Review
Energy expenditure in different patient populations on intensive care
C.M. Mooij, C.J. Beurskens, N.P. Juffermans

Case report
Extravasation injury by norepinephrine
G. van der Wal, J.C. Janssen, P.E. Spronk

Book review
Pediatric Anesthesia, Intensive Care and Pain: Standardization in Clinical Practice
A.P. Bos
Breed toepasbaar bij
- Invasieve candidiasis
- Invasieve aspergillose*
- Empirische antifungale therapie

Antifungale therapie zonder compromis
- Voor volwassenen én kinderen
- Voor neutropenen én niet-neutropenen
- Goed verdragen¹
- Eenvoudige dosering
- Als add-on DBC volledig vergoed²
- 11 jaar klinische ervaring

Referenties:
* Invasieve aspergillose bij volwassen patiënten en kinderen die niet reageren op amfotericine B, toedieningsvormen van amfotericine B met lipiden en/of itraconazol of deze niet verdragen.

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- 11 jaar klinische ervaring (caspofungin, MSD)

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Abstract
Objective: Adequate nutrition has an impact on outcome in critically ill patients. This descriptive literature search investigates whether there are differences in energy expenditure (EE) between specific subgroups of critically ill patients, including patients with sepsis, trauma, burns and cerebrovascular accidents. Also, we summarised specific factors which may influence EE, such as the use of sedation, body temperature and severity of illness.

Design: A descriptive review of studies which have measured EE or oxygen consumption with indirect calorimetry in critically ill patients. Studies were retrieved by a systematic search of the Medline database, using search terms referring to the measurement (energy expenditure), the patient population in general (critically ill patients), and to the four specific subgroups (sepsis, trauma, burns, stroke).

Results: EE in patients with sepsis, trauma and burns was increased (sepsis 102-198%; trauma 110-168%; burns 137-182%; stroke 149% for men and 120% for women) compared with reference values of EE in healthy individuals. Burn patients had the highest EE levels. There was no difference in EE between sepsis and trauma patients. Patients with a cerebrovascular accident had the lowest EE. Half of these patients had an EE that did not exceed EE levels in healthy adults. Use of sedation lowered EE whereas fever increased EE. Uncertainty persists whether treatment of stroke patients with hypothermia decreases EE. According to most studies, higher disease severity scores are associated with higher EE, but one study found that severity of illness is negatively correlated with EE in sepsis.

Conclusions: Data for this review were limited, precluding definite conclusions. However, it is clear EE differs among critically ill patient populations. The use of a ‘one size fits all’ formula to estimate caloric need in the critically ill may not be appropriate in the design of studies on caloric need nor in patient care.

Introduction
In critically ill patients, meeting caloric demand by adequate nutrition is related to better outcome. Therefore, adequately responding to the nutritional demands of patients admitted to the intensive care unit (ICU) should be a daily goal in patient care. However, the optimal amount of calories that should be prescribed to critically ill patients has been a matter of debate. It is thought that the consumption of calories, termed energy expenditure (EE), is increased in critically ill patients compared with the general hospital population, due to high metabolic demands during various inflammatory conditions. A disbalance between high demands and limited energy supply may contribute to organ failure and adverse outcome in ICU patients. In this view, underfeeding could be detrimental. An alternative hypothesis relating to the optimal amount of calories holds that this hypermetabolic state might be harmful and that hypocaloric nutrition reduces hypermetabolism, thereby improving outcome. In both strategies, measuring or estimating energy demands of patients are crucial in determining the optimal amount of feeding.

The EE can be measured in several ways, including indirect calorimetry. Alternatively, the Harris-Benedict equation is used, which calculates the amount of calories needed in ICU patients and estimates an individual’s basal metabolic rate, multiplied by an activity factor. A shortcoming of this formula is the controversy about what exactly this activity factor should be. Also, the formula does not distinguish between specific ICU patient populations. Comparing caloric targets based on calculated calorie need with use of this formula may therefore lead to inadequate conclusions in ICU patients. Given the relation between caloric supply and outcome, it seems paramount to be aware of possible EE differences between different subgroups. This paper summarises data from all available studies which have directly measured EE in four specific subgroups of ICU patients: sepsis, trauma, burns and cerebrovascular accident (CVA).

C. M. Mooij, C.J. Beurskens, N.P. Juffermans
Laboratory of Experimental Intensive Care and Anaesthesiology and the Department of Intensive Care, Academic Medical Center, University of Amsterdam, the Netherlands

Correspondence
C. Beurskens – e-mail: c.j.beurskens@amc.uva.nl

Keywords - Energy expenditure, oxygen consumption, calorimetry, Intensive Care Unit
The Medline database was used to identify medical subject’s headings (MeSH) and select search terms. In addition to MeSH terms, free text words were used. Search terms referred to the measurement: energy expenditure (calorimetry, indirect [MeSH]; energy metabolism [MeSH]; energy metabolism; energy expenditure; indirect calorimetry), to the patient population in general: critically ill patients (critical illness [MeSH]; intensive care unit [MeSH]; critical care [MeSH]; intensive care [MeSH]; critical care unit; critical illness; ICU patients) and to the four specific subgroups (septic shock [MeSH]; bacteremia [MeSH]; sepsis [MeSH]; sepsis; pyemia; septicemia; blood poisoning; severe sepsis; bacteremia; septic shock); (wounds and injuries [MeSH]; trauma; wounds and injuries; severe trauma); (burn, chemical [MeSH]; burn [MeSH]; burn; chemical burns; electric burns; burn wounds); (brain ischemia [MeSH]; cerebral infarction[MeSH]; subarachnoid hemorrhage [MeSH]; intracranial hemorrhage [MeSH]; stroke [MeSH]; stroke; cerebrovascular apoplexy; CVA; cerebrovascular accident; brain infarction; cerebral ischemia; intracranial hemorrhage; subarachnoid hemorrhage; SAH). Search results were limited to adults. Studies were selected when data on EE (kcal/day) or VO₂ were given, mean and SD were calculated. Studies were selected when data on EE (kcal/day) or VO₂ were given, mean and SD were calculated. In patients suffering from sepsis (table 1), all studies except one13 found an increase in measured EE with values ranging from 102-198% compared with the reference value. Three out of the six VO₂ measurements were high, but within the normal range. The other VO₂ measurements slightly exceeded the normal range. In the trauma group (table 2), all studies reported high EE measurements, ranging from 110-68% compared with the reference value. Of the VO₂ measurements, one study reported values within the normal range (153.6 ml/min/m²),29 other studies reported VO₂ values higher than 160 ml/min/m². In the patient population suffering from burns (table 3), EE measurements ranged from 137-182% of the reference values. Two studies reporting VO₂ measurements exceeded the normal range, with values of 131 and 209 compared with the upper limit of the normal range of oxygen consumption of 160 ml/min/m².30,31 In stroke patients (table 4), increased levels of EE of 149% of the reference value for men and 120% for women were found in one study.32 However, the other two studies33,34 found no increased EE levels compared with the reference value. In this patient group, no VO₂ measurements were available.

