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ORIGINAL ARTICLE
Satisfaction of nurses and physicians with the introduction of the Rapid Response System in Dutch hospitals
A.H. Brunsveld-Reinders

CASE REPORT
Treating pulmonary embolism in the intensive care unit: are the guidelines helpful?
A.C.J.M. de Pont

CLINICAL PROBLEM-SOLVING
A severe community-acquired pneumonia during pregnancy
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Inschrijven via www.nvic.nl
CONTENTS

EDITORIAL
156 Management of submassive pulmonary embolism
M. Coppens

REVIEW
159 Patient-related determinants of host response and sepsis outcome
M.A. Wiewel, L.A. van Vught, T. van der Poll, M.J. Schultz

ORIGINAL ARTICLE
165 Satisfaction of nurses and physicians with the introduction of the Rapid Response System in Dutch hospitals
A.H. Brunsveld-Reinders, J. Ludikhuize, M.S. Arbous, M.G.W. Dijkgraaf, E.de Jonge for the COMET study group

PHOTO QUIZ
171 Brain activity in cardiac arrest
J. Horn, M.M. Admiraal

CASE REPORT
172 Treating pulmonary embolism in the intensive care unit: are the guidelines helpful?
A.C.J.M. de Pont, D.P.M. Brandjes

CASE REPORT
176 An unexpected cause of in-hospital cardiac arrest
S. IJmkers, N. van der Lubbe, L. Dawson

CLINICAL PROBLEM-SOLVING
178 A severe community-acquired pneumonia during pregnancy

RESEARCH NEWS
183 When to start renal-replacement therapy in critically ill patients?
H.R.W. Touw, H.M. Oudemans-van Straaten

ANSWER TO PHOTO QUIZ
185 Brain activity in cardiac arrest

CLINICAL IMAGE
186 Successful use of plain subcostal transthoracic echocardiography in VV-ECMO cannula repositioning
F.S. van den Brink, A.H. Swadi, E. Scholten

188 Conference/course agenda
189 Editorial board
189 International advisory board
190 Information for authors

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Management of submassive pulmonary embolism

M. Coppens
Department of Vascular Medicine, Academic Medical Center, Amsterdam, the Netherlands

Correspondence
m.coppens@amc.nl

Keywords - (submassive) pulmonary embolism; low-molecular weight heparin; unfractionated heparin.

Venous thromboembolism (VTE) is the third most common cause of death from cardiovascular diseases after myocardial infarction and ischaemic stroke. The case fatality rate at 30 days after pulmonary embolism (PE) is reported to be around 10%. The majority of VTE related deaths, however, occur in patients who were never diagnosed as having PE. From an epidemiological model it was estimated that each year 370,000 deaths related to VTE occur in six European Union countries with a total population of 454 million. Of these deaths, 34% are caused by sudden fatal PE, in 59% of deaths PE remained undiagnosed during life and only 7% of cases were correctly diagnosed as PE before death. The risk of recurrence or progression of VTE on anticoagulant therapy is highest during the first 14 days and declines thereafter.

In patients with acute severe PE, right ventricular failure is considered the primary cause of death due to the acute increase in pulmonary vascular resistance, which only occurs when more than 30-50% of the cross-sectional area of pulmonary arteries is obstructed by emboli. Secondary PE-induced vasoconstriction, mediated by thromboxane A2 and serotonin release, adds to the right ventricular pressure overload. In the International Cooperative Pulmonary Embolism Registry (ICOPER) risk factors for early death by PE were age >70 years, systolic blood pressure <90 mmHg, respiratory rate >20 breaths/min, cancer, chronic heart failure and chronic obstructive pulmonary disease. The Pulmonary Embolism Severity Index (PESI) is the best validated prognostic model for patients with acute PE and consists of these and other risk factors. With points assigned to individual risk factors, a total score is calculated that puts patients into any of five risk categories. The main strength of the PESI score is that it reliably identifies patients at low risk of death for which home treatment of PE is likely to be safe (PESI classes I and II, corresponding to a 30-day mortality of 0-3.5%). Patients in PESI classes III-V have a higher risk of death at 30 days of 3.2-24.5%. In PE patients with shock or hypotension, defined as a systolic blood pressure <90 mmHg or a systolic pressure drop of ≥40 mmHg for >15 min (not caused by new-onset arrhythmia, hypovolaemia, or sepsis), the European Society of Cardiology (ESC) guideline on acute PE recommends reperfusion therapy by systemic fibrinolysis, usually with recombinant tissue plasminogen activator (rt-PA). For all other patients, treatment with anticoagulation with either unfractionated or low-molecular-weight heparin (LMWH) or with a direct oral anticoagulant is the mainstay of therapy. The recommendation is based on a meta-analysis of randomised trials in which fibrinolysis added to routine anticoagulation reduced the risk of death or recurrent early PE by 55% only in patients with haemodynamically unstable PE but not in haemodynamically stable patients. Still, many haemodynamically stable patients fall into PESI classes III-V and have significant short-term mortality, including patients with tachycardia, severe hypoxia, as well as patients with signs of right ventricular overload and patients with elevated biomarkers such as troponin-T and or N-terminal pro-brain natriuretic peptide. This group of patients are usually referred to as patients with submassive PE. The question remains whether anticoagulation alone is sufficient or that more aggressive therapy is warranted to reduce mortality.

In this edition of the Netherlands Journal of Critical Care De Pont and Brandjes present two cases with submassive PE. Both patients were initially treated with LMWH and developed a major thrombotic complication three and nine days after initiation of therapy. One patient died in spite of attempted rescue fibrinolysis, the other stabilised after a switch from LMWH to intravenous unfractionated heparin (UFH). The authors highlight the importance of prognostic risk stratification in PE patients by using the PESI score and imaging and laboratory markers of right ventricular strain. They further argue that patients with submassive PE admitted to the intensive care unit (ICU) need ‘aggressive anticoagulation’ and suggest that continuous intravenous UFH might be preferred over intermittent subcutaneous LMWH.
In spite of the cases presented, there is no evidence to support that UFH is a more aggressive form of anticoagulation than LMWH. In fact, the Cochrane systemic review of randomised trials that compared LMWH with UFH suggests the opposite. In patients with non-massive PE, LMWH, compared with UFH for initial anticoagulation of acute VTE, reduced the risk of thrombotic complications by 30%, the risk of major bleeding by 42%, and the risk of death by 23%. It is presumed that the superiority of LMWH in these patients is explained by the inherent difficulty of achieving and maintaining the target activated partial thromboplastin time (APTT) in patients treated with UFH. For example, in an observational study in patients treated with UFH who were admitted to the ICU, only 56% of patients achieved a therapeutic APTT within the first 24 hours. Whether UFH would be superior to LMWH in patients with submassive PE admitted to the ICU is speculative and based on pharmacokinetic arguments and some low-quality evidence from observational data. No randomised studies in this subgroup of PE patients have compared the effects of UFH with LMWH.

The cases presented by De Pont and Brandjes also raise an important point with respect to dosing of LMWH in specific patient groups, such as patients with severe renal impairment and (severely) obese patients. UFH is enzymatically degraded while LMWHs are mainly cleared renally. In patients with eGFR <30 ml/min, impaired LMWH clearance may lead to accumulation and increased bleeding risk. In patients with severe obesity, the optimal LMWH dose is similarly challenging due to differences in drug absorption, distribution and elimination in obese versus non-obese patients. The nadroparin product monograph recommends a dose of 86 IU/kg twice daily (bid) and suggests to cap the dose at a maximum of 8550 IU bid in patients weighing 90 kg or over. The rationale for a cap/maximum dose would be that the volume of distribution of LMWH does not further increase with increasing body weight in severely obese patients and consequently, dosing per kg in these patients would lead to over-anticoagulation. However, in a pharmacokinetic study comparing obese (body mass index (BMI) 30-48 kg/m², weight 78-144 kg) with non-obese volunteers (BMI 19-26 kg/m²) treated with enoxaparin, no indication of over-anticoagulation was observed in obese patients. A similar anti-Xa activity was achieved in both groups using weight-based dosing without a maximum dose. In the light of this uncertainty of LMWH dosing in the severely obese, the ESC guideline suggests monitored UFH over unmonitored LMWH in patients with severe obesity, defined as a BMI of 35 kg/m² or higher.

Two randomised studies have compared anticoagulation with UFH with or without systemic fibrinolysis in patients with submassive PE. The first trial included 256 patients with acute PE without shock or hypotension but with signs of right ventricular overload on imaging or electrocardiography. The second trial included a more severe subgroup of 1006 patients with submassive PE with a combination of imaging signs of right ventricular overload and elevated cardiac biomarkers. In both studies, additional fibrinolysis failed to demonstrate a survival benefit over UFH only. While fibrinolytic therapy did reduce the risk of further haemodynamic decompensation, this benefit was offset by a significant increase in major bleeding in the patients treated with fibrinolysis (11.5% vs. 2.4%, OR 5.6, 95% CI 2.3-13.4), including a 2.0% risk of intracranial bleeding. This suggests that systemic fibrinolysis may be too aggressive, in spite of the increased risk of death in patients with submassive PE. An interesting alternative is the use of lower dosages of fibrinolitics, either systemically or delivered locally by a pulmonary artery catheter. Both approaches have demonstrated a reduction in right ventricular overload without an apparent increase in bleeding compared with routine anticoagulation, although neither study was adequately powered to show a difference in clinical endpoints such as thrombotic complications, bleeding or mortality. Alternatively, DS-1040 is an inhibitor of activated thrombin-activatable fibrinolysis inhibitor (TAFI) currently undergoing phase I/II testing in patients with acute PE (clinicaltrials.gov; NCT02923115). TAFI inhibits fibrinolysis in the presence of high thrombin concentrations, i.e. in patients with acute submassive PE. Theoretically, TAFI inhibition could promote fibrinolysis without the increase in bleeding risk induced by systemic fibrinolysis.

In summary, studies in patients with submassive PE have thus far failed to show survival benefit from more aggressive strategies than routine anticoagulation. However, the significant risk of adverse events including death in these patients presents an unmet clinical need, for which more aggressive strategies may be justified. The question which strategy should be used is as yet unsolved and needs to be answered by robust randomised clinical trials.

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**References**


Patient-related determinants of host response and sepsis outcome

M.A. Wiewel1,2, L.A van Vught1,2, T. van der Poll1,2, M.J. Schultz2
1Center for Experimental and Molecular Medicine, 2Center for Infection and Immunity Amsterdam, 3Department of Intensive Care, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands

Correspondence
M.A. Wiewel - m.a.wiewel@amc.uva.nl.

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Abstract
Sepsis is an important cause of morbidity and mortality in intensive care unit patients. In this review, the results of studies with specific research questions performed within a large prospective observational study on sepsis in the Netherlands are discussed. The studies investigated various factors that may affect the host response during sepsis, and may have an impact on the outcome, including prior medication (antiplatelet agents, calcium channel blockers, and statins), HIV infection, and hypothermia. Neither prior medication nor HIV infection were associated with large differences in the host response during sepsis, whereas only prior use of calcium channel blockers was associated with an improved outcome. In addition, while hypothermia was not associated with an altered immune response, there was an independent association between hypothermia and mortality.

Introduction
Worldwide, more than 19 million cases of severe sepsis are estimated to occur annually, resulting in more than 5 million deaths.[1] The incidence rate of sepsis is estimated at 270 per 100,000 person years in high-income countries.[1] The incidence of sepsis has increased over the past decades[2,3] and this trend is expected to continue due to ageing of the population, increased burden of comorbidities, cumulative use of immunosuppressive drugs, chemotherapy, transplantation and invasive procedures.[4] Hence, sepsis is a large burden on human health.

One essence of sepsis pathogenesis lies in the failure of the body to effectively eliminate the invading pathogen, repair tissue and reconstitute homeostasis upon infection. Sepsis is in part the consequence of a dysregulated host response to infection, characterised by disproportionate pro- and anti-inflammatory components, coagulation and complement factors, and disturbed vascular responses, including increased leukocyte adhesion, vasodilation, and loss of endothelial barrier function, leading to tissue and organ damage.[5,6]

This review discusses various studies with specific research questions performed within the ‘Molecular Diagnosis and Risk Stratification of Sepsis’ (MARS) study, a large prospective observational study of sepsis in two academic intensive care units (ICUs) in the Netherlands. Various factors that may have an effect on the host response during sepsis, and may impact outcome were studied, including cardiovascular medication (antiplatelet agents, calcium channel blockers, and statins), HIV infection, and hypothermia (figure 1). These studies were bundled in an academic thesis.

Figure 1. Association between host factors and survival in critically ill patients with sepsis Hypothermia was associated with increased mortality, calcium channel blocker use with reduced mortality. HIV, antiplatelet and statin therapy were not associated with altered mortality. Host response biomarkers were largely similar in patients with and without the particular host factor.

The MARS study
The MARS study was a collaboration of multiple partners and registered at clinicaltrials.gov (identifier NCT01905033). The primary aim of the MARS study was to develop tools that can provide rapid and accurate information on pathogen and host immune response or status. These tools should be easy to use,
available at or close to the bedside, aiding the clinician in the determination of the optimal treatment in an individual patient. From 2011 until 2013, consecutive patients aged 18 years or older and admitted to the mixed medical-surgical ICUs of the Academic Medical Center in Amsterdam and the University Medical Center Utrecht were included if they were expected to have a length of stay of at least 24 hours; the project had no other inclusion and exclusion criteria.\cite{7-11}

Clinical data were prospectively collected from all patients, including demographics, premorbid comorbidities, use of prior (cardiovascular) medication, ICU admission characteristics, daily physiological measurements, disease severity scores, complications such as acute kidney injury and acute respiratory distress syndrome, and microbiology test results and antibiotic prescriptions. For all patients, leftover plasma was stored for protein biomarker analysis, including measurement of cytokines, endothelial activation and coagulation markers; also, whole blood was collected for genome wide RNA expression profiling of leukocytes. During the three-year study period, 6984 unique patients were enrolled in the MARS study, amounting to 8305 ICU admissions.

