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, which 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 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 a 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 effectively antipyretic can decrease temperature?
5） How different is lowering temperature with medications compared 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 critically ill patients (20 years old or older).
- Expected to require intensive care for more than 48 hours.

Note; Re-admission can be used as another entry to FACE study.

Exclusion criteria

- Post brain surgery (craniotomy).
- Suspected or proven brain damage (ischemic brain injury, massive brain edema, cerebral hemorrhage, subarachinoid hemorrhage, and cerebral infarction)
  (Please include patients with abnormality of consciousness due to dug abuse and metabolism abnormality as like hyponatremia, liver dysfunction etc, if investigators think it is reversible)

Note; FACE study wants to exclude cohort who have potential to be a candidate of hypothermia or normothermia therapy to prevent brain damage, as like post cardiac arrest and traumatic brain injury patients.

The study period

Study will start from 1st Sep to 30th Nov 2009.
with 28 days follow up. (FACE will finish 28th Dec 2009)

The information collect in FACE

1) Patients demographics

- Hospital Name (It will be coded as Hospital 1, 2, 3‥in final database and country names, no individual name in database)
- Sex (Male=1, Female=0)
- Age (years old at admission)
- Height (cm)
- Body weight (kg)

2) The reason for ICU admission

A) Medical or surgical admission?

・Post-operative admission (elective or emergency)

=The patients who admitted in ICU after surgical operation

（If patients is admitted in ICU **not** after surgery, but require surgical operation within 6 hours after admission (admission for preparation of surgery), he is categories as “surgical patients”. For these patients, the data collection (such as APACHE II calculation, body temperature etc) will be started from admission after surgery.

・Non-operative admission（from emergency room, ward and another hospital）

=The patients who admitted in ICU not after surgical operation

B) Infection related admission (Y/N)

(Such as sepsis, pneumonia or peritonitis (post surgery) etc.)

C) Trauma (Y/N)

D) Post transplantation (Y/N)

E) Re-admission (Y/N)

Readmission can be used as another entry for FACE study.

F) Main problem for ICU admission

Please select **only one problem** as main issue for ICU admission.

3) Co-morbidity of patients (Y/N)

If patients have co-morbidity shown below please check “Y” and check any

individual morbidity (if any, it can be multiple choice)
Liver cirrhosis, NYHA Class IV, Hugh Jones Class V, Chronic dialysis, AIDS, Hematology malignancy, Metastatic cancer, Immuno-suppression, Chemotherapy, Long term high dose steroids

4) Patients outcome at 28 days

- Die in ICU (if yes, please provide the day of die)
- Die in Ward (if yes, please provide the day of die and discharge from ICU)
- Survive in ICU
- Survive in Ward (if yes, please provide the day of discharge from ICU)
- Discharge from Hospital or transfer to another hospital (if yes, please provide the day of discharge ICU and hospital)

(Transfer to another hospital is considered as “survival discharge from hospital”).
(If patients discharge from hospital before 28 days, they are “alive”. No need to follow up after discharge.)

5） Mechanical ventilation requirement during ICU stay (Y/N)
Duration; please provide the day for starting and day for stopping.
Success for stopping mechanical ventilation defined as weaning from it for more than 48 hours.
(Mechanical ventilation=invasive or non-invasive respiratory support.)

Ex, If patients are ventilated from Dec 1st, extubated at Dec 6th, re-intubated Dec 7th and extubated at Dec 10th. The duration is documented as “Dec 1st –Dec10th”

If patients are ventilated from Dec 1st, extubated at Dec 6th, reintubated Dec 9th and extubated at Dec 10th. The duration should be documented as “Dec 1st–Dec 6th and Dec 9th-Dec 10th”.

6） Renal replacement therapy requirement during ICU stay (Y/N)
Duration; Please provide the day for starting and stopping.
(renal replacement therapy =Continuous renal replacement therapy, SLED, intermittent dialysis or peritoneal dialysis)

7) APACHE II calculation

GCS; If it is unable to assess the GCS so that patients are anesthetized or/and

sedated, please provide GCS before commencement of anesthesia or sedation.
If patient's GCS is 15 before anesthesia, and after operation, he/she is admitted into ICU and sedated for next 30 hours. There are nothing to concern brain damage during operation and first 24 hours of ICU stay. His GCS for APACHE II calculation is 15.

Mechanical ventilation within 24 hours from admission (Y/N)
(Mechanical ventilation=invasive or non-invasive respiratory support.)

B) Information recorded daily during ICU stay up to 28 days.

The information which required **daily** for all patients until the day of ICU discharge or the 28th day of ICU.

1); Requirement of Extra corporeal circuit? (Yes or No)
Hemodialysis, CVVHD, CVVHDF, CVVHF, ECMO etc

2); Requirement of any steroid? (Yes or No)
For Replacement for previous corticosteroid treatment,
For Septic shock
For Fibroproliferative ARDS
For Immunosuppression for prevention or treatment of organ rejection
For Immunosuppression for treatment of inflammatory disease
For Acute exacerbation of COPD
For Acute asthma
Etc

3) Infection data
Not suspected, suspected or culture proven infection.