Clinical conditions influencing EE

The use of sedative medication generally lowers EE.20,21 However, one study showed a positive correlation between sedative dose and EE.35 Different types of sedative medication did not result in differences in EE levels when measurements were corrected for body temperature.36 An increase in EE caused by fever was found in sedated head-injured patients37 and in septic patients.38 Conversely, induced hyperthermia to 33 °C resulted in a significantly lower EE in stroke patients.39 However, not all studies report such a decrease, as Badjatia et al. found no significant differences in EE between the hypothermic (33.5–33.5 °C) and the normothermic (36.5–37.0 °C) stroke patients.40 In this study, shivering as a result of treatment with hyperthermia was clearly shown to increase EE.41

The severity of illness may influence EE. EE was related to either the APACHE II or III for sepsis,42-44 ISS for trauma45 or %BSA for burn patients (table 5). Not all studies mentioned severity scores. In general, however, patients with higher severity scores were more hypermetabolic, which was most distinct in patients with burns.46 An association between severity of illness and EE was also noted in septic trauma patients.47 One study, however, reported a negative correlation between APACHE III scores and resting EE in sepsis.48

Discussion

EE measurements were highest in burn patients, with all studies reporting substantially higher values than reference measurements.49-51

Table 1. Caloric demand in critically ill patients with sepsis

<table>
<thead>
<tr>
<th>References</th>
<th>Number of patients</th>
<th>M/F</th>
<th>EE (kcal/day)</th>
<th>% of reference EE</th>
<th>VO₂ (ml/(min.m²))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zauner et al.23</td>
<td>14</td>
<td>8/6</td>
<td>-</td>
<td>-</td>
<td>135 ±26</td>
</tr>
<tr>
<td>Fernandes et al.35</td>
<td>10</td>
<td>10/0</td>
<td>-</td>
<td>-</td>
<td>168.9 ± 63.1</td>
</tr>
<tr>
<td>Khoiruzaman et al.9*</td>
<td>18</td>
<td>unknown</td>
<td>1982 ± 97</td>
<td>119%</td>
<td>-</td>
</tr>
<tr>
<td>Basile-Filho et al.13</td>
<td>15</td>
<td>11/4</td>
<td>1699 ± 271</td>
<td>102%</td>
<td>-</td>
</tr>
<tr>
<td>Stucky et al.38</td>
<td>21</td>
<td>unknown</td>
<td>2263 ± 599</td>
<td>136%</td>
<td>-</td>
</tr>
<tr>
<td>Frankenfield et al.22</td>
<td>20</td>
<td>17/3</td>
<td>3395 ± 634</td>
<td>198%</td>
<td>-</td>
</tr>
<tr>
<td>Khorram-Sefat et al.8</td>
<td>27</td>
<td>27/0</td>
<td>2878 ± 407</td>
<td>172%</td>
<td>-</td>
</tr>
<tr>
<td>Kiiski et al.32</td>
<td>25</td>
<td>17/8</td>
<td>2071 ± 430</td>
<td>126%</td>
<td>-</td>
</tr>
<tr>
<td>Raurich et al.10*</td>
<td>Total: 26</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>15/5</td>
<td>1900 ± 394</td>
<td>114%</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>15/5</td>
<td>1640 ± 311</td>
<td>110%</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>14/1</td>
<td>163 ± 21.2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>13/2</td>
<td>153 ± 30.4</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td>154</td>
<td></td>
<td></td>
<td></td>
<td>110-188%</td>
</tr>
</tbody>
</table>

Data are mean ± SD; M/F = proportion male/female; in Liigget et al., EE was measured using a pulmonary artery catheter.

Table 2. Caloric demand in critically ill patients with trauma

<table>
<thead>
<tr>
<th>References</th>
<th>Number of patients</th>
<th>M/F</th>
<th>EE (kcal/day)</th>
<th>% of reference EE</th>
<th>VO₂ (ml/(min.m²))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frankenfield et al.22</td>
<td>13</td>
<td>10/3</td>
<td>2754 ± 401</td>
<td>148%</td>
<td>-</td>
</tr>
<tr>
<td>Bruder et al.40</td>
<td>24</td>
<td>19/5</td>
<td>2406 ± 374</td>
<td>148%</td>
<td>203 ± 55</td>
</tr>
<tr>
<td>Shucke et al.37</td>
<td>27</td>
<td>Unknown</td>
<td>2281 ± 599</td>
<td>150%</td>
<td>-</td>
</tr>
<tr>
<td>Uehara et al.34</td>
<td>12</td>
<td>9/3</td>
<td>1953 ± 416</td>
<td>117%</td>
<td>-</td>
</tr>
<tr>
<td>Raurich et al.10*</td>
<td>Total: 26</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>15/5</td>
<td>1900 ± 394</td>
<td>114%</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>15/5</td>
<td>1640 ± 311</td>
<td>110%</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>14/1</td>
<td>163 ± 21.2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>13/2</td>
<td>153 ± 30.4</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td>154</td>
<td></td>
<td></td>
<td></td>
<td>110-188%</td>
</tr>
</tbody>
</table>

Data are mean ± SD; M/F = proportion male/female; in Raurich et al., 40 EE measurements are reported for 26 patients in total. One group of measurements was performed with 20 surgical patients, the other to 20 medical patients.

Table 3. Caloric demand in critically ill patients with burns

<table>
<thead>
<tr>
<th>References</th>
<th>Number of patients</th>
<th>M/F</th>
<th>EE (kcal/day)</th>
<th>% of reference EE</th>
<th>VO₂ (ml/(min.m²))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gnecco et al.39</td>
<td>65</td>
<td>Unknown</td>
<td>3205 ± 599</td>
<td>183%</td>
<td>-</td>
</tr>
<tr>
<td>Khromov et al.44</td>
<td>27</td>
<td>27/0</td>
<td>2878 ± 407</td>
<td>172%</td>
<td>-</td>
</tr>
<tr>
<td>Royall et al.46</td>
<td>22</td>
<td>17/3</td>
<td>2319 ± 553</td>
<td>199%</td>
<td>335 ± 80</td>
</tr>
<tr>
<td>Struck et al.36</td>
<td>12</td>
<td>Unknown</td>
<td>2284 ± 508</td>
<td>137%</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td>67</td>
<td></td>
<td></td>
<td></td>
<td>137-182%</td>
</tr>
</tbody>
</table>

Data are mean ± SD; M/F = proportion male/female;
Table 4. Caloric demand in critically ill patients with cerebrovascular accident

<table>
<thead>
<tr>
<th>Reference</th>
<th>Male</th>
<th>Female</th>
<th>% of reference EE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bardutzky et al.17</td>
<td>50</td>
<td>36</td>
<td>74%</td>
</tr>
<tr>
<td>Stucky et al.18</td>
<td>34</td>
<td>16</td>
<td>98%</td>
</tr>
</tbody>
</table>

