Fever management in ICU

@DogICUma

Dr Paul Young
I have no conflicts of interest to declare
Neurosyphilis resolves after febrile illness

Malaria causes a fever

Malaria therapy for syphilis?

THE VALUE OF FEVER THERAPY FOR GONORRHEA

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Author Affiliations


The Kettering hypertherm with patient in place.
Early peak temperature and mortality in critically ill patients with or without infection

No infection

Infection

n > 500,000
fever is *good* because it helps fight infections
Original Article

Acetaminophen for Fever in Critically Ill Patients with Suspected Infection

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Frank van Haren, M.D., Ph.D., Mark Holliday, B.Sc., Seton Henderson, M.D.,
Diane Mackle, M.N., Colin McArthur, M.D., Shay McGuinness, M.D.,
John Myburgh, M.D., Ph.D., Mark Weatherall, M.D., Steve Webb, M.D., Ph.D.,
and Richard Beasley, M.D., D.Sc., for the HEAT Investigators and the Australian
and New Zealand Intensive Care Society Clinical Trials Group.
It is unclear whether administration of paracetamol to treat fever is beneficial OR harmful
• Phase 2b RCT comparing IV paracetamol with placebo in ICU patients with fever and infection
Hypothesis

In ICU patients with likely infection, using paracetamol to treat fever will ↓ ICU-free days (by 2.2 days)
Inclusion Criteria

Fever

+ Likely infection
Exclusion Criteria

Contraindications or Acute brain pathologies
Paracetamol 1g IV 6hrly
or
Placebo
When study treatment stopped

1. Fever resolved
2. Antimicrobial therapy ceased
3. Discharged from ICU
4. Day 28
5. Contraindication to paracetamol developed
**Fever resolution algorithm**

- **Gave study drug until morning of day 2**
- **Afebrile for 24 hours?**
  - YES: **Continued study drug**
  - NO: **Withheld study drug**
- **Fever within 48 hours?**
  - NO: **Ceased study drug permanently**
  - YES: **Restarted study drug**
- **Assessed patient daily**
Met inclusions (n=3601)

- Met exclusions (n=1674)
  - Contraindications to paracetamol (n=652)
  - Acute brain pathologies (n=519)
- Did not consent (n=174)
- Eligible but missed (n=1053)

Randomised (n=700)
CONSORT

Randomised (n=700)

Paracetamol (n=352)
- Received allocated intervention (n=344)
  - Consent withdrawn (n=6)
  - Analysed (n=346)

Placebo (n=348)
- Received allocated intervention (n=339)
  - Consent withdrawn (n=4)
  - Analysed (n=344)
Treatment groups had similar baseline characteristics
• Age 60 years
• \( \frac{2}{3} \) male
• Most common comorbid conditions were diabetes (25%) & cancer (20%)
• >80% had severe sepsis
• \( \approx 50\% \) invasively ventilated
• \( \approx 50\% \) on inotropes / vasopressors
• APACHE-II scores around 19
Percentage of study patients in ICU receiving study medication

![Graph showing the percentage of study patients in ICU receiving study medication over study days. The graph compares two groups: Paracetamol (blue) and Placebo (red). The percentage drops significantly over the study period from 0 to 28 days.]
Percentage of study patients in ICU receiving open label paracetamol
DESIGN TEMPERATURE EFFECTS

Maximum body temperature

P<0.001

Paracetamol
Placebo

baseline 0 1 2 3 4 5 6 7

study day
Mean body temperature

P<0.001
Primary outcome
<table>
<thead>
<tr>
<th>OUTCOMES</th>
<th>Paracetamol (n=346)</th>
<th>Placebo (n=344)</th>
<th>Difference (96.21%CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU-free days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>23 days [IQR 13-25]</td>
<td>22 days [IQR 11.5-25]</td>
<td>0 days (0 to 1)</td>
<td>0.07</td>
<td></td>
</tr>
</tbody>
</table>
Distribution of ICU-free days by treatment group

ICU-free days

Paracetamol
Placebo
<table>
<thead>
<tr>
<th>Mortality</th>
<th>Paracetamol (n=346)</th>
<th>Placebo (n=344)</th>
<th>Relative Risk (95%CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 28</td>
<td>13.9%</td>
<td>13.7%</td>
<td>1.02 (0.68 to 1.52)</td>
<td>0.94</td>
</tr>
<tr>
<td>Day 90</td>
<td>15.9%</td>
<td>16.6%</td>
<td>0.96 (0.66 to 1.35)</td>
<td>0.84</td>
</tr>
</tbody>
</table>
Kaplan-Meier Survival Curve

