Netherlands Journal of Critical Care

Bi-monthly journal of the Dutch Society of Intensive Care

REVIEW
Central venous catheter associated infections in the ICU: A Dutch approach
M. Kuindersma, E. Kolwijck, J. Ten Oever, J.A. Schouten

ORIGINAL ARTICLE
Network governance of Dutch intensive care units: state of affairs after implementation of the Quality Standard
P.H.J. van der Voort, A.A. de Beer, I. van Stijn, B.J.M. van der Meer

CASE REPORT
How low can your haemoglobin concentration go?
J. Heidt, J. Gunkel, H. Visser, R. van Raalte
CONTENTS

EDITORIAL
76 In networks we trust
V.C.A. Gerardu, I.C.C. van der Horst

REVIEW
80 Central venous catheter associated infections in the ICU: A Dutch approach
M. Kuindersma, E. Kolwijck, J. Ten Oever, J.A. Schouten

ORIGINAL ARTICLE
88 Network governance of Dutch intensive care units: state of affairs after implementation of the Quality Standard
P.H.J. van der Voort, A.A. de Beer, I. van Stijn, B.J.M. van der Meer

ORIGINAL ARTICLE
93 Trust in Dutch intensive care networks: the results of a survey
P.H.J. van der Voort, A.A. de Beer, I. van Stijn, B.J.M. van der Meer

CASE REPORT
98 How low can your haemoglobin concentration go?
J. Heidt, J. Gunkel, H. Visser, R. van Raalte

CASE REPORT
103 The broad differential diagnosis of encephalitis: a case report
I.E. Ghijselings, I.C.M. Hoogland, M.C. Brouwer, P.H.J. van der Voort, J. Horn

CLINICAL IMAGE
107 The white cerebellum sign
J. Gunkel, A.E. Scholtens, J. Heidt

108 NVIC conference and course agenda
109 Editorial board
109 International advisory board
110 Information for authors

Netherlands Journal of Critical Care is indexed in:
In networks we trust

V.C.A. Gerardu, I.C.C. van der Horst
Department of Intensive Care, Maastricht University Medical Center+, Maastricht University, Maastricht, the Netherlands

Correspondence
I.C.C. van der Horst - iwan.vander.horst@mumc.nl

Keywords - networks, intensive care, regionalisation, governance

The best care for critically ill patients depends on several factors, such as the availability of care within a certain distance and time, and offering care on a scale that ensures caregivers will remain adequately skilled. In the Netherlands, we are fortunate to have hospitals, intensive care units (ICUs), and caregivers in the close vicinity for most of the population. Furthermore, in 2016, the National Health Care Institute of the Netherlands - Zorginstituut - Nederland recommended working together in networks of ICUs as part of an implemented quality standard to improve care for patients. Networks are a complex of organisations that work together to achieve a specific goal. The goal here is to strive for an adequate amount of beds occupied during an optimal percentage of the time, as close as possible to a patient’s place of residence.

In past years, we have seen that within these networks, care for ICU patients is transferred to larger and more centrally located hospitals (i.e., regionalisation). One of the consequences of the regionalisation of care is that several ICUs have been closed down. Some evidence supports the rationale of regionalisation and transferring care. For example, there is a volume-outcome relationship among subsets of critically ill patients that supports the regionalisation of care for specific groups of patients to improve patient outcomes. Networks are complex of organisations that work together to achieve a specific goal. The goal here is to strive for an adequate amount of beds occupied during an optimal percentage of the time, as close as possible to a patient’s place of residence.

In this issue of the journal, Van der Voort et al. describe the trust in contemporary Dutch ICU networks. Trust is defined as the ability to allow your work processes to be influenced by others and is a condition that is present in these networks as an organisational form. The authors performed a survey completed by 85 respondents and concluded that caregivers’ trust in the networks and each other is reasonable. Cooperation between intensivists provides the opportunity to discuss care for critically ill patients and to visit ICUs within the network to exchange knowledge informally. Every ICU in the Netherlands has certain specialties in which their care is organised, such as additional training for teams of caregivers, treating specific patient categories, and successful improvement programs. Thus, contact between caregivers allows for optimisation of care in all ICUs by implementing elements of the specialties of others into their own care system, a real example of trust. Regionalisation may result in a reduction of opportunities to cooperate and, therefore, may lead to a decrease in the exchange of knowledge. The ability to consult each other and provide sufficient communication between caregivers may be a reason to strive for an adequate number of ICUs within a network.

Trust in the networks is there. However, in a second article in this issue, Van der Voort et al. show that the governance structure is not optimal at the moment in any of the 15 ICU networks in the Netherlands. The authors concluded that the Dutch ICU networks have different types of governance structures and that these differences can be a risk for the effectiveness of the networks. The method used to study the governance structure was defined by Provan and Kenis and stated that the success of governance depends on several factors of which trust is an important one. Also, the number of organisations within the network, e.g., the ICUs, is a factor as well. The interaction between perceived trust and the number of ICUs has not been studied, and we do not know whether the regionalisation of care leads to a reduction in trust between caregivers.

Another reason to strive for a sufficient number of ICUs within a network is a possible suboptimal occupancy rate of beds. An occupancy rate higher than optimal or even so high that patients can no longer be admitted to the ICU of a hospital in the network does not contribute to the best care. In this case, transferring the patient to an ICU of another hospital is necessary, and by closing ICUs in hospitals, it might be that the next available bed is not nearby. Transfers between hospitals are not uncommon. However, little is known about the influence of inter-hospital transfers on
patient outcomes in patients transferred for logistic reasons only. Most of the data on the effects of regionalisation of ICU care are based on the American healthcare landscape. This system is characterised by a wide variation in the quality of care between hospitals, which leads to a difference in observed mortality, partially attributed to a difference in experience with critical care. The quality of critical care in the Netherlands is frequently monitored, and within networks differences in the outcome of care among ICU’s discussed. Furthermore, in the Netherlands, the distance between hospitals is smaller. Some restraint is needed to directly generalise and extrapolate the available evidence to our unique system. On the other hand, this also calls for obtaining data with regards to the influence of regionalisation of ICUs in the Netherlands.

Several years ago, intensivists were questioned in a survey regarding the perceived barriers to the regionalisation of ICU care. The survey had an effective response rate of 569 out of 1200 intensivists (53%). The most prominent perceived barriers were a personal strain on the patient’s family, the lack of strong central authority, and the potential to overwhelm capacity at large hospitals. Another perceived barrier was the risks accompanying the transport of patients between hospitals. As previously cautioned, these data were obtained in the American system, and not all perceived barriers may be directly transferable to the system in the Netherlands.

Regionalisation is a fact in the current networks. Physicians have trust in these networks, but there is still room for improvement regarding governance structures. Nevertheless, we believe that the optimisation of communication between ICUs, intraregionally and even interregionally, is also necessary to distribute care more efficiently. For this to work, trust is essential, as well. We believe it is an illusion that single ICUs in a large area can take care of all patients in a region. Communication on future strategies of regionalisation and collaboration within the networks seems mandatory too. All of these barriers need to be addressed to allow the success of the currently implemented system and to ensure its sustainability.

Disclosures
All authors declare no conflict of interest. No funding or financial support was received.

References

Central venous catheter associated infections in the ICU: A Dutch approach

M. Kuindersma1, E. Kolwijck2, J. ten Oever3, J.A. Schouten4
1Department of Intensive Care, Gelre Hospital, Apeldoorn, the Netherlands
2Department of Medical Microbiology, 3Department of Internal Medicine, 4Department of Intensive Care, Radboud University Medical Center, Radboud University, Nijmegen, the Netherlands

Correspondence
M. Kuindersma - m.kuindersma@gelre.nl

Keywords - central line associated infections, causative pathogens, diagnosis, empirical therapy

Abstract
Central venous catheters (CVCs) are an indispensable means of intravascular access in the treatment of critically ill patients. Infections associated with these catheters occur most frequently in intensive care unit settings. Despite the successful implementation of infection prevention programs, CVC-associated infections remain relatively common. Thorough knowledge of local epidemiology, diagnosis and treatment of CVC-associated infections is therefore essential for the intensivist. In this paper we present new Dutch data on the epidemiology of causative microorganisms and we summarise the evidence on diagnostic strategy and optimal empirical treatment of CVC-associated infections.

Introduction
Effective treatment of critically ill patients requires reliable vascular access. In Dutch intensive care units (ICUs) at least 29,000 central venous catheters (CVCs) are used annually for this purpose. CVCs pose a risk for central line associated infections, resulting in increased morbidity, prolonged hospitalisation, and increased healthcare expenditure. In the Netherlands the incidence of CVC-associated infections has been 0.8-1.3 infections per (1,000) catheter days on the ICU in the past years.[1] Currently, there is no Dutch guideline for the clinical diagnosis and empirical treatment of a suspected CVC-associated infection. The clinician must rely on a ten-year-old international guideline, while Dutch practice in both diagnostic strategy and empirical treatment may vary considerably from this guideline.[2] In general, empirical antibiotic therapy is based on the local epidemiology and resistance patterns of the most common causative pathogens of the infection. To date, limited data have been published on the most common pathogens of CVC-associated infections in the Netherlands, while these data constitute the cornerstone of determining empirical treatment.

In this paper, we want to respond to the question related to CVC-associated infections that every practising ICU clinician is faced with: What is the optimal diagnostic and therapeutic strategy for a suspected CVC-associated infection?

To be able to do so we need to know first about the aetiology of micro-organisms causing CVC-associated infections in the Netherlands. Further we need to address some other burning management issues related to CVC-associated infections: Should the central venous catheter be removed or retained? In which circumstances is removal mandatory? And when is removal enough as a therapeutic strategy?

Methods/ search strategy
Recent Dutch data on pathogens causing CVC-associated infections were obtained by consulting the national Infectious Disease Surveillance Information System for Antibiotic Resistance (ISIS-AR). The data in this system include all isolates and antibiotic resistance patterns provided by 34 medical microbiological laboratories in the Netherlands and cover 81 hospitals throughout the country. All isolates from 2017 categorised as cultures of the tip of a central venous catheter and blood cultures were selected. A definite CVC-associated infection was defined as a peripheral blood culture and a culture of the tip of the catheter both turning positive within a maximum of 24 hours difference, growing the same microorganism (including skin contaminants).

We also used data of the PREventie van ZIEkenhuisinfecties door Surveillance (PREZIES) system for specific Dutch data on pathogens causing CVC-associated infection. PREZIES is a collaboration of hospitals and the Dutch National Institute for Public Health and the Environment (the RIVM). In this database definite and probable hospital-acquired infections are registered. There are 53 participating hospitals, of which 15 hospitals provided data annually over the period 2014-2018. PREZIES (criteria of version 2017-2019) defines CVC-associated infections as definite...
when clinical signs (fever, chills, hypotension) are documented in combination with positive peripheral blood cultures and cultures of the tip of the CVC. In patients in whom a ‘definite’ CVC-associated infection cannot be diagnosed, due to the lack of appropriate peripheral blood cultures or cultures of the tip of the CVC, a diagnosis of probable CVC-associated infection is made. In the PREZIES data presented here, definite and probable CVC-associated infections are combined. Furthermore, we searched the literature using PubMed and the Cochrane database, for the search strategy used, see Supplement 1. The titles and abstracts of all the articles identified in the electronic search were reviewed. For pragmatic reasons, only articles in English and Dutch were reviewed. Additionally, the reference lists of relevant studies were checked to see if references included reports of other studies that might be eligible for this review. Whenever possible, the studies that seemed to fulfil the criteria of inclusion were obtained in full (figure 1).

**Results**

**Micro-organisms causing CVC-associated infections**

In the ISIS-AR database, 506 CVC-associated infections were identified in 2017. Coagulase-negative staphylococci (CoNS) (56%) was the most common causative pathogen, followed by *Staphylococcus aureus* (18%), *Enterobacterales* (10.6%) and *Enterococcus* spp (6.6%). The 2014-2018 PREZIES database reported on 416 cases of CVC-associated infections in 33,761 CVCs among 25,410 patients from 53 hospitals. A diagnosis of definitive CVC-associated infection was made in 268 cases. A probable CVC-associated infection was established in 148 cases (36%). For definitions used by PREZIES see: www.rivm.nl/documenten/bijlage-2-definities-lijnsepsis-2017.

In the combined group of definitive and probable CVC-associated infections, CoNS (69%) was the most commonly isolated causative pathogen, followed by *Enterococcus* spp (7.5%), *S. aureus* (7.3%), *Enterobacterales* (5.8%) and Candida *albicans* (5.5%). Our literature search resulted in four major retrospective cohort studies about the distribution of pathogens. The combined results are presented in table 1.

Interestingly, the distribution of causative pathogens for CVC-related infections in the Netherlands is somewhat skewed towards Gram-positive microorganisms, especially CoNS, compared with international data (mainly US data). This could be attributable to the use of selective digestive decontamination (SDD) in Dutch hospitals. Unfortunately, no specific Dutch data are available on this potential influence. A recent randomised trial on the effects of long-term use of SDD in a Spanish hospital did describe the influence of SDD on the incidence of CVC-associated infections. More CVC-associated infections were described in the group treated with SDD but no data were shared on the type of microorganisms that were cultured. We presume that these were equally dominated by the Gram-positive spectrum. A shift from Gram negatives to CoNS should be considered ‘desirable’ as the latter rarely cause severe infection and thus only need to be treated in selected cases (see under Empirical treatment).

**Diagnostic strategy**

The diagnosis of a CVC-associated infection is based on 1) establishing the presence of bloodstream infection and 2) demonstrating that the catheter is the source of the infection. Although these directives seem simple, they often pose diagnostic problems in critically ill patients. There are no specific clinical signs that should prompt a high index of suspicion for a CVC-associated infection, with the exception of purulence at the insertion site and catheter dysfunction. In most cases fever is the only presenting symptom and the CVC is one of the possible foci of infection. In these cases, there should be an emphasis on finding the cause of fever with a low threshold for blood cultures. In fact, peripheral blood cultures drawn with a single puncture are imperative to diagnose a microbiologically definite CVC-associated infection. After completing these diagnostics, watchful waiting is a reasonable initial approach.