**Prior cardiovascular medication**

Cardiovascular disease is among the most common premorbid diseases in sepsis patients.\cite{12,13} Preclinical studies using animals and observational studies in humans suggest that several cardiovascular drugs possess anti-inflammatory, antioxidant and other immune-modulatory effects, which, when used during infection, may modify the host response to sepsis.\cite{14-17}

**Antiplatelet therapy**

Besides their role in primary haemostasis, platelets also exert important immune functions.\cite{14,18} While platelets have been implicated in multiple inflammatory and procoagulant reactions, knowledge on effects of antiplatelet therapy on host response in sepsis patients is very limited. In the MARS study it was hypothesised that antiplatelet therapy modifies the host response during sepsis. In the MARS cohort, severity of illness upon ICU admission was similar in antiplatelet users compared with non-users and there was no association with an altered risk of mortality.\cite{19} There was also no association between prior antiplatelet therapy and plasma concentrations of biomarkers indicative of key host responses to severe infection. Specifically, antiplatelet therapy was not associated with alterations in systemic inflammation, coagulation, endothelial activation, or renal injury during sepsis.

Previous observational studies investigating associations between antiplatelet therapy and outcomes in patients admitted to an ICU with sepsis have reported variable results.\cite{20-23} Two of these studies used propensity matching to correct for baseline differences between antiplatelet users and non-users.\cite{21,23} One of them entailed patients admitted to a medical ICU with severe sepsis or septic shock, and observed no influence of antiplatelet therapy after adjusting for the propensity to receive antiplatelet therapy and severity of illness, calculated using the APACHE III score.\cite{21} The other one encompassed patients admitted to the ICU with systemic inflammatory response syndrome (SIRS), a subgroup of which was classified as sepsis; propensity analysis revealed a mortality reduction in acetylsalicylic acid users in both the overall SIRS population and the sepsis subgroup.\cite{22} While both studies adjusted for concurrent statin use, other prior medication use, such as beta-blockers, calcium channel blockers, and ACE inhibitors, was not taken into account.\cite{21,23}

The third study consisted of a regression analysis to establish the impact of prior antiplatelet therapy on sepsis outcome showing an association between low-dose acetylsalicylic acid therapy with decreased hospital or ICU mortality.\cite{22} Another study concerning the continuous use of acetylsalicylic acid during ICU stay reported similar findings.\cite{24} Lastly, an investigation reported an association between prior antiplatelet treatment and reduced sepsis mortality using a medical claims database.\cite{26} The analysis of the MARS data was different from these previous reports in several aspects. First, in the MARS study patients were prospectively enrolled and classified based on strict diagnostic criteria and post-hoc assessment of trained research physicians, taking into account all available clinical and microbiological information. Second, propensity matching allowed us to compose comparable patients cohorts with respect to multiple relevant patient characteristics. Sepsis patients are heterogeneous in terms of age, comorbidity, genetic background, severity, site and microbiology, and plasma biomarker levels demonstrated variability between patients, which may explain the lack of effect by prior antiplatelet therapy. Nonetheless, these data argue against a beneficial effect of prior antiplatelet therapy on sepsis severity and outcome. To our knowledge no randomised controlled trials of antiplatelet therapy have been performed in critically ill sepsis patients.

**Statins**

Several investigators have looked at the association between prior statin use and outcome in hospitalised patients with infections. Considering the abundant literature on pleiotropic non-lipid-lowering properties of statins, the MARS study was used to explore associations between prior statin use and host response characteristics in critically ill patients with sepsis. For this, plasma biomarkers were measured to provide insight into systemic inflammatory reactions, activation of the endothelium and the coagulation system, and studied whole genome expression profiles in blood leukocytes. Sepsis patients who were on prior statin therapy prior to admission were compared with those who were not on prior statin therapy, in both the complete and in a propensity score matched cohort. The results of this analysis suggest that prior statin therapy does not affect any of the host response pathways in ICU patients with sepsis.
(as yet unpublished data). In the MARS cohort, prior statin use was not associated with altered mortality either.

Previous investigations in patients with infection and/or sepsis studying the association between statin use and host response biomarkers were small or limited in the number of biomarkers studied. Only one study focused on sepsis patients admitted to the ICU, which showed that atorvastatin treatment was neither associated with altered plasma IL-6 levels nor survival.[25] Prior statin therapy, however, was associated with low baseline plasma IL-6 levels and continuation of atorvastatin in this cohort was linked to improved survival.[25]

Most observational studies have shown a survival benefit for patients with sepsis on prior statin therapy, with recent meta-analyses reporting an overall lower risk of sepsis and infection-associated death in prior statin users.[26,27] Several trials were undertaken, demonstrating no therapeutic effect of statins on sepsis outcome.[22,24] Heterogeneity of the study groups was an important limitation of the meta-analysed observational studies. Therefore, in the MARS study the analyses were adjusted for important co-variables, including many comorbidities and prior (cardiovascular) medication. Also, ‘healthy user’ effects cannot be ruled out, which may have influenced the protective effect of statins in some studies, and publication bias may have occurred. Altogether, these data suggest that statin therapy does not influence the host response to sepsis in patients requiring ICU admission.

Calcium channel blockers

Studies in animals have suggested that calcium channel blockers (CCBs) can lower mortality induced by endotoxaemia or sepsis by restoring intracellular calcium homeostasis,[29–33] however, knowledge on the association between prior CCB use and outcome in humans with sepsis is limited. Therefore, this association was studied in the MARS cohort of critically ill patients with sepsis. Prior use of CCBs was associated with improved survival in multivariable analysis of the complete cohort as well as in analysis of a cohort in which CCB users were matched to controls by demographics, comorbidities and prior medication.[34] The influence of CCBs on three key host response systems implicated in sepsis pathogenesis was studied (i.e., activation of the cytokine network, the vascular endothelium and the coagulation system) by measuring biomarkers indicative of these responses during the first four days after ICU admission. Biomarkers were similar in propensity-matched CCB users and non-users except for less reduction in antithrombin levels relative to normal values in CCB users. In the unmatched cohort, CCB use was associated with reduced cytokine release and blunted reductions in the anticoagulant proteins antithrombin and protein C, which suggests some effect of CCBs in patients who also receive other cardioprotective and/or vasoactive drugs. Since the finding on the potential beneficial effect of prior CCB use in patients with sepsis was the first report on this association, these data should be confirmed in another sepsis cohort. One earlier study reported on the link between CCB use and outcome of severe infection. This retrospective analysis of the clinical records of 388 bacteraemic patients caused by aerobic Gram-negative bacilli and Staphylococcus aureus, prior CCB use was not associated with altered mortality in multivariate analysis.[30] This study differed from the MARS study in various ways, i.e., its retrospective nature, and patient inclusion criteria (only bacteraemic patients and the absence of information about the type of care).[35] In multivariate analyses the relation between prior use of other cardioprotective medication and sepsis mortality was investigated. In particular the role of beta-blocker therapy in sepsis is currently under debate; a randomised controlled trial demonstrated a significant difference in 28-day mortality between septic shock patients treated with esmolol (49.4%), compared with the placebo group (80.5%).[36] In the MARS cohort, prior use of beta-blockers was not associated with altered 30-day mortality. One earlier observational study reported on prior beta-blocker use and sepsis outcome.[37] Patients previously prescribed beta-blockers had a lower frequency of death at 28 days than those previously untreated. Of importance, patients in this study were included based on hospital discharge records versus prospective inclusion by dedicated research physicians in the MARS study, and the fact that all hospitalised patients were enrolled versus ICU patients.[37] In a cohort of patients with pneumonia, prior beta-blocker use was not associated with mortality.[38] This study is different to the MARS study in that only pneumonia patients requiring hospital admission were included, whereas the MARS study was conducted in sepsis patients requiring intensive care and with different sources of infection.

HIV infection

The epidemiology of sepsis in patients infected with the human immunodeficiency virus (HIV) has changed dramatically upon the introduction of combination antiretroviral therapy.[39] The incidence of opportunistic infections has decreased and long-term survival improved; however, invasive bacterial infections and sepsis remain an important cause of morbidity and mortality in HIV patients.[40,41] The MARS investigators studied the impact of chronic HIV infection on the presentation, outcome and host response of sepsis patients.[42] ICU admissions of HIV-positive patients for sepsis more often involved pneumonia compared with admissions of HIV-negative patients. There were no significant differences in mortality up to one year after admission between HIV-positive and HIV-negative patients in the total sepsis cohort, as well as in the pneumosepsis subgroup. In ICU patients with sepsis, HIV/AIDS was independently associated with in-hospital mortality in other studies.[43–45] However, these differed from the MARS investigation in patient
selection and setting resulting in a cohort of patients with more severe disease. Over time, standards of care for HIV patients have improved considerably and studies suggest that survival of critically ill HIV-infected patients has improved in the era of widespread cART availability. These findings indicate that in a setting with excellent access to care and HIV treatment, the prognosis of sepsis patients with HIV infection admitted to the ICU has become similar to that of patients without HIV infection.

As there were large demographic differences between HIV-positive and -negative patients, a control cohort of 90 admissions of HIV-negative pneumonia patients matched for age, sex and race was composed to study the host response. The levels of most host response biomarkers were similar in admissions of HIV-positive and HIV-negative patients, with the exception of interferon-γ and soluble ICAM-1, which were higher in HIV-positive patients at day 0 and 2.

Two earlier studies on the host response in adult HIV patients with sepsis have been published, reporting plasma cytokine levels. HIV status had little impact; one of these studies reported elevated plasma IL-10 levels in the presence of unaltered plasma IL-6 levels in HIV-positive patients with sepsis. However, these only included patients with advanced AIDS defining disease and high mortality rates (around 50%). Chronically infected HIV infection seems to induce endothelial cell activation and disturbances, responses that are also observed in patients with sepsis. In Malawian children with severe bacterial infection, plasma angiopoietin-2, an angiogenic peptide that increases endothelial activation and vascular permeability, was more elevated in patients with HIV co-infection compared with controls. In the adult ICU patients with pneumosepsis from the MARS cohort, HIV status did not influence plasma levels of specific endothelial cell activation markers (angiopoietin-1 and -2, and soluble E-selectin). Interestingly, HIV-positive patients displayed higher circulating levels of soluble ICAM-1, which can be shed by both endothelial cells and leukocytes. HIV infection can enhance the release of exosomes containing ADAM17 (ADAM metallopeptidase domain 17), the cleaving protease for ICAM-1, which promotes ICAM-1 shedding. Increased levels of IFN-γ, as observed in the MARS study, may also contribute to the release of sICAM-1.

Hypothermia

Patients with sepsis can display profound hypothermia, being observed in 9-35% of septic patients, the underlying mechanism of which is poorly understood. Immune suppression, due to an excessive anti-inflammatory response, has been proposed as a mechanism for hypothermia. Also, a recent study showed that hypothermia was associated with lymphopenia following diagnosis of sepsis, thereby potentially accounting for the association with adverse outcome. The MARS study aimed to determine risk factors of the occurrence of hypothermia during the first 24 hours of ICU admission and to characterise the host response in patients with hypothermic sepsis. Lower body mass index, hypertension and chronic cardiovascular insufficiency were associated with hypothermic sepsis. Hypothermia was independently associated with mortality in multivariate analysis, confirming previous studies.

In order to obtain insight into the pathophysiological mechanisms, pro- and anti-inflammatory cytokines and endothelial activation markers were measured. Pro- or anti-inflammatory cytokine levels were not different between hypothermic and non-hypothermic patients in the MARS study, even after correction for disease severity, which is in line with a study in hypothermic patients reporting no difference in circulating levels of proinflammatory cytokines. The host response biomarkers were similar in groups of patients with and without hypothermia, except for plasma fractalkine, which was higher in patients with hypothermia, and this difference remained after correction for disease severity. Fractalkine is a chemokine that has been implicated as a mediator in a diverse spectrum of inflammatory conditions and is associated with adverse outcome in critically ill patients with sepsis.

Endothelial cells have been described as an important source of fractalkine. Considering the presence of mainly cardiovascular risk factors in patients with hypothermia, the MARS data may suggest that the endothelium is implicated in hypothermia. The association between hypothermia and enhanced circulating levels of fractalkine in a population with significantly increased disease severity requires further evaluation.

Discussion

Within the MARS consortium a large prospective cohort of critically ill patients was studied, in which patients were methodically categorised and followed by committed research physicians. Besides information on demographics, comorbidities, and other patient-related factors, the MARS database also included extensive data on the septic episodes, i.e., timing of the infection, sepsis-induced organ failure and causative pathogens. In addition, a large set of host response biomarkers were measured, which provided further insight into the immune response of sepsis patients admitted to the intensive care unit. Although the studies on the association between prior medication, disease severity, host response and outcome were performed in an extensive cohort of patients, the observational nature of MARS studies does not allow for assessment of causal relationships. Propensity score matching was implemented to enable estimation of the independent effect of individual factors. The size of the MARS study population allowed it to perform matching by many important covariates; however, bias can remain as a result of unmeasured confounders. Another limitation involves the fact that this study was performed in two centres in the Netherlands, limiting generalisability of the results.
Conclusion
In the future, the number of patients who will present with sepsis is likely to increase due to ageing of the population, aggressive therapies for chronic diseases (most notably cancer) and the emergence of multidrug resistant pathogens. As a consequence, the management of sepsis will remain an important issue in the years to come. In the MARS study several ‘external’ and host factors that might influence sepsis outcome and the accompanying host response were studied, particularly prior medication (antipatelet agents, CCBs, statins) and comorbidity (HIV infection). None of these factors had a major impact on the host response to sepsis, while only the use of CCBs was associated with an altered (improved) outcome. In addition, the influence of an acute manifestation of severe infection (i.e., hypothermia) on sepsis outcome and the host response was examined, revealing an independent association between hypothermia and mortality without evidence for an altered immune response. Sepsis patients are heterogeneous in terms of comorbidity, age and host response, therefore adjuvant therapies for sepsis may differ from patient to patient. Great advances have been made in terms of understanding the pathogenesis of sepsis in recent years, and implementation of this increased knowledge in clinical practice will likely facilitate individualised treatment of patients with sepsis.

Disclosures
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Satisfaction of nurses and physicians with the introduction of the Rapid Response System in Dutch hospitals

A.H. Brunsveld-Reinders¹, J. Ludikhuize¹, M.S. Arbous¹,², M.G.W. Dijkgraaf³, E.de Jonge¹ for the COMET study group
¹Department of Intensive Care, Leiden University Medical Center, Leiden, the Netherlands
²Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, the Netherlands
³Clinical Research Unit, Academic Medical Center, Amsterdam, the Netherlands

Correspondence
A.H. Brunsveld-Reinders - A.H.Brunsveld-Reinders@lumc.nl

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Abstract
Background: Rapid Response Systems (RRSs) have been introduced in hospitals to improve recognition of and response to deteriorating hospital ward patients. The value of an RRS depends not only on relevant patient outcomes but also on how satisfied nurses and physicians are with the system. The aim of the study was to measure the degree of satisfaction with an RRS and analyse factors influencing the degree of implementation.

