Supplementary Online Content


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This supplementary material has been provided by the authors to give readers additional information about their work.
eAppendix 1: Treatment guidelines

Antimicrobial therapy

Cardiovascular care

- Fluid resuscitation to maintain adequate fluid balance
- Maintain mean arterial pressure between 70-100 mmHg. Use norepinephrine if necessary
- In case of septic shock, low dose steroids with HSHC 50mg every 6 hours, plus 9α fludrocortisone

Respiratory care

- Maintain PaCO2 between 35-40 mmHg

Metabolic care

- Maintain glycemia below 8 mmol/L
- Maintain natremia to normal range 140-145 mmol/L
- Maintain magnesemia in normal range 0.75-1 mmol/L
- Maintain phosphoremia above 0.6 mmol/L

Neurologic care

- Perform cerebral CT-scan before lumbar puncture immunocompromised patient, history of CNS disease, new onset of seizure, papilledema, abnormal level of consciousness (GCS < 10) or focal neurologic deficit.
- Dexamethasone 10mg IV every 6 hours during 4 days, initiated before or with the first dose of antibiotics.
- In patients with high risk of brain herniation, consider use of osmotic diuretics.
- Anticonvulsivant therapy in case of seizure (clinically or electrically confirmed).
- Deep sedation (Ramsay score 6) in the control group for almost 48 hours.
- Maintain normothermia

Other

Otorhinolaryngology consultant in case of paracerebral infection requiring specific treatment
eAppendix 2: Adverse event definitions

Nosocomial infections

Nosocomial infection was defined as an infection occurring at least 72 hours after hospital admission and not present or incubating at randomization

1. Surgical wound infection
   
   Superficial wound infection: purulent discharge or presence of polymorphonuclear from the wound or from fascia or skin, with or without a microorganism.
   
   Deep wound infection: purulent discharge or presence of polymorphonuclear from a drain under the fascia

2. Urinary tract infection:
   
   Asymptomatic bacteriuria
   
   - Patient has had an indwelling urinary catheter within 7 days before the culture: positive urine culture that is > 10^5 microorganisms per cm^3 of urine
   
   - Patient has not had an indwelling urinary catheter within 7 days before the first: least two positive urine cultures, that is, > 10^5 microorganisms per cm^3 of urine with repeated isolation of the same microorganism

   Symptomatic urinary tract infection
   
   Patient has at least one of the following signs or symptoms with no other recognized cause
   
   - fever (.38°C)
   
   - urgency
   
   - frequency
   
   - dysuria
   
   - or suprapubic tenderness
   
   Patient has a positive urine culture, that is, > 10^5 microorganisms per cm^3 or urine with no more than two species of microorganisms or pyuria (urine specimen with > 10 WBC/mm^3 or > 3 WBC/high power field of unspun urine)

3. Bloodstream infection
   
   A least one positive blood culture (with or without clinical signs or symptoms). For the following microorganisms, at least 2 positive blood cultures with bacteria having the same biotype and susceptibility profile: coagulase negative staphylococci, Bacillus sp, Propionibacterium sp, non-baumannii Acinetobacter, non-aeruginosa Pseudomonas.
   
   Bloodstream infections could be primary (no identified focus) or secondary, including those related to catheter infection
4. Catheter-related infections

Catheter colonization was defined as a quantitative catheter-tip culture yielding at least 1000 colony-forming units (CFUs)/mL.

Catheter-related bloodstream infection was defined as a combination of (1) or more positive peripheral blood cultures sampled immediately before or within 48 hours after catheter removal, (2) a quantitative catheter-tip culture testing positive for the same microorganisms (same species and same susceptibility pattern), and (3) no other infectious focus explaining the positive blood culture result.

5. Lower respiratory tract infection

Development of a new pulmonary infiltrate on chest-X-ray and either positive quantitative cultures of distal pulmonary secretion samples, obtained by fiberoptic bronchoscopy, of bronchoalveolar lavage fluid (significant threshold $\geq 10^4$ colony-forming units/mL), or with a protected specimen brush or catheter (significant threshold $\geq 10^3$ colony-forming units/mL, or from tracheal aspirates (significant threshold $\geq 10^7$ colony-forming units/mL).

Isolation of bacteria in pleural fluid or from lung sample obtained through transbronchial biopsy or from lung abscess

Isolation of *Legionella* sp, *Aspergillus* sp or *Mycobacterium* sp from sputum or tracheal aspirates.

*Legionella pneumophila* diagnosed through positive urine antigen test or serology

Purulent tracheal aspirate and fever $> 38.5^\circ$ and positive blood culture without any other obvious site of infection.