Total 94

EE values. Also, EE values of burn patients were higher than EE values in most studies describing sepsis or trauma patients. A probable explanation is that burned patients are highly stressed and have hypermetabolic and catabolic.23 In both the sepsis and trauma patient populations we found increased EE values compared with the EE levels in healthy adults. Patients suffering from sepsis do not have consistently higher EE values than trauma patients. As expected, EE measurements in the CVA group of patients we found increased EE values compared with healthy patients. As expected, fever increases EE values.21 Another study found no significant difference in EE between no-sepsis and hypertensive, which was attributed by the authors to the heterogeneity of the patient population.22 The positive correlation between body temperature and EE can be explained by thermogenesis. Of note, we found that EE was positively correlated to the severity of illness in the majority of the reviewed studies, suggesting the trends in EE were related to clinical condition, also disease severity should be taken into account when estimating the caloric need. However, it should be considered that this approach is also being widely used in EE estimation in burn patients, we feel that it would be best to measure EE in each individual patient when assessing the amount of nutrition. When predictive equations are used instead of indirect calorimetry, factors can be added correcting for the patient’s type of lesion and for clinical conditions such as the use of sedation, severity of illness and body temperature. However, various recommendations on estimating EE in patients have been made. According to some, predicting the individual EE by using an equation is not possible, because of the variation in EE in critically ill patients and the quantity of factors influencing EE. Therefore, it was proposed to use the same predictive equations for all patients without adding factors. On the other hand, others hold that factors attributing to differences in energy expenditure between critically ill patients should be better understood to allow more accurate estimation of the caloric needs of individual patients.24 In burned patients, it was recommended to use equations that do not give higher predictions of EE than 1.5-1.6 times basal EE to avoid overfeeding.25 Taken together, there is no consensus on what the correcting factors should be. The summary of our findings points towards a patient-tailored approach, taking into account the clinical condition as well as disease severity.

Besides patient care, our findings may also have implications for future research. In studies comparing the impact of hyper- versus hypo-calyoric nutrition on outcome, it should be considered that EE differs between patient populations. The use of predictive equations in such studies is inappropriate in predicting the actual EE and thus the caloric demand of individual patients. However, some of these studies claim a relation between predictive equations and outcome.26 When the ‘less than goal’ and ‘near goal’ amount of calories is based on those predictions and is related to outcome, results may be confounded. Therefore, indirect calorimetry seems the best way to estimate the nutritional status of a patient and provide tailored care to possibly improve outcome. There are several limitations to this review. The amount of data on measured EE or VO2 is limited. Therefore, patient numbers are small. The most important limitation is that statistical analysis of the data was limited as individual patient data were not available, rendering this study a descriptive review. Also, the ratio between male and female was not always given. Most collected measurements were performed during the first week. Varying results reported in the reviewed studies, conclusions of this study only pertain to the first week following admission. Another limitation is that several factors such as age, body weight, types of nutrition, presence of shock, administration of medications such as insulin or inotropes and the use of mechanical ventilation were not considered. Patients and circumstances were quite heterogeneous and EE measurements were not corrected for that. However, we corrected for sex, which importantly determines EE.27 There is a great need for collecting more data to improve the limited knowledge, before adapting this in daily ICU care. Future research should ideally include the influence of mechanical ventilation and inotropic drugs on EE values.

Noneetheless, this study attempts to give an indication of differences in EE between different groups of patients. Despite the limitations of this study, results may have implications for estimating energy expenditure in clinical practice and for research goals. Conclusion

Energy expenditure differs between and within patient populations. The use of sedatives, body temperature and severity of illness have an impact on EE values. The use of the same formula to calculate caloric need for each patient may not be appropriate.

References

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A restrictive transfusion policy in the paediatric intensive care unit: safe and effective

L. de Vetten,1 M.C.J. Kneyber,2 R.Y.J. Tammenga3
Departments 1 of Paediatrics, 2 Paediatric Intensive Care and 3 Haematology and Oncology, the Beatrix Children’s Hospital, University Medical Centre of Groningen, the Netherlands

Correspondence
L. de Vetten – e-mail: lianne.devetten@znb.nl

Keywords – Transfusion, red blood cell, paediatric intensive care unit

Abstract
Background: Red blood cell transfusions are frequently used in the paediatric intensive care unit (PICU) with a primary goal of increasing oxygen delivery to the tissues. There are several disorders in which a high haemoglobin level is suggested to improve outcome, including sepsis and cardiac disease. Nevertheless, red blood cell transfusions are associated with a higher morbidity and mortality rate in critically ill children and adults. In our article, we will give a narrative review of the existing literature on a restrictive transfusion policy in the PICU. Methods: A literature search was done using the terms “red blood cell transfusion” or “erythrocyte transfusion” and “pediatric” or “child” in the Cochrane, Sumsearch, Trip and PubMed medical databases. Review of literature: The TRIP-CICU study offers the largest number of patients in whom a restrictive transfusion policy was concluded to be as safe and effective as a liberal transfusion policy. Several sub-studies were extracted from the TRIP-CICU database, focusing on specific groups of patients, e.g. sepsis patients, patients with non-cyanotic heart disease who underwent cardiac surgery and patients who underwent general surgery. One additional study focused on cyanotic heart disease, using higher haemoglobin levels than the studies named before. In all sub-categories a restrictive transfusion policy was found to be safe and effective. Conclusion: We conclude that it is safe to work with a haemoglobin threshold of 4.3 mmol/l for children admitted to the PICU with burns, sepsis or after general and cardiac surgery, and 5.6 mmol/l for patients with cyanotic heart disease.

Introduction
Up to 50% of the critically ill children admitted to the paediatric intensive care unit (PICU), receive one or more red blood cell (RBC) transfusions. After a stay of more than seven days in the PICU, this amount increases up to 75%.1-3 Red blood cell transfusions can cause serious side effects.1,4 Nevertheless, no international consensus exists on a haemoglobin threshold for administering RBC transfusions to critically ill children.5 Previous research has shown that there are quite some differences between doctors’ usage of RBC transfusions, and that the volume given is often not adapted to the degree of anaemia.4,6 A clear guideline on the usage of RBC transfusions at the PICU is desirable.

Little information is known on the subject of a restrictive transfusion policy in critically ill children. In September 2011 the renewed Dutch consensus on Blood Transfusions was published.7 This extensive guideline includes information about the patient population admitted to the PICU. The consensus concludes that a restrictive transfusion policy is safe for patients in the PICU based on literature published until the year 2008. We want to support and emphasise this statement by offering a narrative review on the subject of a restrictive transfusion policy in the PICU. We will also describe more recent literature, making a more specific usage of RBC transfusions possible.

Methods
The Cochrane, Sumsearch, Trip and PubMed medical databases were used during the literature search. We used the following terms in searching the databases “red blood cell transfusion” or “erythrocyte transfusion” and “pediatric” or “child”. We then confined the results to articles comparing a restrictive and liberal transfusion policy. We excluded literature on neonates, premature neonates and children admitted elsewhere than the PICU. We focused on randomised clinical trials for our review and used citations from associated articles.