Methods: Questionnaires were distributed among physicians and nurses on medical and surgical wards participating in the COMET study at 7 and 14 months after introduction of a Rapid Response Team (RRT). The questionnaires included 24 questions regarding the use and the degree of satisfaction with the Modified Early Warning Score MEWS/SBAR tool and the RRT.

Results: The response rate was 1005/1920 (52%). Satisfaction with implementation of the RRS was generally higher at t=14 compared with t=7 months and in respondents working on surgical versus medical wards. In a multivariate analysis, independent predictors of high satisfaction were timing of the questionnaire (14 months versus 7 months after the start of an RRT), the support of the RRT system by local ward management, and having an RRT that was considered to be open and approachable.

Conclusions: Our findings show that healthcare workers on hospital wards are generally very satisfied with the services offered by the RRT, the use of the MEWS instrument to recognise deteriorating patients and the SBAR communication tool to improve communication between nurses and doctors. Satisfaction with the RRT was higher at 14 months compared with 7 months.

Introduction
Rapid Response Systems have been introduced in hospitals to improve recognition of and response to deteriorating hospital ward patients. An RRS can be seen as an intensive care-based, organisation-wide preventive approach to the management of deteriorating patients, and implementing the RRS requires more than just standardisation of ‘calling criteria’ and the rapid response of a dedicated acute care team. The RRS consists of three important components. The afferent limb is designed to identify the deteriorating patient by using calling criteria such as the Modified Early Warning Score (MEWS) card and to trigger a response. The efferent limb involves directed action of the Rapid Response Team (RRT) and the third component includes measures to improve the quality of care on the ward, training and feedback. An optimal RRS should ensure 1) the support of all physicians and nurses, 2) leadership and support from senior hospital executives, 3) 24/7 response by staff with appropriate skills, knowledge and experience, and 4) the promotion of hospital-wide awareness of the system.

The effectiveness of RRSs has not yet been proven conclusively. So far, the effectiveness of the introduction of RRSs in hospitals was shown in only two studies. The study by Priestly showed a reduction in hospital mortality, while the study by Ludikhuize et al. showed a reduction of the composite endpoint including cardiac arrest, death and unplanned ICU admission. Another multicentre randomised study conducted by Hillman in Australia could not demonstrate a benefit of the introduction of a medical emergency team based RRS.

Besides effects on relevant patient outcomes, the value of an RRS also depends on how satisfied nurses and physicians are with the system. Satisfaction of healthcare workers with the RRSs is not only a subjective measure of contentment with the support the RRS offers to the care of their patients, it also is a prerequisite for a good implementation and performance of the RRS. Nurses will only call an RRT if they expect to be supported by it. Fear of being criticised by members of an RRT for their care of deteriorating patients was reported to be a barrier for implementing an RRS.

In the Netherlands, we recently implemented an RRS in 12 hospitals. The aim of this study was to measure the degree of
satisfaction of nurses and physicians with the implementation of an RRS and the perceived benefit of the system.

**Material and methods**

**Design, setting, participants**
This study is part of the Cost and Outcome Medical Emergency Team (COMET) study which was conducted in the Netherlands from 2009 to 2011. The COMET study was a pragmatic prospective before-after multicentre study in which 12 Dutch hospitals participated. The before period in which baseline characteristics were collected lasted five months. Subsequently, the RRS was introduced in a two-step fashion. First, in the MEWS/SBAR phase, which lasted 7 months, the Modified Early Warning Score (MEWS) card and the Situation Background Assessment Recommendation (SBAR) communication tool were introduced to identify patients at risk and to facilitate communication between nurses and physicians. Secondly, the RRT was implemented and this phase lasted 17 months; it was divided into two periods, namely RRT implementation and the Final RRT phase. In each participating hospital, patients of 18 years and older who were admitted to two surgical and two medical wards, the so-called COMET wards, were included. A full description of the study design has been published previously.

**Intervention**

The questionnaires included 24 questions covering three aspects: 1) questions on how respondents used the MEWS/SBAR tools and RRT, 2) level of satisfaction with MEWS/SBAR and RRT, and 3) characteristics of the respondents (physician/nurse, working on medical/surgical ward, gender, age, experience since graduation (years), employment in the hospital and current ward (years)). Responses to the questions were scored on a scale from 0-10 (0 = totally disagree or never, 10 = totally agree or always).

**Ethical consideration**

The medical ethics committee of the Academic Medical Centre in Amsterdam waived the need for formal evaluation of the study due to the observational nature of the study. Consequently, the need for informed consent was not applicable.

**Statistical analysis**

Descriptive analyses are presented as raw numbers and percentages. Continuous data were presented as medians with interquartile range (IQR) due to non-normally distributed data. A bootstrap independent t-test was used for comparison of the time points, drawing 1000 samples of the same size as the original samples and with replacement, stratified by the timing of questionnaire. The generalised estimating equation (GEE) was applied to estimate the univariable association between predictors as measured by the questionnaire and satisfaction. The predictors used in GEE were 1) timing of questionnaire (7 and 14 months), 2) gender of respondent, 3) surgical/medical ward, 4) number of patients with MEWS ≥3 assessed by nurse or physician in the last 2 weeks, 5) age (years) of respondent, and 6) work experience (years) of respondent.

In the GEE, a binomial distribution was assumed after recoding the questions scored on a scale from 0 to 10 into a dichotomous

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**Figure 1. Design of the COMET study**

Following the baseline period of 5 months, the Modified Early Warning Score (MEWS)/Situation-Background-Assessment-Recommendation (SBAR) was implemented for 7 months and subsequently followed up for 17 months in which the rapid response team (RRT) was available. Effects of the RRT on outcomes were measured during the last 5 months and compared with the 5-month baseline period. During the entire length of the study, data were collected on all the endpoints. For further clarification, hospitals were able to start the study in a 3-month time period. The total study took 30 months, in which each hospital participated for 27 months. Log Rank (Mantel-Cox analysis) p=0.004

During the second phase of the COMET study, questionnaires were distributed to nurses and physicians in all 12 participating hospitals to measure the satisfaction with the RRS on two different time points: 7 and 14 months after introduction of the RRT. On each occasion, participating hospitals distributed 80 questionnaires on the four COMET wards to nurses and physicians. The questionnaires were completed anonymously.

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**Table 1. Demographics**

<table>
<thead>
<tr>
<th>Questionnaire</th>
<th>RRT implementation phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respondent, n (% of total)</td>
<td>492 (51)</td>
</tr>
<tr>
<td>Gender, male, n (%)</td>
<td>55 (11)</td>
</tr>
<tr>
<td>Age, mean ± SD</td>
<td>32.8 ± 10.5</td>
</tr>
<tr>
<td>Reporter, n (%)</td>
<td></td>
</tr>
<tr>
<td>Physicians</td>
<td>52 (11)</td>
</tr>
<tr>
<td>Nurses</td>
<td>421 (85)</td>
</tr>
<tr>
<td>Other or unknown</td>
<td>19 (4)</td>
</tr>
<tr>
<td>Ward</td>
<td></td>
</tr>
<tr>
<td>Non-surgical ward</td>
<td>231 (47)</td>
</tr>
<tr>
<td>Surgical ward</td>
<td>251 (51)</td>
</tr>
<tr>
<td>Not reported</td>
<td>10 (2)</td>
</tr>
<tr>
<td>Experience since graduation (years), mean ± SD</td>
<td>8.6 ± 9.2</td>
</tr>
<tr>
<td>Employment in the hospital (months), mean ± SD</td>
<td>96.9 ± 105.2</td>
</tr>
<tr>
<td>Employment on current ward (months), mean ± SD</td>
<td>65.9 ± 74.7</td>
</tr>
</tbody>
</table>
Table 2. Characteristics of questionnaires, answers given by professionals

<table>
<thead>
<tr>
<th>Questionnaire</th>
<th>7 Months</th>
<th>14 Months</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Use of MEWS/SBAR</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If my patient has a MEWS ≥3, I always call the ward physician immediately</td>
<td>6.44 (6.19-6.66)</td>
<td>6.87 (6.65-7.06)</td>
<td>0.006</td>
</tr>
<tr>
<td>I always use the SBAR communication tool in the communication between the nurse and physician</td>
<td>5.29 (5.05-5.54)</td>
<td>5.49 (5.23-5.73)</td>
<td>0.245</td>
</tr>
<tr>
<td>The RRS is fully incorporated in the daily care we provide to our patients on the ward</td>
<td>5.49 (5.28-5.68)</td>
<td>6.26 (6.06-6.46)</td>
<td>0.001</td>
</tr>
<tr>
<td>The ward management supports the RRS concept</td>
<td>7.55 (7.36-7.74)</td>
<td>7.87 (7.71-8.03)</td>
<td>0.006</td>
</tr>
<tr>
<td>Explaining the MEWS/SBAR and RRT procedure to a new colleague is not a problem</td>
<td>6.52 (6.31-6.74)</td>
<td>6.91 (6.75-7.09)</td>
<td>0.006</td>
</tr>
<tr>
<td><strong>Satisfaction using MEWS/SBAR and RRT procedure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>What is your general opinion about the MEWS tool?</td>
<td>7.17 (7.05-7.31)</td>
<td>7.55 (7.42-7.67)</td>
<td>0.001</td>
</tr>
<tr>
<td>What is your general opinion about the use of SBAR communication tool?</td>
<td>6.99 (6.85-7.16)</td>
<td>7.08 (6.93-7.21)</td>
<td>0.462</td>
</tr>
<tr>
<td>What is your general opinion about the RRT?</td>
<td>7.33 (7.18-7.47)</td>
<td>7.69 (7.56-7.81)</td>
<td>0.001</td>
</tr>
<tr>
<td>The use of the MEWS/SBAR tool and RRT procedure creates an unbalanced increase in workload</td>
<td>3.71 (3.46-3.93)</td>
<td>3.32 (3.11-3.54)</td>
<td>0.016</td>
</tr>
<tr>
<td>Using the MEWS/SBAR tool, deteriorating patients were identified earlier</td>
<td>6.74 (6.56-6.91)</td>
<td>7.16 (6.99-7.31)</td>
<td>0.002</td>
</tr>
<tr>
<td>The RRT is of added value over using the MEWS/SBAR tool in early recognition and treatment of deteriorating patients</td>
<td>6.73 (6.55-6.91)</td>
<td>7.02 (6.87-7.17)</td>
<td>0.015</td>
</tr>
<tr>
<td>The presence of the RRT procedure in our hospital ensures that physicians review deteriorating patients earlier than before</td>
<td>6.08 (4.69-6.88)</td>
<td>6.79 (6.63-6.95)</td>
<td>0.352</td>
</tr>
<tr>
<td>The RRS is very relevant for my daily activities and I will keep using this in the future</td>
<td>7.01 (7.62-7.79)</td>
<td>7.44 (7.28-7.58)</td>
<td>0.001</td>
</tr>
<tr>
<td>The RRS is an essential part of the daily care and should be employed in all hospitals</td>
<td>7.28 (7.12-7.43)</td>
<td>7.72 (7.58-7.84)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Rapid Response Team</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The members of the RRT are kind and helpful during consultation</td>
<td>7.19 (7.03-7.35)</td>
<td>7.54 (7.41-7.76)</td>
<td>0.001</td>
</tr>
<tr>
<td>The members of the RRT have a low threshold to contact and are approachable</td>
<td>7.22 (7.04-7.38)</td>
<td>7.48 (7.37-7.60)</td>
<td>0.017</td>
</tr>
<tr>
<td>The members of the RRT give sufficient and high-quality bedside teaching during consultation</td>
<td>6.43 (6.23-6.62)</td>
<td>6.51 (6.34-6.68)</td>
<td>0.583</td>
</tr>
<tr>
<td><strong>Negative experiences with the members of the RRT in the previous three months?</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The members of the RRT are unfriendly and not cooperative to the ward nurse and physician during consultation</td>
<td>2.14 (1.90-2.41)</td>
<td>2.09 (1.88-2.31)</td>
<td>0.799</td>
</tr>
<tr>
<td>Members of the RRT give the feeling that they were called unnecessarily</td>
<td>2.52 (2.29-2.77)</td>
<td>2.39 (2.18-2.60)</td>
<td>0.424</td>
</tr>
<tr>
<td>The members of the RRT give the impression that the daily care on the ward is insufficient</td>
<td>2.56 (2.32-2.80)</td>
<td>2.64 (2.45-2.86)</td>
<td>0.555</td>
</tr>
<tr>
<td><strong>Possible delays in the RRS protocol</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nurses frequently activate the RRT instead of physicians</td>
<td>3.27 (3.04-3.49)</td>
<td>3.74 (3.54-3.96)</td>
<td>0.005</td>
</tr>
<tr>
<td>The ward physicians adhere to the timeframe to call the RRT</td>
<td>4.91 (4.72-5.09)</td>
<td>4.78 (4.57-4.97)</td>
<td>0.350</td>
</tr>
<tr>
<td>The RRT is always present within 10 minutes after the RRT call</td>
<td>6.87 (6.69-7.07)</td>
<td>6.98 (6.80-7.16)</td>
<td>0.142</td>
</tr>
</tbody>
</table>

Questionnaire 7 and 14 months after implementation of RRT. Response to questions was scored on a scale from 0-10 (0=totally disagree or never, 10=totally agree or always). All data are presented as mean and 95% CI. Data were derived from answers to questions 3-21 of the questionnaire.

Results
The response rate was 51% at 7 months and 53% at 14 months after RRT implementation. Of the returned questionnaires, 85% were filled in by nurses. Further details on the respondents are given in table 1.

Responses to the questionnaires at 7 months and 14 months are given in table 2. According to their own answers, respondents were more likely to call the RRT if patients had a MEWS ≥3 points, and the RRS was more fully incorporated on the wards at 14 months compared with 7 months after its introduction. Also, at 14 compared with 7 months, support by the management on the ward was higher and it was more often considered ‘no problem’ to explain the RRS to colleagues. Satisfaction with the RRS was generally higher at 14 months. Concerning the perceived attitudes of members of the RRT, respondents tended to be more positive at 14 months than at 7 months.

