

The Fever and Antipyretic in Critically illness Evaluation study

(The FACE study)

Rationale; Fever is associated with various critically ill conditions. The incidence of mild hyperthermia (defined more than 38.0- 38.5 degree) varies from 15 % to 70%, and with an incidence of 8-17% for moderate hyperthermia (defined more than 39.0-39.5 degree).

Hyperthermia may cause discomfort and impose undue metabolic stress on non-neurological critically ill patients. On the other hand, fever is a normal host response to infection and its presence or absence may be used as a means of assessing the activity of infection. Furthermore, there is evidence, at least in animal models, that fever is a beneficial host response to infection.

However, antipyretic therapy for fever in non-neurological ICU patients is routinely performed in the ICU patient. The cost for of antipyretic therapy has been reported to be between \$10,000 and \$29,000 per year in one 18-bed ICU.

What is known in this area (SYSTEMATIC REVIEW)

We performed a systematic MEDLINE and PUBMED search (1978 – 2008) using the following key words: “hyperthermia”, “fever”, “temperature”, “intensive care”, “critically ill”, “ICU”, “death”, “mortality”.

We found 24 papers to assess the relationship between fever and mortality in non-neurological ICU patients. However, none of them had any information of antipyretic therapy. There were only 2 small single center RCT to assess the effect of antipyretic strategy on mortality.

In the first randomized study, 38 surgical ICU patients without neuro-trauma or severe hypoxemia and with fever were randomized to either external cooling (n=18) or no antipyretic treatment (n=20). In this trial, temperature and discomfort decreased similarly in both groups after 24 hours. No significant differences in recurrence of fever, incidence of infection, antibiotic therapy, intensive care unit and hospital length of stay, or mortality were noted between the groups (Arch Intern Med 2001;161:121-123).

In the second RCT, 82 patients admitted to the Trauma Intensive Care Unit without traumatic brain injury were randomized into aggressive or permissive groups. The aggressive group (n=44) received acetaminophen 650 mg every 6 h for a temperature of >38.5 and a cooling blanket was added for a temperature of >39.5. The permissive group (n=38) received no treatment for temperature of >38.5, but instead had treatment initiated at temperature of >40.0, at which time

acetaminophen and cooling blankets were used until temperature was <40.0 . There were seven deaths in the aggressive group and only one death in the permissive group (aggressive vs permissive; 7/44 (16%) vs 1/38 (2.6%) $p = 0.06$). The study was stopped after the first interim analysis due to the mortality difference (Surg infect(Larchmt) 2005;6:369-75)

In summary,

- There are number of studies to assess the relationship between fever and mortality in non-neurological ICU.
- However, all of them did not have any information of antipyretic therapy.
- There are two small, single center RCT, which suggested a potential risk for antipyretic therapy
- A large RCT might be ethically difficult.

It is unfortunate that there is not enough information on how we should control body temperature in non-neurological critically ill patients, because fever is a very common physiological abnormality in this cohort. From the beginning, it would, therefore, be desirable to understand several aspects of fever and antipyretic therapy in ICU patients

- 1) How often fever occurs in our ICUs
- 2) To what degree fever is independently associated with mortality?
- 3) How often antipyretic therapy is prescribed?
- 4) How antipyretic can decrease temperature?
- 5) How different is medication with cooling?
- 6) To what degree antipyretic is independently associated with mortality?

Thus, we plan to address these questions by conducting a multi-national multi-center prospective observational trial, named “The Fever and Antipyretic in Critically illness evaluation study” (The FACE study).

Inclusion criteria

- Adult non-neurological critically ill patients (20 years old or older).
- Expected to require intensive care for more than 48 hour.

The study period (plan)

2009 Sep-Nov (3 months)

with 28 days follow up. (FACE will finish 27th Dec)

The information collect in FACE

A)Patients demographics at admission

- Age
- Sex
- Body weight& heights
- APACHE II score (using first 24 hour data)
- The reason for admission
 - /surgical or medical
 - /elective surgical or emergency surgical
- Infection related admission (Y/N)
(such as sepsis, pneumonia or peritonitis (post surgery) etc.)
- T. Bil, Cre and BUN measured at preadmission (last data measured within 3 months or just at admission) to assess their liver and Kidney function.

B) Information recorded daily while in ICU for up to 28 days.

1) Temperature data

Recorded every four hours and maximum temperature. (Core temperature) with the type of device. (See below)

2) Daily laboratory data (if possible)

3) Antipyretic information

- Medical antipyretic; daily dose of NSAIDs, Acetaminophen, cold fluids and Others.
- Cooling; duration of cooling.
- Complication of treatment
 - * Hypothermia (defined as less than 36 °C)
 - * Hypotension (defined as mean blood pressure less than 50 mmHg, or requiring vasopressor to maintain blood pressure or increasing the dose of vasopressor.)
 - * Decreasing urinary output (defined as less than 0.5

mg/kg/hr during at least consequence 4 hours)

- * Bleeding
- * Allergies (Shock, asthma etc)

4) the therapy contributing to the fever.

Daily dose of steroids

Daily duration on extra corporeal circuit.

4) Infection related information

1) Lung (sputum), 2) blood, 3) urinary tract, 4) other

- The day of diagnosis of infection
- Suspected or proven?

5) Patients outcome

- The day of admission to hospital
- The day of admission to ICU
- The day of start of ventilation
- The last day of ventilation (if they tolerate more than 24 hours without re-intubation)
- The day of discharge from ICU (death or alive)
- The day of discharge from Hospital (death or alive)

Statistical plan (association of fever and antipyretic with outcome)

- Univariate analysis of temperature and antipyretic indices between survivors and non-survivors.
- If any significant difference, multivariate analysis will be performed to adjust patients demographics with survival to 28 days, time to death, time in ICU, time in Hospital, time on ventilator as outcome measures.