To establish if the CVC is in fact the source of infection, the catheter should be cultured as well. There are two ways to culture the CVC: by culturing the tip of the catheter or by drawing cultures from all lumina of the CVC. Although drawing cultures from the CVC might seem to be an attractive option, to diagnose a definite CVC-associated infection in this way, strict criteria should be met: 1. Presence of clinical signs and symptoms; 2. Cultures drawn from all lumina of the CVC at exactly the same time as peripheral blood cultures are drawn; 3. Strict laboratory criteria (i.e. simultaneous (semi) quantitative cultures drawn from the CVC with a colony count that is at least threefold greater than colony count of peripheral blood
culture or positive cultures drawn from the CVC that become positive at least 2 h before peripheral blood cultures become positive).\[2,15\] Unfortunately these criteria are rarely feasible in clinical practice. Furthermore, this approach risks cultures from the CVC becoming positive as a result of colonisation, while peripheral blood cultures remain negative. Rather than performing this elaborate and error-prone procedure to establish a diagnosis of CVC-related infection, pulling the CVC is easy and often therapeutic by reducing the microbial load in a true CVC-associated infection. In which circumstances a CVC should be retained or pulled directly will be discussed in the section on removal of the CVC (see under Empirical treatment). Finally, it is important to emphasise that the underlying goal, when drawing cultures from a CVC, is that the line is to be retained. This is often desirable in clinical settings outside of the ICU where the threshold for removing and replacing a CVC is much higher. The literature that supports this practice is indeed predominantly non-ICU based.\[17,18\] In an ICU setting, there should generally be a much lower threshold to remove the CVC.

In the rare instances in which no peripheral blood cultures can be taken, cultures can only be drawn from the CVC. Results of cultures drawn from a catheter without concomitantly drawn peripheral cultures have a low positive predictive value for CVC-associated infections. In a systematic review of 2677 paired blood cultures obtained from a CVC and a peripheral venepuncture, diagnostic accuracy was compared with true bacteraemia. True bacteraemia was defined on the basis of the number of positive cultures, the type of micro-organism isolated and the clinical evaluation of the patient. Based on this review, cultures drawn from the CVC have an excellent negative predictive value 97-99% for a CVC-associated infection. However, the positive predictive value is low (17-58%).\[16,19,20\]

Culturing the CVC tip without a concomitant peripheral blood culture is discouraged, given the very poor positive predictive value of tip cultures (55%, range 24-70%).\[21-24\] Positive tip cultures without concomitant positive peripheral blood cultures will rarely have clinical consequences, except for when \textit{S. aureus} and \textit{Candida} are cultured (see below).

### Table 1. Definitions of catheter-related infections

<table>
<thead>
<tr>
<th>Possible CVC-associated infection</th>
<th>Definite (laboratory-confirmed) CVC-associated infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>• CVC has been in place for more &gt;48 hours before bloodstream infection</td>
<td>• Meeting criteria possible CVC-associated infection PLUS</td>
</tr>
<tr>
<td>• CVC is in place or was in place one day before</td>
<td>• ≥ 1 (preferentially 2) set(s) of positive blood culture(s) from peripheral vein</td>
</tr>
<tr>
<td>• Clinical manifestations of infection (i.e. fever, chills, and/or hypotension)</td>
<td>• Positive (semi)quantitative culture(s) of the tip of the CVC with same microorganism as in blood culture</td>
</tr>
<tr>
<td>• No apparent other source of bloodstream infection</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2. Definitions of catheter-related infections

<table>
<thead>
<tr>
<th>Pathogens causing CVC-associated infections</th>
<th>[1,3-7]</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISIS-AR PREZIES 2014-2018*</td>
<td>Combined literature</td>
</tr>
<tr>
<td>N</td>
<td>506</td>
</tr>
<tr>
<td>Gram-positive micro-organisms</td>
<td>%</td>
</tr>
<tr>
<td>CoNS</td>
<td>56</td>
</tr>
<tr>
<td>\textit{S. aureus} (incl MRSA)</td>
<td>18</td>
</tr>
<tr>
<td>\textit{Enterococcus} spp.</td>
<td>6.6</td>
</tr>
<tr>
<td>\textit{E. faecium}</td>
<td>4.0</td>
</tr>
<tr>
<td>\textit{E. faecalis}</td>
<td>2.4</td>
</tr>
<tr>
<td>Other</td>
<td>0-0.2</td>
</tr>
<tr>
<td>\textit{Corynebacterium} spp.</td>
<td>0.2</td>
</tr>
<tr>
<td>Enterobacteriales</td>
<td></td>
</tr>
<tr>
<td>\textit{E. coli}</td>
<td>2.4</td>
</tr>
<tr>
<td>\textit{Enterobacter} spp.</td>
<td>2.6</td>
</tr>
<tr>
<td>\textit{Klebsiella} spp.</td>
<td>3.4</td>
</tr>
<tr>
<td>\textit{Serratia} spp.</td>
<td>1.8</td>
</tr>
<tr>
<td>\textit{Proteus mirabilis}</td>
<td>0.4</td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>Non-fermenting bacteria</td>
<td></td>
</tr>
<tr>
<td>\textit{Pseudomonas} aeruginosa</td>
<td>2.4</td>
</tr>
<tr>
<td>Other</td>
<td>0.6</td>
</tr>
<tr>
<td>Yeast/fungi</td>
<td></td>
</tr>
<tr>
<td>\textit{Candida} spp</td>
<td>4</td>
</tr>
</tbody>
</table>

### Empirical treatment

#### Removal of the CVC

Removing a CVC is a crucial step in treating a CVC-associated infection. In fact, the delayed removal of a source of bacteraemia is associated with an elevated mortality rate and complications of infection.\[25-27\] How fast a CVC needs to be removed depends on the clinical circumstances. Immediate removal of a CVC is warranted in the setting of a tunnel abscess, suppurrative thrombophlebitis, endocarditis or evidence of metastatic infection. Persistent bacteraemia after 72 hours of antimicrobial therapy, infections due to \textit{Pseudomonas} aeruginosa, \textit{S. aureus} or fungi, sepsis with haemodynamic instability or severe clinical deterioration are other reasons to remove the CVC immediately.\[12,28\] If fever is the only clinical sign pointing towards a CVC-associated infection and the CVC is clinically indicated, watchful waiting after taking peripheral blood cultures is a reasonable initial approach. In a small randomised study of 80 suspected CVC-associated infections in 64 patients in which fever was the only presenting symptom, this strategy resulted in
a 62% reduction of unnecessary CVC removals compared with immediate CVC exchange with no change in defervescence or complications.\[14\]

In the case of an infection with CoNS, which rarely causes complicated infection in patients without prosthetic valves or other prostheses, many clinicians will withhold antibiotic treatment after removal of the catheter. There is, to our knowledge, only one small trial to endorse this common practice.\[29\] Despite the lack of evidence, the revised Dutch Working Party on Antibiotic Policy (SWAB) sepsis guideline advises that in uncomplicated CVC-associated infection with CoNS, removal alone is acceptable practice.\[2,29,30\] In patients with prosthetic valves or other prostheses, the CVC should be removed and antibiotic therapy is mandated (see under Empirical antibiotic treatment).

**Empirical antibiotic treatment**
Antibiotic therapy for a CVC-associated infection is most often initiated empirically and should only be started with a high index of clinical suspicion. Immediate empirical treatment of a CVC-associated infection is warranted in the settings of sepsis, haemodynamic instability or severe clinical deterioration.

To our knowledge, there are no randomised controlled trials available on empirical therapy for CVC-associated infections. Empirical therapy should therefore be based on epidemiological data of causative pathogens and their resistance patterns. In the ICU, regular colonisation cultures may also guide the choice of empirical therapy for CVC-related infections. In the available studies, CoNS, *S. aureus*, *Enterobacteriales* and *Enterococcus* spp. were the most common causative micro-organisms in the Netherlands. CVC-associated infections with *Candida* are relatively uncommon.\[1,3\]

Although it seems appropriate to empirically cover all these pathogens, this is not necessary in most cases. In patients with a low risk of complicated enterococcal or CoNS infection, (e.g. without prosthetic valves and prosthetic joints), empirical therapy covering these pathogens can be withheld.
In three recent studies, empirical coverage of CoNS and Enterococcus spp. was not associated with an improved outcome.[30, 31,32] Given the lack of benefit, even the single dose of vancomycin which is common practice at the time of line removal is discouraged in patients with a low risk of complicated enterococcal or CoNS infections.[33] There is no evidence that any ‘single dose’ at the time of line removal is rational. However, in patients with an elevated risk of complicated enterococcal or CoNS infections (e.g. prosthetic valves and prosthetic joints), empirical treatment should be initiated and should include a glycopeptide.[34]

Based on the pathogens found in the Netherlands, empirical antimicrobial treatment should at least cover S. aureus and Enterobacterales. Current international guidelines advise empirical therapy with glycopeptides to cover S. aureus in the setting of high prevalence of methicillin-resistant staphylococcus aureus (MRSA). This advice would lead to gross overtreatment in the Netherlands, given the low prevalence of MRSA (1.4%).[33] For adequate coverage of S. aureus, fluclaxocillin (or cefazolin in case of penicillin allergy) is an appropriate initial choice. Empirical coverage of S. aureus can be attained with a third-generation cephalosporin as well.

The initial choice for coverage of Enterobacterales should be based on local resistance patterns but would conventionally mean a third-generation cephalosporin or an aminoglycoside. De-escalation should be performed as soon as culture and susceptibility data become available.[31]

Concerning Candida spp., it is important to note that early and adequate antifungal therapy is an important determinant of survival in patients with candidaemia.[30,35] Bearing in mind the survival benefit of early treatment, it is advised that in high-risk groups (i.e. patients with total parenteral nutrition, haematological malignancy, receipt of bone marrow or solid-organ transplant) who present with sepsis, empirical therapy for possible candidaemia is started.[30] The presence of a femoral line as the suspected site of infection is not sufficient to define initiation of empirical treatment for Candida spp.[36] In the general ICU population with ICU-acquired sepsis and who are colonised with Candida spp., it is unclear whether to initiate antifungal therapy. In two randomised trials, empirical treatment (in suspected fungal infection in ICU patients with sepsis) with micafungin or fluconazole showed no clinical benefit compared with placebo.[17,18] Therefore antifungal therapy should not automatically be initiated in colonised ICU patients while awaiting blood culture results. A practical guide of the recommendations on diagnosis and treatment is given in figure 2.

Special considerations
As a consequence of the culture strategy, in which CVCs are often promptly removed, it is possible that culture(s) of the tip of the CVC become positive while blood cultures remain negative. Whether treatment is warranted in these circumstances depends on the pathogens found. If S. aureus is found, treatment for a minimum of five days is advised pending peripheral blood cultures, given the elevated risk (4.8-24%) of S. aureus bacteraemia, even after catheter removal.[39-42] For the treatment of isolated line tips with Gram-negative pathogens (including Pseudomonas spp.) there is insufficient evidence of clinical benefit to start treatment.[43] All studies on subsequent bacteraemia after a positive tip culture have to be interpreted with caution: for instance, it is not always clear whether a blood culture was taken in all patients and not all antibiotic use is always registered. If a tip culture grows Candida spp., the risk of a positive candidaemia is about 4-8%.[44,45] Given the increased mortality of untreated candidaemia it may be considered to start treatment with a positive line tip for seven days while awaiting definitive blood cultures. If blood cultures remain negative, empirical therapy for candidaemia should be stopped.

Conclusions
Establishing whether fever in ICU patients is due to a CVC-associated infection is a common diagnostic challenge in an ICU population. The focus in these cases should be on performing adequate diagnostics and making it plausible that the line is the source of infection. If fever is the only clinical sign indicating a CVC-associated infection, watchful waiting after taking peripheral blood cultures is a reasonable initial approach. Removal of the CVC is advocated in sepsis with haemodynamic instability or severe clinical deterioration if the CVC is the suspected source of infection. In this setting, the clinician should also initiate empirical antibiotic therapy, based on epidemiological data. In the Netherlands, the most common pathogens are CoNS S. aureus, Enterobacterales and enterococci. Empirical therapy should cover S. aureus and Enterobacterales with a third-generation cephalosporin or fluclaxocillin/cefazolin combined with an aminoglycoside. Empirical treatment should not cover enterococci or CoNS, even in complicated line infections such as those associated with sepsis, unless the patient has mechanical heart valves or joint prostheses.

Disclosures
All authors declare no conflicts of interest. No funding or financial support was received.

References
Network governance of Dutch intensive care units: state of affairs after implementation of the Quality Standard

P.H.J. van der Voort¹,², A.A. de Beer¹, I. van Stijn¹, B.J.M. van der Meer³,⁴
¹Department of Intensive Care, OLVG, Amsterdam, the Netherlands
²Department of Critical Care, University Medical Center Groningen, University of Groningen, the Netherlands
³TIAS School for Business & Society, Tilburg University, Tilburg, the Netherlands
⁴Department of Intensive Care, Amphia Hospital, Breda, Oosterhout and Etten-Leur, the Netherlands

Correspondence
P.H.J. van der Voort - phjvdvoort@upcmail.nl

Keywords - network; governance; intensive care; cooperation

Abstract
Objective: To study the current state of affairs concerning Dutch intensive care network governance in relation to known effective governance structures of network organisations.

Methods: Six characteristics of intensive care networks were defined to determine the four contingency factors from the Provan & Kenis network governance models. The contingency factors were determined for all Dutch intensive care networks. An overview of the networks and characteristics was created by triangulation, using information from two national intensive care network meetings (November 2017 and June 2018) and semi-structured interviews by telephone with 10 network intensivists and / or network managers.

Results: Based on the chosen characteristics, none of the Dutch intensive care networks has a governance structure according to one of the Provan & Kenis successful forms of governance. Each of the present networks has a governance structure with elements from two or three different types. Characteristics of the network administrative organisation and shared governance form overlap in 10 out of 15 networks. All networks have a form of governance in which at least one intensivist is represented.

Conclusion: After implementation of the Quality Standard, the presence of networks of intensive care units covering the Netherlands is a fact. The network governance that has developed varies but none of the networks has a governance structure that matches with a proven effective governance structure. Based on theory, the network administrative organisation seems to be the most effective for larger networks, and shared governance for smaller networks.