Table 3 reports the results of the GEE analysis. In the table, the RR for agreement with a certain statement of the survey is given for time of questionnaire (14 months versus 7 months), gender (female versus male), ward (surgical versus medical), observing patients with a MEWS ≥3 in the last week (≥1 patient versus 0 patients), age and work experience (years) are reported. For almost all statements, compliance of respondents and ward.

one. Score from 0 to 5 meant never or totally disagree and score from 6 to 10 meant always or totally agree. We indicated the reference category as the one which contained the most answers. Furthermore, a GEE was applied to estimate the multivariable association between demographic and process related items and overall satisfaction with the RRT. Associations were reported as relative risks (RR). Associations with p-values >0.1 were manually removed (backward stepwise) from the GEE. The level of significance was set at p<0.05. Statistical analysis was done using SPSS version 20.0 (Armonk, New York, USA).
Table 3. Association of characteristics of respondents with Rapid Response System-related behaviour and satisfaction

<table>
<thead>
<tr>
<th>Use of MEWS/SBAR</th>
<th>Timing (14 months vs. 7 months)</th>
<th>Female vs. male</th>
<th>Surgical vs. medical</th>
<th>Experience with patients with MEWS &gt;3</th>
<th>Age (years)</th>
<th>Work experience (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR (95%CI) p-value</td>
<td>RR (95%CI) p-value</td>
<td>RR (95%CI) p-value</td>
<td>RR (95%CI) p-value</td>
<td>RR (95%CI) p-value</td>
<td>RR (95%CI) p-value</td>
<td>RR (95%CI) p-value</td>
</tr>
<tr>
<td>If my patient has a MEWS ≥3, I always call the ward physician immediately</td>
<td>1.182 (0.974-1.034) 0.091 NS</td>
<td>1.389 (1.168-1.650) 0.000 NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>I always use the SBAR communication tool in the communication between the nurse and physician</td>
<td>NS</td>
<td>NS</td>
<td>1.157 (1.029-1.302) 0.015 NS</td>
<td>NS</td>
<td>1.008 (1.004-1.013) 0.000</td>
<td></td>
</tr>
<tr>
<td>The RRS is fully incorporated in the daily care we provide to our patients on the ward</td>
<td>1.429 (1.271-1.605) 0.000 NS</td>
<td>1.406 (1.179-1.678) 0.000 NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>The ward management supports the RRS concept</td>
<td>NS</td>
<td>NS</td>
<td>4.878 (2.597-9.091) 0.000 1.326 (0.959-1.835) 0.089 1.018 (0.998-1.038) 0.084 0.979 (0.959-1.000) 0.051</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Explaining the MEWS/SBAR and RRT procedure to a new colleague is not a problem</td>
<td>1.311 (1.086-1.605) 0.005 1.383 (1.001-1.908) 0.049 1.585 (1.2591.996) 0.000 NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Satisfaction using MEWS/SBAR and RRT procedure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>What is your general opinion about the MEWS tool?</td>
<td>1.479 (1.059-2.066) 0.021 NS</td>
<td>2.141 (1.277-3.597) 0.004 NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>What is your general opinion about the use of SBAR communication tool?</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>0.982 (0.962-1.004) 0.110 1.024 (1.002-1.047) 0.036</td>
<td></td>
<td></td>
</tr>
<tr>
<td>What is your general opinion about the RRT?</td>
<td>1.887 (1.403-2.532) 0.000 NS</td>
<td>2.475 (1.479-4.149) 0.001 NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>The use of the MEWS/SBAR tool and RRT procedure creates an unbalanced increase in workload</td>
<td>0.723 (0.873-0.958) 0.001 NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>0.985 (0.975-0.995) 0.004</td>
<td></td>
</tr>
<tr>
<td>Using the MEWS/SBAR tool, deteriorating patients are identified earlier</td>
<td>1.344 (1.044-1.733) 0.022 NS</td>
<td>1.451 (1.156-1.821) 0.001 NS</td>
<td>1.013 (1.002-1.025) 0.021 NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>The RRT is of added value over using the MEWS/SBAR tool in early recognition and treatment of deteriorating patients</td>
<td>1.460 (1.209-1.761) 0.000 NS</td>
<td>1.855 (1.600-2.146) 0.000 NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>The presence of the RRT procedure in our hospital ensures that physicians review deteriorating patients earlier than before</td>
<td>NS</td>
<td>NS</td>
<td>1.975 (1.634-2.347) 0.000 NS</td>
<td>NS</td>
<td>1.013 (1.003-1.024) 0.010</td>
<td></td>
</tr>
<tr>
<td>The RRS is very relevant for my daily activities and I will keep using this in the future</td>
<td>1.773 (1.294-2.427) 0.000 NS</td>
<td>2.793 (1.887-4.132) 0.000 NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>The RRS is an essential part of the daily care and should be employed in all hospitals</td>
<td>1.520 (1.224-1.887) 0.000 NS</td>
<td>2.801 (1.898-4.132) 0.000 NS</td>
<td>0.979 (0.956-1.003) 0.087 1.025 (1.002-1.049) 0.037</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Rapid Response Team</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The members of the RRT are kind and helpful during consultation?</td>
<td>1.848 (1.253-2.725) 0.002 1.821 (1.295-2.564) 0.001 1.645 (1.095-2.463) 0.016 1.534 (0.980-2.398) 0.061 NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>The members of the RRT have a low threshold to contact and are easily reachable</td>
<td>1.555 (1.175-2.058) 0.002 1.502 (1.013-2.227) 0.043 1.563 (1.171-2.088) 0.002 1.412 (1.048-1.923) 0.028 NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>The members of the RRT give sufficient and high-quality bedside teaching during consultation</td>
<td>NS</td>
<td>NS</td>
<td>1.524 (1.181-1.969) 0.001 NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td><strong>In the last three months negative experiences with the members of the RRT?</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The members of the RRT were unfriendly and not cooperative to the ward nurse and physician during consultation</td>
<td>NS</td>
<td>NS</td>
<td>0.618 (0.321-1.190) 0.150 NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Members of the RRT gave the feeling that they were called unnecessarily</td>
<td>NS</td>
<td>NS</td>
<td>0.613 (0.421-0.894) 0.011 NS</td>
<td>1.018 (1.001-1.035) 0.040 NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>The members of the RRT gave the impression that the daily care on the ward is insufficient</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>1.000 (0.990-1.010) 0.962 NS</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Is there any delay in the process?</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nurses frequently activate the RRT instead of physicians</td>
<td>1.073 (1.013-1.138) 0.017 NS</td>
<td>1.093 (0.999-1.196) 0.053 0.872 (0.822-0.925) 0.000 0.994 (0.991-0.997) 0.000 1.004 (1.000-1.008) 0.017</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The ward physician adhere to the time frame to call the RRT</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>1.008 (1.000-1.016) 0.045 0.993 (1.000-1.001) 0.097</td>
<td></td>
</tr>
<tr>
<td>The RRT is always present within 10 minutes after the RRT call</td>
<td>1.200 (0.996-1.449) 0.056 NS</td>
<td>1.307 (1.124-1.522) 0.001 NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Relative risk (RR) of characteristics of respondents with RRS-related behaviours and satisfaction. RR >1 indicates higher satisfaction or agreement with statement. Response to questions was originally scored on a scale from 0-10 (0=totally disagree or never, 10=totally agree or always). For this analysis answers were dichotomously recoded in a way that scores from 0-5 mean no or disagree and 6-10 means yes or agree. Data were derived from answers to question 3-21 of the questionnaire.
Table 4. Multivariate analysis exploring the association of different aspects of the Rapid Response System (demographic and process related items) and overall satisfaction with RRS

<table>
<thead>
<tr>
<th>Description</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Support of RRS by ward management</td>
<td>3.497 (1.802-6.803)</td>
</tr>
<tr>
<td>The members of the RRT are kind and helpful during consultation</td>
<td>4.149 (1.825-9.434)</td>
</tr>
<tr>
<td>The members of the RRT have a low threshold to contact and are easily reachable</td>
<td>NS</td>
</tr>
<tr>
<td>The members of the RRT give sufficient and high-quality bedside teaching during consultation</td>
<td>NS</td>
</tr>
<tr>
<td>Members of the RRT give the feeling that they were called unnecessarily</td>
<td>NS</td>
</tr>
<tr>
<td>The members of the RRT give the impression that the daily care on the ward is insufficient</td>
<td>NS</td>
</tr>
<tr>
<td>Nurses frequently activate the RRT instead of physicians</td>
<td>NS</td>
</tr>
<tr>
<td>The ward physician sticks to the timeframe to call the RRT</td>
<td>NS</td>
</tr>
<tr>
<td>The RRT is always present within 10 minutes after the RRT call</td>
<td>NS</td>
</tr>
<tr>
<td>Timing of questionnaire (14 months versus 7 months)</td>
<td>1.495 (0.959-2.331)</td>
</tr>
<tr>
<td>Surgical versus medical ward</td>
<td>NS</td>
</tr>
</tbody>
</table>

Relative risk (RR) of characteristics of respondents with RRS-related behaviours and satisfaction. RR > 1 indicates higher satisfaction of agreement statement. Response to questions was originally scored on a scale from 0-10 (0=totally disagree or never, 10=totally agree or always). For this analysis answers were dichotomously recoded in a way that scores from 0-5 mean ‘no or disagree’ and 6-10 means ‘yes or agree’. Data were derived from answers to questions that were related in our opinion to the process.

In this study we found that nurses and physicians working on hospital wards in the Netherlands are generally very satisfied with the services offered by the RRT, with the MEWS instrument to recognise patients at risk and with the SBAR communication tool to improve communication about deteriorating patients between nurses and doctors. At 14 months after implementation of the RRT, respondents valued these components of the RRS even more than at 7 months after implementation. Accordingly, we found high agreement of respondents with the statement that RRTs should be installed in all hospitals and that they were willing to use it in the future.

Our findings from the Netherlands are in agreement with earlier reports on attitudes of healthcare workers regarding RRTs. Studies from Saudi Arabia,[11] Australia,[9,12] Italy[13] and Canada[8] and the USA[14] all reported very high satisfaction with RRTs by nurses and doctors. RRTs were believed to prevent cardiac arrests[8,12] and allowed nurses to seek help if they were worried about their patients.[8] We found that nurses and physicians on surgical wards expressed higher satisfaction with the RRT than colleagues on medical wards. The use of the different components of the RRT system was also higher on surgical wards and the management on the surgical ward was more supportive regarding the RRT than on medical wards. The same difference in attitudes towards the RRT between surgical and medical wards was also reported in studies from Italy, Australia and Canada.[8,13,15] It has been suggested that the benefits from an RRT may be more pronounced on a surgical ward because surgeons are more often busy in the operating room and not available for care on the ward. Furthermore, many doctors and nurses of surgical wards feel inadequate in managing critical patients and are accustomed to relying on external consultants for managing medical problems.[13] As severe adverse events are common after surgery, RRTs may be especially beneficial in these patients. Indeed, Bellomo and co-workers reported that an RRT resulted in a 58% relative risk reduction in adverse outcomes and a 44% reduction in emergency ICU admissions after major surgery.[16]

In general, no association was found between satisfaction with RRT and either gender, experience with more than one deteriorating patient in the last two weeks, age of the respondent or years of experience in healthcare. Only a few individual statements showed such an association. More years of experience were associated with more agreement with the statement ‘I always use the SBAR communication tool in the consultation between nurse and physician’, and also with the statement ‘an RRT in the hospital means that deteriorating patients are reviewed earlier’. In other studies seniority of nurses was shown to be associated with a higher appreciation of the RRT.[15] In our multivariate analysis, an RRT considered to be ‘open’ and ‘approachable’ during consultation was associated with higher overall satisfaction with the RRT by healthcare workers. This can be a direct positive effect of being kind and helpful. If so, RRTs should be urged to be kind and helpful to facilitate implementation of the rapid response system in hospitals. Alternatively, it is also possible that nurses and doctors who are satisfied with the RRT for other reasons are also more positive about how the RRT operates.

The high satisfaction with an RRT found in our study is not necessarily representative for large-scale implementation in real-life settings. We cannot exclude that implementation
measures such as information and education were more intense and local management was more involved because our implementation of RRTs was part of a scientific study. However, we believe that this was unlikely. First, as this was a large study in 12 hospitals involving 166,569 patients, without external funding, implementation measures were mostly limited to informing all nurses and physicians and offering pocket cards with a MEWS and SBAR summary. This would not be very different in ‘normal’ implementations. Second, implementation was mainly done in the first months before and after the start of the RRT; if our study had applied unrealistic implementation measures, one would expect the highest appreciation of the RRT in the first period. In contrast, we found that satisfaction with the RRT actually increased over time between 7 and 14 months after the start of the RRT. In our study, questionnaires were distributed anonymously among physicians and nurses. Clearly, satisfaction by healthcare workers alone does not justify the implementation of RRTs. The effect of RRTs has been studied in the Netherlands in the COMET study in which a total of 166,569 patients were included. The composite endpoint of the RRT; if our study had applied unrealistic implementation

Conclusion

Our findings show that healthcare workers on hospital wards are generally very satisfied with the services offered by the RRT, the use of the MEWS instrument to recognise deteriorating patients and the SBAR communication tool to improve communication between nurses and doctors. Satisfaction with the RRT was higher at 14 months compared with 7 months.

Members of the COMET study group

M.A. van Putten, R. Adams (MSc) - Academic Medical Center; S.E.J.A. de Rooij (MD, PhD) - UMCG Groningen, C. Kerkhoven - Catharina Hospital; A. Braber, (MD) - Gelre Hospital; FJ. Schoonderbeek, (MD, PhD) - Ikazia Hospital; B.M. Kors, (MD) - Kennemer Gasthuis; D.P. Sep, (MD) – Noord West Hospital; J.W. Vermeijden, (MD, PhD) - Medical Spectrum Twente; B.G. Fikkers, (MD, PhD) - Radboud University Medical Center; P. Tångkau, (MD) - Reinier de Graaf Hospital; P.K.C. van der Weijden, (MD) - Rijnland Hospital; S. Koenders, (MD) - Rivas Beatrix Hospital; M. Meertens, (MD) - Sint Lucas Andreas Hospital; A.H. Brunsveld-Reinders, (PhD) - University Medical Center Leiden; M. Hoeksema, (MD) - Zaans Medical Center; S.M. Smorenburg, (MD, PhD) - Ben Saetcentrum.