Survival Probability

Days

P=0.80

Paracetamol
Placebo

Censored
<table>
<thead>
<tr>
<th></th>
<th><strong>Paracetamol (n=346)</strong></th>
<th><strong>Placebo (n=344)</strong></th>
<th><em><em>Exponent</em> (95%CI)</em>*</th>
<th><strong>P value</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ICU length of stay (days)</strong></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Non-survivors</strong></td>
<td>Median: 10.4 days [IQR, 4.1-16.9]</td>
<td>Median: 4.0 days [IQR, 1.7-9.4]</td>
<td>2.12 (1.43 to 3.13)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Survivors</strong></td>
<td>Median: 3.5 days [IQR, 1.9-6.9]</td>
<td>Median: 4.3 days [IQR, 2.1-8.9]</td>
<td>0.84 (0.70 to 0.99)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

*The exponent of the difference can be interpreted as the ratio of the means*
<table>
<thead>
<tr>
<th></th>
<th>Paracetamol (n=346)</th>
<th>Placebo (n=344)</th>
<th>Odds Ratio (95%CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver Dysfunction</td>
<td>8.1%</td>
<td>9.9%</td>
<td>0.89 (95% CI: 0.69 to 1.16)</td>
<td>0.40</td>
</tr>
</tbody>
</table>
Paracetamol did not alter ICU-free days in patients with fever and likely infection.
Paracetamol appears to have a modest antipyretic effect in adult ICU patients with fever and likely infection.
Paracetamol appears to be well tolerated in adult ICU patients with fever and likely infection.
fever is bad because it increases metabolic & physiological demands
if an illness is reversible, ICU therapy allows patients to survive
...if they can be supported long enough to recover
fever is common
tolerance of the physiological demands created by fever may be poor
one potential way to protect patients from the physiological demands of fever...
is to systematically prevent & treat fever
IBUPROFEN


<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>IBUPROFEN NO. OF PATIENTS</th>
<th>MORTALITY (95% CI)</th>
<th>PLASICO NO. OF PATIENTS</th>
<th>MORTALITY (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>224</td>
<td>37 (31-44)</td>
<td>231</td>
<td>40 (34-45)</td>
</tr>
<tr>
<td>Shock</td>
<td>146</td>
<td>42 (34-51)</td>
<td>147</td>
<td>45 (37-53)</td>
</tr>
<tr>
<td>No shock</td>
<td>78</td>
<td>28 (19-40)</td>
<td>84</td>
<td>31 (22-42)</td>
</tr>
<tr>
<td>Black race</td>
<td>72</td>
<td>42 (26-59)</td>
<td>58</td>
<td>57 (37-75)†</td>
</tr>
<tr>
<td>Hypothermia</td>
<td>24</td>
<td>54 (20-85)</td>
<td>20</td>
<td>50 (44-99)†</td>
</tr>
<tr>
<td>Positive blood culture</td>
<td>75</td>
<td>45 (34-57)</td>
<td>68</td>
<td>40 (28-52)</td>
</tr>
<tr>
<td>Negative blood culture</td>
<td>149</td>
<td>34 (26-42)</td>
<td>163</td>
<td>40 (32-45)</td>
</tr>
</tbody>
</table>

* CI denotes confidence interval.
† P = 0.06 for the comparison with the ibuprofen group.
‡ P = 0.02 for the comparison with the ibuprofen group.
Risks / benefits

- Least sick patients
- Most sick patients

Benefits of fever (infection)
Benefits of fever (no infection)

Costs of fever exceed benefits (i.e. fever should be treated)
How to monitor temperature
core vs.
peripheral
Take home point #1: The conversion from peripheral temp to core temp by adding 0.5°C is not supported by evidence.
tympanic vs. bladder
axillary vs. bladder
nasopharyngeal vs. bladder
Take home point #2: The temperature on the ICU chart is not as accurate as you think.
Accuracy of Peripheral Thermometers for Estimating Temperature
A Systematic Review and Meta-analysis

Daniel J. Niven, MD, MSc; Jonathan E. Gaudet, MD, MSc; Kevin B. Laupland, MD, MSc; Kelly J. Mrklas, MSc; Derek J. Roberts, MD, PhD; and Henry Thomas Stelfox, MD, PhD

Background: Body temperature is commonly used to screen patients for infectious diseases, establish diagnoses, monitor therapy, and guide management decisions.

Purpose: To determine the accuracy of peripheral thermometers for estimating core body temperature in adults and children.

Data Sources: MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, and CINAHL Plus from inception to July 2015.

Study Selection: Prospective studies comparing the accuracy of peripheral ( tympanic membrane, temporal artery, axillary, or oral) thermometers with central (pulmonary artery catheter, urinary bladder, esophageal, or rectal) thermometers.

Data Extraction: 2 reviewers extracted data on study characteristics, methods, and outcomes and assessed the quality of individual studies.

