Some like it HOT!

Revelations in Managing Fever in the ICU.

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Fever in Critical Illness

1. Normal Thermoregulation
2. Physiology of Fever
3. Costs and **BENEFITS** of Fever
4. When & How to Treat a Fever
Normal is ......
36.3 °C to 37.8 °C

Cellular function is best when body temperature is within this range.

Thermoregulation is a VITAL body function.

The body will do anything and everything to defend core body temperature at the HYPOTHALAMIC SET POINT.
Measures Body Temperature

Determines SET POINT

Hypothalamus

Perception of Hot or Cold

Warm Sensitive Neurons (WSN)

Core body
Hypothalamus (OVLT)
Abdomen
(via vagus & splanchnic nerves)

Skin

Perception of Hot or Cold

Warm Sensitive Neurons (WSN)

Shivering

Cardiac Thermogenesis

BAT Thermogenesis

Vasomotor Control

Sweating

Measures Body Temperature

Measures

Body Temperature

Set Point

Hypothalamus

Perception of Hot or Cold

Warm Sensitive Neurons (WSN)

Core body
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(via vagus & splanchnic nerves)

Skin

Perception of Hot or Cold

Warm Sensitive Neurons (WSN)
Vasomotor Control

This is a cross section of the Cutaneous layer

Cold
- blood flow to ½ L/min
- insulation & heat loss
- The cutaneous layer becomes a **THICK WOOL COAT**

Hot
- blood flow to 7.8L/min
- insulation & heat loss
- The cutaneous layer becomes a **RADIATOR**
Sweating Buckets

We can sweat as much as

1L/hr to 1.8L/hr

1%-2% of 70 kg is

0.7L to 1.4L

Brown Adipose Tissue (BAT)

- Primary job is THERMOGENESIS
- Packed with specialized mitochondria
- Does NOT make ATP (UCP-1)
- Makes HEAT (300x better than any other cell)
- Highly vascular
- Highly innervated (WSN - inhibitory)

LOCATED ➔
**BAT Thermogenesis**

*Turns on with COLD.* + *Turns up With A Fever!*

When febrile UNSEDATED patients are cooled to treat a fever metabolic rate **INCREASED by 35% to 40%** prior to the onset of shivering.


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**Turning off BAT Thermogenesis**

*No Ice Without Snow*

20 febrile ICU patients, who received moderate to heavy sedation and analgesia where also cooled externally from 39 C to 37 C. 17 patients had an average of **12 % decrease in O2 consumption.**

Cardiac Thermogenesis

- Innervated in parallel with BAT
- Stimulated in THERMOGENESIS
- SA node stimulated to increase HR
  - Increase blood supply to meet demand
  - Circulate warmed blood
  - **CREATES HEAT**
    - Why your heart races when you jump in the lake
    - Why you see tachycardia with fever.

Shivering

Shivering starts when the core body temperature is 1 °C to 2.5 °C below the **HYPOTHALAMIC SETPOINT**.
Shivering

will increase the basal metabolic rate by 100% to 200%
(equal to an aerobic workout)

2. Physiology of Fever

- Thermoregulation happens in exactly the same way whether the person is febrile or afebrile.

- The only difference is the hypothalamic set point is > 38.3°C instead of 37°C.

- **FEVER IS NOT Hyperthermia**
Causes of Fever

- **Not all infections cause fever**
  - 55% of septic patients are febrile
  - 35% are normothermic
  - 10% are hypothermic

- **Not all fever is caused by infection**
  - 25% to 40% of all fevers are caused by non-infectious sources

Non-Infectious Causes of Fever

- **GENERALLY** they follow the 102 °F rule (except drug fevers) \(102^\circ\text{F} = 38.9^\circ\text{C}\)

- **A VERY long list...but generally its** INFLAMATION
  - all the itis's
  - any tissue damage
  - necrotic tissue anywhere
  - extra vascular blood
  - cancer
Physiology of Fever

Hypothalamus

PYROGENIC CYTOKINES
- Interleukin 1
- Interleukin 6

CRYOGENIC CYTOKINES
- Glucocorticoids
- Vasopressin
- Other mediators (indirectly HSP)

Blood flow

Tissue Injury or Infection

Epithelium of hypothalamus

Set Point

Epithelium of hypothalamus

Set Point

Prostaglandin E₂

Cytokine Receptors

Epithelium of hypothalamus

Set Point

Hypothalamus

preoptic area of anterior hypothalamus
Physiology of Fever

Hypothalamus
preoptic area of
anterior hypothalamus

37°C

Set Point

Toll-Like
Receptors

Prostaglandin E₂

37°C

Hypothalamus
preoptic area of
anterior hypothalamus

Set Point

Physiology of Fever

ACETAMINOPHEN
Blocks Prostaglandin E

Prostaglandin E
Antipyretic Related Hypotension in some ICU Patients with SIRS

- M. Boyle, S. Hundy, T.A. Torda (1997)
- 23 febrile ICU patients, all given an antipyretic (Paracetamol) and BP was monitored
  - on average 10% drop in systolic BP & 7% drop in MAP (including treatments initiated)
  - 8 of 23 (34%) patients required treatment for hypotension following Paracetamol administration (fluid bolus and/or vasoactive infusions)