Background
Anaemia is defined as a haemoglobin (Hb) level in the blood that is lower than two standard deviations below the median of the age-dependent reference. Anaemia is common in children admitted to a PICU. At admission, already 33% of these children
have anaemia and after 48 hours, another 18% have developed anaemia.15 The pathogenesis of anaemia in critically ill children is multi-factorial, including poor nutritional state, changes in iron metabolism, lowered erythropoietin production and response, blood loss and frequent blood tests in the PICU.15

Physiological changes
Hb is of importance for the delivery of oxygen (DO2) to tissues and thereby maintaining an adequate organ function. At low serum Hb levels, less oxygen can be transported to the tissues. The tissues will extract proportionally more oxygen from the blood resulting in an increased concentration of deoxyhaemoglobin in the red blood cells. This process stimulates the production of 2,3-diphosphoglycerate (2,3-DPG). 2,3-DPG ensures a shift of the oxygen-dissociation curve, making it easier for the tissues to extract oxygen from the blood. Other compensating mechanisms to ensure an adequate DO2 are a redistribution of blood flow and an increase in cardiac output.16

High haemoglobin target level
Based on pathological changes, it seems reasonable to strive for a high Hb level to ensure adequate tissue oxygenation in at least two categories of PICU patients. The first category consists of septic patients. During sepsis, endotoxins, tumour necrosis factor-alpha and nitrogen-oxygen molecules are released, causing mitochondrial depression and thereby an increased oxygen demand of the tissues. Yet, the oxygen supply is limited through decreased myocardial function and maldistribution of blood flow in the microcirculation results. The second category consists of patients who have undergone cardiac surgery. A compromised respiratory and cardiac condition results in limited oxygenation of the blood. The percentage of unsaturated blood is even higher in patients with a mixed circulation. Decreased contractility of the myocardium and/or arhythmia can contribute to a decreased cardiac output. For both categories of patients it seems that a higher Hb level is able to compensate for the restricted oxygen delivery to the tissues.17

Effects of RBC transfusions
The primary goal of RBC transfusions is to preserve organ function by ensuring an adequate oxygen supply. Yet, for the individual patient, it is unknown at which haemoglobin threshold the oxygen supply to the tissues becomes critical. Also, RBC transfusions seem to have a limited effect on improvement in the oxygen supply to the tissues.1 Three mechanisms can explain this limited effect. First, the storage of red blood cells leads to a depletion of 2,3-DPG in a couple of days. We explained earlier that 2,3-DPG is necessary for the maintenance of red blood cells. A depletion of 2,3-DPG in a couple of days leads to a depletion of 2,3-DPG in red blood cells. This process stimulates the production of 2,3-diphosphoglycerate (2,3-DPG). 2,3-DPG ensures a shift of the oxygen-dissociation curve, making it easier for the tissues to extract oxygen from the blood. Other compensating mechanisms to ensure an adequate DO2 are a redistribution of blood flow and an increase in cardiac output.16

Adverse effects of RBC transfusions
Different studies in adults as well as children show that RBC transfusions are associated with a longer duration of hospital stay and a higher morbidity and mortality. RBC transfusions are associated with a longer duration of ventilatory need, an increased usage of vasoactive medication and longer duration of stay in the PICU, independent of severity of illness.15,16,18 For some adverse effects of RBC transfusions, a clear causal mechanism is known. For example, cardiac decompensation can be the result of volume load in critically ill patients. Disturbances in electrolytes and/or coagulation originate from the dissimilarity in composition of stored blood products compared with fresh blood. The mechanisms causing non-haemolytic fever and transfusion-related immunomodulation are less clear. It has been postulated that the leukocytes and cytokines that are released from the blood product cause an inflammatory cascade.19,20 This immunomodulation is associated with an increased risk for nosocomial infections and multi-organ failure.21,22 Nevertheless, two recent studies have shown that leukocyte-depleted RBC transfusions are also associated with nosocomial infections.23,24 Because of this controversy with respect to leukocyte depletion, more research is desired. In addition, a longer storage time of blood products seems to be associated with a worse outcome, but this has not been confirmed universally.15,16 Until more research is done, it seems recommendable to use fresh leukocyte-depleted RBC transfusions when treating critically ill children. In the Netherlands this is already standard practice.

Restrictive transfusion strategy
Several articles have been published on a restrictive transfusion strategy in critically ill adults and children. In the year 1999, the TRICC study (Transfusion Requirements in Critical Care)10 compared a traditional transfusion policy (liberal strategy: Hb threshold of 10 g/dl or 6.2 mmol/l) with a restrictive transfusion strategy (Hb threshold of 7 g/dl or 4.3 mmol/l) in adults. According to this multicentre, prospective, randomised trial, a restrictive strategy is as effective and safer than the traditional policy. The TRICC motivated different researchers to evaluate the transfusion policy in critically ill children. We will now describe the published literature on restrictive transfusion strategies in children. From each study, patient characteristics, transfusion information and outcome parameters are assembled in table 1, table 2 and table 3, respectively.

First indications, 2007
The first study on a restrictive transfusion strategy in children concerned a population of burn patients. In a retrospective review two groups of patients were compared who were treated in a burns centre for children in the period of 2000-2006.25 The first group (traditional group, n=146) received a RBC transfusion at a Hb threshold of 10 g/d (6.2 mmol/l). In the second group (restrictive group, n=127) this Hb threshold was lowered to 7 g/d (4.3 mmol/l). No differences were found in outcome parameters such as duration of stay, duration of ventilation, amount of surgery needed and mortality. The restrictive transfusion strategy did lead to a greater decrease in

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<th>Table 1. Patient characteristics per study*</th>
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<td>Randomised sepsis patients</td>
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* Plus–minus values are means ± SD. Total percentage can differ from 100% because of rounding. * Scores of the Pediatric Risk of Mortality (PRISM) range from 0 to 76, with higher scores indicating a higher risk of death. Score taken at the moment of randomisation. # Before randomisation. ◊ Before randomisation. 0 At the moment of randomisation. nS = not significant.
the amount of RBC transfusions resulting in cost saving. An important point of concern is the time frame of the study. The traditional group was treated in the period 2000–2003, while the restrictive group was treated in the period 2003–2006. Changes in the general treatment of burn patients could very well have influenced the outcome of this study.

TRIPICU study

After the TRICC study, a comparable research was designed for critically ill children in 2007. The TRIPICU study (Transfusion Requirements in the Pediatric Intensive Care Unit) included more than 600 stable but critically ill children who were admitted to the PICU.14 Patients were considered stable if the mean systemic arterial pressure was not less than 2 SD below the normal mean for age and if cardiovascular treatments had not been increased for at least two hours. The patients were randomised in a liberal transfusion group (Hb threshold 9.5 g/dl or 5.6 mmol/l) and a restrictive transfusion group (Hb threshold 7.0 g/dl or 4.3 mmol/l). RBCs were transfused when the haemoglobin concentration fell below 7.0 g/dl or 4.3 mmol/l. Patients were not transfused if the haemoglobin concentration had not been increased for at least two hours. The patients were randomised in a liberal transfusion group (Hb threshold 9.5 g/dl or 5.6 mmol/l) and a restrictive transfusion group (Hb threshold 7.0 g/dl or 4.3 mmol/l). In the restrictive group, 30 of 68 patients received a blood transfusion, compared with 68 of 69 patients in the liberal group. No differences were found in mortality, MODS and length of hospital stay (table 3).

Cardiac surgery patients

From the TRIPICU study, another subgroup of post-cardiac surgery patients was analysed, using the same Hb threshold as described above.15 In the restrictive transfusion group, twice as much MODS was found than in the liberal group but because of the small number of patients this was not statistically significant. No difference was found in mortality or in the secondary outcomes of length of hospital stay and length of ventilation. As described before, an important restriction is the exclusion of patients with cyanotic heart disease.

A second, smaller study on RBC transfusions in children after cardiac surgery was published in 2011.16 In this study, 60 patients who underwent a cavopulmonary connection were randomised in a restrictive and a liberal transfusion group, receiving leukocyte-depleted RBC transfusions. These patients all suffered from cyanotic heart disease. Therefore, higher Hb thresholds were used, 9.0 g/dl (5.6 mmol/l) and 13.0 g/dl (8.1 mmol/l) for the restrictive and the liberal group, respectively. No differences were found in the outcomes of oxygen saturation, mortality, length of stay on the PICU and length of ventilation. Side effects, for example nosocomial infections, were not described in this study.