Questionnaire

You will find the questionnaire: http://njcc.nl/25/5/appendix.pdf

Disclosures

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References

PHOTO QUIZ

Brain activity in cardiac arrest

J. Horn, M.M. Admiraal
Department of Intensive Care, Academic Medical Center, Amsterdam, the Netherlands

Correspondence
J. Horn - j.horn@amc.uva.nl

Case
A 59-year-old male patient without any medical history was admitted to our intensive care unit (ICU) after an out-of-hospital cardiac arrest. He had collapsed unwitnessed but was found by the medical services with ventricular fibrillation. After seven rounds of electrocardioversion, administration of two doses of norepinephrine, and one of amiodarone, spontaneous circulation returned. On admission he was in coma with a Glasgow Coma Scale score of 3. After successful cardiological intervention he was admitted to the ICU, where he was treated with target temperature management aiming at a temperature of 36°C and continuous EEG monitoring was started. The patient was haemodynamically stable and the EEG showed a nice continuous pattern. Then suddenly everything changed and we saw the picture in figure 1.

What is your diagnosis?

Answer
You will find the answer on page 185 in this issue.

Figure 1. Suddenly changing EEG trace of a patient after successful resuscitation.
Treating pulmonary embolism in the intensive care unit: are the guidelines helpful?

Abstract
Patients admitted to the intensive care unit (ICU) with pulmonary embolism (PE) usually have an increased mortality risk. This risk can be estimated by the Pulmonary Embolism Severity Index (PESI), composed of clinical features such as tachycardia, tachypnoea, hypotension, altered mental status and decreased arterial oxygen saturation. Patients with persistent hypotension (systolic blood pressure <90 mmHg for ≥15 min) carry the highest mortality risk and in the absence of contraindications, international guidelines recommend to treat these patients with fibrinolysis. Choosing the best anticoagulation strategy for patients with acute PE can be difficult, especially in patients with severe obesity and those with contraindications to anticoagulation. Although the guidelines suggest that intermittent subcutaneous and continuous intravenous anticoagulant treatment are equally effective, the intermittent subcutaneous treatment does not warrant continuous protection against clinical deterioration. To illustrate this problem, we present two case histories.

Case 1
A 49-year-old woman with a body mass index (BMI) of 43.5 kg/m² (height 176 cm, weight 135 kg) was admitted to the hospital because of chest pain and dyspnoea. Her body temperature was 37.1°C, heart rate 143/min, blood pressure 118/71 mmHg and respiratory rate 18/min. Based on age and heart rate, a PESI score of 69 could be calculated (class II) (table 1). CT angiography demonstrated large emboli in the left and right pulmonary arteries (figure 1). Laboratory results showed a

Introduction
Pulmonary embolism (PE) covers a wide spectrum of clinical severities, ranging from low-risk to life-threatening. The severity of PE is classified according to its short-term mortality risk: low (<1%), intermediate (3-15%) and high (>15%). Patients with low-risk PE are characterised by a normal blood pressure, normal biomarkers and no right ventricular dysfunction. Patients with high-risk PE can be identified by clinical features such as tachycardia, tachypnoea, hypotension, altered mental status and decreased arterial oxygen saturation, parameters incorporated in the Pulmonary Embolism Severity Index (PESI) (table 1). Patients in circulatory shock carry the highest risk of short-term mortality (>15%). Although this classification is clear-cut, choosing the right anticoagulant strategy for a particular ICU patient with PE can be difficult. To illustrate this problem, we present two case histories.

Table 1. PESI score

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Age in years</td>
</tr>
<tr>
<td>Male gender</td>
<td>+10</td>
</tr>
<tr>
<td>Cancer</td>
<td>+30</td>
</tr>
<tr>
<td>Chronic heart failure</td>
<td>+10</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>+10</td>
</tr>
<tr>
<td>Heart rate &gt;110/min</td>
<td>+20</td>
</tr>
<tr>
<td>Systolic blood pressure &lt;100</td>
<td>+30</td>
</tr>
<tr>
<td>Respiratory rate &gt;30/min</td>
<td>+20</td>
</tr>
<tr>
<td>Temperature &lt;36°C</td>
<td>+20</td>
</tr>
<tr>
<td>Altered mental status</td>
<td>+60</td>
</tr>
<tr>
<td>SaO2 &lt;90%</td>
<td>+20</td>
</tr>
</tbody>
</table>

Class I: ≤65 points: very low 30-day mortality risk (0-1.6%)
Class II: 66-85 points: low mortality risk (1.7-3.5%)
Class III: 86-105 points: moderate mortality risk (3.2-7.1%)
Class IV: 106-125 points: high mortality risk (4.0-11.4%)
Class V: >125 points: very high mortality risk (10-25%)

PESI = Pulmonary Embolism Severity Index; SaO2 = arterial oxygen saturation.
leukocyte count of 12.8 x 10^9/l and an hs-troponin-T level of 0.073 mg/l. The patient was treated with 5000 IU unfractionated heparin (UFH) intravenously, followed by nadroparin 9500 IU subcutaneously twice daily on the first day of admission and 7600 IU thrice daily the day after. On the third day of admission the patient experienced renewed chest pain along with dyspnoea, nausea and dizziness. Monitoring showed a temperature of 38.1°C, heart rate of 117/min, blood pressure of 98/69 mmHg, respiratory rate of 20/min and peripheral oxygen saturation of 95%. There were no clinical signs of infection and the anti-Xa activity was 0.01 U/ml. The patient was admitted to the ICU, treated with UFH intravenously and the symptoms subsided. Three days later, she could return to the ward and ten days later, she left the hospital.

**Case 2**

A 63-year-old man with a BMI of 24 (height 195 cm, weight 91 kg) had a right-sided hemicolectomy because of colonic cancer. On the third postoperative day he was admitted to the ICU because of fever, chills and desaturation. He had a body temperature of 38.5°C, heart rate of 117/min, blood pressure of 134/95 mmHg, respiratory rate of 20/min and peripheral oxygen saturation of 90%. Based on age, male gender, cancer and heart rate, a PESI score of 123 could be calculated (class IV) (table 1). The next day, CT angiography showed large emboli in the arteries of the lower right lobe and both left lobes. The patient was treated with subcutaneous nadroparin, 5700 IU twice daily. A week after the operation, the nadroparin dose was increased to 7600 IU twice daily, acenocoumarol was added and the patient was transferred to the ward.

Two days later, the patient experienced acute dyspnoea. Monitoring showed a heart rate of 150/min, respiratory rate of 40/min and oxygen saturation of 88%. Oxygen was applied through a non-rebreather mask and the patient was admitted to the ICU. Because massive PE was suspected, the patient was treated with 5000 IU UFH and 100 mg recombinant tissue plasminogen activator intravenously. Nevertheless, the heart rate and blood pressure dropped until cardiac arrest with pulseless electric activity occurred. The resuscitation no-shock block was started according to the guideline of the European Resuscitation Council (ERC). Despite adequate basic life support and repeated administration of epinephrine intravenously, echocardiography showed no cardiac activity, a dilated right ventricle and collapse of the left ventricle, compatible with massive PE. After 40 minutes, the resuscitation was ended and the patient was pronounced dead.

**Discussion**

In both cases described here, PE was accurately diagnosed. Both patients were admitted to the ICU and treated with anticoagulants. However, the first patient recovered, while the second patient died. This prompted us to investigate whether treatment for PE in the ICU can be optimised.

Patients with suspected PE should be stratified according to their short-term mortality risk. For this purpose, PESI can be used (table 1). When calculated for our patients, the first patient had a PESI score of 69 points (class II), corresponding to a low mortality risk (1.7-3.5%), whereas the second patient had a PESI score of 123 (class IV), corresponding to a high mortality risk (4.1-11.4%). When interpreting these scores, we have to keep in mind that in PESI classes I-IV, the score has a negative predictive value ranging from 76 to 92%, whereas the positive predictive value ranges from 27 to 50%.

Several investigators have tried to improve the predictive value of PESI by adding biomarkers or information derived from imaging. By adding troponin, BNP or leukocyte count to the PESI score, its predictive value could be improved. In addition, cardiac chamber sizes measured during CT angiography were demonstrated to have a predictive value for outcome: a left atrial volume ≤62 ml, a left ventricular volume ≤67 ml and a right to left atrial ratio >2.1 were associated with hazard ratios for 30-day mortality ranging from 1.8 to 2.4. A right atrium to ventricle ratio <1.01 was predictive of 30-day mortality. Right ventricular strain, defined as a right to left ventricle ratio ≥1, was identified as a predictor of negative outcome with an odds ratio of 9.2.

The American Heart Association (AHA), the European Society of Cardiologists (ESC) and the American College of Chest Physicians (ACCP) have all published guidelines for the management of pulmonary embolism. All three guidelines recognise the impact of right ventricular dysfunction and elevated cardiac markers such as troponin and natriuretic peptide on short-term mortality. However, the routine determination of these items is not recommended because of their low positive predictive value.

Patients with established PE should receive prompt and appropriate anticoagulation. Anticoagulant strategies comprise...
intravenous UFH and subcutaneous fondaparinux, low-molecular-weight heparin (LMWH) or UFH. The three guidelines recommend fibrinolysis for patients with acute PE associated with shock (defined as a condition of inadequate tissue perfusion) or hypotension (defined by the ESC guideline as a blood pressure <90 mmHg for ≥15 minutes or a systolic pressure drop by ≥40 mmHg for ≥15 minutes, if not caused by new-onset arrhythmia, hypovolaemia or sepsis) and no contraindications. In these patients, the ESC guideline recommends anticoagulation with UFH because of its short half-life, the ease of monitoring its anticoagulant effects, and its rapid reversal by protamine.[12] Patients with acute PE without hypotension should be stratified by means of PESI and markers of right ventricular strain to determine their eligibility for fibrinolysis.[12,13] In patients with a high mortality risk, the AHA guideline suggests heparin anticoagulation, while the ACCP guideline suggests ‘aggressive anticoagulation’ without further specification.[2,12,13] The ESC guideline recommends UFH for patients in whom primary reperfusion such as thrombolysis or embolectomy is considered, as well as for those with serious renal impairment (creatinine clearance <30 ml/min) or severe obesity (BMI >35 kg/m²).[12] In patients with renal impairment, decreased heparin clearance may lead to heparin-associated bleeding. Therefore, UFH by continuous infusion has to be monitored by means of the activated partial thromboplastin time (APTT) or the activated clotting time.[14] Several authors have described the possibility to estimate the risk of bleeding in patients with venous thromboembolism. Kooiman et al. demonstrated that patients with a HAS-BLED score >3 had an increased risk of bleeding.[15] Among acutely ill medical patients, Guijarro et al. demonstrated an increased risk of bleeding in males, patients with ischaemic heart disease, upper gastrointestinal disease, liver disease, coagulation disorders and anemia, with odds ratios ranging from 1.09 to 3.01.[16] In patients with morbid obesity (BMI >40 kg/m²), the effect of subcutaneously administered LMWH is delayed, and is best described by a three compartment model.[17] If there is a compelling reason to choose LMWH in a patient with morbid obesity, anti-Xa monitoring is recommended, aiming at an anti-Xa level of 1.3 IU/ml four hours after the subcutaneous dose.[14,18] For patients with cancer-associated PE, the three guidelines recommend LMWH as the therapy of choice.[2,12,13]

When we reconsider the treatment of our patients, the first patient had a BMI of 43.5 and a low mortality risk (1.7-3.5%) based on a PESI score of 69 (class II). According to the ESC guideline, she should have been treated with UFH, preferably a bolus of 60 IU/kg, followed by a continuous infusion of 12 IU/kg/h.[19] If there is a compelling reason to choose for LMWH, the recommended daily subcutaneous nadroparin dose is 171 IU/kg, aiming at an anti-Xa level of 1.3 IU/ml four hours after the subcutaneous dose.[2,18] It should be noted that intermittent subcutaneous dosing of LMWH leads to anti-Xa trough and peak levels between 0 and 1.7 IU/ml, whereas an anti-Xa level of 1.0±0.2 IU/ml is needed for an adequate anticoagulant effect.[18,20] The anti-Xa level in our patient was 0.01 IU/ml 5 hours after the subcutaneously administered nadroparin.

Our second patient underwent surgery for colonic cancer and according to the three guidelines, LMWH was the treatment of choice.[2,12,13] This patient had a PESI score of 123 (class IV) and therefore a high mortality risk (4-11.4%). For high-risk patients, the AHA guideline recommends aggressive anticoagulation without further specification. When nadroparin is chosen as first-line therapy, the recommended daily dose is 171 IU/kg, which comes down to 15,561 IU per day for our patient. The prescribed subcutaneous dose of 5700 IU nadroparin twice daily was therefore too low. In patients with cancer, aggressive anticoagulation is important, since both cancer and failure to rapidly achieve therapeutic levels of anticoagulation independently predict an increased risk of recurrence.[12,21-23] In a large case-cohort study, Heit et al. found a hazard ratio of 3.5 (95% CI 1.86-6.66) for recurrence of thromboembolism among patients with stage 4 cancer, and a hazard ratio of 1.6 (95% CI 1.12-2.39) for patients failing to reach a therapeutic APTT within 24 hours.[21] In an earlier study, Heit et al. found a hazard ratio of 0.57 (95% CI 0.34-0.97) for recurrence of thromboembolism among patients reaching an APTT ≥58 s. within 24±4 hours, which corresponded to an anti-Xa level of ≥0.3 IU/ml.[22] For treatment with LMWH, however, routine anti-Xa monitoring is not recommended. Moreover, the correlation between anti-Xa level and antithrombotic activity is weak.[20,24] The question remains how we can be sure that the chosen anticoagulant strategy adequately protects our patients from recurrent thromboembolism. When we choose UFH by continuous infusion, the risk of recurrent thromboembolism decreases by 43% when an APTT ≥58 s. is reached, whereas we cannot be sure about the risk of recurrence when intermittent subcutaneous LMWH is used.

