

Improving Decision Making in Intensive Care

Iwan Meynaar



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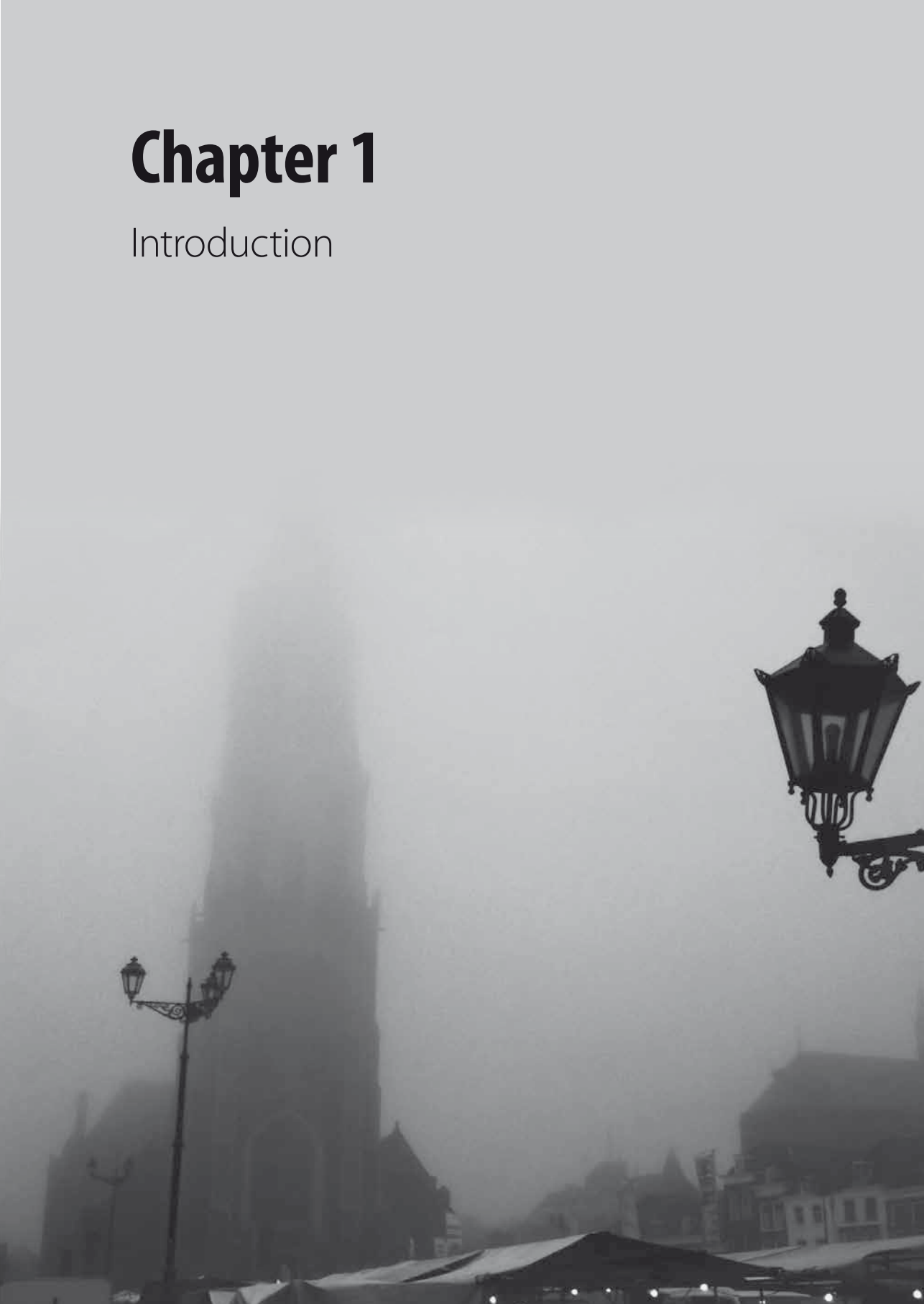
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Chapter 1

Introduction



Many decisions are made during a day's work in critical care. Should this octogenarian with pneumonia and cancer be admitted to the ICU or left on the ward with palliative care? And if admitted to the ICU, will she benefit from being ventilated or should she only be treated with antibiotics and inotropes? How long should we continue administering antibiotics in a patient with peritonitis due to anastomotic leakage after low anterior resection? Will antibiotics do the job or does he have to go back to the operating theatre? Should we give more fluids in a patient with shock, should we start vasoconstrictors or vasodilators or should we accept this low blood pressure? Continue treatment with a curative intent or accept the inevitable? Act on a laboratory result or stop 'just treating the numbers'?