Introduction
The Quality Standard ‘Organisation of Intensive Care’, which was adopted in 2016 stated: ‘A nationwide network system should be set up to maximise the efficiency and outcomes of intensive care’. This was the official introduction of intensive care unit networks in the Dutch intensive care community. There has been cooperation between intensive care units for much longer but formalising network relationships aiming at improving the efficiency and (joint) outcomes of intensive care was new. Between 2016 and 2019, a nationwide intensive care network cooperation and governance has grown. During a network meeting of the Healthcare Institute on 30 November 2017, a map of the Dutch intensive care networks was built (figure 1).

Network organisations are developing not only among intensive care units but more broadly in healthcare. According to management scientist Mintzberg, this is a natural development since patients are often not limited to a single medical specialty or pathophysiological ‘pigeonholes’ on which our healthcare system is designed. The Parkinson’s network and the COPD chain organisation are examples in which multidisciplinary cooperation takes place to obtain the best result for the patient. A network can be defined as a complex of organisations that work together to achieve a specific goal. The aim of networking in intensive care medicine is, according to the Quality Standard, to provide the right care at the right time in the right place.

Provan & Kenis studied the governance of networks to find out what the best kind of ‘governance’ is for a network organisation to achieve the intended objective(s). Unfortunately, there is no uniform answer for all network organisations. These researchers state that the success of a form of governance depends on four structural factors of relations (contingency factors). The contingency factors are: 1) mutual trust between the different organisations, 2) the number of organisations within the network, 3) consensus on the objective of the network (goal consensus), and 4) the need to work together as a network (need for network level competencies). These factors are summarised in figure 2.
Network governance of Dutch ICUs

**Figure 1.** Overview of Dutch Intensive Care networks as presented at the National Network Meeting: Landelijke Netwerk bijeenkomst Zorg Instituut Nederland, November 2017

**Figure 2.** The Provan & Kenis network governance model NAO = network administrative organisation

### Key Predictors of Effectiveness of Network Governance Forms

<table>
<thead>
<tr>
<th>Governance Forms</th>
<th>Trust</th>
<th>Number of Participants</th>
<th>Goal Consensus</th>
<th>Need for Network-Level Competencies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shared governance Lead organization</td>
<td>High density</td>
<td>Few</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Low density,</td>
<td>Moderate number</td>
<td>Moderately low</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>highly centralized</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Network administrative organization</td>
<td>Moderate density,</td>
<td>Moderate to many</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>NAO monitored by members</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Provan & Kenis define three proven effective basic forms of network governance based on the four factors above. These are:

- **Shared governed network**: The board is formed by the network members themselves. This kind of governance includes, for example, partnerships between physicians and paramedics that aim to improve care through coordinated collaboration without setting up a separate organisation.

- **Lead organisation-governed network**: Important activities and decisions are made by one of the participating network organisations, which acts as the leading organisation. Examples of this are the Education and Training Regions for the training of medical specialists where the academic centres are the lead organisations.

- **Network administrative organisation (NAO)**: In this governance form, there is a separate administrative entity that manages the network and organises the activities. This ‘NAO’ is not part of the primary process of the network. An example of this is the National Acute Care Network, which organises the network activities for the acute care regions.

The aforementioned four contingency factors determine the effectiveness of network governance. The aim of this study is to investigate how the current intensive care networks develop within the Quality Standard and what we can learn about network governance from the described governance models. The primary endpoint is the classification of the networks according to the Provan & Kenis model.

### Methods

An overview of the Dutch intensive care networks was created by combining information obtained from three sources (triangulation). First, information collected during the National Healthcare Institute (Zorginstituut Nederland) meeting in November 2017, second information from the national intensive care network meeting in June 2018 and third information from semi-structured interviews by telephone with 10 network intensivists and/or dedicated network managers who are responsible for organising the network activities on behalf of the network. The interviewer made inquiries about the way in which the network was formed, about the current agreements within the network and about the criteria necessary for classification according to the Provan & Kenis model, as shown in *Table 1*.

The Provan & Kenis model does not in itself describe the criteria by which the contingency factors can be interpreted. For the intensive care networks, information as shown in *table 1* was collected. An arbitrary choice was made for the variables, by consensus with the research group, that describe the contingency factors in the specific intensive care unit setting, as well as for the scoring that determines the classification. The

### Table 1. Characteristics of the intensive care networks for the contingency factors

<table>
<thead>
<tr>
<th>Contingency factor</th>
<th>Criterion</th>
<th>Score</th>
<th>Type of governance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trust density</td>
<td>Do the intensivists of the network visit other network partners?</td>
<td>0 = no 1 = only for scientific meetings 2 = to watch and learn from each other</td>
<td>0 = LO 1 = NAO 2 = SG</td>
</tr>
<tr>
<td>Number of participants’</td>
<td>How many ICs participate in the network?</td>
<td>Number of ICs</td>
<td>≤3 = SG 4-6 = LO ≥7 = NAO</td>
</tr>
<tr>
<td>Goal consensus</td>
<td>Does an agreement exist for cooperation in the network signed by all organisations? Did the network cooperation start before the Quality Standard?</td>
<td>0 = no 1 = yes</td>
<td>0 = LO 1 = NAO 2 = SG</td>
</tr>
<tr>
<td>Need for network level competencies</td>
<td>Is an academic hospital present in the network? Does the network have a dedicated network manager?</td>
<td>0 = no 1 = yes</td>
<td>0 = SG 1 = LO 2 = NAO</td>
</tr>
</tbody>
</table>

LO = lead organisation; NAO = network administrative organisation; SG = shared governance

*bold when ≥2 factors are present.*

### Table 2. Results for the contingency factors per network

<table>
<thead>
<tr>
<th>Network number</th>
<th>Trust density</th>
<th>Number of participants</th>
<th>Goal consensus</th>
<th>Need for network level competencies</th>
<th>Best fitting type of network governance*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>10</td>
<td>2</td>
<td>2</td>
<td>NAO / SG</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>NAO / SG / LO</td>
</tr>
<tr>
<td>3</td>
<td>NA</td>
<td>3</td>
<td>NA</td>
<td>2</td>
<td>NA</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>7</td>
<td>1</td>
<td>1</td>
<td>NAO / LO</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>9</td>
<td>2</td>
<td>1</td>
<td>NAO / SG / LO</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>8</td>
<td>2</td>
<td>1</td>
<td>NAO / SG / LO</td>
</tr>
<tr>
<td>7</td>
<td>2</td>
<td>9</td>
<td>2</td>
<td>2</td>
<td>NAO / SG</td>
</tr>
<tr>
<td>8</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>NAO / SG / LO</td>
</tr>
<tr>
<td>9</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>NAO / SG</td>
</tr>
<tr>
<td>10</td>
<td>NA</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>11</td>
<td>2</td>
<td>7</td>
<td>1</td>
<td>1</td>
<td>NAO / SG / LO</td>
</tr>
<tr>
<td>12</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>NAO / SG / LO</td>
</tr>
<tr>
<td>13</td>
<td>NA</td>
<td>7</td>
<td>1</td>
<td>1</td>
<td>NA</td>
</tr>
<tr>
<td>14</td>
<td>1</td>
<td>7</td>
<td>1</td>
<td>1</td>
<td>NAO / LO</td>
</tr>
<tr>
<td>15</td>
<td>1</td>
<td>4</td>
<td>1</td>
<td>0</td>
<td>NAO / SG / LO</td>
</tr>
</tbody>
</table>

NA = not available; LO = lead organisation; NAO = network administrative organisation; SG = shared governance
The results for the contingency factors are summarised in Table 2. In the last column, the network governance model that fits best, based on the contingency factors, is shown in bold type. Less well fitting types of network governance - with few features of a proven model - are given as well, but in standard font. Getting to know each other, as a method of building trust, appears to be encouraged in all networks through joint meetings. In addition, people visit each other actively in six networks. This can be seen as a way to become oriented to the work processes of other intensive care units. This can be focused on a specific topic, or in some cases the exchange of nursing staff for a fixed period of time. Getting to know each other professionally is also achieved by organising joint scientific meetings. Two-thirds of the networks emphasised that knowing each other is a contributory factor for network success.

Six of the networks have a network manager for coordinating tasks. The network managers indicate that their presence facilitates accessibility to contact at the organisational level between the networks themselves. These contacts between network managers resulted in the National Consultation Intensive Care Regions, a consultative body, under the flag of the Dutch Intensive Care Society (NVIC). In meetings of this National Consultation experiences and developments concerning network formation are shared and, if necessary, discussed with the NVIC. Table 3 shows, for every contingency factor, the classification of each network according to the different forms of governance of Provan & Kenis.

### Discussion

The main finding from our analysis of intensive care networks is that none of the networks is organised according to one of the network governance structures as described by Provan & Kenis. Characteristics of the NAO and shared governance form overlap in 10 out of 15 networks. A larger network makes its management more complex due to an increase in the number of inter-organisational relationships. Hence, according to Provan & Kenis, larger networks (more than 6-8 organisations) benefit from an NAO or lead organisation governance and smaller networks suffice with a shared governance model because mutual coordination is easier with fewer parties.

Consensus on the objectives to be achieved results in more efficient cooperation. Under NAO and shared governance, active participation of the network participants is required and a higher degree of alignment will be needed. With a lesser degree of consensus, collaboration can still be successful with a lead organisation governance structure. A lead organisation is able to make strategic and operational decisions more objectively, which produces results in the short term. It is important that mutual relationships are well managed.

NAO appears to be the most effective form of management because of the relatively large number of intensive care units per network in combination with the, for some, dependent position...
Network governance of Dutch ICUs

of the smaller or the academic intensive care departments within the network. One lead organisation within the network that performs administrative tasks and facilitates network tasks is a possibility when mutual trust has to be worked on and when shared goal consensus has not yet been achieved. A shared governance model can be successful in a small network with three equal intensive care departments with a great deal of mutual trust and with agreement about the objectives to be achieved. Our study is the first one to summarise the current state of affairs concerning intensive care networks after the implementation of the Quality Standard. Various forms of networks have emerged. Our study has limitations concerning a number of issues. First, data were collected from a combination of sources in which subjective assessment by network spokespersons played a role. Some inaccuracy may therefore be present. We think it is likely, however, that a good overall picture has emerged about the network cooperation of intensive care units in the Netherlands. The field is moving so that this report should be seen as a snapshot. The chosen model of Provan & Kenis has the advantage that a classification based on proven effectiveness of network governance is given. However, it has not previously been used and validated for intensive care networks. It is therefore possible that other forms of network governance in the intensive care setting are also effective. We have chosen a limited number of arbitrary criteria to determine the contingency factors. Other choices could have been made as well. Finally, we have not tested our classification against measures of effectiveness such as treatment duration or mortality.

We believe that our overview can help to look carefully at the design of network governance and to develop the most appropriate type of network governance. The purpose is to create effective intensive care networks that truly achieve a maximum efficiency and the best outcomes for intensive care patients. Our study suggests that in creating a network, the first step is to generate insight into the characteristics of the participating organisations (both the intensive care units and the hospital as a whole) within the network. It seems important to aim for goal consensus in the next step and to study complementarity within the collaboration. Mutual relationships and the associated trust are likely to grow by working together during these steps.

Conclusion
After implementation of the Quality Standard, a network governance structure of intensive care departments covering the Netherlands has been established. The networks are managed in different ways. For larger networks, theoretically the NAO type of governance seems to be the most effective and for small networks, when consisting of equivalent intensive care units, this is the shared governance form. Nine intensive care networks have characteristics of this type of network. However, most networks overlap in type of governance structure, which can be a risk for the effectiveness of the network. According to Provan & Kenis, governance is an underexposed topic in the literature of network organisations, while effective governance contributes to the success of a network. The next step is to study the efficiency and outcomes of the networks in relation to their governance structure. In addition, intensive care networks might learn about their governance structure with and from each other.

Disclosures
All authors declare no conflict of interest. No funding or financial support was received.

References
2. Mintzberg H. Managing the Myths of Health Care: Bridging the Separations between Care, Cure, Control and Community. Oakland, USA: Berret-Koehler Publisher; 2017.
3. https://www.parkinsonnet.nl/
Trust in Dutch intensive care networks: the results of a survey

P.H.J. van der Voort1,2,3, A.A. de Beer1, I. van Stijn1, B.J.M. van der Meer1,4
1Department of Intensive Care, OLVG, Amsterdam, the Netherlands
2Department of Critical Care, University Medical Center Groningen, University of Groningen, the Netherlands
3TIAS School for Business & Society, Tilburg University, Tilburg, the Netherlands
4Department of Intensive Care, Amphia Hospital, Breda, Oosterhout and Etten-Leur, the Netherlands

Correspondence
P.H.J. van der Voort - phjvdvoort@upcmail.nl

Keywords - intensive care; network; trust

Abstract

Introduction: Dutch ICUs have been enrolled in network organisations since the Quality Standard of 2016. In networks, intensivists have to cooperate to provide a high quality of care for all patients in their network. Trust is essential to cooperate effectively in a network. It is unknown what the degree of trust is in Dutch ICU networks.

Methods: A survey was composed using the questionnaire by Cummings, measuring the experience of trust, and the questionnaire by Currall, measuring the willingness to show behaviour that is consistent with trust. Two overall questions concerning the feeling of being part of the network and the overall level of trust were added. All questions were answered on a 7-point Likert scale. Network managers passed the questionnaire to intensivists in the network.

Results: The overall level of trust showed a mean of 5.5 (SD 1.2), similar to the mean of the Cummings questionnaire (5.3; SD 0.9). Academic intensivists had a significantly higher level of trust than intensivists from other hospitals (5.9 vs 5.0 and 5.3; p=0.009). The questions covering ‘surveillance’, which measures the need for control, scored lowest with 3.8 (SD 1.3). Intensivists feel the need to make formal agreements and they experience a relatively intense need to control these agreements.

Conclusion: Intensivists experience a reasonable level of trust within their network. However, intensivists feel the need to make formal agreements and they experience a relatively intense need to control these agreements. This suggests that the actual trust is conditional. Academic intensivists showed the highest level of trust.

Introduction

In 2015, Dutch medical associations did not succeed in developing a guideline for the organisation and quality of adult intensive care units. As a result, the Quality Institute defined a Quality Standard in 2016.[1] An important recommendation in this standard is that intensive care departments must work together in networks.