Data Synthesis: 75 studies (8682 patients) were included. Most studies were at high or unclear risk of patient selection bias (74%) or index test bias (69%). Compared with central thermometers, peripheral thermometers had pooled 95% limits of agreement (random-effects meta-analysis) outside the predefined clinically acceptable range (±0.5°C), especially among patients with fever (−1.44°C to 1.46°C for adults; −1.49°C to 0.43°C for children) and hypothermia (−2.07°C to 1.90°C for adults; no data for children). For detection of fever (bivariate random-effects meta-analysis), sensitivity was low (64% [95% CI, 55% to 72%]; $P = 0.01$, $P < 0.001$) but specificity was high (96% [CI, 93% to 97%]; $P = 0.01$, $P < 0.001$). Only 1 study reported sensitivity and specificity for the detection of hypothermia.

Limitations: High-quality data for some temperature measurement techniques are limited. Pooled data are associated with interstudy heterogeneity that is not fully explained by stratified and metaregression analyses.

Conclusion: Peripheral thermometers do not have clinically acceptable accuracy and should not be used when accurate measurement of body temperature will influence clinical decisions.

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For author affiliations, see end of text.
Axillary temperature monitoring
• Death associated with very high body temperature
• Intermittent monitoring of axillary temperature failed to detect a potentially life threatening fever
Take home point #3: If the axillary temperature exceeds 39°C consider continuous monitoring.
How I treat fever
think of sepsis
very high fever
acute brain pathologies
Take home point #4: If I make a clinical decision that controlling fever is important then I typically administer paracetamol regularly.
Physical cooling
The problem with surface cooling
Take home point #5: In morbidly obese patients with very high temperature external cooling stimulates intense vasoconstriction & can make the core temperature rise initially.
NSAIDS
Ibuprofen
800mg Q6hrly
Take home point #6: 48 hours of ibuprofen appears to be safe and well-tolerated in sick ICU patients
costs of fever exceed benefits (i.e. fever should be treated)
Randomised Evaluation of Active Control of Temperature vs. ORDinary temperature management (REACTOR)
multi-centre, phase II, open-label, feasibility trial...
...comparing combined prophylactic IV paracetamol and early targeted physical cooling to treat fever
...with standard temperature management
...in mechanically ventilated adults without acute brain pathologies who are expected to be ventilated beyond the day after randomisation
Inclusion Criteria

- ≥18 years
- Invasive ventilation in ICU
- Expected to remain ventilated beyond the next calendar day
- Temp 37.8°C or more in the previous 12 hours
Exclusion Criteria

- Acute brain pathologies
- Recent cardiac arrest
- Regular paracetamol contraindicated
- Dying
- Previously enrolled
- Eligible >24 hrs ago
• Standard care
• If paracetamol is used it should be PRN
• Avoid paracetamol by the IV route unless there is a specific indication
FEVER CONTROL ALGORITHM FOR PATIENTS RANDOMISED TO THE INTERVENTION ARM ONLY

**Intervention**

- **Regular IV Paracetamol**: 1gm 6 hourly until day 14 or ready for ICU discharge (whichever is sooner)

**Flowchart**

1. **Temperature ≥ 37.8°C?**
   - **YES**: Physical cooling NOT needed
   - **NO**:
     - **Extubated AND off vasopressors/inotropes?**
       - **YES**: Use simple cooling measures* AND if temperature reaches ≥38°C add a physical cooling device, targeting 36.5-37°C
       - **NO**: Temp < 37.8°C for 48 hours OR patient extubated & off vasopressors/inotropes?
         - **YES**: Physical cooling NOT needed
         - **NO**: Continue physical cooling

*Simple cooling measures include:
- Removal of clothing & sheets
- Using a sponge or wet towel
- Using a fan

Note: If use of a physical cooling device provokes shivering this should be treated using opioids +/- sedation +/- paralysis. If none of these treatments are clinically appropriate or if shivering cannot be controlled, use of the physical cooling device should be ceased.
• Temporal artery & axillary thermometers should not be used
• Continuous monitoring of core temperature while ventilated
• Tympanic when core not possible
Intervention

- Shivering treatment:
  (i) Opioid bolus
  (ii) Sedation
  (iii) Neuromuscular paralysis
Temp $\geq 37.8^\circ C$ should trigger investigation for new infection and consideration of empirical therapy for new sepsis
The between group difference in *mean body temperature* calculated from the body temperatures measured six hourly for seven days (168 hours) or until ICU discharge whichever is sooner.
Secondary outcome

- ICU-free days
- In hospital mortality
- Survival time to day 28 (censored at hospital discharge)
Sample size & recruitment

184 patients
90% power
12 sites
1.5 patients per site per month
10 months total
Sick people should have core temperature monitoring

Aggressive treatment of fever may benefit patients with limited physiological reserves (especially in the absence of infection)