Whether or not we know the answers to these questions, practitioners in critical care make decisions to the best of their knowledge. When you as an intensivist are called to the bedside of this 83 year old very friendly and very dyspnoeic lady that reminds you of your grandmother, this lady with pneumonia and cancer, but alas she was operated on 6 months ago, a left sided colectomy and seems cured from the cancer, you will either admit her to your ICU or not, but you will have to decide. Some decisions are made by others: surgeons who have decided to attempt (or refrain) from surgery, patients who have made their own choices. Some decisions are ready made by adhering to local or international guidelines, customs and protocols. Sometimes additional investigations or consultations can help in choosing the right track. Some decisions are made through experience or by listening to senior staff or to one's gut feeling and last but not least some decisions turn out later to be wrong.

Off course, some decisions are not for the intensivist or the team alone to make. If our 83 year old lady, apparently she has not completely recovered after the operation 6 months ago and she has been admitted to a nursing home only temporarily though, is not too ill she might be able to express her preferences. For her to make an informed decision she will need information on her chances of survival with and without intensive care and on the quality of life afterwards should she indeed survive. She might want to know something about the duration and the burden of the intensive care treatment. She may specifically tell us what she would want us to do in case of cardiac arrest. She will ask us many questions and essentially she needs the same information as the intensivist needs to come to a decision, even if patient and doctor may decide differently based on the same data. Not always will the patient be able to help the intensivist decide. Sometimes the patient is just too sick to express his wishes. Sometimes the doctor will decide not to offer a certain treatment because she judges this treatment to be futile in this particular patient. But most day to day decisions are to be made by the treating nurses, doctors, physiotherapists etcetera: which antibiotic to use, which blood pressure level to aim for, what to do with a test result, this is what society expects us to study, understand and decide upon.

This is the era of evidence based medicine. Whereas medicine has traditionally been thought from master to apprentice, with the advent of evidence based medicine we no longer believe what the master tells us just because it is he who says so. Also pathophysiological reasoning is not enough. We need evidence, meaning results of well conducted studies of large numbers of patients just like the patient that we are presently debating. For studies comparing different treatments we prefer patients and treating physicians both to be blinded in a conclusive randomized controlled trial. The patients are followed up until a meaningful endpoint, like (the absence of) death or disability, not just some laboratory or radiological test result. And even if this trial is available skeptics will say that one trial is not enough to change practice and that a confirmatory study is needed. For diagnostic questions the problem is sometimes even greater: what good is a better diagnosis if this does not result in a better treatment with a better outcome? And it is indeed very difficult to prove the benefit of organizational changes unequivocally.

Still, thanks to many, many studies medical knowledge has increased tremendously, although the more we know, the more we know what we do not know. Also, many long held beliefs from the masters have been proved wrong by investigative apprentices. Medical specialties like cardiology and oncology have used this tool of clinical epidemiology to maximize their knowledge base and to the advantage of their patients. Unfortunately, many critical care practices have not (yet?) been studied rigorously and our specialty of critical care has not been able to take full advantage of the possibilities of evidence based medicine. The enormous amount of studies and data that is present in for instance cardiology is lacking in intensive care. This can be explained by the difficulty in performing these studies, lack of resources, the absence of expensive drugs and the accompanying funds from the industry, the heterogeneity of patients and studies and more excuses, but this leaves us with many unanswered questions to day to day questions. The studies presented in this thesis are all attempts to answer clinical questions in daily care about what to do, what to expect, what makes the difference or a combination of the three. In other words about organization and decision making, prognosis and risk factors. The tools used are those handed to us by clinical epidemiology.

The first study tries to answer a commonly encountered question in comatose survivors of cardiac arrest treated in the ICU. Most professionals know and most laymen do not know that resuscitation attempts in people who suffer from cardiac arrest often fail. If however cardiopulmonary resuscitation successfully returns spontaneous circulation and the patient reaches the intensive care unit, many patients will turn out to have irreversible brain damage due to postanoxic encephalopathy. The damaged brain releases neuron specific enolase (NSE) into the circulation. In this study we hypothesized that based on an increased serum NSE we would be able to identify patients who would not regain consciousness and for whom continuation of intensive treatment would be futile.