4) 4 hourly temperature data
Please recode body temperature at every four hours.

5) Type of device used to measure body temperature.
Please circle one device.

- B; Blood temperature as like using pulmonary artery thermistor
- U; Bladder catheter thermistor
- E; Esophageal temperature
- O; Oral temperature
- R; Rectal probe
- T; Tympanic membrane temperature
- A; Axillary temperature

Please select one device for temperature measurement at 0:00. Please use most reliable temperature, when you measure two or more than 2 temperatures. Please see the statement of reliability of body temperature measurements shown below.

When you change the place of body temperature measurements, please document

as like bellow

Patient is admitted in ICU at 9:00 and his temperature is measured by urinary bladder catheter thermistor. His urinary bladder catheter is removed at 11:00 next day of admission then, Axillary temperature is used. He discharges from ICU at 14:00 of 2nd day.

Place of measure at 0:00 or admission	0:00	4:00	8:00	12:00	16:00	20:00
B(U), E, O, R, T, A	℃	℃	℃	36.8 ℃	37.8 ℃	38.2 ℃
B(U), E, O, R, T, A	38.5 ℃	37.5 ℃	38.2 ℃	(A) 37.4 ℃	37.5 ℃	37.8 ℃
B, U, E, O, R, T, (A)	38.6 ℃	37.6 ℃	38.3 ℃	38.4 ℃	℃	℃

Please document the place of measurement, when it is changed

6) Antipyretic information

The method, time and the temperature start antipyretic therapy.

Methods

EX; External cooling; Cooling blanket, ice pack etc

IN; Internal cooling; Cold gastric lavage, cold fluid infusion etc

NSAIDS; Non steroid anti inflammatory drugs

Ace; Acetaminophen

Steroid Steroid just for antipyretic

Oth; Other cooling methods

Statistical plan （association of fever and antipyretic with mortality）

How to use axillary temperature.

Axillary temperature was reported to be 0.4℃ lower than core temperature in average. Thus, in FACE study, Axillary temperature+0.4℃ will be used as surrogate of core temperature.

Indices for fever.

For each patient, maximum and minimum body temperature ($BT_{Max,}$ BT_{Min}), body temperature at admission (BT_{adm}), time weighted average of body temperature(BT_{Ave}), the duration BT and time weighted BT above 38.0℃, 38.5℃, 39.0℃, 39.5℃ and 40.0℃ and complexity of variability of body temperature.were obtained.

1;Whether patients developed fever defined above 38.0℃, 38.5℃, 39.0℃, 39.5℃ and 40.0℃.

2;The duration of body temperature above 38.0℃, 38.5℃, 39.0℃, 39.5℃ and 40.0℃ per total ICU duration.

3;The time weighted area above＞38.0℃, 38.5℃, 39.0℃, 39.5℃ and 40.0℃.

Indices for antipyretic

1; Whether antipyretic therapy is prescribed above 38.0℃, 38.5℃, 39.0℃, 39.5℃ and 40.0℃.

2; Whether external cooling is prescribed above 38.0℃, 38.5℃, 39.0℃, 39.5℃ and 40.0℃.

3; Whether internal cooling is prescribed above 38.0℃, 38.5℃, 39.0℃, 39.5℃ and 40.0℃.

4; Whether NSAIDS is prescribed above 38.0℃, 38.5℃, 39.0℃, 39.5℃ and 40.0℃.

5; Whether acetaminophen is prescribed above 38.0℃, 38.5℃, 39.0℃, 39.5℃ and 40.0℃.

<u>Statistical methods</u>

Fever; To compare the mortality between patients cohorts between no fever cohorts and patients whose BT_{Max} are more than 38.0℃, 38.5℃, 39.0℃, 39.5℃ and 40.0℃

BT＞38.0, 38.5 and 39.0℃ is an independent predictor of increased mortality in multivariate analysis.

Antipyretic;

The odds ratio for antipyretic use on mortality when BT is above 38.0℃ will be calculated. The multivariate analysis will be performed to determine adjusted odds ration for antipyretic therapy prescribed when BT is above 38.0℃

Same analysis will be performed for physical cooling (external and internal), NSAIDs and acetaminophen, then compared their odds ratio.

Same analysis will be performed for BT is above 38.5℃, 39.0℃, 39.5℃ and 40.0℃, then compared their odds ratio.

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 one of 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 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 devise as independent factors to adjust device related bias.

How to measure fever

Blood temperature; most authorities consider the thermistor of a pulmonary artery catheter or central venous 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. 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 an electronic 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 vancomycin-resistant 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 thermometer; axillary temperature 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.)
First draft 2008, July 6th.
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