General surgery patients

A third subcategory of the TRIPICU study includes a group of 124 children who underwent general surgery.17 This group was also randomised in a liberal transfusion group (Hb threshold 9.5 g/dl or 5.9 mmol/l) and a restrictive transfusion group (Hb threshold 7.0 g/dl or 4.3 mmol/l). In the restrictive group, 30 of 60 patients received an RBC transfusion, compared with 62 of 64 patients in the liberal group. No differences were found in mortality and MODS. A difference in length of hospital stay was found in favour of the restrictive transfusion policy.

Conclusion

The literature described above clearly indicates that a restrictive transfusion policy is effective in the treatment of stable critically ill children admitted to the PICU. From the number of adverse effects of RBC transfusions, including nosocomial infections, duration of ventilatory support and occurrence of MODS, it can be concluded that a restrictive policy is as safe as a liberal policy. We therefore support the CBO consensus with the addition that a restrictive transfusion policy can also be used in specified groups of patients, such as sepsis patients and general and cardiac surgery patients. It must be noted that in the subcategory of cardiac surgery patients, more MODS was found in the restrictive group. This finding was not found to be significant, yet a greater number of patients should be included to further investigate this finding. The studies described above advise to use a haemoglobin threshold of 4.3 mmol/l in PICU.
patients, decreasing the exposure to RBC transfusions and their possible side effects. For patients with cyanotic heart disease, a haemoglobin threshold of 5.6 mmol/l can be used. Multicentre studies with greater numbers of patients are recommended to confirm these findings.

References


CASE REPORT
Extravasation injury by norepinephrine: a case report and treatment options

G. van der Wal, J.C. Janssen, P.E. Spronk
Department of Intensive Care Medicine, Gelre Hospitals Apeldoorn, the Netherlands

Correspondence
G. van der Wal – e-mail: g.van.der.wal@gelre.nl

Keywords: Extravasation injury, norepinephrine, skin necrosis

Abstract
In this case report we describe a patient with extravasation injury with norepinephrine given through a peripheral catheter in an emergency setting, awaiting placement of a central venous catheter. Delayed recognition and management of extravasation injury may result in serious consequences. It is important to be familiar with the treatment options to prevent further damage. We describe local treatment using the ‘flush-out technique’ with good results.

Introduction
Extravasation of medication given via the intravenous route occurs when the medication given accidently flows out of the blood vessel into the surrounding tissue. Recognition of extravasation injury can be difficult but is important because skin necrosis can be prevented with immediate treatment in some cases.

We describe a patient with extravasation injury following norepinephrine infusion through a peripheral catheter and outline treatment options of extravasation injury.

Case report
A 65-year-old woman was admitted to the ICU with respiratory failure because of exacerbation of her chronic obstructive pulmonary disease. Despite non-invasive ventilation, intubation and mechanical ventilation was needed. After intubation, a subclavian central venous catheter was inserted, but placement was aborted because it was complicated by a tension pneumothorax with haemodynamic deterioration. Volume resuscitation was started and a thoracic drain was inserted immediately. Because of severe hypotension while placing the thoracic drain, norepinephrine was started for haemodynamic support through a peripheral intravenous catheter. The haemodynamic situation in the patient stabilised immediately after placement of the thoracic drain. The nurse noticed that the skin was pale and cold around the puncture of the peripheral catheter located in her left underarm, suggesting subcutaneous extravasation of norepinephrine (infusion of 0.1 mg (0.5 ml) in max. 15 minutes) (figure 2a). The norepinephrine infusion was promptly stopped and transferred to the central catheter, which had been inserted in the meantime. No fluids could be aspirated from the peripheral catheter and the line was removed.

The extravasation injury was treated by the subcutaneous ‘flush-out technique’ described by Gault. 1 Little incisions were made around the affected area, the subcutaneous tissue were made permeable by blunt cannulation and physiological saline was slowly infused. Of the other incisions. Follow-up after irrigation (figure 2b) showed improvement of the local skin perfusion. Five days later (figure 2a) and after four months (figure 2b) good healing was seen and skin necrosis had been prevented. After two days she was extubated. She recovered well and was discharged from the hospital 16 days after ICU admission.

Discussion
Extravasation injury results from a combination of factors (including 1) solution osmolality (e.g. potassium chloride, sodium bicarbonate, calcium, glucose (≥10%), hypertonic saline and total parenteral nutrition), 2) local tissue toxicity (cytotoxic agents), 3) vasoconstrictor properties (epinephrine, norepinephrine), 4) infusion pressure (radiographic contrast media) and 5) regional anatomical peculiarity (thin skin or places with little soft-tissue coverage). 1, 2, 3, 4 Extravasation injury should be recognised as soon as possible to prevent further damage. Norepinephrine is a vasopressor (alpha adrenergic agonist) commonly used in haemodynamically unstable patients in the intensive care unit (ICU). Other aforementioned medications are also widely used in the ICU and they are in general administered through a central venous catheter for rapid dilution and to prevent the risk of extravasation injury. 1, 2, 3, 4 Extravasation with norepinephrine may cause severe local tissue ischaemia mediated by vasoconstriction, which can
result in severe skin necrosis. Ischaemic necrosis can also occur when the peripheral catheter is in place without extravasation, because of local stasis and concentration of the drug in case of low blood flow. The extent of damage is dependent on the dilution, volume, time of infusion and the localisation of the peripheral catheter. The severity of injury immediately after extravasation is not always predictable and frequently underestimated. An early warning sign might be pain at the site of infusion, local swelling or a change of skin colour. However, most ICU patients are unable to localise, as in our case, because of their decreased level of consciousness. Delayed recognition and management or mismanagement may therefore have serious consequences from scarring, damage to the underlying tendons and nerves, contracture, marked soft tissue loss requiring skin grafting to amputate and permanent disability. No randomised controlled trials exist about the management of extravasation injuries. Consequently, treatment strategy is mostly based on empirical research. In case of extravasation injury the medication should be discontinued quickly and the extravasation area and a large amount (500 ml) of physiological saline solution is flushed with a blunt tipped catheter through the subcutaneous tissue flowing out of the other incisions. This should be repeated through the other incisions. Care should be taken that the fluids do not accumulate and a sterile procedure should be used. The incisions are allowed to close spontaneously. If saline flush-out and hyaluronidase are insufficient, liposuction under local or general anaesthesia can be used to aspirate the extruded material and subcutaneous fat. Administration of a vasodilator such as phentolamine 5-10 mg (an alpha adrenergic antagonist) is also recommended in case of extravasation injury with vasoconstrictors which give local vasoconstriction and hyperaemia. In more severe cases with blistering and necrosis, the treatment should be surgical: debridement, eventually followed by skin grafting or flap reconstruction.

It is not exactly known which patients will have serious damage after extravasation and who needs aggressive treatment, but when necrosis develops it is too late to save the skin. In our case it was sufficient to use the saline flush-out technique with good result. We made the subcutis permeable with a blunt instrument because hyaluronidase was not available at the time of the injury.