Selective decontamination of the digestive tract (SDD) is a strategy to reduce infections in the critically ill that consists apart from hygiene, microbiological surveillance and administration of enteral antibiotics of a short course of intravenous cefotaxim, a third generation cephalosporin. Third generation cephalosporins are otherwise not used in prophylaxis and reserved for treatment of bacteria resistant to first or second generation cephalosporins. Because administration of third generation cephalosporins was seldom necessary in our hospital, we hypothesized that intravenous cefotaxim might be replaced by first generation cefazoline. This hypothesis was tested in the second study.

The hallmark of the ICU is the ability to react to a change in patient's situation immediately and to do so 24/7 and this is most important in the first hours of intensive treatment. We hypothesized in the third study that the quality of care might be so much different during office hours as compared to off hours that this would be reflected in a difference in outcome.

Sepsis is one of the ICUs most life threatening illnesses and many resources are utilized in recognition and treatment of sepsis. Identifying patients with sepsis can be difficult because signs and symptoms are not specific. In the fourth study we tested the hypothesis that serum procalcitonin might be useful in confirming or rejecting the diagnosis of sepsis in ICU patients and we compared procalcitonin with C-reactive protein, interleukin 6 and lipopolysaccharide binding protein.

In the fifth study we describe the results of implementing a medical emergency system in the Reinier de Graaf Hospital to enable early identification and treatment of patients who are at risk of developing cardiac arrest. In the sixth study long term survival of patients who were treated in the ICU and discharged alive from the hospital is analyzed.

The second part of the thesis is about glucose management. In 2001 van den Berghe *et al.* published their hallmark study in which an improved outcome was seen for patients in whom serum glucose was maintained in the normal range of 4.4-6.1 mmol/L as opposed to starting insulin therapy only when serum glucose was as high as 12 mmol/L. Intensive cares worldwide wanted to copy these impressive results but faced various difficulties. One problem was how to give the right amount of insulin without causing hypo- or hyperglycemia. We developed and introduced a computerized insulin dosing protocol and this is described in the seventh study. Another problem, which is the subject of the eighth study, is the accuracy of the bedside glucose measurement device. And finally a national database is explored to study the effect of glucose variability on outcome in the ninth study.