Collaboration in a network is, following the Quality Standard, not only necessary for intensive care units (ICUs) but has consequences for intensivists as well. Intensivists will have to communicate and cooperate with other intensivists from ICUs in the network. Different types of network governance have been shown to be successful, although none have been investigated in an acute care setting.[2] Research on network cooperation between intensive care units is virtually lacking. In the Netherlands, current cooperation is mainly based on professional equality between intensivists from the cooperative ICUs. An important aspect in this cooperation is trust.[2] Trust is a condition that is present in the network as an organisational form, between ICUs and between individual intensivists. Trust has many definitions. Sobel defined trust as ‘the willingness to permit the decisions of others to influence your welfare’.[3] In the intensive care network setting trust is the willingness to permit other intensivists and other ICUs to influence your work processes and maybe even patient outcomes.

In this study we explored trust within Dutch intensive care network cooperation as it is being experienced by intensivists. We studied whether available validated questionnaires regarding trust are applicable to the Dutch intensive care network setting and what the degree of trust is.
Methods

Questionnaires were sent to intensivists in the Netherlands in an online survey tool (SurveyMonkey®) as a ‘closed survey’. We sent a link to the online questionnaire to the coordinating intensivist of the network or to the network coordinator with the request to send this questionnaire to all intensivists in the network. Reminders were not sent and incentives were not offered. Data collection was closed after approximately six months. As patients were not involved and the questionnaire was voluntary, institutional review board approval and informed consent was not necessary. The respondents were anonymous for the researchers; data are securely stored and unavailable to others than the researchers.

Questionnaires

A number of validated questionnaires that measure trust between organisations within a partnership are available. The questionnaires from Cummings and Currall are complementary in the measurement of trust within organisations that cooperate. In particular, Cummings determines the experience of trust and Currall determines the willingness to show the behaviour which is appropriate in case of trust. In addition, Currall classifies the questions by category of communication, informal agreement and control (surveillance). Currall also describes two categories about executives in the partnership. These two categories turned out to have little relevancy for the current intensive care networks so these questions were deleted in the present study. The questions from the original lists of both Cummings and Currall were translated into Dutch as precisely as possible.

In addition to the validated questionnaires, two summarising questions were asked about the network. Firstly ‘I feel part of the network’ and secondly ‘How much trust do you have in the network in general?’

Measurement scale

A 7-point Likert scale was used for all questions. A number of questions were asked in a positive sense regarding trust in the network and a number were asked in a negative way. The negative questions were coded in reverse before the analysis to ensure that higher scores in the results are always indicative of a higher level of trust.

Statistics

Descriptive statistics were calculated for all measured variables and individual questions. Data are given as mean and standard deviation (SD) in case of normal distribution. For other distributions median and interquartile range (IQR) are given. Groups were compared with the Mann-Whitney U test, Fisher’s exact test, Wilcoxon or Kruskal-Wallis test where appropriate. The internal consistency using the Cronbach alpha was determined for the three categories of the Currall questionnaire and for the Cummings questionnaire. Cronbach alpha was interpreted as follows: 0.81 to 1.00 very high, 0.61 to 0.80 high, 0.41 to 0.60 medium, 0.21 to 0.40 low and 0.01 to 0.20 very low. In case of a Cronbach alpha lower than 0.6, one or more questions were removed in order to increase the internal consistency to a value of 0.6 or higher.

Correlation was determined using Pearson’s correlation coefficient. In all tests, a two-sided alpha of 5% was taken as significance level.

Results

Baseline

Fifteen intensive care networks were formed after the Quality Standard was implemented. Eight networks are centred around an academic hospital. The questionnaire was presented to the network managers with the request to offer the link to the intensivists in the network. Therefore, it is unknown how many intensivists received the survey. Eighty-five anonymous surveys were completed and analysed online.

The baseline results are summarised in table 1. In summary, 72% were male and 48% of the respondents were in the category 40-50 years. Academic intensivists and intensivists from the smaller hospitals affiliated with the cooperating general hospitals (in Dutch the SAZ) were equally represented and intensivists from the larger cooperating top clinical hospitals (in Dutch the STZ) represented 56% of the respondents. The work experience, measured in categories of five years, was more or less equally divided across all categories in numbers of respondents.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>24%</td>
</tr>
<tr>
<td>30-40</td>
<td>48%</td>
</tr>
<tr>
<td>40-50</td>
<td>23%</td>
</tr>
<tr>
<td>50-60</td>
<td>5%</td>
</tr>
<tr>
<td>&gt;60</td>
<td></td>
</tr>
</tbody>
</table>

Gender M (%)  

<table>
<thead>
<tr>
<th>Work experience (years)</th>
<th>22%</th>
<th>28%</th>
<th>26%</th>
<th>24%</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-10</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10-15</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;15</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Number of ICUs in the network, mean (SD) 7.5 (2.6)

<table>
<thead>
<tr>
<th>Type of hospital</th>
<th>Academic</th>
<th>Top clinical</th>
<th>General</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>22%</td>
<td>56%</td>
<td>22%</td>
</tr>
</tbody>
</table>

Table 1. Baseline characteristics of the respondents

SD = standard deviation
Table 2. Results of the questionnaires adapted from Currall and from Cummings

<table>
<thead>
<tr>
<th>Original English text</th>
<th>Translated Dutch text</th>
<th>Questionnaire</th>
<th>Mean</th>
<th>SD</th>
<th>Median</th>
<th>IQR</th>
</tr>
</thead>
<tbody>
<tr>
<td>I give to the network all known and relevant information about important issues even if there is a possibility that it might jeopardise the network</td>
<td>Ik geef binnen het netwerk alle mij bekende en relevante informatie over belangrijke zaken, ook als er een kans bestaat dat dit het IC netwerk benadeelde</td>
<td>Communication (Currall)</td>
<td>4.4</td>
<td>1.3</td>
<td>4.0</td>
<td>4-5</td>
</tr>
<tr>
<td>I give to the network all known and relevant information about important issues even if there is a possibility that it might jeopardise my job as intensivist in the network</td>
<td>Ik geef binnen het netwerk alle mij bekende en relevante informatie over belangrijke zaken, ook als er een kans bestaat dat dit mijn baan als intensivist binnen het IC netwerk benadeelde</td>
<td>Communication (Currall)</td>
<td>4.0</td>
<td>1.5</td>
<td>4.0</td>
<td>3-5</td>
</tr>
<tr>
<td>I minimise the information I give to the network</td>
<td>Ik minimaliseer de informatie die ik aan het IC netwerk geef</td>
<td>Communication (Currall)</td>
<td>5.4</td>
<td>1.3</td>
<td>6.0</td>
<td>4-6</td>
</tr>
<tr>
<td>I deliberately withhold some information when communicating within the network</td>
<td>Ik houd opzettelijk sommige informatie achter wanneer ik communiceer in het IC netwerk</td>
<td>Communication (Currall)</td>
<td>5.8</td>
<td>1.2</td>
<td>6.0</td>
<td>5-7</td>
</tr>
<tr>
<td>I enter into an agreement with the network even if his/her future obligations concerning the agreement are not explicitly stated.</td>
<td>Ik ben bereid om een overeenkomst met het IC netwerk aan te gaan als de toekomstige verplichtingen betreffende de overeenkomst niet uitdrukkelijk bekend/geformuleerd zijn.</td>
<td>Informal agreement (Currall)</td>
<td>3.7</td>
<td>1.6</td>
<td>4.0</td>
<td>2-5</td>
</tr>
<tr>
<td>I enter into an agreement with the network even if I think other people might try to persuade someone to break the network agreement</td>
<td>Ik ben bereid om een overeenkomst met het netwerk aan te gaan, ook als ik denk dat iemand zal proberen anderen binnen het IC netwerk over te halen dit te dwarsbomen</td>
<td>Informal agreement (Currall)</td>
<td>4.3</td>
<td>1.4</td>
<td>4.0</td>
<td>4-5</td>
</tr>
<tr>
<td>I enter into an agreement with the network even if it is unclear whether the network would suffer any negative consequences for breaking it</td>
<td>Ik ga een overeenkomst aan met het IC netwerk ook al is het onduidelijk of het netwerk negatieve consequenties ondervindt bij het verbreken er van.</td>
<td>Informal agreement (Currall)</td>
<td>3.9</td>
<td>1.2</td>
<td>4.0</td>
<td>3-4</td>
</tr>
<tr>
<td>I decline the network’s offer to enter into an unwritten agreement</td>
<td>Ik wijs een uitnodiging aan een ongeschreven overeenkomst binnen het IC netwerk af.</td>
<td>Informal agreement (Currall)</td>
<td>5.3</td>
<td>1.5</td>
<td>5.0</td>
<td>4-7</td>
</tr>
<tr>
<td>I watch the intensivists in the network attentively in order to make sure that they do not do something detrimental to the network</td>
<td>Ik bekijk de intensivisten in het netwerk aandachtig om er zeker van te zijn dat hij/zij niks schadelijks doet voor het netwerk</td>
<td>Surveillance (Currall)</td>
<td>4.3</td>
<td>1.5</td>
<td>4.0</td>
<td>4-5</td>
</tr>
<tr>
<td>I keep surveillance (i.e. look over the shoulder) over the network after asking the network to do something</td>
<td>Ik houd het IC netwerk in de gaten nadat ik het netwerk gevraagd heb om iets uit te voeren. (Over de schouder meekijken)</td>
<td>Surveillance (Currall)</td>
<td>3.8</td>
<td>1.3</td>
<td>4.0</td>
<td>3-4</td>
</tr>
<tr>
<td>I check with other people about the activities of the network to make sure the network is not trying to ‘get away’ with something</td>
<td>Ik vraag bij collega intensivisten na of de activiteiten van het IC netwerk worden uitgevoerd, om ervoor te zorgen dat het niet blijft liggen</td>
<td>Surveillance (Currall)</td>
<td>3.5</td>
<td>1.1</td>
<td>3.0</td>
<td>3-4</td>
</tr>
<tr>
<td>In situations other than contract negotiations, I check records to verify facts stated by the network</td>
<td>In situaties anders dan contractonderhandelingen controleer ik de documenten om de door het IC netwerk genoemde feiten te controleren</td>
<td>Surveillance (Currall)</td>
<td>3.5</td>
<td>1.4</td>
<td>4.0</td>
<td>2.2</td>
</tr>
<tr>
<td>I think that people in the network tell the truth in negotiations</td>
<td>Ik denk dat mensen binnen het IC netwerk de waarheid spreken in onderhandelingen</td>
<td>Cummings</td>
<td>4.9</td>
<td>1.1</td>
<td>5.0</td>
<td>4-6</td>
</tr>
<tr>
<td>I think that the network meets its negotiated obligations to our department</td>
<td>Ik denk dat het IC netwerk haar onderhandelde verplichtingen aan onze afdeling tegemoet komt</td>
<td>Cummings</td>
<td>5.2</td>
<td>1.1</td>
<td>5.0</td>
<td>4-6</td>
</tr>
<tr>
<td>In my opinion, the network is reliable</td>
<td>Ik ben van mening dat het IC netwerk betrouwbaar is</td>
<td>Cummings</td>
<td>5.4</td>
<td>1.0</td>
<td>5.0</td>
<td>5-6</td>
</tr>
<tr>
<td>I think that the people in the network succeed by stepping on other people</td>
<td>Ik denk dat mensen in het IC netwerk succesvol zijn ten koste van anderen</td>
<td>Cummings</td>
<td>5.3</td>
<td>1.1</td>
<td>5.0</td>
<td>4-6</td>
</tr>
<tr>
<td>I think that the network takes advantage of our problems</td>
<td>Ik denk dat het IC netwerk voordeel haalt uit de problemen van onze afdeling</td>
<td>Cummings</td>
<td>4.9</td>
<td>1.6</td>
<td>5.0</td>
<td>4-6</td>
</tr>
<tr>
<td>I think that the network will keep its word</td>
<td>Ik heb het gevoel dat het IC netwerk zich aan zijn woorden houdt</td>
<td>Cummings</td>
<td>5.3</td>
<td>1.0</td>
<td>5.0</td>
<td>4-6</td>
</tr>
<tr>
<td>I think the network does not mislead us</td>
<td>Ik heb het gevoel dat het IC netwerk onze afdeling niet misleidt</td>
<td>Cummings</td>
<td>5.3</td>
<td>1.2</td>
<td>5.5</td>
<td>4-6</td>
</tr>
<tr>
<td>I feel that the network tries to get out of its commitments</td>
<td>Ik heb gevoel dat het IC netwerk probeert om onder haar verplichtingen uit te komen</td>
<td>Cummings</td>
<td>5.8</td>
<td>1.3</td>
<td>6.0</td>
<td>6-7</td>
</tr>
<tr>
<td>I feel that the network negotiates joint expectations fairly</td>
<td>Ik heb het gevoel dat het IC netwerk onze gezamenlijke verwachting eerlijk uit onderhandelt.</td>
<td>Cummings</td>
<td>5.2</td>
<td>1.0</td>
<td>5.0</td>
<td>4-6</td>
</tr>
<tr>
<td>I feel that the network takes advantage of people who are vulnerable</td>
<td>Ik heb het gevoel dat het IC netwerk voordeel haalt ten koste van kwetsbare afdelingen</td>
<td>Cummings</td>
<td>5.5</td>
<td>1.3</td>
<td>6.0</td>
<td>4-7</td>
</tr>
<tr>
<td>I feel part of the network</td>
<td>Ik voel me onderdeel van het netwerk</td>
<td>Overall part of the network</td>
<td>5.1</td>
<td>1.8</td>
<td>6.0</td>
<td>4-7</td>
</tr>
<tr>
<td>How much trust do you have in the network in general?</td>
<td>Hoe groot is uw vertrouwen in het netwerk in het algemeen</td>
<td>Overall trust</td>
<td>5.5</td>
<td>1.2</td>
<td>6.0</td>
<td>5-6.0</td>
</tr>
</tbody>
</table>
question improved the Cronbach alpha from 0.56 to 0.68. In the surveillance category, the removal of one question improved the Cronbach alpha from 0.56 to 0.66. The Cummings list had a very high Cronbach alpha of 0.94 after reduction of the numbers of questions from 12 to 10. Table 2 summarises the results of the questionnaire.