Reconsidering the three international guidelines for the management of PE, subtle differences in the recommendations for the treatment of severely obese patients and high-risk patients are noticed. Obviously, these guidelines are based on large populations of patients who were not necessarily critically ill. When treating our critically ill PE patients, we should realise that in general, they have a higher mortality risk than the average PE patient included in a treatment trial and that, therefore, our patients have to be treated more aggressively. When choosing an anticoagulant for our critically ill PE patient, we should take into account body mass index, disease severity and risk of recurrence, both for the individual patient and the anticoagulant strategy chosen.
Conclusion
Critically ill patients with pulmonary embolism usually have a higher mortality risk than the average patient included in a treatment trial. Therefore, guidelines for the treatment of pulmonary embolism are often not aggressive enough for our high-risk ICU patients. When we treat ICU patients with acute PE, we have to take into account the BMI, disease severity and risk of thromboembolic recurrence. For the estimation of disease severity, PESI may be helpful. In both severely obese and high-risk ICU patients with pulmonary embolism (PESI classes IV and V), we should choose an anticoagulant strategy minimising the risk of thromboembolic recurrence, such as UFH by continuous infusion, reaching an APTT ≥58 s. within 24 hours.

Disclosures
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References

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Pulmonary embolism in the ICU
CASE REPORT

An unexpected cause of in-hospital cardiac arrest

S. IJmkers, N. van der Lubbe, L. Dawson
Department of Intensive Care Medicine, Reinier de Graaf Hospital, Delft, the Netherlands

Correspondence
S. IJmkers - susanneijmkers@gmail.com

Keywords - in-hospital cardiac arrest, cervical spinal cord injury, causes of cardiac arrest, ligamentous injury

Abstract
We describe a patient admitted with pneumonia two weeks after falling down stairs. On admission, spinal cord injury was excluded by computed tomography (CT). At day 3 of admission in-hospital cardiac arrest occurred. With this case, we want to create awareness that even two weeks post trauma, spinal cord injury can be missed on CT with fatal consequences. We advocate an MRI in patients with persistent localised neck pain or neurological deficits as well as in patients with altered mental status to exclude soft tissue injuries.

Introduction
The incidence of traumatic spinal cord injury (SCI) in the Netherlands is among the lowest in the world. There is an increase in age at time of injury with same-level falls becoming a more important cause of SCI.[1] A multi-detector row computed tomography (CT) scan is generally accepted as a valid tool to rule out SCI.[2] Magnetic resonance imaging (MRI) is more sensitive than CT in discerning purely ligamentous injuries. A recent study reported that CT scan alone appeared to be safe in clearance of the cervical spine in intoxicated patients with no gross motor deficits, therefore avoiding prolonged and unnecessary immobilisation.[3] However, a thorough approach to these patients is of utmost importance because cervical SCI may have devastating consequences. Cardiac arrest can occur in the acute phase due to disruption of central sympathetic control and the concomitant unopposed vagal outflow.[4] Considering the low incidence, resuscitation teams may have little experience of SCI. Identifying the aetiology of cardiac arrest can be of great significance. Another study demonstrated substantial benefit in survival in in-hospital cardiac arrest (IHCA) patients whose causes were recognised by emergency teams during advanced life support.[5] In this case, we present a patient with unrecognised cervical SCI.

Case history
A 62-year-old male was admitted with dyspnoea, fever and confusion. His medical history included alcohol abuse and atrial fibrillation for which he used vitamin K antagonists. Inflammatory parameters were elevated (C-reactive protein 243 mg/l, leukocytosis 19.0 x 10^9/l) and chest X-ray showed bilateral consolidation. Cefuroxime and clarithromycin were started according to the local guidelines on community-acquired pneumonia. On day 2 of admission the patient complained of neck pain. The patient's history was incomprehensive due to delirium, but he reported falling down the stairs two weeks before admission. A neurologist was consulted and a neck collar was adjusted to stabilise the cervical spine. Apart from cervical midline tenderness and a radiating sensation between the patient's shoulder blades during neck flexion, neurological examination was without abnormalities. Multi-detector row CT of the brain and cervical spine revealed cervical spondylosis (figure 1a). His neck collar was removed and his neck pain was ascribed to tendomyalgia.

Figure 1a. CT cervical spine on admission demonstrates spondylosis, but normal alignment without fracture.
Figure 1b. CT cervical spine post cardiac arrest demonstrates atlantoaxial dislocation with compression on the myelum and lower brainstem.
MRI of the cervical spine was scheduled for day 3 to exclude spondylosis/spondylodiscitis. Diagnostic lumbar puncture was considered but not performed since clinical suspicion of meningitis was low, the INR was elevated (3.7) and the inflammatory parameters as well as the dyspnoea were decreasing. At day 3, completely unexpectedly, asystolic witnessed cardiac arrest occurred and cardiopulmonary resuscitation (CPR) was initiated. The cause of cardiac arrest was not immediately evident to the emergency team. After 18 minutes of advanced life support, return of spontaneous circulation was achieved. The patient was intubated and transferred to the intensive care unit where he received a jugular central venous catheter for administration of inotropic drugs. Despite our respiratory and haemodynamic support, he remained hypotensive with recurrent episodes of bradycardia. Several causes of shock were excluded. Neurogenic shock was considered because of his recent fall together with unresponsiveness, apnoea and noteworthy bradycardia. Also, after evaluation, the patient appeared to have warned the nurses directly prior to cardiac arrest that he was unable to move his legs. Lumbar puncture was performed after correction of the INR, and showed macroscopic red blood cells after which another CT was performed to exclude subarachnoid haemorrhage. Surprisingly this CT revealed atlantoaxial (C1-C2) dislocation with a relatively high position of the dens in the foramen magnum compromising the myelum and lower brainstem (figure 1b). The patient did not qualify for neurosurgical intervention due to his comorbidity and poor overall clinical condition with locked in syndrome. Shortly after initiation of palliative treatment he died. Postmortem a subtle bruise was noticed beneath the beard under his chin (figure 2).

**Discussion**

When IHCA occurs, information regarding patient comorbidity and preceding signs can be obtained by the resuscitation team to provide insight into the aetiology. In this case no preceding vital functions were determined. There were, however, preceding subjective signs such as the acute loss of motor function indicated by the patient directly prior to cardiac arrest, unfortunately unknown to the emergency team at time of CPR. The patient was primarily admitted with pneumonia. Suspection of spinal cord injury (SCI) was low since repeated neurological examination and the initial CT showed no objective abnormalities two weeks post trauma. The bruise on his chin could have exposed the impact of the trauma, indicative of hyperextension with severe mechanical force exerted on the spinal cord. In elderly patients with spondylosis, even relatively mild trauma can cause SCI. [3,4] In case of clinoradiological mismatch in a patient with previous blunt trauma such as our patient, careful protocollled evaluation and management is warranted including consultation of a trauma surgeon. [7,8] First a neck collar is indicated to maintain spine immobilisation and secondly an MRI has to be performed to detect soft tissue injuries including haemorrhage, oedema, and injuries to the adjacent ligaments or spinal cord itself. [4,8]

Retrospective evaluation of clinical signs and symptoms of our patient finally resulted in the diagnosis of cervical SCI and neurogenic shock leading to IHCA. We believe that this patient was predisposed to SCI due to ligamentous injury not observed on the initial CT scan. Furthermore, we hypothesise that atlantoaxial dislocation originated directly prior to cardiac arrest but we cannot exclude that it occurred during intubation, transport to the ICU or insertion of the central venous catheter. Oedema, haemorrhage with prolonged INR or contusion could also have led to acute exacerbation of the SCI. In this case, MRI in an early stage could have revealed unstable SCI.

With this case we want to illustrate that even two weeks post trauma, SCI with unknown ligamentous injury can be a cause of cardiac arrest. Therefore we propose that when a clinoradiological mismatch is present, even two weeks after an accident, MRI should be obtained to exclude ligamentous or soft tissue injury. The recent trauma and the bruise on the patient’s chin appeared not to be an innocent bystander but the clue to an unexpected cause of IHCA.

**Disclosures**

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

**References**

A severe community-acquired pneumonia during pregnancy

D.W. Oostwoud,1,2 S. Achterberg1, C. Savelkoul1, D.H.T. Tjan3, D.W. de Lange1
1Department of Intensive Care Medicine, University Medical Center Utrecht, Utrecht, the Netherlands
2Department of Intensive Care Medicine, Onze Lieve Vrouwe Gasthuis, Amsterdam, the Netherlands
3Departement of Intensive Care Medicine, Gelderse Vallei Hospital, Ede, the Netherlands

Keywords - pneumonia, pregnancy, pre eclampsia, legionella

A 39-year-old pregnant woman (G3P2, gestational age 28 weeks) visited her general practitioner with a three-day history of fever, malaise and flu-like symptoms. A common flu was suspected and a re-evaluation was planned for the next day. The next day the symptoms were rapidly progressive and she was seen by her obstetrician.

Physical examination at that time showed a blood pressure of 121/77 mmHg, heart rate 109 beats/min and a temperature of 39.5 °C. She complained about abdominal tenderness in her left and right upper quadrant.

Laboratory results: haemoglobin 7.1 mmol/l (normal range at 28 weeks of pregnancy 6.8-8.7 mmol/l); hematocrit 0.32 l/l (>0.32); MCV 90 fl; leucocytes 11.7 /nl; CRP 245 mg/l, lactate 0.7 mmol/l, bilirubin 9 µmol/l, troponin-1 <0.0450 µg/l, NT-pro-BNP 67 pmol/l. Arterial blood gas analysis: pH 7.41 (7.35-7.45), pCO2 3.2 kPa (4.5-6.0), pO2 12.7 kPa (9.5-13.0), HCO3 15.1 mmol/l (22.0-26.0), base excess -7.9 mmol/l (-2.0-2.0), O2 saturation 98% (92-99) (Table 1).

Urine analysis: Protein (quantitative) 2.0 g/l (0.0-0.15 g/l), leucocytes negative, erythrocytes negative, nitrite negative.

Abdominal ultrasound showed no abnormalities. A chest X-ray showed a right middle lobe infiltrate (figure 1).

Table 1. Overview of arterial blood gas analysis prior to admission to the ICU

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
</tr>
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<tbody>
<tr>
<td>18:49</td>
<td>7:10</td>
<td>16:23</td>
<td>17:20</td>
<td>18:16</td>
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<tr>
<td>pH (7.35-7.45)</td>
<td>7.41</td>
<td>7.39</td>
<td>7.41</td>
<td>7.34</td>
</tr>
<tr>
<td>pCO2 (4.5-6.0 kPa)</td>
<td>3.2 kPa</td>
<td>3.4 kPa</td>
<td>4.0 kPa</td>
<td>5.0 kPa</td>
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<tr>
<td>pO2 (9.5-13.0 kPa)</td>
<td>12.7 kPa</td>
<td>12.5 kPa</td>
<td>13.3 kPa</td>
<td>9.0 kPa</td>
</tr>
<tr>
<td>HCO3 (22.0-26.0 mmol/l)</td>
<td>15.1 mmol/l</td>
<td>14.8 mmol/l</td>
<td>18.5 mmol/l</td>
<td>19.9 mmol/l</td>
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<tr>
<td>Base excess (-2.0-2.0 mmol/l)</td>
<td>-7.9 mmol/l</td>
<td>-8.5 mmol/l</td>
<td>-4.8 mmol/l</td>
<td>-4.8 mmol/l</td>
</tr>
<tr>
<td>Saturation</td>
<td>98%</td>
<td>98%</td>
<td>98%</td>
<td>99%</td>
</tr>
<tr>
<td>Lactate (0.5-1.7 mmol/l)</td>
<td>0.7 mmol/l</td>
<td>0.8 mmol/l</td>
<td>0.7 mmol/l</td>
<td>0.6 mmol/l</td>
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</table>

Due to severe hypoxic respiratory failure (table 1) she was then admitted to the intensive care unit (ICU) where she was intubated and mechanically ventilated. She was ventilated with pressure controlled ventilation (PCV) with PEEP at 18 cm H2O, pressure control at 20 cm H2O, FiO2 of 100%, respiratory rate 22/ min and tidal volume of 6 ml/kg of ideal body weight. Because clavulanic acid. Initially her clinical condition briefly improved and her fever disappeared. However, one day after admission her symptoms worsened with progressive dyspnoea and hypoxaemia and internal medicine was consulted. She was then admitted to the general medical ward. In the following hours her respiratory rate increased to 32 breaths/min and her saturation measured by pulse oximetry dropped to 77%.

A newly performed chest X-ray now showed bilateral infiltrates (figure 2).

Due to severe hypoxic respiratory failure (table 1) she was then admitted to the intensive care unit (ICU) where she was intubated and mechanically ventilated. She was ventilated with pressure controlled ventilation (PCV) with PEEP at 18 cm H2O, pressure control at 20 cm H2O, FiO2 of 100%, respiratory rate 22/ min and tidal volume of 6 ml/kg of ideal body weight. Because
Severe community-acquired pneumonia during pregnancy of persistent hypoxaemia with a PaO$_2$/FiO$_2$ <100, ventilation in the prone position was started. The antimicrobial agents were switched from amoxicillin/clavulanic acid to cefotaxime, erythromycin and oseltamivir after taking new cultures, swabs for polymerase chain reaction (PCR) testing and urinary antigen tests (for *Legionella* type 1 and *pneumococci*).

Assessment by the obstetrician including foetal ultrasound showed no abnormalities concerning the condition of the foetus.

This 39-year-old pregnant woman was admitted to the obstetric ward because of community-acquired pneumonia (CAP). Two questions arise here. First, why did this young woman get CAP? The incidence of CAP is highest at a very young age and at old age (>65 years). Was this patient immunocompromised? The reported estimated prevalence of antepartum pneumonia is similar to that in the non-pregnant population at 0.78 to 2.7 per 1000.[1] Pregnancy is considered to be an important risk factor for severe complications following influenza virus infection.[2] During the H1N1 influenza pandemic of 2009-2010, pregnant women had an increased risk to be hospitalised or admitted to ICUs due to an influenza pneumonia, and were at higher risk of death compared with non-pregnant adults.[2]

Some studies show that pregnant women respond differently to pathogens than non-pregnant women. One theory is that placental immune response and its tropism for specific viruses and pathogens affect the pregnant woman’s susceptibility to and severity of certain infectious diseases. But up to now no real pathophysiological mechanism has been elucidated.[3]

Secondly, the severity of the pneumonia was underestimated. The obstetrician initially saw the patient and decided to admit her to the obstetric ward. A formal risk score was not quantified at that point. The attending physicians were misled by the initial clinical signs. Current guidelines suggest using a severity of illness model to evaluate the severity of pneumonia. Contemporary risk prediction models are the Pneumonia Severity Index (PSI) and the CURB-65.[4,5] Both models depend mainly on age, comorbidity and derangements of physiology. Especially young and otherwise healthy patients obtain few points for the age component and therefore only extremely severe illness is then recognised as severe CAP (PSI class 5 or CURB-65 >3).[6] This explains the overrepresentation of rather young patients who, despite a low PSI or CURB-65, still require treatment in the ICU.[7] In this particular instance, the initial PSI score was 44 points (Class I low risk, 0.1% 30-day mortality) and the CURB-65 was 0 points (0.6% 30-day mortality). Upon admission to the ICU the PSI score was 89 points (Class III, low risk, 0.9% 30-day mortality) and the CURB score was 1 point (low risk group: 2.7% 30-day mortality).