3. Costs of Fever

- Increases basal metabolic rate by 10% to 13% for every 1 °C increase in core temperature
- Increases myocardial workload
- When there is neurological insult, Fever enhances inflammation in the brain ....
  ➔ Worsening neurological outcomes.
Benefits of Fever

• Acts directly on bacteria
  - replication of bacteria and viruses are altered at temperatures >38°C

Even if microbes replicate, they are more susceptible to antibiotics

Acts to stimulate immune function
  - enhances neutrophil migration
  - enhances production of antibacterial substances
  - enhances production and function of interferon
  - enhances T-cell proliferation
  - release of *Heat Shock Proteins*

(Mackowiak, Marling-Cason & Cohen, 1982)
Heat Shock Proteins (HSP)

- In every cell of the body & is released when the body is exposed to temp $> 37^\circ C$.
- An adaptive response to protect cells from excessive stress.
- Can be induced after as little as 15 minutes of heat stress.
- Remains active for 1 to 3 days.

Roles of HSP

**WITHIN THE CELL**
- Chaperones
- Mr. Fix-it
  - Folding or refolding damaged proteins
- Garbage Collectors
  - Removes proteins that are too damaged

**OUTSIDE THE CELL**
- Stress Observation System
- Regulates the inflammatory response.

**WHAT NEXT?**
Fever as THERAPY???

- When you up-regulate HSP, (pre-treat with heat) you have improved outcomes.
  
  (in a study by Villar, Ribeiro, Mullen, Kuliszewski, Post & Slutsky (1994))

- 142 rats, 1/2 Controls, 1/2 were treated with heat stress (temp up to 42°C for 15 minutes)
  
  - Later all were given a perforated bowel

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<thead>
<tr>
<th></th>
<th>Control group</th>
<th>Heat Pre-treated group</th>
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<tbody>
<tr>
<td>18 hour mortality</td>
<td>25%</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p&lt;0.005</td>
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<tr>
<td>7 day mortality</td>
<td>69%</td>
<td>21%</td>
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<td></td>
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<td>p&lt;0.01</td>
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The ICU Study!!

- In a Study by, CI Schulman, N Namias, J Doherty, RJ Manning, P Li, A Alhaddad, D Lasko, J Amortegui, CJ Dy, L Dlugasch, G Barracco & SM Cohn (2005)

- Randomized prospective study

- Trauma ICU patients who had a fever on day 3 of their ICU stay divided into 2 group
  
  - Aggressive group 650 mg acetaminophen q6h for temp >38.5°C and a cooling blanket was added for temp >39.5°C
  
  - Permissive group had no treatment until pt temp was >40°C at which point acetaminophen and cooling was provided to bring pt temp < 40°C
THE RESULTS

- 82 pt enrolled in the study,

<table>
<thead>
<tr>
<th></th>
<th>Aggressive Group</th>
<th>Permissive Group</th>
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<tbody>
<tr>
<td>Participants</td>
<td>44</td>
<td>38</td>
</tr>
<tr>
<td>Infections</td>
<td>131 (4±6)</td>
<td>85 (3±2)</td>
</tr>
<tr>
<td>(p=.26)</td>
<td></td>
<td>(p=0.007)</td>
</tr>
<tr>
<td>Days on antibiotics</td>
<td>77.2%</td>
<td>70.9%</td>
</tr>
<tr>
<td>(p=0.007)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deaths</td>
<td>7 DEATHS (p=.06)</td>
<td>1 DEATH (p=0.06)</td>
</tr>
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4. How to Treat Fever

- Find the cause.
  - blood, urine & sputum cultures and other indicators of infection.
  - explore possible non-infectious causes.
  - examine fever patterns.
    - i.e., low, mid or high grade fevers.
    - when did it spike, or resolve.

- Treat the cause with appropriate antimicrobial therapies.

- Optimize O2 Supply /Demand (& nutrition)
Weigh the Costs & Benefits

- **COSTS**
  - Increases myocardial workload
  - Increases basal metabolic rate (O2 Demand)
  - Increase Cerebral O2 Consumption & Cerebral INFLAMMATION

- **BENEFITS**
  - Enhances immune function
  - Inhibits microbial growth
  - Cross-protection of HSP
  - Possible better regulation of the inflammatory response with HSF

How to treat

- Treat with antipyretic drugs first.
- **NO ICE without SNOW!**

When to treat

- When cost outweigh benefits
  - CEREBRAL INJURY
  - O2 SUPPLY/DEMAND MISMATCH
    - SEVERE ARDS
    - SEVERE SEPSIS
    - MI
    - Very high fever???

ANTIPYRETIC treatments are not benign.

NEVER cool unless your patient is adequately sedated. Unsedated patients will INCREASE metabolism to counteract the cold.
Some like it HOT!

The End

Thank you.

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