Results of the questionnaires
The questions regarding sharing of information and regarding conducting transparent communication scored an average of 4.9 out of 7 on all questions and respondents. The questions on formal or informal agreements scored an average of 4.3 and the questions about exercising surveillance scored a 3.8 on average (table 2).

Trust in the communication category was significantly higher than in the agreement category (p<0.001) and also higher than in the surveillance category (p=0.001). The agreement category scored significantly higher than surveillance (p=0.025).

The Cummings questionnaire scored an average of 5.3 on all seven questions of all respondents on a scale of 7. The question concerning overall trust in the network was rated with an average of 5.5 on a scale of 7. The feeling of being part of the network scored an average of 5.1. Gender and age were unrelated to these outcomes. The analysis per hospital type showed that intensivists from academic hospitals expressed a significantly higher level of trust than those from top clinical and general hospitals (STZ and SAZ) hospitals respectively (5.9 vs 5.0 vs 5.3; p=0.009).

Correlation
In a correlation matrix, the Cummings questionnaire showed the highest correlation with the level of overall trust (r²=0.28). The two general questions concerning feeling part of the network and overall level of trust correlated best with r²=0.38. The analysis of the baseline variables and the questionnaires showed that age was unrelated to the mean score of all questions of the Cummings questionnaire (p=0.06) but the overall level of trust was highest in intensivists of age category 40-50 years (p=0.019). Gender was unrelated to the mean score of all questions of the Cummings questionnaire (p=0.54) and to the mean overall level of trust (p=0.32).

Discussion
This study shows that intensivists experience a reasonable level of trust within their network.

Our study on trust within intensive care networks in the Netherlands is a first cautious attempt to quantify research concerning the level of trust between intensive care units and intensivists. With our study, we have shown that the Cummings questionnaire is the most consistent questionnaire in this setting. This questionnaire focuses on the experience of trust. The final question on the overall level of trust in the network is in fact a measurement of the perception of trust. It is therefore expected that the Cummings questionnaire and the question to the overall level on trust show the highest correlation with each other. The questions in the Currall questionnaire determine whether the respondents concede to displaying behaviour that is consistent with a high level of trust. This questionnaire shows that intensivists feel the need to make formal agreements and they experience a relatively intense need to control these agreements. This in itself does not tell us whether there is actual trust. Moreover, it is uncertain to what extent socially desirable answers have been given.

Altogether, there appears to be a reasonable degree of perception of trust within intensivists who work together in an intensive care network. This is also apparent from the question on the overall level of trust. Academic intensivists have significantly more trust in the network than intensivists from other hospitals.

The scores measuring the degree of behaviour associated with trust that intensivists want to show are between 3.8 and 4.9, which is slightly lower than the scores on the experience of trust. This behaviour manifests more in the communication category than in other categories. Signs of lower levels of trust are the need that intensivists feel to make formal agreements and that intensivists experience a relatively intense need to control these agreements. In fact, the surveillance category shows that control is important, which suggests that the actual trust is conditional[6] and needs confirmation by applying surveillance measures. Conditional trust is trust that persists when behaviour is consistent with the expectations. Apparently, this consistency is checked by formal agreements and their control.

The response rate is limited, which may have affected the results. On the other hand, the distribution of the intensivists is representative in work location and age. We translated the questions into Dutch. Table 2 shows both Dutch and English questions. This translation might have affected the validity of the questionnaires. However, the internal consistency, shown by Cronbach alpha, was sufficient for the Dutch questionnaires.

Several factors drive the level of trust. Expertise, benevolence or intention and integrity are the main drivers.[7] We did not study which of these drivers is key in the development of trust in intensive care networks. The construct of trust also implies a risk that is taken in the future.[7] In the network setting, intensivists in the network are more or less willing to take this risk in future situations when cooperation is needed. Our finding that agreements and controlling the agreements are important can be seen as ways to minimise the risk within the network cooperation.

This research leaves many questions unanswered and raises several new questions. It should therefore be seen as a first exploratory study of possible methods to be used and to measure the level of trust in intensive care networks.
Conclusion
Intensivists experience a reasonable level of trust within their network. The behaviour that demonstrates trust mainly concerns communication and exchange of information. Signs of lower levels of trust are the need that intensivists feel to make formal agreements and that intensivists experience a relatively intense need to control these agreements. Academic intensivists showed the highest level of trust.

Disclosures
All authors declare no conflict of interest. No funding or financial support was received.

References
CASE REPORT

How low can your haemoglobin concentration go?

J. Heidt1, J. Gunkel1, H. Visser2, R. van Raalte1

1Department of Intensive Care, 2Department of Gynaecology, Tergooi Hospital, Hilversum, the Netherlands

Correspondence
J. Heidt - jheidt@tergooi.nl

Keywords - haemorrhagic shock, severe anaemia, uterine leiomyoma, cardiac ischaemia, organ dysfunction

Abstract
A 48-year-old female presented to the emergency department in severe haemorrhagic shock with associated altered mental status. She had suffered severe vaginal blood loss for the past two days. A CT scan did not show any signs of active bleeding, but revealed a large uterine leiomyoma, likely to have caused the severe vaginal blood loss. She was admitted to the intensive care unit for resuscitation with multiple transfusions. The first haemoglobin concentration was 0.9 mmol/l. She developed major cardiac ischaemia and severe acidosis due to the haemorrhagic shock, but survived. Severe anaemia, especially in acute onset due to major haemorrhage, is associated with high mortality and morbidity. In our medical practice to date, we have never encountered such an extreme case of anaemia compatible with life.

Introduction
Severe anaemia, especially in acute onset due to major haemorrhage, is associated with high mortality and morbidity such as cardiac ischaemia and multi-organ dysfunction, as presented in this case.

Case report
A 48-year-old female presented to the emergency department in severe haemorrhagic shock with associated altered mental status. She had suffered major vaginal blood loss with large clots for the past two days but did not consult the general practitioner or emergency services until the time of presentation. She is para 2 with no medical history and reported no use of medication. Physical examination on presentation showed extreme pallor, anxiety and restlessness, tachypnoea (respiratory rate of 23/min), hypoxaemia (SatO2 of 92% with 15 l/min oxygen on a non-rebreather-mask), hypotension (70/35 mmHg) with a weak pulse (heart rate 90/min) and no capillary refill, and hypothermia (33.0 °C). Although she was disorientated and anxious she was still able to speak coherently, mentioning feeling cold and thirsty. We suspected major internal haemorrhage with hypovolaemic shock and started resuscitation with infusion of crystalloid fluids (500 ml Ringer’s lactate solution, on top of the 1000 ml administered by the ambulance personnel in the prehospital setting) and norepinephrine. We aimed at permissive hypotension with a target systolic blood pressure (SBP) of 100 mmHg, in order to minimise blood loss and limit infusion of crystalloid fluids to prevent further haemodilution and coagulopathy. The patient was gradually warmed up using a Bair Hugger™. Concomitantly, we activated our major haemorrhage protocol and started resuscitation with transfusion of O-negative packed red blood...
cells (PRBCs), pending blood group typed and cross-matched PRBCs (figure 1).
A CT scan of the chest and abdomen did not show extravasation of contrast fluid and ruled out aortic dissection, ruptured abdominal aneurysm, intestinal bleeding, extra-uterine pregnancy and active bleeding in utero. It did reveal uterine leiomyoma (figure 2). In the absence of active haemorrhage that would require surgical intervention, the patient was admitted to the intensive care unit (ICU) for further resuscitation and transfusion. While inserting venous and arterial lines we observed backflow of extremely diluted blood. The first laboratory results (table 1) showed a haemoglobin concentration of 0.9 mmol/l, haematocrit of 0.06 l/l and thrombocytopenia with a platelet count of 110 x 10^9/l. After one unit of PRBCs was administered, the haemoglobin concentration increased to 1.4 mmol/l with a haematocrit 0.09 l/l. Further blood analysis revealed severe lactic acidosis (pH 7.07, serum lactate 20.6 mmol/l), acute renal failure and elevated cardiac enzymes (table 1). An electrocardiogram (ECG) showed signs of subendocardial pan-ischaemia (figure 3). In total six units of PRBCs (two O-negative), two of fresh frozen plasma, one unit of platelets, two grams of fibrinogen, two grams of calcium gluconate and one gram of tranexamic acid were administered. This resulted in a stable haemoglobin concentration of 4.6 mmol/l (figure 1). Since the pH was still above 7.00 we decided not to actively correct the metabolic/lactic acidosis with sodium bicarbonate. Our patient gradually improved. We diagnosed a severe uterine haemorrhage due to uterine leiomyoma. Secondary to the extreme anaemia she not only developed lactic acidosis as a sign of disturbed oxygen delivery and tissue oxygenation, but also massive subendocardial ischaemia with elevated cardiac enzymes (table 1) and signs of subendocardial ischaemia on the ECG (figure 3). She rapidly recovered, with normalisation of the ECG, and was discharged to the gynaecological ward within 24 hours after presentation. Echocardiography showed normal function and dimensions of the heart, and ultimately there was complete recovery of cerebral, renal and liver function. Analysis by the haematologist ruled out coagulation disorders (e.g. Von Willebrand Factor activity 140%). Histological analysis of the endometrium confirmed the diagnosis of uterine leiomyoma with ischaemic changes. She was treated with lynestrenol (Orgametril®) and scheduled for hysterectomy.

**Discussion**
Severe anaemia, especially due to acute major haemorrhage, is associated with high morbidity (such as myocardial infarction, arrhythmia, congestive heart failure, infections) and mortality. Case reports of extreme anaemia in surgical and trauma patients and perioperative reports of anaemia in Jehovah’s Witnesses showed increased mortality and morbidity when haemoglobin concentrations dropped below 3.1 mmol/l.[1-4]

Patients with acute major haemorrhage are at risk of severe cardiovascular deterioration as a result of hypovolaemic shock and compromised oxygen transport. If not treated in time, irreversible damage to vital organs may occur, subsequently leading to multiple organ failure and death. We present a case of a 48-year-old woman with severe anaemia (haemoglobin concentration 0.9 mmol/l) due to severe haemorrhage from uterine leiomyoma, resulting in anaemia and hypovolaemia, coagulopathy, tissue malperfusion, severe acidosis, further progression of bleeding and finally cardiac, cerebral, renal and liver dysfunction. Menorrhagia is a known complication of uterine leiomyoma and can lead to anaemia. Although extremely rare, spontaneous rupture of vessels overlying uterine leiomyoma causing severe vaginal blood loss or haemoperitoneum and hypovolaemic shock has been documented.[5-9]
In our case, the first haemoglobin concentration of 0.9 mmol/l (haematocrit 0.06 l/l) after one unit of PRBCs was administered, suggesting the first sample analysis was accurate. To eliminate potential erroneous results, in our hospital all haemoglobin concentrations <4.0 mmol/l are routinely executed twice (XN-analyser). These routine control samples confirmed the low first haemoglobin concentration of 0.9 mmol/l and subsequently 1.4 mmol/l.

In our case, the first haemoglobin concentration of 0.9 mmol/l (haematocrit 0.06 l/l) was followed by 1.4 mmol/l (haematocrit 0.09 l/l) after one unit of PRBCs was administered, suggesting the first sample analysis was accurate. To eliminate potential erroneous results, in our hospital all haemoglobin concentrations <4.0 mmol/l are routinely executed twice (XN-analyser). These routine control samples confirmed the low first haemoglobin concentration of 0.9 mmol/l and subsequently 1.4 mmol/l.

We assume our patient gradually developed chronic anaemia due to menorrhagia, leading to physiological adaptation enabling her to still circulate, oxygenate and retain consciousness after two days of extensive blood loss,
ultimately resulting in this severe anaemia. Haemodilution due to the initial resuscitation with crystalloid fluids probably also played a role in this severe anaemia. Adaptation to chronic anaemia consists of several different processes: 1) activation of oxygen-sensing mechanisms, resulting in an increase of renal erythropoietin production to restore haemoglobin concentration and an increase in cardiac output; 2) respiratory adaptation with increased minute ventilation, ensuring optimal SatO₂ is maintained with a reduced haemoglobin to maximise blood oxygen content; 3) hypoxia-sensing cells activating the sympathetic nervous system, increasing cardiac output and reducing systemic vascular resistance; 4) increased tissue oxygen extraction; 5) metabolic cellular adaptations, resulting in reduced tissue oxygen consumption by several organs to maintain maximum global oxygen utilisation to the vital organs such as the heart and the brain.[10,11]

Despite these possible adaptive mechanisms, our patient not only developed severe acidosis with a raised lactate level as a sign of disturbed oxygen delivery and tissue oxygenation, but also massive subendocardial demand ischaemia with elevated cardiac enzymes (table 1) and an abnormal ECG (figure 3). We hypothesise that the adaptive processes fell short due to major haemorrhage resulting in this severe anaemia with a haemoglobin concentration well below the critical limit of 3.1 mmol/l as mentioned in previous reports.[3,4,10]

We assume ‘only’ six units of PRBCs were necessary during resuscitation to accomplish a stable haemoglobin concentration of 4.6 mmol/l because of spontaneous cessation of ongoing active bleeding at the time of presentation and during resuscitation. Acute coagulopathy in severe haemorrhage is a well-known phenomenon, especially in traumatology.[12] Causal factors are acidosis, hypothermia, resuscitation-associated dilutional coagulopathy and severe depletion of red blood cells, platelets and coagulation factors. Rapid intravenous infusion of crystalloid or colloid fluids is generally applied during ongoing haemorrhage to establish haemodynamic stability, restore adequate intravascular volume and improve oxygen tissue delivery.[13] When given in large volumes, however, crystalloid or colloid fluids initiate dilution of clotting factors resulting in coagulopathy.[14-16] Furthermore, the use of colloid fluids has proven to negatively influence coagulation capacity and endothelial function.[17,18] Caution should be exercised with aggressive fluid resuscitation. Additionally, rapid consumption of fibrinogen, clotting factors and platelets as a result of persistent blood loss, aggravates coagulopathy.[15] These findings have led to less aggressive fluid resuscitation in patients with traumatic and postpartum haemorrhagic shock.[19,20] In light of this, we initially aimed at maintaining permissive hypotension with infusion of crystalloid fluids and norepinephrine, starting transfusion with O-negative PRBCs as soon as possible to prevent further worsening of the coagulopathy and bleeding.