Statistical hypothesis.

Fever;

BT > 38.0, 38.5 and 39.0°C is predictors of increases mortality in univariate analysis.

BT > 38.0, 38.5 and 39.0°C is predictors of increases mortality in multivariate analysis.

Maximum temperature when antipyretic (medical or cooling) is used is predictors of increases mortality in univariate and multivariate analysis.

Antipyretic;

Antipyretic (medical or cooling) used when BT is > 38.0, 38.5 and 39.0°C is predictors of increases mortality in univariate analysis.

Antipyretic (medical or cooling) used when BT is > 38.0, 38.5 and 39.0°C is predictors of increases mortality in multivariate analysis.

Antipyretic used (or non-used) when BT is Maximum during ICU stay is predictors of increases mortality in multivariate analysis for adjusting maximum temperature as well.

Temperature indices

- Body temperature at admission
- Max temperature (band analysis in each 0.5°C)
- Min temperature (band analysis in each 0.5°C)
- Mean temperature (band analysis in each 0.5°C)
- Duration > 38.0, 38.5 and 39.0°C

Antipyretic indices (BT=body temperature)

- Whether antipyretic is used during ICU stay.
- The first antipyretic strategy (dose, type etc) prescribe from BT>38.0 to BT<38.0.
- The antipyretic strategy (dose, type etc) prescribe from Max BT to BT<38.0.

Power calculation

If one assume fever ($BT > 38.5^{\circ}\text{C}$) occurred in 50% on non-critically ill patients, half of them were prescribed antipyretic therapy and the mortality of non-neurological ICU patients required ICU more than 48 hours is 10%.

- **Assuming 7% increase in ICU mortality with antipyretic, a power of 0.80, and an α level of 0.05, we require 1200 participants.**
- **Assuming 6% increase in ICU mortality with fever ($BT > 38.5$), a power of 0.90, and an α level of 0.05, we require 1200 participants.**

To conduct the multicenter study for fever, one of difficulties is to standardize the device for measuring body temperature. The text below shows the recommendation for devices.

I would like to propose that all participated units can use 7 devices (1;Pulmonary artery thermistor, 2;Urinary bladder catheter thermistor, 3;Esophageal probe, 4;Rectal probe, 5;Oral probe, 6;ear thermometry(Tympanic membrane temperature), 7 Axillary's thermometer) as following their standard care. All ICUs record the temperature and device every 2 hours. The variation of device might create bias for the results. Therefore, we will perform multivariate analysis including the device as independent factors to adjust device related bias.

How to measure fever

PA catheter ;Most authorities consider the thermistor of a pulmonary artery catheter to be the standard for measuring core temperature against which other devices must be compared.

Bladder Catheter; Thermistors in indwelling bladder catheters provide essentially identical readings to thermistors in intravascular sites, are less invasive, provide continuous readings, and provide stable measurements, regardless of urine flow rate. However, bladder thermistor catheters are costly and require a monitor.

Esophageal probes; Esophageal probes placed in the distal third of the esophagus provide readings comparable with thermistors in intravascular sites and with bladder catheters. In addition, they are uncomfortable in alert or spontaneously breathing patients. The theoretical risk of an esophageal probe eroding or perforating the esophagus when left in place for extended periods of time makes this probe impractical for use in the critically ill patient.

Rectal probes; Rectal temperatures obtained with a mercury thermometer or anelectronic probe (intermittent or continuous) are traditional measurement devices. Readings from the rectum are often a few tenths of a degree higher than core temperature. The patient often perceives rectal temperature measurement as unpleasant and intrusive. Access to the rectum may be limited by patient position. Moreover, there is a small risk of trauma or perforation to the rectum, which is a particular problem in patients who are neutropenic, coagulopathic, or who have had recent rectal surgery. Rectal temperature measurements have also been implicated in spreading enteric pathogens such as *Clostridium difficile* or vancomycinresistant enterococci via the device or the operator.

Oral temperature measurement; Oral temperature measurement is safe,

convenient, and familiar for alert and cooperative patients. Mouth breathing, heated gases, and hot or cold fluids can distort the reading. Oral probes can damage oral mucosa, especially in patients with abnormal mucosa due to trauma, thermal injury, infection, surgery, cancer, or cytotoxic drugs. In critically ill patients, oral temperatures are often not practical due to intubation or inability of the patient to cooperate.

Tympanic membrane temperature; Tympanic membrane temperature is believed to reflect the temperature of the hypothalamus and, thus, the core body temperature. Direct measurement of the tympanic membrane temperature requires an electronic probe, is painful in awake patients, and risks trauma to the tympanic membrane. Infrared ear thermometry is also available to detect radiant energy from the tympanic membrane and ear canal through an otoscopic probe. These devices are not accurate if inflammation of the auditory canal or tympanic membrane is present or if there is obstruction of the external canal. Tympanic membrane and infrared devices do not always agree with other measurement devices. Multiple studies have shown consistently poor agreement between measurements made by infrared ear devices and those made by pulmonary artery catheters

Axillary's thermometer

Axillary's measurements have not recommended to be used in the ICU (level 2). However, this method is also acceptable in FACE, when it is the only way to measure temperature.

Table1; Accuracy of methods used for measuring temperature

Most accurate

Pulmonary artery thermistor

Urinary bladder catheter thermistor

Esophageal probe

Rectal probe

Other acceptable methods in order of accuracy

Oral probe

Infrared ear thermometry

Other methods less desirable

Temporal artery thermometer

Axillary thermometer

Note; Our research group should be tightly connected and worked for each other not for individual advantage. The publication from their research works should be “FACE study group with Korean and Japanese collaboration research team”, not with individual names.

(Written by M.E.)

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