Another, rather pragmatic approach is that all patients who require ICU admission are considered to have a ‘severe CAP’. Determination of the severity of the pneumonia is essential as the empirical antimicrobial coverage is broadened when a patient has ‘severe CAP’. In such instances atypical pathogens also need to be covered. When the patient was transferred to the ICU the antimicrobial agents were switched from amoxicillin/clavulanic acid to cefotaxime and erythromycin.

In case of a severe CAP (requirement of ICU treatment) with an unknown pathogen, the current Dutch antibiotic guidelines (SWAB) advise to use the following first-line antimicrobial therapy: monotherapy with a quinolone (levofloxacin or moxifloxacin); or combination therapy with penicillin (or amoxicillin) and ciprofloxacin; or combination therapy with a second or third generation cephalosporin and a macrolide.[8] Fluoroquinolones, however, are contraindicated during pregnancy because they were associated with foetal harm in animal studies. We therefore chose for treatment with a combination of a cephalosporin and a macrolide, despite the higher risk of drug-drug-interactions (cytochrome P450 3A4 interactions) between macrolides and various other medications (with e.g. midazolam, fentanyl and more). Because the patient was admitted during the flu season, additional treatment with oseltamivir is also advised in order to cover for a possible influenza infection. PCR for viral and atypical pathogens is strongly advised.

**Day 1 in the ICU**

Despite aggressive treatment the patient’s condition deteriorated rapidly. She was on pressure-controlled ventilation with PEEP at 20 cm H$_2$O, pressure control at 20 cm H$_2$O, FiO$_2$ 100%, respiratory rare 26/min and tidal volume of 6 ml/kg of ideal body weight. With these settings she had a P/F ratio of 132 and hypercapnia (8.5 kPa) with concomitant acidosis.

![Figure 2. A chest X-ray repeated after clinical deterioration the following day shows bilateral infiltrates](image_url)
This patient had severe ARDS based upon the Berlin criteria. There was a deterioration in her respiratory symptoms within one week of the initial clinical event, bilateral opacities on the chest X-ray, severe hypoxaemia and the respiratory failure was not due to cardiac failure or fluid overload. Anticipating that further treatment such as veno-venous extracorporeal membrane oxygenation (VV-ECMO) and complex neonatal care for the premature infant could be needed, the decision was made to transfer the patient to an academic centre the same day.

At what point should a caesarean section be considered? This patient has severe ARDS on top of a restrictive pulmonary function (due to pregnancy) and sepsis. This is a life-threatening situation for both mother and child. Therefore caesarean section should be considered. At the moment the Dutch guidelines (NVOG richtlijn Perinataal Beleid bij Extreme Vroeggeboorte) advise to consider a caesarean section from the gestational age of 24 0/7 weeks.

Early delivery of a premature baby can lead to more neonatal complications such as respiratory distress syndrome. However, delaying delivery in an attempt to allow foetal maturation could place the mother at risk of multi-organ failure. Delaying caesarean section also prolongs the time that a foetus is in a potentially harmful environment in the uterus. This may result in an intrauterine death due to severe hypoxia or an acute event such as placental abruption.

The timing of performance of a caesarean section is a matter of ongoing controversy. Obviously, there is insufficient evidence about the effects of either approach on stillbirth or death after delivery in these cases. There is some circumstantial evidence from a 2013 Cochrane systematic review, however, to suggest that a policy of delaying delivery reduces the morbidity of neonates. Babies in the delayed delivery group were less likely to be admitted to the neonatal ICU and when admitted had a shorter length of stay. There were insufficient data to draw conclusions about the effect of expectant management on maternal outcome.

Because of the risk of an emergency delivery of a premature child, corticosteroids (betamethasone 6 mg four times a day) were administered in order to stimulate foetal lung maturation.

Day 2 in the ICU
Upon arrival at the academic centre oxygenation initially worsened. The P/F ratio at that point was 80 with PEEP at 20 cm H2O. She was put into the prone position in an air-fluidised bed and neuromuscular blocking agents were administered. Subsequently, in the following hours we saw significant improvement of oxygenation and ventilation and ventilator settings were reduced to PEEP at 18 cm H2O, pressure control at 15 cm H2O, tidal volume of <4-5 ml/kg of ideal body weight and FiO2 50%.

The Pneumococcus and Legionella urine antigen tests were reported to be negative.

Day 3 in the ICU
The microbiology lab revoked the negative result of the Legionella urine antigen test. Repeat Legionella urine antigen test was positive and the PCR on nasal lavage fluid also turned out to be positive for Legionella pneumophila. The antimicrobial chemotherapy was switched to macrolide monotherapy. Further investigation revealed that she had been working in the cleaning service and that she may have been exposed to Legionella pneumophila while cleaning air-conditioned office buildings. Hence she was diagnosed with Legioniennairs’ disease with concomitant ARDS.

In the following days oxygenation improved significantly in response to the treatment. Because she responded so well to treatment, it was concluded that VV-ECMO would not be necessary.

Is the management of the pregnant patient with ARDS the same as for the non-pregnant patient? Optimal treatment consists of ‘protective ventilation,’ small tidal volumes (<6 ml/kg of ideal body weight), ventilation in the prone position, high PEEP and the use of neuromuscular blocking agents during the first 48-72 hours. Placing a pregnant patient in the prone position can be done safely.

In the treatment of severe ARDS permissive hypoxaemia and permissive hypercapnia are accepted strategies to reduce the risk of ventilator-induced lung injury. However, during pregnancy these strategies can be harmful to the foetus. Foetal gas exchange is dependent on diffusion across the surface between the maternal sinuses and the foetal capillaries. Maintaining an adequate gradient of pCO2 and pO2 is crucial. In normal physiology during pregnancy, maternal hyperventilation results in a mild respiratory alkalosis with maternal pCO2 around 3.8-4.3 kPa, which increases the gradient favouring CO2 transfer. Adequate buffering is achieved by compensatory renal excretion of bicarbonate. The decrease in pCO2 on the foetal side of the circulation assists oxygen loading. The increase in pCO2 in the maternal intervillous sinuses assists oxygen unloading. This is referred to as the Bohr effect, and facilitates the reciprocal exchange of O2 for CO2.

Furthermore, maternal acidosis is associated with lower foetal pH and foetal acidosis in turn is associated with foetal distress, poor Apgar scores and adverse neonatal outcome. Therefore permissive hypoxaemia and permissive hypercapnia can lead to foetal hypoxaemia and acidosis, which consequently can lead to an increased risk of preterm delivery and foetal morbidity or mortality. Our strategy in this case was that the
occurrence of hypercapnia and acidosis with pH <7.3 would be the point that VV-ECMO would be started.

Our recommendation is as follows: aim for the maintenance of normal pH levels (7.3-7.4) and normocapnia (4.6-6.0 kPa), on the condition that protective ventilation is preserved. This, obviously, is a matter of opinion based on the physiological principles previously explained and comparative studies are lacking.

Foetal monitoring in the prone position was challenging because of frequent loss of signal and artefacts. We recommend using an air-fluidised bed when placing a pregnant patient in the prone position as this will better distribute the pressure that is put on the abdomen. Regular assessment of foetal well-being and maternal monitoring with multidisciplinary consultations are essential. Intermittent cardiotocography and assessment by the obstetrician is the best alternative to continuous foetal monitoring.

While sedated with propofol and remifentanil the patient developed high blood pressure with a systolic pressure ≥160 mmHg, which did not react to appropriate levels of analgosedation. She had no history of hypertension and had been normotensive since admission. We started magnesium sulphate and labetalol to manage her hypertension. Urine protein showed proteinuria 1.06 g/l and protein/creatinine ratio of 119.2 mg/mmol. Protein in a 24-hour specimen was 0.8 grams. The platelet count was 332 x 10^9/l (150-450 x 10^9/l), ASAT 53 U/l (0-30 U/l), and ALAT 30 U/l (0-35 U/l). There were no signs of acute kidney injury and the urinary analysis showed no casts.

The hypertension did not respond to analgosedation, and therefore could possibly be caused by preeclampsia. Preeclampsia refers to the new onset of hypertension and proteinuria (table 2) or hypertension and end-organ dysfunction with or without proteinuria after 20 weeks of gestation in a previously normotensive woman.

<table>
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<th>Proteinuria in preeclampsia can be defined as any of the following [17]:</th>
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<td>• Persistent ≥1+ (0.3 g/l) on a paper test strip dipped into a fresh, clean voided midstream urine specimen</td>
</tr>
<tr>
<td>• Random protein: creatinine ratio &gt;0.3 mg protein/mg creatinine</td>
</tr>
<tr>
<td>• ≥0.3 grams protein in a 24-hour urine specimen</td>
</tr>
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</table>

Table 2. Definition of proteinuria in preeclampsia

Nonetheless, proteinuria may also be explained as the result of infection. Especially for patients with streptococcal disease, a post-streptococcal glomerulonephritis can be encountered. In such patients proteinuria usually develops after 1–2 weeks. This patient, however, had not been ill for that long. Moreover, the diagnosis of Legionnaires’ disease had already been confirmed, which made a streptococcal glomerulonephritis highly unlikely. Sepsis or septic shock are associated with kidney damage and subsequent proteinuria, but the amount of proteinuria in such patients is not well established.[18]

Day 4 in the ICU

The patient has Legionnaires’ disease, severe ARDS superimposed on restrictive pulmonary function (due to pregnancy) and possible preeclampsia. Despite finally achieving adequate oxygenation, ventilation and pH, this was at the cost of relatively high ventilator pressure levels, possibly required for an extended period of time due to the severity of her illness. Regarding preeclampsia, the only cure is to deliver the baby. Occasionally, performance of a caesarean section can be postponed while closely monitoring the condition of the mother and foetus. In this case, however, the combination of pathologies had the potential for serious adverse outcome. Taking this into consideration, the decision was made to perform a caesarean section in the ICU. The procedure was uncomplicated. She gave birth to a daughter (gestational age 28 weeks and 5 days). The APGAR score (10 points maximal) was 5 after 1 minute and 6 after 5 minutes. Because of respiratory insufficiency, the baby was intubated and ventilated. Immediately after the caesarean section we continued mechanical ventilation in the prone position and applied the usual permissive hypoxaemia and hypercapnia strategies. Strikingly, we were able to reduce the ventilator support levels. The blood pressure normalised within hours and she no longer needed antihypertensive medication. Antimicrobial therapy was switched from erythromycin to levofloxacin with the intent to optimise the treatment of the Legionella infection. The patient was extubated one day after the caesarean section and she was discharged to the obstetric ward the following day. She received antibiotic treatment for a total duration of 14 days. The PCR on Legionella pneumophila DNA on placenta, amniotic fluid and cord blood was negative. The baby was not treated for Legionella. The baby was ventilated for a couple of days and spent almost three months on the neonatal ward with a seemingly full recovery. There were no signs of neurological damage to the child.

Although there are some reports in the medical literature on horizontal nosocomial spread of Legionella,[19] there are no reports on vertical transmission of Legionella from the mother to the baby. The PCRs on placenta, amniotic fluid and cord blood are in concordance with previous findings that Legionella is not a blood transmissible disease.[20] Treatment of the baby is, therefore, not necessary. The mother was treated with the usual protective ventilation strategies and usual antimicrobial chemotherapy after delivery of the baby. Fluoroquinolones are thought to carry little risk from breast feeding to the baby. The
calcium in the milk is thought to bind the quinolones, reducing their bioavailability to the baby. Currently, there is insufficient evidence to approve or disapprove this assertion.\textsuperscript{[11]}

**Discussion**

Is there an association between pneumonia and the subsequent development of preeclampsia?

Current theories for the pathophysiological basis for preeclampsia include a number of potential causes, including abnormal placentation, cardiovascular maladaptation to pregnancy, genetic and immune mechanisms, an enhanced systemic inflammatory response, and nutritional, hormonal, and angiogenic factors. There are hypotheses that infection in pregnancy may be involved in the aetiology of preeclampsia. Some studies have shown that urinary tract infection and periodontal disease during pregnancy are associated with an increased risk of preeclampsia.\textsuperscript{[18]} Causality has not yet been proven and the mechanism remains unknown. Currently, to our knowledge, there are no studies that show a clear association between other maternal infections and preeclampsia. Therefore the question remains whether Legionnaires’ disease was the trigger for preeclampsia.

Managing critically ill obstetric patients in the ICU can be challenging because of their altered physiology, different normal ranges for laboratory and clinical parameters during pregnancy, and potentially harmful effects of medications and interventions to the foetus. This is illustrated by the various treatment challenges encountered in this patient, such as 1) whether or not to perform a caesarean section, 2) treatment of *Legionella* infection during pregnancy, 3) management of preeclampsia and 4) the management of ARDS during pregnancy. What is also noteworthy is the emotional impact this all has on the whole team.

It is important to consider that emergency delivery is not routine for most ICUs. The ICU needs to prepare for an emergency caesarean section (e.g. instrumentation), keep an incubator in standby mode, and be equipped with appropriate material for the airway management of a premature infant. A multidisciplinary approach with a team consisting of the intensivist, obstetrician, anaesthesiologist, neonatologist, and nurse is key to optimise outcome\textsuperscript{[19]} and, as always, ‘hope for the best but prepare for the worst’.

**Disclosures**

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**References**

When to start renal-replacement therapy in critically ill patients?

H.R.W. Touw, H.M. Oudemans-van Straaten
Departments of Intensive Care Medicine, Amsterdam Cardiovascular Sciences, Amsterdam Infection and Immunity Institute, VU University Medical Center, Amsterdam, the Netherlands.

Correspondence
H.R.W. Touw – h.touw@vumc.nl

Keywords - renal replacement therapy, acute kidney injury, continuous venovenous hemofiltration, KDIGO guidelines

Article
Optimal timing of renal replacement therapy initiation in acute kidney injury: the elephant felt by the blindmen? Published in Critical Care in June, 2017.[1]

Why was this research done?
When to start renal-replacement therapy (RRT) in critically ill patients who have acute kidney injury (AKI) but without potentially life-threatening complications directly related to renal failure is still a matter of debate. Recently Shiao et al. published an interesting viewpoint in the journal of Critical Care on this topic, primarily discussing the two large RCTs published in 2016.[1] The question of the optimal timing of the initiation of RRT has not been solved yet. Several authorities have described this topic to be an important research question and randomised multicentre controlled trials are warranted.