The goal of permissive hypotension is to maintain the minimal blood pressure necessary to perfuse the vital organs. The rationale is that elevations in blood pressure before adequate haemostasis is achieved may compromise a tenuous clot and exacerbate blood loss.[29] Although most research has been

![Figure 3. ECG on ICU admission, showing diffuse ST-segment depression and ST-segment elevation in aVR, suspect for subendocardial pan-ischaemia](image-url)
Table 1. Laboratory results on presentation and during/after resuscitation and transfusion, with reference values and time points

<table>
<thead>
<tr>
<th>Laboratory results</th>
<th>On presentation</th>
<th>+ 45 minutes</th>
<th>+ 1 hour and 45 minutes</th>
<th>+ 2 hours</th>
<th>+ 5 hours and 30 minutes</th>
<th>+ 6 hours</th>
<th>+ 9 hours and 30 minutes</th>
<th>+ 10 hours</th>
<th>+ 13 hours</th>
<th>Reference values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin</td>
<td>0.9</td>
<td>1.4</td>
<td>3.5</td>
<td>4.6</td>
<td>4.6</td>
<td>4.6</td>
<td>7.5-10.0 mmol/l</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haematocrit</td>
<td>0.06</td>
<td>0.09</td>
<td>0.19</td>
<td>0.23</td>
<td>0.23</td>
<td>0.22</td>
<td>0.35-0.45 l/l</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets</td>
<td>110</td>
<td>107</td>
<td>81</td>
<td>95</td>
<td>85</td>
<td>74</td>
<td>150-450 x10^9/l</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INR</td>
<td>1.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT</td>
<td>14.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>13.8</td>
<td>9.9-11.8 sec</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>APTT</td>
<td>17</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>23</td>
<td>22-28 sec</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>2.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.0-4.0 g/l</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactate</td>
<td>20.6</td>
<td>13.6</td>
<td>4.0</td>
<td></td>
<td></td>
<td></td>
<td>&lt;2.2 mmol/l</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium</td>
<td>133</td>
<td>135</td>
<td>135</td>
<td>136</td>
<td>136</td>
<td>136</td>
<td>133-142 mmol/l</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potassium</td>
<td>5.2</td>
<td>5.3</td>
<td>4.6</td>
<td>4.4</td>
<td>4.0</td>
<td></td>
<td>3.5-5.0 mmol/l</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chloride</td>
<td>99</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>98-107 mmol/l</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium ion</td>
<td>1.08</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.10-1.30 mmol/l</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phosphate</td>
<td>3.39</td>
<td></td>
<td></td>
<td>1.40</td>
<td></td>
<td></td>
<td>0.74-1.52 mmol/l</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Magnesium</td>
<td>1.11</td>
<td></td>
<td></td>
<td>0.91</td>
<td></td>
<td></td>
<td>0.70-1.00 mmol/l</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urea</td>
<td>10.0</td>
<td></td>
<td></td>
<td>10.0</td>
<td></td>
<td></td>
<td>2.5-6.7 mmol/l</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>195</td>
<td></td>
<td></td>
<td>110</td>
<td></td>
<td></td>
<td>50-95 μmol/l</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin</td>
<td>&lt;5</td>
<td></td>
<td></td>
<td>17</td>
<td></td>
<td></td>
<td>5-20 μmol/l</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AF</td>
<td>60</td>
<td></td>
<td>72</td>
<td>74</td>
<td></td>
<td></td>
<td>30-120 U/l</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GGT</td>
<td>8</td>
<td></td>
<td>15</td>
<td>10</td>
<td></td>
<td></td>
<td>&lt;27 U/l</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASAT</td>
<td>2237</td>
<td></td>
<td>3596</td>
<td>4384</td>
<td></td>
<td></td>
<td>&lt;30 U/l</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALAT</td>
<td>1821</td>
<td></td>
<td>2412</td>
<td>2884</td>
<td></td>
<td></td>
<td>&lt;35 U/l</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LD</td>
<td>4245</td>
<td></td>
<td>7057</td>
<td>&gt;7500</td>
<td></td>
<td></td>
<td>&lt;250 U/l</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CK</td>
<td>241</td>
<td></td>
<td>828</td>
<td>1529</td>
<td></td>
<td></td>
<td>&lt;122 U/l</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CK-MB % total CK</td>
<td>97</td>
<td></td>
<td>115</td>
<td>94</td>
<td></td>
<td>6</td>
<td>&lt;4%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Troponin-I (HS)</td>
<td>313</td>
<td></td>
<td>9056</td>
<td>7608</td>
<td></td>
<td></td>
<td>&lt;26 ng/ml</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.07</td>
<td>7.16</td>
<td>7.39</td>
<td>7.42</td>
<td>7.47</td>
<td>7.47</td>
<td>7.36-7.44</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>4.0</td>
<td>7.1</td>
<td>16.0</td>
<td>18.8</td>
<td>21.6</td>
<td></td>
<td>23-27 mmol/l</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(arterial)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Base excess</td>
<td>-23.7</td>
<td>-19.9</td>
<td>-8.1</td>
<td>-5.0</td>
<td>-1.7</td>
<td>-3.0</td>
<td>-3.0-3.0 mmol/l</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PaCO2</td>
<td>1.8</td>
<td>2.7</td>
<td>3.6</td>
<td>3.9</td>
<td>3.9</td>
<td>4.5-6.1 kPa</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PaO2</td>
<td>37.6</td>
<td>12.1</td>
<td>7.2</td>
<td>7.7</td>
<td>8.6</td>
<td>10.0-13.5 kPa</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sato2</td>
<td>1.00</td>
<td>0.98</td>
<td>0.92</td>
<td>0.93</td>
<td>0.95</td>
<td>0.95-0.98</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anion gap</td>
<td>31.30</td>
<td>26.40</td>
<td>15.60</td>
<td>13.50</td>
<td>10.20</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

conducted in animal models, a few studies in trauma patients show that delayed fluid resuscitation (versus immediate fluid resuscitation) and resuscitation with permissive hypotension with systolic blood pressure (SBP) goals down to 70 mmHg (versus non-limited SBP) resulted in no difference in mortality and even improved survival in both intervention groups compared with the control groups.\textsuperscript{[21-23]} In trauma patients it has been shown that aggressive volume administration, often initiated in the pre-hospital setting, increased the incidence of secondary compartment syndrome, damage-control laparotomy, coagulopathy, multi-organ failure, nosocomial infections, the number of blood component transfusions as well as the number of massively transfused patients and prolonged the length of ICU and hospital stays.\textsuperscript{[24]} Therefore, the recent 2019 ‘European guideline on management of major bleeding and coagulopathy following trauma’ advocates the concept of
‘damage-control resuscitation’ for initial treatment of trauma-induced hypotension, with restricted volume replacement and permissive hypotension with a target systolic blood pressure of 80–90 mmHg (mean arterial pressure 50–60 mmHg) until major bleeding has been stopped in the initial phase following trauma without brain injury.\textsuperscript{24}

Although our patient was not a trauma patient, we assume that the pathophysiological mechanisms of acute haemorrhage and resuscitation are comparable, and that these findings may also be applied to patients with non-traumatic types of haemorrhagic shock. In our case we achieved clinical stability retaining consciousness of the patient with permissive hypotension with a target SBP of 100 mmHg and therefore refrained from further lowering the blood pressure.

Conclusion

Severe anaemia, especially in acute haemorrhage with haemoglobin concentrations dropping to 3.1 mmol/l, is associated with high mortality and morbidity. These patients are at risk of severe cardiovascular complications due to hypovolaemic shock and compromised oxygen transport and delivery resulting in acute organ dysfunction. As in our patient, they are at increased risk of cardiac ischaemia (and possible cardiac arrest), cerebral hypoxia, kidney and liver dysfunction and severe acidosis. Limiting infusion of crystalloid or colloid fluids during resuscitation should be considered to prevent further worsening of the coagulopathy and bleeding. Permissive hypotension with target SBP 80–90 mmHg is recommended.

In our medical practice to date, we have not encountered a case of such severe anaemia with a haemoglobin concentration of 0.9 mmol/l without concomitant mortality.

Disclosures

All authors declare no conflict of interest. No funding or financial support was received.

References

CASE REPORT

The broad differential diagnosis of encephalitis: a case report

I.E. Ghijselings1, I.C.M. Hoogland2, M.C. Brouwer2, P.H.J. van der Voort1,4, J. Horn3

1Department of Intensive Care, OLVG, Amsterdam, the Netherlands
2Departments of 3Neurology and 4Intensive Care, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands
4Department of Critical Care, University Medical Center Groningen, University of Groningen, the Netherlands

Correspondence
I.E. Ghijselings – idris.ghijselings@gmail.com

Keywords - autoimmune encephalitis, anti-N-methyl-D-aspartate receptor encephalitis, differential diagnosis, tuberculous meningitis

Abstract
A 31-year-old previously healthy woman presented with hallucinations and altered mental status, which was eventually found to be due to anti-N-methyl-D-aspartate receptor encephalitis. In this case report, we discuss the broad differential diagnosis of encephalitis with infectious and autoimmune causes. Furthermore, we consider empirical treatment options in case a definite diagnosis is hard to be made.

Introduction
When a patient presents to the emergency department with clinical signs of meningoencephalitis, a bacterial or viral cause is often initially suspected. As time to treatment is an important prognostic factor in bacterial meningitis, treatment with amoxicillin and a third-generation cephalosporin plus dexamethasone is initiated immediately. Acyclovir is frequently added to treat herpes simplex encephalitis, while awaiting cerebrospinal fluid (CSF) culture and polymerase chain reaction results. However, the differential diagnosis of encephalitis also includes other infectious and autoimmune causes, which may be difficult to diagnose.

We describe a case of a patient presenting with encephalitis, who deteriorated clinically despite antibiotic and antiviral therapy. Intensive care unit (ICU) admission was required because of severely altered mental status, loss of consciousness and autonomic instability. We discuss the broad differential diagnosis and consequences in terms of treatment. The patient's family consented to the publication of this case report.

Case report
A 31-year-old Caucasian woman without a medical history was brought to the emergency department with headache, dizziness, tinnitus, vomiting and fever for two weeks. The day of presentation, she developed diplopia, echolalia and auditory hallucinations. Upon physical examination she was obese (body mass index of 38.6 kg/m²) and had a right-sided abducens nerve palsy. Cranial CT showed no abnormalities after which a lumbar puncture was performed. The CSF showed an elevated leucocyte count (98% mononuclear cells), slightly elevated protein and slightly decreased CSF/blood glucose ratio (table 1). The patient was admitted and treated for meningoencephalitis with amoxicillin, ceftriaxone, dexamethasone and acyclovir (figure 1). Additional hetero-anamnesis revealed no allergies, no alcohol or drug abuse and no recent foreign travel. She had a dog, but no other contact with animals. She smoked five to ten cigarettes a day. She was a social worker and had close contact with homeless people including a recent relationship with a homeless person.

In the following two days she developed anxiety, agitation and involuntary urinary loss. The level of consciousness fluctuated, and she developed orofacial dyskinesias and rhythmic contractions of her right hand, for which midazolam was given with good effect. The electroencephalogram (EEG) showed no epileptic activity. Repeated lumbar punctures revealed a high opening pressure, an increase in leucocyte count and a normal protein (table 1). On day 3 after admission her consciousness deteriorated (Glasgow Coma Scale (GCS) E1M4V1) after which she was transferred to the ICU and intubated.

At the ICU, the patient had a GCS of three, had opisthotonic posturing, intact brainstem reflexes, adduction position of her right eye, regular non-rhythmic vertical movements of the eyes with a rotatory component and regular, supinating movements of both arms with extension of the fingers. MRI of the brain showed enhancement of the leptomeninges, both supratentorially and infratentorially. EEG was repeated three times during admission showing a slow background pattern but
Differential diagnosis of encephalitis

no epilepsy. CT scan of the thorax and abdomen showed no abnormalities, HIV test was negative.

Autoimmune encephalitis (e.g. anti-NMDA, anti-AMPA, leucine-rich glioma-inactivated protein, Hashimoto) was deemed to be likely at that moment. However, given her social contacts, bacterial meningitis due to uncommon pathogens such as *M. tuberculosis* or *L. monocytogenes*, cryptococcal meningitis and herpes encephalitis was still a possibility. Awaiting results the patient was given methylprednisolone for three days to treat autoimmune encephalitis; amphotericin B and flucytosine to treat cryptococcal meningitis; ethambutol, isoniazid, pyrazinamide and rifampicin to treat tuberculous meningitis (TBM) (figure 1).

On day 10 after admission, CSF and serum tests came back positive for NMDA antibodies, leading to a diagnosis of anti-NMDA receptor encephalitis. A course of intravenous immunoglobulin was started and antimicrobial treatment was stopped (figure 1). As the patient did not recover, a high-dosed methylprednisolone pulse treatment was repeated and rituximab was started. Further tumour screening was performed including MRI of the ovaries, whole body 18-Fluorodeoxyglucose PET-CT scan and biopsy of a mass in the breast. No malignancies were found.

During admission to the ICU, the patient developed severe autonomic dysfunction including hypersalivation, bradycardia and tachycardia, hypotension and hypertension. The hyperthermia posed a clinical challenge because of the differential diagnosis of infections in a now immunocompromised patient. Cultures of blood, urine and sputum were done every three days and were all negative. Hyperthermia above 41°C was treated with extracorporeal cooling. The hypersalivation was treated with botulinum toxin injections in the parotid glands. The bradycardias and tachycardias spontaneously normalised, frequently within 30 minutes. The orofacial dyskinesias and the dyskinesias of her arms were severe and responded well to propofol and midazolam treatment.

The patient slowly improved and on day 21 all sedative medication could be discontinued after which she was successfully weaned from mechanical ventilation. The dyskinesias diminished after which midazolam boluses could be tapered. On day 35 she opened her eyes when spoken to and she intermittently performed tasks at request.