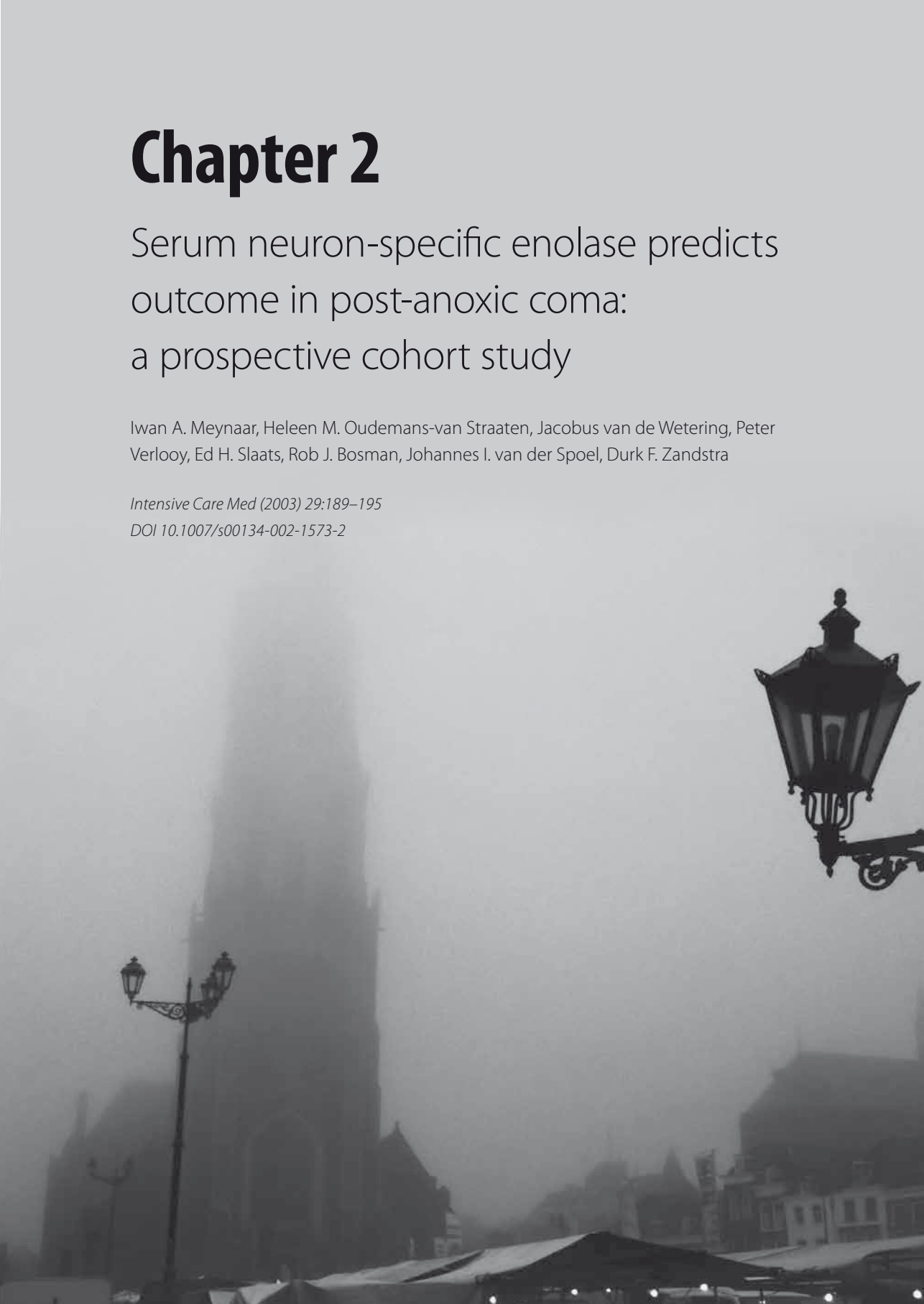
Chapter 2

Serum neuron-specific enolase predicts outcome in post-anoxic coma: a prospective cohort study

Iwan A. Meynaar, Heleen M. Oudemans-van Straaten, Jacobus van de Wetering, Peter Verlooy, Ed H. Slaats, Rob J. Bosman, Johannes I. van der Spoel, Durk F. Zandstra

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ABSTRACT

Objective

The aim of this study was to investigate whether serial serum neuron-specific enolase (NSE) can be used to predict neurological prognosis in patients remaining comatose after cardiopulmonary resuscitation (CPR).

Design

Observational cohort study. Clinicians were blinded to NSE results.

Setting

Eighteen-bed general ICU.

Patients

Comatose patients admitted to the ICU after CPR.

Interventions

Serum NSE was measured at admission and daily for 5 days.

Measurements and results

Patients received full intensive treatment until recovery or until absence of cortical response to somatosensory evoked potentials more than 48 h after CPR proved irreversible coma. Of the 110 patients included (mean GCS at ICU admission 3, range 3–9), 34 regained consciousness, five of whom died in hospital. Seventy-six patients did not regain consciousness, 72 of whom died in hospital. Serum NSE at 24 h and at 48 h after CPR was significantly higher in patients who did not regain consciousness than in patients who regained consciousness (at 24 h: median NSE 29.9 µg/l, range 1.8–250 vs 9.9 µg/l, range 4.5–21.5, $P < 0.001$; at 48 h: median 37.8 µg/l, range 4.4–411 vs 9.5 µg/l, range 6.2–22.4, $P = 0.001$). No patient with a serum NSE level >25.0 µg/l at any time regained consciousness. Addition of NSE to GCS and somatosensory evoked potentials increased predictability of poor neurological outcome from 64% to 76%.

Conclusions

High serum NSE levels in comatose patients at 24 h and 48 h after CPR predict a poor neurological outcome. Addition of NSE to GCS and somatosensory evoked potentials increases predictability of neurological outcome.