Research question?
Is mortality lower when applying delayed RRT compared with an early strategy in patients with severe AKI without potentially life-threatening complications?

How was this investigated?
The multicentre randomised trial from France included patients with severe acute kidney injury (KDIGO stage 3[2]) who required mechanical ventilation and/or catecholamine infusion and did not have potentially life-threatening complications related to AKI. The early strategy RRT was started within six hours of randomisation and in the delayed strategy RRT was initiated in case of severe hyperkalaemia, metabolic acidosis, pulmonary oedema, blood urea nitrogen higher than 40 mmol/l, potassium 5.5 mmol/l despite medical treatment, a pH below 7.15, pulmonary oedema due to fluid overload responsible for severe hypoxaemia of oliguria for more than 72 hours after randomisation.[3]

Main conclusions
In this selected population with AKI, no significant difference with regard to mortality was found between an early and a delayed strategy for the initiation of RRT on day 60. Furthermore, in half of the patients in the delayed strategy group the need for RRT was diverted.

A salient detail was that the patients who never received RRT were less ill at baseline compared with patients who received RRT late.

Thus, this study shows that some patients with AKI will benefit from delaying or diverting RRT, e.g. the less severely ill without impending life-threatening complications.

A week later, another randomised trial was published on the timing of RRT. This is interesting because this trial is representative for the Dutch situation. All patients in the German trial received continuous venovenous haemofiltration (CVVH) as RRT, while only 30% of the patients received continuous RRT as the sole method in the French trial. This German trial compared early RRT (within eight hours of diagnosis of KDIGO stage 2[2]) with delayed RRT (12 hours of stage 3 KDIGO[2] or no initiation).

Although not a multicentre study, the German trial showed that early RRT reduced mortality over the first 90 days.[6] Besides the use of CVVH, the difference could be explained by an additional inclusion criterion, neutrophil gelatinase-associated lipocalin level higher than 150 ng/ml (a biomarker to detect patients who will develop severe, dialysis-dependent AKI). The SOFA score was also higher in the German trial: 15.8 vs. 10.8.

These findings underline the current NVIC guideline on CVVH ‘timing and dosing’ (2012) which recommends considering RRT in patients with AKI and persistent metabolic derangement and/or fluid overload, and not to apply RRT if AKI is mild and probably transitory.[6]
Consequences for daily practice

The decision to start RRT in critically ill patients with severe AKI is complex and requires considering the whole patient. It depends on the severity of AKI (life-threatening renal complications) and whether concomitant organ failure is ongoing or improving.

Disclosures

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

References

Brain activity in cardiac arrest

**Keywords** - continuous EEG monitoring, cardiac arrest, resuscitation, hypoxic-ischemic brain injury

**Diagnosis**
Initially, the EEG showed a continuous EEG pattern and on the co-registered ECG a normal sinus rhythm was seen. The ECG pattern suddenly changed to ventricular fibrillation, after which the EEG pattern changed gradually. This slowed down and became isoelectric after 26 seconds. When chest compressions were started this led to considerable disturbance of the EEG signal. Cardiopulmonary resuscitation was successful and the patient made a good recovery. He was discharged to the cardiology ward with short-term memory impairment that recovered over time.

This EEG registration clearly shows that brain cells are extremely susceptible to hypoxic-ischaemic injury. The main reason for this phenomenon is the lack of energy resources within the brain cells. Already after several seconds a gradual slowing of the EEG pattern occurs, progressing to an isoelectric EEG within 30 seconds. Patients admitted to the ICU after cardiac arrest often recover heart function. Other organs, such as kidneys and liver, also endure the period of anoxaemia with relatively little damage. The brain is often severely injured leading to persisting coma. Especially a delay in starting basic or advanced life support is one of the main factors associated with poor outcome.[3]

In many ICUs patients admitted after cardiac arrest are currently monitored with continuous electroencephalography. This technique allows monitoring of the evolution of EEG patterns over time.[2] In the first few hours after admission an isoelectric or low voltage EEG can often be found which slowly improves when brain function recovers. When a continuous pattern is found 12 hours after cardiac arrest the brain damage is not severe and a good outcome can be expected.[3] On the other hand, if after 24 hours the EEG pattern has not recovered to a continuous pattern this is indicative of severe brain injury and a poor outcome is highly likely.

**References**

**Figure 2.** Suddenly changing EEG trace of a patient after successful resuscitation.
Successful use of plain subcostal transthoracic echocardiography in VV-ECMO cannula repositioning

F.S. van den Brink, A.H. Swadi, E. Scholten
Departments of 1Cardiology and 2Intensive Care, St Antonius Hospital, Nieuwegein, the Netherlands

Correspondence
F.S. van den Brink – f.van.den.brink@antoniusziekenhuis.nl

Keywords - TTE; VV-ECMO; cannula

Case
A previously healthy 62-year-old male with recently diagnosed rapidly progressive pulmonary fibrosis was hospitalised and accepted for lung transplantation. During admission his pulmonary function critically deteriorated due to an intercurrent pneumonia which necessitated additional respiratory support. In order to avoid physical deconditioning inherent to invasive mechanical ventilation and analgesedation, the patient was not intubated. Instead it was decided to follow an awake extra corporal membrane oxygenation (ECMO) strategy, which is increasingly being used as a bridge to lung transplant and allows active participation of the patient, including physical therapy and training.[1] He was put on veno-venous ECMO (VV-ECMO) using a single site double lumen cannula (Avalon Elite®) in the right jugular vein.[2] During daily care, the VV-ECMO flow suddenly dropped from 4.3 litres per minute to 2.7 litres per minute. This was followed by a significant desaturation in oxygen levels from 99% to around 75%. The patient became unresponsive and to avoid possible aspiration of stomach contents, transoesophageal echocardiography was deemed too dangerous. Transthoracic echocardiography only produced good subcostal views, due to the patient’s supine position.

Figure 1A shows a subcostal view. The right atrium (RA in red), right ventricle (RV in red), left atrium (LA in red), and left ventricle (LV in red) are indicated as well as the tricuspid valve in blue and the liver and the diaphragm. The cannula position (white arrow) is in front of the right atrium passing from the superior caval vein to the inferior caval vein during the initial echo images. The ECMO flow is indicated by the yellow arrow. Figure 1B shows the same image with colour Doppler in which the VV-ECMO cannula is retracted and turned directing the flow towards the inferior caval vein. Figure 1C shows the cannula after slight twisting and pushing it somewhat deeper in the right jugular vein with colour Doppler signal aimed more towards the tricuspid valve (red arrow). Figure 1D shows the ECMO colour Doppler signal directed towards the tricuspid anulus and across after further repositioning (red arrow). The images are an example of so-called re-circulation.[3] A situation in which part of the ECMO flow from the exit cannula containing oxygen rich blood is being directed towards the entry cannula and thus re-circulates within the ECMO circuit. This was caused by the shift in cannula position due to daily care. In the process the patient is being deprived of oxygen rich blood. This together with the decrease in flow caused the sudden deterioration in oxygen saturation.

After repositioning of the VV-ECMO cannula, using only subcostal views due to patient and technique related circumstances, flow of the VV-ECMO circuit normalised completely and the patient recovered. He was transferred to a designated lung transplantation centre in order to receive a lung transplantation.

Plain subcostal transthoracic echocardiography can be successfully used in double lumen Avalon cannula repositioning in VV-ECMO when placed in the right internal jugular vein.
Disclosures
All authors declare no conflict of interest. No funding or financial support was received.

References


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<table>
<thead>
<tr>
<th>Course</th>
<th>Dates</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NVIC Basiscursus echografie</strong></td>
<td>Wednesday 14 November - Thursday 15 November 2018</td>
</tr>
<tr>
<td><strong>NVIC Cursus Luchtwegmanagement op de IC</strong></td>
<td>Wednesday 14 November - Thursday 15 November 2018</td>
</tr>
<tr>
<td><strong>NVIC Consolidatiecursus echografie</strong></td>
<td>Friday 15 December 2017</td>
</tr>
<tr>
<td><strong>NVIC FCCS cursus</strong></td>
<td>Tuesday 10 July - Wednesday 11 July 2018</td>
</tr>
<tr>
<td><strong>NVIC Intensivistendagen 2018</strong></td>
<td>Thursday 1 February - Friday 2 February 2018</td>
</tr>
<tr>
<td><strong>NVIC Najaarscongres 2018</strong></td>
<td>Thursday 13 September 2018</td>
</tr>
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### COURSES AND CONFERENCES | OTHER

<table>
<thead>
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<th>Conference</th>
<th>Dates</th>
</tr>
</thead>
<tbody>
<tr>
<td>30th ESICM Annual Congress Vienna</td>
<td>Saturday 23 - Wednesday 27 September 2017</td>
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<tr>
<td>13th WFSICCM congress</td>
<td>Thursday 9 - Saturday 11 November 2017</td>
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<tr>
<td>NICE Discussiebijeenkomst 2017 – NBC Nieuwegein</td>
<td>Thursday 7 December 2017</td>
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Information for authors

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 around 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 of the accepted manuscripts 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, if appropriate, that animals were treated 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 editors reserve the right to amend manuscripts if necessary.

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 & 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 full data 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/); and
- 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 keyword(s), 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.

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.

Editor correspondence

Editor correspondence provides an opportunity to debate published articles. This should not exceed 500 words, 5 references and 1 figure or table. Editor 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 Netherlands Journal of Critical 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 pages, 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 (noum), and practise (verb). This should be used consistently. Use the s-form spelling, e.g. minimisation/re 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, 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
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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 copyediting. The 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>
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<tbody>
<tr>
<td>AIDS</td>
<td>acquired immunodeficiency syndrome</td>
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<tr>
<td>ALI</td>
<td>acute lung injury</td>
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<tr>
<td>ARDS</td>
<td>adult respiratory distress syndrome</td>
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<tr>
<td>APACHE</td>
<td>acute physiology and chronic health evaluation</td>
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<tr>
<td>BIPAP</td>
<td>biphasic positive airways pressure</td>
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<tr>
<td>COPD</td>
<td>chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>CT</td>
<td>computed tomography</td>
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<tr>
<td>ECG</td>
<td>electrocardiogram</td>
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<tr>
<td>ECMO</td>
<td>extracorporeal membrane oxygenation</td>
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<tr>
<td>EEG</td>
<td>Electroencephalogram</td>
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<tr>
<td>ELISA</td>
<td>enzyme-linked immunosorbent assay</td>
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<tr>
<td>ETOCO2</td>
<td>end-tidal carbon dioxide</td>
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<tr>
<td>HIV</td>
<td>human immunodeficiency virus</td>
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<tr>
<td>IC</td>
<td>intensive care</td>
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<tr>
<td>ICU</td>
<td>intensive care unit</td>
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<tr>
<td>IM</td>
<td>Intramuscular</td>
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<td>INR</td>
<td>international normalised ratio</td>
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<tr>
<td>IPPV</td>
<td>intermittent positive pressure ventilation</td>
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<tr>
<td>IV</td>
<td>Intravenous</td>
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<tr>
<td>MAP</td>
<td>mean arterial pressure</td>
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<tr>
<td>MODS</td>
<td>multiorgan dysfunction syndrome</td>
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<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
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<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>PIRS</td>
<td>severe adult respiratory syndrome</td>
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<tr>
<td>SIRS</td>
<td>systemic inflammatory response syndrome</td>
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<tr>
<td>SOFA</td>
<td>sequential organ failure assessment</td>
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<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>
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</tbody>
</table>
Antifungale kracht in drie formuleringen
Geïndiceerd voor volwassenen voor:¹
- profylaxe van invasieve schimmelinfecties* 
- refractaire behandeling van aspergillose en andere schimmelinfecties**

<table>
<thead>
<tr>
<th>Indicaties</th>
<th>NOXAFIL® Suspensie voor oraal gebruik</th>
<th>NOXAFIL® Maagsapresistente tablet</th>
<th>NOXAFIL® Concentraat voor oplossing voor infusie</th>
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<tr>
<td>Profylaxe van invasieve schimmelinfecties*</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
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<tr>
<td>Refractaire behandeling van invasieve aspergillose, fusariose, chromoblastomycose, mycetoom en coccidioidomycose**</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
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<tr>
<td>Behandeling van orofaryngeale candidiasis***</td>
<td>✔</td>
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NOXAFIL tabletten zijn het voorkeurspreparaat voor optimalisering van de plasmaconcentraties

¹ - Patiënten die remissie-inductiechemotherapie krijgen voor acute myelogene leukemie (AML) of myelodysplastische syndromen (MDS) waarvan verwacht wordt dat ze leiden tot aanhoudende neutropenie en die een hoog risico hebben op het ontwikkelen van invasieve schimmelinfecties;
   - Patiënten die hematopoëtische stamceltransplantaties (HSCT) ontvangen hebben en die een immunosuppressive therapie met hoge dosering ondergaan voor graft-versus-host-ziekte en die een hoog risico hebben op het ontwikkelen van invasieve schimmelinfecties

** - Invasieve aspergillose bij patiënten met een ziekte die ongevoelig is voor amfotericine B of itraconazol of bij patiënten die deze geneesmiddelen niet verdragen;
   - Fusariose bij patiënten met een ziekte die ongevoelig is voor amfotericine B of itraconazol of bij patiënten die deze geneesmiddelen niet verdragen;
   - Chromoblastomycose bij patiënten met een ziekte die ongevoelig is voor itraconazol of inderdaad niet verdragen;
   - Coccidioidomycose bij patiënten met een ziekte die ongevoelig is voor amfotericine B, itraconazol of fluconazol of bij patiënten die deze geneesmiddelen niet verdragen.

*** Als eerstelijnsbehandeling bij patiënten die een ernstige ziekte hebben of die immuungecompromitteerd zijn, bij wie verwacht wordt dat de respons op lokale therapie zwak is.

1. SPC NOXAFIL, Tabletten, IV en Suspensie

Raadpleeg de volledige productinformatie (SPC) alvorens NOXAFIL voor te schrijven.

Voor meer productinformatie zie verkorte SPC elders in dit blad.