In conclusion, extravasation injury with nor epinephrine may result in serious skin necrosis when not recognised rapidly and treated correctly. The best way of treating an extravasation injury is to prevent it. This case underlines the importance of giving high-risk medications through a central venous catheter. When, like in our case, these medications need to be given as an emergency through a peripheral catheter, the puncture site should be monitored closely. Although evidence for treatment is limited, it is good to be familiar with the treatment possibilities that are described to be able to prevent further damage.

References
Intravenous lipid emulsion in the treatment of verapamil intoxication

M.A.J. Assink1, P.E. Spronk1, H.J.M. van Kan2, A. Braber1
Departments of 1intensive care and 2clinical Pharmacy, Gelre Hospitals, Apeldoorn, the Netherlands

Correspondence
A. Braber – e-mail: a.braber@gelre.nl

Keywords – Verapamil intoxication, calcium channel blockers, intralipid, 4-aminopyridine

Abstract
Calcium channel blockers are commonly used in a variety of cardiovascular diseases. Their extensive clinical use concurs with an increase in the incidence of deliberate and accidental poisonings. Intoxication with non-dihydropyridine calcium channel blockers is currently treated with supportive therapies, since no antidote is available. When conventional therapies fail to be successful, alternative approaches should be considered. In this case report we describe the effect of continuous renal replacement therapy and intravenous lipid emulsion in the treatment of severe verapamil intoxication. High-volume continuous venovenous haemofiltration did not have a substantial effect on verapamil clearance. However, after intravenous administration of lipid emulsion the haemodynamics stabilised, which suggests that this intervention is beneficial after life-threatening verapamil intoxication, although the exact underlying mechanism remains to be elucidated.

Introduction
The incidence of cardiovascular disease, especially hypertension and congestive heart failure, is increasing. Calcium channel blockers are commonly used in a variety of cardiovascular diseases, including angina pectoris, supraventricular tachycardias and hypertension, and in non-cardiac conditions such as migraine and Raynaud’s phenomenon. Their extensive clinical use concurs with an increase in the incidence of deliberate and accidental poisonings.6 Overdosage of the non-dihydropyridine calcium channel blocker verapamil causes a variety of symptoms including cardiogenic shock, arrhythmias, conduc tance disturbances, vasodilatation, central nervous system depression, pulmonary oedema and paralytic ileus (table 2). Treatment of intoxication with calcium channel blockers is controversial.10 Generally, accepted treatment options are prevention of absorption by giving active charcoal, and supportive care including calcium suppletion, glucagon and insulin infusion.1 Recently, high-dose lipid solutions have been advocated in these intoxications. In this case report we describe the use of intravenous lipid emulsion in a severe verapamil intoxication and discuss the potential benefit of this intervention to improve outcome.

Case description
A 68-year-old man was brought to the emergency room one hour after a suicide attempt by ingestion of 6700 mg of verapamil, of which 6300 mg (94%) in extended-release capsules. Four weeks previously he was diagnosed with AV-nodal re-entrant tachycardia for which verapamil was prescribed. On evaluation we saw a drowsy man. His blood pressure was 80/50 mmHg, pulse rate 70 beats/min with sinus rhythm, and respiratory rate 19 breaths/min with oxygen saturation 98% while breathing 5 litres O2. Examination of heart, lungs, abdomen and extremities was unremarkable. Laboratory tests on arrival showed normal serum potassium and glucose levels, and an increased level of lactate. Gastric lavage did not show traces of the consumed medication. Supportive treatment was started, including volume resuscitation and administration of low-dose nor epinephrine. Absorption prevention was attempted by colon lavage. Despite this treatment, the patient deteriorated and developed deep vasoplastic shock within a few hours after admission to the ICU. High doses of inotropes and vasopressors, and respiratory support were necessary (figure 1). Thrombocytopenic echocardiography, while substantial amounts of inotropes were administered, showed relatively normal contractility of the right and left ventricle without valve pathology. Eight hours later, an external pacemaker was introduced because of severe bradycardia, followed by ventricular fibrillation requiring resuscitation by defibrillation and basic life support for one hour.

High-volume continuous venovenous haemofiltration (HCVVH; substitution fluid rate 9.4 litre/h) was started because of severe metabolic acidosi s due to vasoplastic shock (lactate 11 mmol/l). Twelve hours after intake of verapamil, intravenous lipid emulsion 20% (Intralipid®) was administered, starting with a bolus of 1.5 ml/kg, followed by 0.25 ml/kg/h. During continuous venovenous haemofiltration MAP and norverapamil concentrations were measured in the serum and ultrafiltrate (table 2). There was no substantial amount of verapamil or norverapamil ultrafiltrated, resulting in a low sieving coefficient.

Table 2. Concentrations of verapamil (V) and norverapamil (NV) in serum and ultrafiltrate (UF) and the resulting sieving coefficients (Si) during continuous venovenous haemofiltration

Time (h) Serum V (μg/l) Serum NV (μg/l) UF V (μg/l) UF NV (μg/l) Si V Si NV
0 359 370 29 0.11 0.13
1 529 546 34 0.11 0.12
10 594 646 36 0.12 0.11
20 689 793 40 0.13 0.10
30 793 800 43 0.11 0.09
40 846 900 46 0.10 0.08
50 891 946 49 0.10 0.08
60 936 993 52 0.10 0.09
70 981 1025 55 0.10 0.08
80 1025 1070 58 0.10 0.08
90 1070 1118 61 0.10 0.08
100 1118 1165 64 0.10 0.08
120 1165 1212 67 0.10 0.08
180 1212 1259 70 0.10 0.09
240 1259 1306 73 0.10 0.10
360 1306 1353 76 0.11 0.09
480 1353 1400 79 0.11 0.10
600 1400 1447 82 0.10 0.09
720 1447 1494 85 0.10 0.09

Table 1. Symptoms caused by verapamil intoxication

Clinical features
Altered mental status, dizziness, seizures
Respiratory depression
Nausea, vomiting, abdominal pain
Physical examination
Hypotension, bradycardia, cardiogenic shock
Paralytic ileus
Jugular venous distension
Pulmonary crackles
Diagnoses
Electrocardiogram: conduction abnormalities of the SA/Av nodes, idioventricular arrhythmias
Laboratory results: hyperglycaemia, metabolic acidosis, elevated transaminase values
Chew X-ray: pulmonary oedema