### Table 1. Cerebrospinal fluid (CSF) characteristics

<table>
<thead>
<tr>
<th>CSF</th>
<th>Day 0</th>
<th>Day 3</th>
<th>Day 5</th>
<th>Day 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opening pressure (cmH2O)</td>
<td>x</td>
<td>48</td>
<td>37</td>
<td>29</td>
</tr>
<tr>
<td>Leukocytes (x10^6 cells/l)</td>
<td>238</td>
<td>417</td>
<td>251</td>
<td>179</td>
</tr>
<tr>
<td>Total protein (g/l)</td>
<td>0.6</td>
<td>0.3</td>
<td>0.5</td>
<td>0.2</td>
</tr>
</tbody>
</table>
On day 43 she could be discharged from the ICU to the neurology department. There she improved further. She made eye contact, showed emotion and tried to speak. Because of the severity of the disease and the very slow improvement, she was treated with intravenous cyclophosphamide on day 54 after admission (figure 1).

On day 60 after admission the patient was readmitted to the ICU because of hyperthermia and respiratory distress. Shortly after arrival to the ICU she collapsed and cardiopulmonary resuscitation was started due to cardiac arrest with pulseless electric activity. Thrombolysis was given for a tentative diagnosis of pulmonary embolism, but the patient ultimately died.

Discussion
A young patient with a highly likely autoimmune receptor encephalitis but also a possible infectious meningoencephalitis leads to a complex situation. Ideally, immune suppressive treatment is started as soon as possible to prevent further neurological deterioration. But high-dosed methylprednisolone or other immune suppressive therapies will likely lead to an acute aggravation of the infectious disease. It often takes several days for the results of the diagnostic tests to become available, so a strategy has to be developed while awaiting the results.

At presentation to the emergency department our patient had a two-week history of flu-like symptoms, had been in contact with several homeless people, had unprotected sexual contact and had cranial nerve palsy. Her CSF characteristics were more typical for TBM than for autoimmune encephalitis. An increased intracranial pressure, a high leucocytosis and a low CSF/blood glucose ratio are uncommon in autoimmune encephalitis. Furthermore, the MRI of the brain showed pachymeningitis. Because the definite diagnosis remained uncertain, lumbar puncture was repeated several times and empirical treatment was started as soon as possible. Treatment with corticosteroids reduces the mortality and morbidity of HIV-negative patients with TBM. The advised dosage to start with is prednisone 1g/day to simultaneously treat the suspected autoimmune encephalitis. For suspected bacterial meningitis, a third-generation cephalosporin combined with amoxicillin is the standard therapy. When cultures are negative after 48 hours, the cephalosporin can be stopped. As Listeria monocytogenes is notoriously difficult to culture, the amoxicillin should be continued for 14 days. Other infectious causes for meningoencephalitis are rare but should be kept in mind. Due to the complex social situation of this patient, TBM was one of the possibilities.

TBM typically presents as subacute meningitis where symptoms often precede for seven days or longer. Non-specific symptoms such as fever, headache, nausea and vomiting are common. Also epileptic seizures and cranial nerve palsy are relatively common. Risk factors for TBM are contact with patients with open tuberculosis, tuberculosis in the past medical history, HIV infection, drug addiction and being homeless. CSF characteristics of TBM are a lymphocytic leucocytosis (usually 100-2000 x 10^6 cells/l), an increased protein and a low CSF/blood ratio. We repeated the CSF testing to increase the sensitivity.

In our patient we combined a treatment with immune suppression with antibiotic therapy for tuberculosis. This led to a combination of an impressive number of drugs. When the results were positive for anti-NMDA antibodies and enough certainty was obtained to rule out TBM, all antibiotics except amoxicillin were stopped. Anti-NMDA receptor encephalitis is an autoimmune receptor encephalitis that is more frequent in young women and is associated with ovarian teratomas or other tumours, and viral infections. Specific IgG antibodies are formed as a paraneoplastic phenomenon against neurological tissue in teratomas and target the NMDA receptor in the brain. This results in internalisation of the receptor and reduced NMDA effect. Low activity of NMDA receptors has been associated with psychiatric symptoms such as schizophrenia. The clinical course of anti-NMDA encephalitis typically consists of different phases. About 70% of patients have a nonspecific flu-like prodrome, with symptoms as fever, headache and fatigue. Within a few days, this is followed by psychiatric and behavioural symptoms (psychotic phase) such as confusion, anxiety, fear, insomnia, paranoid thoughts, disorientation, visual and auditory hallucinations, stereotypical behaviour and short time memory loss. A rapid disintegration of language, varying from reduction of verbal output and echolalia to mutism, is frequent in this phase. The next phase consists of decreases of consciousness, epileptic seizures, hypoventilation, autonomic instability and dyskinesia.

Multiple ancillary investigations may provide valuable information for diagnosing anti-NMDA receptor encephalitis. CSF tests can show a mild-to-moderate lymphocytic leucocytosis, a mild increase of protein concentration and CSF-specific oligoclonal bands. Abnormal MRI findings are present in 30 to 50% of cases and are often mild, transient and nonspecific. Most often, the EEG shows focal or generalised slow activity with or without epileptic discharges. An extreme delta brush is rather rare (30% of cases) but regarded a unique EEG pattern of anti-NMDA receptor encephalitis. The definite diagnosis can be made by positive anti-NMDA receptor antibodies in serum or CSF by immunohistochemistry or cell-based assay, but test results may take a couple of days until known.

Treatment consists of three modalities: first- and second-line immunotherapy, if applicable tumour resection and treatment of complications such as autonomic instability, epileptic seizures, hypoventilation and dyskinesia. This case of encephalitis is characterised by a broad differential diagnosis and a subsequent therapeutic dilemma. Although the probability of cryptococcal meningitis was low,
we decided to treat awaiting the CSF cryptococcal test result. Furthermore, the immunological status of the patient was not clear since haematological malignancy was still in our differential diagnosis. Similarly, the probability of TBM was low. Nevertheless we decided to treat for several reasons. First, the diagnosis of TBM is often made too late since a previous tuberculous infection is known in only 10% of patients with TBM, and the presentation of TBM is often atypical. Second, the prognosis of untreated TBM is poor: 25-50% of patients die or have severe neurological damage.[15]

**Conclusion**

We present a case report of a young woman with autoimmune encephalitis. The presenting symptoms were typical, but due to the patient’s social history and absence of positive test results other causes had to be taken into account. When the differential diagnosis remains broad, all possible causes of meningoencephalitis should be treated empirically until a definitive diagnosis can be made. Waiting until tests become positive may result in a harmful delay in necessary treatment.

**Disclosures**

All authors declare no conflicts of interest. No funding or financial support was received.

**References**

The white cerebellum sign

J. Gunkel1, A.E. Scholtens2, J. Heidt1
1Department of Intensive Care, Tergooi Hospital, 2Department of Radiology, Hilversum, the Netherlands

Correspondence
J. Gunkel - juliagunkel@gmail.com

Keywords - neuroimaging, computed tomography, white cerebellum sign, cardiac arrest, prognostic marker

Case presentation
A 78-year-old man presented to the emergency room (ER) after an out-of-hospital cardiac arrest. His medical history included diabetes mellitus, iron-deficiency anaemia, vascular dementia and an ischaemic stroke of the left hemisphere. He was found unresponsive in his wheelchair in his care home for an unknown amount of time. Upon arrival of the ambulance the first registered rhythm was asystole. Return of spontaneous circulation was achieved after 10 minutes.

Physical examination in the ER revealed a SatO2 of 92% with 40% supplemental oxygen via mechanical ventilation, diffuse bilateral rhonchi, a heart rate of 102 beats/min, blood pressure of 100/60 mmHg and a basal body temperature of 37 ºC. He had fixed, dilated pupils, absent cornea reflexes and a Glasgow Coma Scale score of three. Based on the electrocardiogram and echocardiography findings, myocardial infarction was deemed unlikely and thus acute coronary angiography was not performed. Due to ensuing hypotension, cerebral and thoracic computed tomography (CT), as part of the routine diagnostic work-up, were postponed. The following day, a thoracic CT scan showed no abnormalities. The non-enhanced cerebral CT scan revealed diffuse oedema with effacement of sulci, loss of grey and white matter differentiation, compression of the lateral ventricles and mild hyperdensity of the cerebellum ('white cerebellum sign', figure 1). Enhanced cerebral CT angiography confirmed progressive cerebral oedema and significant reduction in the intracerebral arterial blood circulation. Brain stem reflexes were persistently absent. Due to this extensive brain damage and poor prognosis, life-prolonging treatment was ceased. The patient passed away shortly after.

Discussion
White cerebellum sign is an infrequently described, yet ominous finding in neuroradiology. On cerebral CT imaging it is seen as hypootenuation of the cerebral hemispheres sparing infratentorial structures and leading to the characteristic lighter aspect of the cerebellum and/or the brain stem.[1,2] It is often interchangeably mentioned with ‘reversal sign’, a finding in which there is diffuse hypodensity of the cortical grey matter relative to the adjacent white matter.[1-4] The white cerebellum sign and reversal sign may occur together, however have also been separately reported.[1,3] The exact pathophysiological mechanism of white cerebellum sign is unclear.[1,2] One proposed mechanism suggests redistribution of cerebral blood flow to the posterior circulation, due to cerebral oedema in hypoxic-ischaemic events.[4] It has been described in cases of severe head trauma, perinatal asphyxia or asphyxia, drowning, hypothermia, status epilepticus, cerebral infections and post-anoxic encephalopathy.[1,4,6] White cerebellum sign is an important diagnostic marker that may aid in therapeutic and prognostic decision-making as it is indicative of severe and often irreversible brain injury with poor neurological outcome.[4-6]

Nevertheless, cessation of life-prolonging therapies should not be solely based on this marker. In our case, due to the subtle nature of the white cerebellum sign, we additionally conducted cerebral CT angiography to confirm compromised cerebral arterial blood flow and in light of persistent absent brain stem reflexes, treatment was withdrawn.

Disclosure
All authors declare no conflict of interest. No funding or financial support was received.

References
NVIC CONFERENCE AND COURSE AGENDA

COURSES AND CONFERENCES | NVIC

**NVIC Basiscursus echografie**
- Tuesday 16 June - Wednesday 17 June 2020
- Tuesday 1 September - Wednesday 2 September 2020
- Tuesday 3 November - Wednesday 4 November 2020
- Tuesday 1 December - Wednesday 2 December 2020
- Tuesday 30 June - Wednesday 1 July 2020
- Tuesday 25 August - Wednesday 26 August 2020
- Wednesday 9 September - Thursday 10 September 2020
- Thursday 1 October - Friday 1 October 2020
- Wednesday 28 October - Thursday 29 October 2020
- Tuesday 17 November - Wednesday 18 November 2020
- Wednesday 9 December - Thursday 10 December 2020

**NVIC Cursus Luchtwegmanagement op de IC**
- Wednesday 11 November - Thursday 12 November 2020
- Tuesday 31 March - Wednesday 1 April 2020
- Thursday 16 April - Friday 17 April 2020
- Wednesday 13 May - Thursday 14 May 2020
- Wednesday 3 June - Thursday 4 June 2020
- Wednesday 11 November - Thursday 12 November 2020
- Tuesday 30 June - Wednesday 1 July 2020
- Tuesday 25 August - Wednesday 26 August 2020
- Wednesday 9 September - Thursday 10 September 2020
- Thursday 1 October - Friday 1 October 2020
- Wednesday 28 October - Thursday 29 October 2020
- Tuesday 17 November - Wednesday 18 November 2020
- Wednesday 9 December - Thursday 10 December 2020

**NVIC FCCS cursus**
- Tuesday 31 March - Wednesday 1 April 2020
- Thursday 16 April - Friday 17 April 2020
- Wednesday 13 May - Thursday 14 May 2020
- Wednesday 3 June - Thursday 4 June 2020
- Tuesday 30 June - Wednesday 1 July 2020
- Tuesday 25 August - Wednesday 26 August 2020
- Wednesday 9 September - Thursday 10 September 2020
- Thursday 1 October - Friday 1 October 2020
- Wednesday 28 October - Thursday 29 October 2020
- Tuesday 17 November - Wednesday 18 November 2020
- Wednesday 9 December - Thursday 10 December 2020

**Congressen | Overig**
- EuroNeuro 2020 - Parijs
- Wednesday 22 April 2020 - Friday 24 April 2020
- Vitamine C symposium - Amsterdam
- Friday 24 April 2020
Editorial board of the Netherlands Journal of Critical Care

Dirk Donker, Editor in Chief
Dept. of Intensive Care Medicine, Div. of Anesthesiology, Intensive Care and Emergency Medicine
University Medical Center Utrecht
PO Box 85500
3508 GA Utrecht

Walter van den Bergh, Section Editor General
Dept. of Critical Care
University of Groningen
Hanzeplein 1
9700 RB Groningen

Dennis Bergmans, Section Editor Infection and Inflammation
Dept. of Intensive Care
Maastricht University Medical Center+
P. Debyelaan 25
6229 HX Maastricht

Frank Bosch, Section Editor Imaging
Dept. of Internal Medicine
Rijnstate Hospital
PO Box 9555
6800 TA Arnhem

Diederik van Dijk, Section Editor Cardiоanesthesia
Dept. of Intensive Care Medicine, Div. of Anesthesiology, Intensive Care and Emergency Medicine
University Medical Center Utrecht
PO Box 85500
3508 GA Utrecht

Maarten van Eijk, Associate Section Editor Anesthesiology
Dept. of Intensive Care Medicine
University Medical Center Utrecht
PO Box 85500
3508 GA Utrecht

Janneke Horn, Section Editor General
Dept. of Intensive Care
Amsterdam UMC location AMC
University of Amsterdam
Meibergdreef 9
1105 AZ Amsterdam

Can Ince, Section Editor Physiology
Dept. of Physiology
Amsterdam UMC location AMC
University of Amsterdam
Meibergdreef 9
1105 AZ Amsterdam

Evert de Jonge, Section Editor Scoring and quality assessment
Dept. of Intensive Care Medicine
Leiden University Medical Center
PO Box 9600
2300 RC Leiden

Nicole Juffermans, Section Editor Hemostasis and Thrombosis
Dept. of Intensive Care Medicine
Amsterdam UMC location AMC
University of Amsterdam
Meibergdreef 9
1105 AZ Amsterdam

Michael Kuiper, Section Editor Neurology
Dept. of Intensive Care Medicine
Medical Center Leeuwarden
PO Box 888
8901 BR Leeuwarden