**Hemorrhage** was defined as bleeding requiring a blood transfusion of 2 red cell packs for 2 consecutive days.

**Cardiac arrhythmias** were defined by one the following: atrial flutter, atrial fibrillation, ventricular tachycardia or bradycardia below 50 pulse/min.
eAppendix 3: Detailed futility analysis

Triangular test

For all the following results, it has to be taken into account the study power at the moment of the present analyses (43%)

The first intermediate analysis was planned after obtaining the principal endpoint for the 106th patient included in the study (GOS at 3 month).

The present analyses were performed after complete follow up of the 98th included patient (due to the early stop of the study on the advice of the DSBM).

Notes

*upper panel legend*: area where the control arm was more efficiency than the hypothermia arm

*lower panel legend*: area where the hypothermia arm was more efficiency than the control arm

The intermediate area is the futility area.

**Model specifications and hypothesis: Study design**

The study was designed to have two arms for the dichotomy favorable outcome at 3 months (GOS at 3 month being of a value 5 vs. 1, 2, 3, 4) with a double triangular sequential design (Whitehead & Stratton, 1983)

Study hypothesis on the difference of proportion of patients with an unfavorable outcome at 3 month was that the difference was of at least of 15 points

**Probability model**

Predefined parameters of the study were:

- Power : 80%
- Type I error (alpha) : 5%
- Theta \( \theta \) (minimum detectable level of proportions to show) : -0.15 (negative 0.15)

Hypothesis testing would be double tailed, with null (H0) and alternative (H1) hypothesis defined as follows

\[
H0 : \theta = 0
\]

\[
H1 : |\theta| \neq 0.15
\]
Stopping rules for the 3 planned analyses were as shown in the following table

<table>
<thead>
<tr>
<th></th>
<th>a</th>
<th>b</th>
<th>c</th>
<th>d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time 1 (N= 106)</td>
<td>-0.21</td>
<td>-0.05</td>
<td>0.05</td>
<td>0.21</td>
</tr>
<tr>
<td>Time 2 (N= 212)</td>
<td>-0.13</td>
<td>-0.08</td>
<td>0.08</td>
<td>0.13</td>
</tr>
<tr>
<td>Time 3 (N= 318)</td>
<td>-0.11</td>
<td>-0.11</td>
<td>0.11</td>
<td>0.11</td>
</tr>
</tbody>
</table>

where a, b, c, d are the stopping rules for each intermediate analyses

**Observed probabilities**

Power of the study is of 43% at 3 month of the 98th included patient

The estimated difference $\theta$ is of 0.12 (positive 0.12)
We stress that $\theta$ is positive unlike the hypothesis on $\theta$ of -0.15 (negative -0.15).
Differences between arms are not statistically significant

We agree with the expert: comparison between the two arms is not significant, and even if the results favor the control group, this study cannot conclude neither about the effectiveness of hypothermia, nor about its harmlessness.
As requested, given the observed results (98 patients), 2 interim analysis at $N = 106$ and $N = 212$, and the preplanned protocol assumptions (probability of bad outcome in hypothermia group: 0.20, probability of bad outcome in control group: 0.35), we calculated probabilities of the various possible outcomes:

**Probabilities at the first stage (N = 106):**
- probability to stop in favor of hypothermia group at the first stage: 0
- probability to stop in favor of control group at the first stage: 0
- probability to stop for futility at the first stage: 0.007
- probability to continue to second stage: 0.993

**Probabilities at the second stage (N = 212):**
- probability to stop in favor of hypothermia group at the second stage: 0.009
- probability to stop in favor of control group at the second stage: 0
- probability to stop for futility at the second stage: 0.884
- probability to continue to last stage: 0.10

**Probabilities at the last stage (N = 318):**
- probability to conclude in favor of hypothermia group at the last stage: 0.014
- probability to conclude in favor of control group at the last stage: 0
- probability to not conclude at the last stage: 0.086

**Overall probabilities:**
- probability to conclude in favor of hypothermia group: 0.023
- probability to conclude in favor of control group: 0
- probability to conclude futility: 0.977
<table>
<thead>
<tr>
<th>Presumed causes of death</th>
<th>Hypothermia group (n)</th>
<th>Control group (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Systemic cause</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Septic shock</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Multiorgan failure</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Others</td>
<td>2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Neurologic cause</strong></td>
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<tr>
<td>Diffuse cerebral edema</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Life support withdraw</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>because of poor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>neurologic outcome</td>
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<tr>
<td>Brain death</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>

<sup>a</sup>Hypothermia group: 1 aortitis, 1 ventricular fibrillation with cardiac arrest

<sup>b</sup>Control group: 1 mesenteric ischemia, 1 recurrent myeloma, 1 recurrent infection
eFigure 1: Glycemia follow-up (morning measure)
eFigure 2: Glycemia follow-up (evening measure)
eFigure 3: Natremia over time

Natremia over time

- Hypothermia group
- Control group

Mean natremia (mmol/L)

Number of data on the hypothermia group:
48 44 42 41 40 37 35 18 7

Number of data on the control group:
48 47 44 42 41 34 29 13