Discussion
Verapamil is a non-dihydropyridine 1-type calcium-channel blocker, acting on myocardial muscle, the conduction system and vascular smooth muscle. Verapamil antagonises calcium channels and inhibits calcium influx into myocardial and vascular tissue. The negative inotropic and chronotropic effects of verapamil result in bradycardia, decreased cardiac output, vasodilatation of smooth muscle and cardiovascular collapse (table 2).1 Only 13-65% of a normal verapamil dose reaches the systemic circulation after absorption in the gastrointestinal tract due to an extensive first-pass effect in the liver, via multiple cytochrome P450 (CYP) isoenzymes. These enzymes,
The application of plasmapheresis, as a method of detoxification, is gaining attention. In patients who have ingested substances that are highly lipophilic, plasmapheresis is more effective than haemodialysis because in plasmapheresis clearance is achieved through the longer total blood-filter time compared with intermittent haemodialysis.14 Plasmapheresis resulted in cardiovascular stability in three cases with severe verapamil intoxication; unfortunately verapamil and norverapamil levels were not measured in the ultrafilter, only in serum.15 In our case, we started HVCVFH in an attempt to correct metabolic acidosis. The low sieving coefficient of verapamil and norverapamil, calculated using preliminary case reports, is 9-16% of the excreted dose.16 Treatment of verapamil intoxication consists of several supportive interventions, such as intubation and mechanical ventilation, in order to prevent respiratory insufficiency and hyperglycaemia, which may worsen intoxication.17 Besides the aforementioned treatment modalities, other strategies may be considered, such as levosimendan, which acts as an inotropic agent; it induces a positive inotropic effect.18,19,20,21,22 Infusion of lipid emulsion in an animal model of severe verapamil toxicity resuscitated with atropine, calcium and saline.23 In cases with delayed absorption, 4-aminopyridine is effective in removing verapamil and the active metabolite (norverapamil).14 It has been claimed that 4-aminopyridine improves adenosine triphosphate (ATP) synthesis in mitochondria by increasing the number of ATP synthase molecules and inhibiting the electrochemical gradient.24 The infusion of lipid emulsion (a ‘lipid sink’) decreases the apparent volume of distribution of verapamil and norverapamil, which has been shown in several studies.25 The section on cardiac arrest associated with toxic ingestions of the American Heart Association guidelines mentions the use of lipid emulsion as possibly beneficial in the treatment of beta-blocker overdose, when other standard therapies are not effective.26 Lipid emulsion is not mentioned in the treatment of intoxication with calcium-channel blockers.27 In our patient, 4-aminopyridine was administered 12 hours after arrival on the ICU. A few hours after administration of lipid emulsion, the norepinephrine dose could be tapered (figure 1). A positive response to lipid emulsion seems likely. Although circulating levels of verapamil and norverapamil were already decreasing prior to the start of the intralipids, there was an obvious direct correlation between stabilising haemodynamic parameters and the infusion of lipid emulsion (figure 1). The lipid sink theory only applies to the 10% of unbound verapamil, so beneficial effects could also be caused due to unmeasurable effects, e.g. the intracellular or receptor-mediated effects. In theory, the use of lipid emulsion after intoxication with calcium channel blockers should be evaluated against standard therapy to evaluate the effect, side effects and potential interactions. However, since this intoxication is relatively rare, it is important to draw upon our experience and the inclusion of intravenous lipid emulsion in treatment guidelines. Nevertheless, publication bias should be taken into account.

In conclusion, intoxication with calcium channel blockers such as verapamil should be managed with conventional therapies. When these therapies are insufficient to reach haemodynamic stability, alternative therapies are indicated. High-volume continuous venovenous haemofiltration did not show a substantial effect on verapamil and norverapamil clearance, resulting in a low sieving coefficient. Administration of intravenous lipid emulsion may be beneficial and it may be considered as treatment for life-threatening intoxication with verapamil.

References

Statins for sepsis?

D. Pretorius, P. Pickkers
Department of Intensive Care Medicine, Radboud University Nijmegen, Medical Centre, Nijmegen, The Netherlands

Statins inhibit the enzyme HMG-CoA reductase and thereby exert their well-known effect on cholesterol metabolism. In addition, statins may also exert anti-inflammatory, immune-modulating, and antioxidant effects, known as pleiotropic effects. The mechanism of action by which statins modulate the inflammatory pathways is complex and involves increased gene expression of NfκB, lowered expression of P-selectin influencing leukocyte-endothelium interaction, attenuation of up-regulation of Toll-like receptors and subsequent cytokine production, less platelet aggregation and less expression of tissue factor, less iNOS expression and augmented extracellular adenosine formation.1,2 These effects raise the question if statins may play a role in the treatment of sepsis patients.

Several animal sepsis models have shown improved outcome with statin pre-treatment. It was also demonstrated that mice treated with statins six hours after a septic insult had improved outcome, although not as good as with statin pre-treatment.3,4 In addition, there have been several observational studies that showed an association between statin treatment and improved outcome in humans. The largest of these observational studies was a cohort study from a Canadian administration database, with almost 70,000 patients.5 There are two problems with these studies: First, their observational nature makes them prone to bias (for example, patients from a higher socioeconomic background are more likely to use statins and have a more beneficial prognosis compared with patients from a lower socioeconomic background) and second, the patients were already on chronic statin treatment and therefore no conclusions can be drawn on the acute effects of statins in sepsis patients. Over the past few years, several small, single-centre acute intervention studies were conducted. The ASEPSIS trial had fewer conversions from sepsis to severe sepsis in the atorvastatin group,6 and in the HARP study,7 the simvastatin group suffered less non-pulmonary organ dysfunction. However, these studies were too small to be able to detect effects on hard endpoints.

In April of this year, Kruger and co-workers published the first large, multicentre randomised trial that looked at the effect of a statin (atorvastatin) on intensive care patients with severe sepsis.8 Patients already on statin therapy were also randomised, which meant that half of chronic statin users had to stop their statins. Patients had to be randomised within 48 hours of the start of their sepsis, and statins were continued for 14 days. The primary endpoint was the effect on interleukin-6 levels, as a measure of the immune response. Secondary endpoints were C-reactive protein concentrations, sequential organ failure assessment scores, intensive care unit (ICU) and hospital length of stay, and ICU, hospital, 28-day and 90-day mortality. The investigators found no differences between the intervention (n=123) and control (n=127) group in the course of interleukin (IL)-6 levels. The patients on chronic statin therapy had lower IL-6 concentrations, regardless of whether they were subsequently randomised to the statin or control group. There were no differences in the secondary endpoints between the two groups. In subgroup analyses, the patients on chronic statin therapy, who were randomised to the intervention group (so who continued statin therapy), had a lower 28-day mortality. As the survival benefit was only found in patients who were already on statins, while their IL-6 was similar to prior statin users who were randomised to placebo, these results suggest that the value of IL-6 as a marker of the statin effect is limited. In conclusion, this study suggests that initiation of statin therapy within 48 hours of the start of their sepsis, and statins were continued for 14 days. The primary endpoint was the effect on interleukin-6 levels, as a measure of the immune response. Secondary endpoints were C-reactive protein concentrations, sequential organ failure assessment scores, intensive care unit (ICU) and hospital length of stay, and ICU, hospital, 28-day and 90-day mortality. The investigators found no differences between the intervention (n=123) and control (n=127) group in the course of interleukin (IL)-6 levels. The patients on chronic statin therapy had lower IL-6 concentrations, regardless of whether they were subsequently randomised to the statin or control group. There were no differences in the secondary endpoints between the two groups. In subgroup analyses, the patients on chronic statin therapy, who were randomised to the intervention group (so who continued statin therapy), had a lower 28-day mortality. As the survival benefit was only found in patients who were already on statins, while their IL-6 was similar to prior statin users who were randomised to placebo, these results suggest that the value of IL-6 as a marker of the statin effect is limited. In conclusion, this study suggests that initiation of statin therapy within 48 hours of the start of the SIRS response and treatment continued up to day 14 is not beneficial in sepsis patients. However, if a patient is already on statin therapy, the study suggests that when sepsis develops, continuation of statin therapy might be beneficial for the patient.