Nuray Kusadasi, Associate Section Editor Hemato-Oncology
Dept. of Intensive Care Medicine
University Medical Center Utrecht
PO Box 85500
3508 GA Utrecht

Christian Meuwese, Associate Section Editor Cardiology
Dept. of Intensive Care Medicine
University Medical Center Utrecht
PO Box 85500
3508 GA Utrecht

Marike van der Schaaf, Section Editor Rehabilitation
Dept. of Rehabilitation
Amsterdam UMC location AMC
University of Amsterdam
Meibergdreef 9
1105 AZ Amsterdam

Peter Spronk, Section Editor General
Dept. of Intensive Care Medicine
Gelre Hospital, location Lukas
PO Box 9014
7300 DS Apeldoorn

Ilse van Stijn, Managing Editor
Dept. of Intensive Care Medicine
OLVG
PO Box 95500
1090 HM Amsterdam

International advisory board

Jan Bakker
Professor of Intensive Care
Columbia University Medical Center, New York University Medical Center, New York, USA
Pontificia Universidad Católica de Chile, Santiago, Chile
Erasmus MC University Medical Center, Rotterdam, Netherlands

Charles Hinds
Professor of Intensive Care Medicine
St. Bartholomew’s Hospital West Smithfield,
London, UK

Patrick Honoré
Professor of ICU Medicine
Director of Critical Care Nephrology Platform
ICU department
Universitair Ziekenhuis Brussel, VUB University
Brussels, Belgium

Alun Hughes
Professor of Clinical Pharmacology
University College London
London, UK

Manu Malbrain
Dept. of Intensive Care Unit
Hospital Netwerk Antwerp
Campus Stuivenberg Antwerp, Belgium

Paul Marik
Associate Professor
Dept. of Medicine and Medical Intensive Care Unit
University of Massachusetts
St. Vincent’s Hospital, Worcester, USA

Greg Martin
Dept. of Medicine
Division of Pulmonary, Allergy and Critical Care
Emory University School of Medicine
Atlanta, USA

Ravindra Mehta
Professor of Clinical Medicine
Associate Chair for Clinical Research
Department of Medicine
UCSD Medical Centre
San Diego, USA

Xavier Monnet
Service de réanimation médicale
Centre Hospitalier Universitaire de Bicêtre
Le Kremlin-Bicêtre, France

Jean-Charles Preiser
Dept. Intensive Care
Erasme University Hospital
Brussels, Belgium

Yasser Sakr
Dept. of Anaesthesia and Intensive Care
Friedrich-Schiller University Hospital
Jena, Germany

Hannah Wunsch
Dept. of Anaesthesia
New York Presbyterian Columbia New York, USA

Netherlands Journal of Critical Care
The Netherlands Journal of Critical Care (NJCC) is the official journal of the Dutch Society of Intensive Care (Nederlandse Vereniging voor Intensive Care-NVIC). The journal has a circulation of about 1750 copies bimonthly in the Netherlands and Belgium.

High-quality reports of research related to any aspect of intensive care medicine, whether laboratory, clinical, or epidemiological, will be considered for publication in the NJCC. This includes original articles, reviews, and meta-analyses. Case reports, clinical images, book reviews, editorials, letters to the editor, clinical problem solving, research news and correspondence are also welcome. All manuscripts pass through an independent review process managed by the editorial board. The journal does not have any publication fees, and colour figures are reproduced free of charge. The journal is indexed by Embase, Emcare and Scopus. A Medline annotation is in preparation.

Ethical standards
Manuscripts reporting original research must contain a statement that all human and animal studies have been approved by the appropriate ethics committees and that all procedures were performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Where appropriate, it should also be stated in the text that all persons gave their informed consent prior to their inclusion in the study. If possible, the Journal aims to also include informed consent of individuals described in case reports. Details that might disclose the identity of the subjects under study should be omitted.

The editors reserve the right to reject manuscripts that do not comply with the above-mentioned requirements. The author will be held responsible for false statements or failure to fulfil the above-mentioned requirements. The editor adheres to the guidelines laid down by the International Committee of Medical Journal Editors (www.icmje.org), concerning authorship and scientific conduct.

Types of papers
The following manuscript types are considered for publication: original articles, review articles, systematic reviews, meta-analyses, editorials, case reports, clinical images, book reviews, letters to the editor, clinical problem solving, research news and correspondence.

Original articles
Original articles should not exceed 3000 words (excluding abstract, references, tables and legends). The manuscript should be clear in outline (with subheadings) for maximum clarity. The text should follow the IMRAD format and contain an abstract, introduction, materials (patients) and methods, results, discussion section and references. This should be followed by tables and figures (maximum of 6 in total) with titles above and legends below these elements. The abstract should not exceed 250 words and should be structured: background, methods, results, conclusions. Do not include references in the abstract. Authors should provide a minimum of 3 keywords, a running title, and a list of not more than 30 references. Original articles must meet the following criteria:
- the manuscript presents the results of primary scientific research;
- the results have not been published in full elsewhere;
- analyses are described in full in the manuscript;
- conclusions are presented in a clear and concise manner and are supported by the data;
- the research meets all applicable ethical standards;
- the article adheres to appropriate reporting guidelines and community standards for fiscal disclosure;
- when reporting the results of a randomised controlled trial, author(s) should use the CONSORT statement as a guide to preparing the manuscript (http://www.consort-statement.org/);
- conflicts of interest should be clearly stated in the manuscript (see below).

The authors are encouraged to refer to national and international registries of trials in their papers (such as clinicaltrials.gov), where applicable.

Review articles
Review articles, systematic reviews and meta-analyses should not exceed 3000 words (excluding abstract, references, tables and legends). The manuscript should contain subheadings. A maximum of 6 tables and figures (in total) are allowed. Please provide titles above and legends below these elements. The abstract should not exceed 250 words and should be structured: background, methods, results, conclusions, with the exception of a non-systematic review, which may contain a non-structured abstract. No references should be included in the abstract. Authors should provide a minimum of 3 keywords, a running title, and a list of not more than 70 references. The authors are encouraged to refer to national and international registries of trials in their papers (such as clinicaltrials.gov), where applicable.

Editorials
Editorials are always commissioned by the Editors and comment on one or more articles in the same issue of the Journal or to a subject with high news value. Editorials should not exceed 1500 words and may include up to 15 references. Editorials have a maximum of 3 authors and no abstract. Please provide 2-3 key words.

Case reports
The text of a case report should include an abstract, introduction, case report/case history, discussion, tables and figures (2 in total), and references. The main text may be up to 2000 words; the abstract should not exceed 150 words and may be unstructured. Please provide a minimum of 3 keywords and a list of not more than 30 references. Please include an informed consent statement from the patient described in the case.

Clinical problem-solving
These manuscripts consider the step-by-step process of clinical decision-making. Information about a patient is presented to an expert clinician or clinicians in stages (indicated by boldface type in the manuscript) to simulate the way such information emerges in clinical practice. The clinician responds (in regular type) as new information is presented, sharing his or her reasoning with the reader. The text should not exceed 2500 words, and there should be no more than 15 references. Please include an informed consent statement from the patient described in the case.

Research news
Research news should be a review of a manuscript which has appeared in the past two months. It contains sections on why this study was done, the research question, how this was investigated, conclusions and the impact of the study on clinical practice. The text should not exceed 800 words with a maximum of 5 references. Contributions for this section will be commissioned; however, inquiries about contributions can be sent to a.p.vlaar@amc.uva.nl.

Clinical images
A clinical image should contain one or two pictures with a legend and a short case history, and should preferably not be referenced. The manuscript should succinctly present relevant clinical information, including a short description of the patient's history, relevant physical and laboratory findings, clinical course, response to treatment (if any), and condition at last follow-up. Please provide a minimum of 3 keywords. The text should not exceed 500 words. Please include an informed consent statement from the patient described in the case.

Photo quiz
In this section relevant images for critical care medicine (e.g. flow and pressure curves of mechanical ventilation or haemodynamic indices, radiological images or laboratory results) will be accompanied by a short introduction of the context. The introduction will be followed by 'what is your diagnosis?'. The answer will include a brief discussion of the literature. A photo quiz should not exceed 500 words and contain no more than two figures, and five references conform the Vancouver style. Abbreviations of measurements should be quoted in SI units.

Book reviews
A book review should not exceed 300 words. Please mention in the header: title, author, edition and year. Scan the cover in high resolution (300 dpi/1 mb) and send with the text. With an online review, the cover can usually be downloaded. Details with the cover: title, author, edition, year, publisher, number of pages, price and ISBN number. Conclude with the name and affiliation(s) of the reviewer.

Letters to the editor
Letters to the editor provide an opportunity to present results of scientific value where a short format is most appropriate. They should not exceed 1000 words, 5 references and 1 figure or table.

Correspondence
Correspondence provides an opportunity to debate published articles. This should not exceed 500 words, 5 references and 1 figure or table. Correspondence is sent to the authors for rebuttal, and a final decision on publication is made at the end of this process, by the editor.

General information
Each manuscript should be accompanied by a cover letter stating the following: the complete postal address, email address and telephone number of the corresponding author and, if it is a resubmission, the previous Neth J Crit Care number and year. The language of the journal is British English. Authors who are unsure of proper English usage should have their manuscript checked by someone proficient in the English language. All text should be double spaced. The manuscript, including references and legends, should be sequentially numbered throughout.
General guidelines on house style

- The title of the 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.
- Write 'the Netherlands', without capitalising the t.
- Generally, abbreviations should not be used in the title (see Table of standard abbreviations for exceptions).
- The corresponding author only provides his/her email address on the title page.
- Please provide a minimum of three keywords and a running title.
- The abstract of original and review articles should be written in a structured format.
- Unstructured abstracts should take the form of a single paragraph.
- Headings must be in bold. Use no more than two levels of headings.
- Paragraphs starting immediately under headings and subheadings should begin at the left margin. Subsequent paragraphs should be indented.
- Non-standard abbreviations (see table of standard abbreviations) should always be explained and their use kept to a minimum.
- Use British English spelling – except in titles of institutions that have chosen to use US spelling, e.g. Academic Medical Center, Amsterdam. Examples: anaemia (instead of anemia), oesophagus (instead of esophagus), litre (instead of liter), colour (instead of color), labelling (instead of labeling), practice (noun), and practise (verb). This should be used consistently. Use the s-form spelling, e.g. minimisation (not minimisation).
- Do not use full stops in initials, abbreviations and academic titles.
- References are numbered sequentially in the text and placed in square brackets after the punctuation. [...] Genus names should be written 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 italics; do not use a capital letter, e.g. see table 2.

Tables

Tables are to be numbered independently of the figures with Arabic numbers and are uploaded as separate documents.

- Tables should be laid out in Word, using the table function. Other tables (e.g. in pdf format or PowerPoint) will not be accepted;
- Do not use internal horizontal or vertical lines;
- Do not use spaces, tabs or hard returns in tables;
- Each piece of data must be contained in its own cell;
- Numbers and percentages are presented in the same cell;
- Tables should always be cited in the text in consecutive numerical order;
- For each table, please supply a title explaining the components of the table;
- Any abbreviations used in the table must be defined in a legend;
- Tables should not exceed the printed area of the page (174 x 234 mm).

Figures

Figures should also be numbered with Arabic numbers and are uploaded in separate documents. Legends should be given in the document that contains the text, references, and tables. Authors wishing to include figures or tables that have already been published elsewhere are required to obtain permission from the copyright owner and provide evidence that such permission has been granted when submitting their paper. Colour figures can be published. Short, clear legends make additional description in the text unnecessary. Figures should be provided in electronic format (TIFF or JPEG).

Conflict of interest

Authors must indicate any conflict of interest. This includes a financial relationship with an organisation that sponsored the research (funding, speakers fee, consultancy fee), management relations with the organisation that sponsored the research (consultant, member of board). All sources of funding obtained for the research should also be stated. A conflict of interest statement can be downloaded from the website. The completed and signed form should be uploaded as a separate document when submitting the manuscript. If no conflict exists, authors should state: All authors declare no conflicts of interest. No funding or financial support was received.

Author agreement

All authors must certify they have seen and approved the manuscript being submitted. All authors warrant that the article is the authors' original work, has not been published previously and is not under consideration for publication elsewhere. The author agreement form can be downloaded from the website. An agreement form is required when submitting the paper. Colour figures can be published. Short, clear legends make additional description in the text unnecessary. Figures should be provided in electronic format (TIFF or JPEG).

Copyright

Copyright ownership is to be transferred in a written statement, which must accompany all manuscript submissions and must be signed by all authors. The agreement should state: 'The undersigned authors transfer all copyright ownership of the manuscript (title of article) to the Netherlands Journal of Critical Care. Any relevant papers that may be considered as duplicating in part the current submission should be reported.'

References

*Neth J Crit Care* uses the Vancouver style of referencing. Only articles cited in the text are to be listed. They should be arranged in order of appearance in the text and numbered consecutively. Only the reference number should appear in the text between brackets. [...] Include all author names (unless there are more than six, in which case abbreviate to three and add ‘et al.’), and page numbers. Use the Medline abbreviation for names of journals.


*How to submit*

Please submit manuscripts directly to the Editorial Office through our online submission system at www.njcc.nl.

*Peer review*

All papers are subject to a peer-review system handled by the editors. Authors are encouraged to resubmit, when invited, the revised paper within two weeks after the editorial decision. The changes made in the revised paper should be highlighted and the manuscript accompanied by a letter with a point-to-point rebuttal.

*Proofs*

The corresponding author will receive proofs of accepted papers by email. Corrected proofs should be returned within 48 hours of receipt.

*Production process*

Decisions of the editors are final. All material accepted for publication is subject to copying/editing. *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 the proof to correcting errors and to clarifying misleading statements.

Table of commonly used 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>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>computed tomography</td>
</tr>
<tr>
<td>ECG</td>
<td>electrocardiogram</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>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 normalised 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 organ failure assessment</td>
</tr>
<tr>
<td>SPECT</td>
<td>single-photon emission computed tomography</td>
</tr>
<tr>
<td>TIA</td>
<td>transient ischaemic attack</td>
</tr>
<tr>
<td>TRALI</td>
<td>transfusion-related acute lung injury</td>
</tr>
</tbody>
</table>