Preclinical pharmacodynamic experiments with HMG-CoA reductase blockers suggested that it could be the sepsis-wonder drug. Animal and observational studies also looked promising; however, once again, from evidence obtained in randomised prospective studies, the role of statins in sepsis appears to be limited. Larger multicentre prospective trials would be needed to demonstrate possible beneficial clinical effects and mortality advantages with the use of statins in septic patients. For now, continuation of statin therapy in a patient with sepsis could be recommended.

References

References: see page 25.
### References for sepsis (p. 22)

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Decisions of the editors are final. All material accepted for publication is subject to copyediting. The original manuscript will be discarded one month after publication unless the publisher is requested to return the originals to the author Neth J Crit Care reserves the right to edit for house style, clarity, precision of expression, and grammar. Authors review these changes at the proof stage but must limit their alterations in proof to correcting errors and to clarifying misleading statements. For guidelines on the NJCC’s house style see website

General guidelines on house style
• The title of manuscript should be in typeface Times New Roman, size 20. With the exception of the first word and proper nouns, initial capitals are not used in the title.
• The names of departments should be in typeface Times New Roman, size 12.
• The names of hospitals should be written in English.
• Generally, abbreviations should not be used in the title (see Table of standard abbreviations) for exceptions.
• The corresponding author need only provide their e-mail address on the title page.
• Please provide a minimum of three keywords and a running title.
• In addresses write The Netherlands. In running text, the Netherlands.
• The abstract should be written in the structured format (with the exception of case reports).
• Unstructured abstracts should take the form of a single paragraph.
• The abstract should be bold typeface Times New Roman, size 12.
• Headings must be in bold.
• Non-standard abbreviations (see Table of standard abbreviations) should always be explained and their use kept to a minimum.
• Please use British English spelling, except in titles of institutions that have chosen to use US spelling, e.g. Academic Medical Center, Amsterdam.
• The journal uses British English spelling, e.g. aetiology, oestriadiol, anaemia, haemorrhage, oesophagus, practice (noun), practise (verb), fetus. This should be used consistently. Use z-spellings, e.g. anaemia, haemorrhage, oesophagus, practice (noun), practise (verb).
• Numbers (5 mice, 6 rats, 12 gerbils).
• Numbers under 10 are spelled out except for measurements with a unit (10 mmol/l) or age (4 weeks old), or when in a list with other numbers (5 mice, 6 rats, 12 gerbils).
• When referring to tables or figures in the text use a capital letter, e.g. see Table 2.

Guidelines on writing style for Dutch-speaking authors
• Following English language convention prof. dr. should be written as Professor.
• The gender of an author is not specifically reported. Do not use Ms or Mrs in front of Professor or Doctor.
• Spell check your article before submission using UK English (references keep original spelling).
• Avoid “he” as a general pronoun. Make nouns and pronouns plural, use “they”. If this is not possible then use “he or she”.
• Drugs should be referred to by their English language non-proprietary names, e.g. not fosfomycin but phosphomycin.
• Brackets. In English, information in brackets is not crucial to the meaning of the sentence and may be omitted without detracting from its meaning. The Dutch convention of using brackets to contain information crucial to the sentence should not be applied, e.g. (immuno) histology should be written as immunohistology and histology, (un) sterile gloves as sterile or unsterile gloves.
• Apostrophe. In English the apostrophe is used to indicate possession or omission, e.g. the patient’s notes, not to form a plural, e.g. ECG’s should be ECGs.
• “False friends.” Please be aware that although some words sound like they have the same meaning they do not, e.g. adequate is not always synonymous with adequate (adequate = toereikend), e.g. “Bij 98% werd technisch adequate wervelmorfometrie verricht” becomes “In 98% spinal morphology was technically successful.” “Klachten” may not universally be translated as “complaints”; please use “signs and/or symptoms” where appropriate.
• ± is a mathematical symbol and should not be used in a non-mathematical context to mean approximately or about.
• Generally, organizations and groups of people take single verbs, e.g. the team has researched.

Guidelines on abbreviations
• Avoid “full stops in initials, abbreviations and academic titles.
• Reference numbers go after commas and full stops, before semicolons and colons.
• Quotation marks – please use double, not single, inverted commas for reported speech. Full stops go inside quotation marks.
• Genus names should be in italics, e.g. Staphylococcus aureus, S. aureus.
• Numbers under 10 are spelled out except for measurements with a unit (10 mmol/l) or age (4 weeks old), or when in a list with other numbers (5 mice, 6 rats, 12 gerbils).
• When referring to tables or figures in the text use a capital letter, e.g. see Table 2.

Table of abbreviations

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS</td>
<td>acquired immunodeficiency syndrome</td>
</tr>
<tr>
<td>ALI</td>
<td>acute lung injury</td>
</tr>
<tr>
<td>ARDS</td>
<td>adult respiratory distress syndrome</td>
</tr>
<tr>
<td>APACHE</td>
<td>acute physiology and chronic health evaluation</td>
</tr>
<tr>
<td>BIPAP</td>
<td>biphasic positive airways pressure</td>
</tr>
<tr>
<td>CCU</td>
<td>coronary care unit</td>
</tr>
<tr>
<td>COPD</td>
<td>chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>CPAP</td>
<td>continuous positive airway pressure</td>
</tr>
<tr>
<td>CT</td>
<td>computerized or computed tomography</td>
</tr>
<tr>
<td>ECMO</td>
<td>extracorporeal membrane oxygenation</td>
</tr>
<tr>
<td>EEG</td>
<td>electroencephalogram</td>
</tr>
<tr>
<td>ELISA</td>
<td>enzyme-linked immunosorbent assay</td>
</tr>
<tr>
<td>ETCO2</td>
<td>end-tidal carbon dioxide</td>
</tr>
<tr>
<td>HDU</td>
<td>high dependency unit</td>
</tr>
<tr>
<td>HIV</td>
<td>human immunodeficiency virus</td>
</tr>
<tr>
<td>IC</td>
<td>intensive care</td>
</tr>
<tr>
<td>ICU</td>
<td>intensive care unit</td>
</tr>
<tr>
<td>IM</td>
<td>intramuscular</td>
</tr>
<tr>
<td>INR</td>
<td>international normalized ratio</td>
</tr>
<tr>
<td>IPPV</td>
<td>intermittent positive pressure ventilation</td>
</tr>
<tr>
<td>IV</td>
<td>intravenous</td>
</tr>
<tr>
<td>MAP</td>
<td>mean arterial pressure</td>
</tr>
<tr>
<td>MODS</td>
<td>multiorgan dysfunction syndrome</td>
</tr>
<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>PACU</td>
<td>post anaesthesia care unit</td>
</tr>
<tr>
<td>PEEP</td>
<td>positive end expiratory pressure</td>
</tr>
<tr>
<td>PET</td>
<td>positron emission tomography</td>
</tr>
<tr>
<td>SARS</td>
<td>severe adult respiratory syndrome</td>
</tr>
<tr>
<td>SIRS</td>
<td>systemic inflammatory response syndrome</td>
</tr>
<tr>
<td>SOFA</td>
<td>sequential or gan failure assessment</td>
</tr>
<tr>
<td>SPECT</td>
<td>single-photon emission ct</td>
</tr>
<tr>
<td>TIA</td>
<td>transient ischemic attack</td>
</tr>
<tr>
<td>TRALI</td>
<td>transfusion-related acute lung injury</td>
</tr>
</tbody>
</table>