INTRODUCTION

Following the return of spontaneous circulation after cardiopulmonary resuscitation (CPR), the majority of resuscitated patients will be comatose as a result of post-anoxic encephalopathy. Many of them will not regain consciousness and will subsequently die or remain in a permanent vegetative state. For several reasons, it is important to differentiate between comatose patients after CPR who have no chance of regaining consciousness and those who may regain consciousness. Scarce medical resources such as intensive care treatment should be allocated to those who might benefit most and futile therapy should be withheld if possible. Several criteria to predict neurological outcome in unconscious patients after CPR have been studied. Absence of pupillary light reactions, low Glasgow Coma score (GCS), a poor motor response in particular, as well as alpha coma pattern or burst-suppression pattern electro-encephalogram, all predict poor outcome with variable accuracy. At present, the bilateral absence of cortical response to somatosensory evoked potentials (SSEP) in comatose patients after CPR is regarded as the most accurate predictor of a bad neurological outcome [1, 2]. False positive test results for SSEP in the prediction of a poor outcome after CPR have only been reported when the test was done within the first 24 h after CPR [1, 3]. Some authors, however, advocate the use of SSEP even in the first hours after CPR [4]. SSEP is not always available and the sensitivity of the test is low. Therefore, clinicians are unable to confidently identify all patients comatose after CPR with irreversible brain damage and it is just as difficult to identify the patients who will regain consciousness. There is clearly a need for more prognostic accuracy.

Neuron-specific enolase is an enzyme that is almost exclusively located in neurons and other cells of neuroectodermal origin. Serum NSE levels are low in normal healthy individuals. NSE can be measured both in cerebrospinal fluid and serum and is elevated following injury to the brain such as stroke, intracerebral haemorrhage, and after CPR [5]. Studies on the use of serum NSE in the prediction of outcome in post-anoxic coma have been small and non-conclusive [6]. The aim of the present prospective observational cohort study was to determine whether serum NSE, in combination with GCS and SSEP, can be used to predict outcome in unconscious patients admitted to the ICU after CPR.

PATIENTS AND METHODS

Patients

From October 1st 1997 until January 1st 2001 all patients were enrolled in the study if they were admitted to the ICU immediately following CPR after circulatory arrest for any cause and if they were comatose on arrival in the ICU. The unit is an 18-bed mixed

surgical-medical closed format intensive care unit. The study was approved by the Medical Ethics committee of the hospital and the need for informed consent was waived.

Somatosensory evoked potentials (SSEP)

SSEPs were performed more than 48 h after CPR in all patients who were still unconscious at that time (GCS E=1, M<=4 V<=2). Silver electrodes were located at C3' and C4' (2 cm behind C3 and C4), Fz' (between Fz and Fpz), and C2 and Erb's point. The bandpass was 5–1,000 Hz and analysis time 50 ms. The median nerve at both sides was stimulated separately, with a stimulus frequency of 2 Hz, stimulus duration of 0.2 ms, and intensive enough to yield a clear twitch of the thumb. At least two sets of 512 averages were performed. The N20 (short latency) SSEP was judged to be absent when a cortical response could not be elicited after stimulation of either the right or left median nerve, while at the same time the cervical response was present. Electroencephalograms were also performed but not included in this study.

Treatment protocol

All patients were mechanically ventilated and treated with volume resuscitation, inotropic and vasoactive drugs, dexamethasone 1 mg/kg once at ICU admission, selective decontamination of the digestive tract, systemic cefotaxime, and enteral nutrition. A pulmonary artery catheter or non-invasive cardiac output monitoring were used when deemed necessary. Hypothermic patients were warmed using a thermal ceiling, thermal mattress, heated inspired air, and heated fluids. Continuous venovenous hemofiltration was available round the clock and performed as necessary to treat acute renal failure, refractory shock, and/or pulmonary oedema. Sedation was not used other than necessary to facilitate mechanical ventilation in patients with severe respiratory failure or to treat convulsions that could not be controlled by anticonvulsant therapy alone. A complete neurological examination was performed at least once a day. The GCS was measured every 3 h on the first day and every 24 h on subsequent days. The verbal score in intubated patients was estimated as one, three or five. An awake patient who could communicate with the investigator through signs and movement was scored 5 points for the verbal evaluation in the Glasgow coma scale. Patients who were responsive but who appeared confused were scored a 3. Patients who did not obey commands (with a motor response of less than 6) were judged to have a verbal score of 1. Patients remained mechanically ventilated until they regained consciousness and cardiopulmonary condition permitted withdrawal of ventilatory support. Patients who remained unconscious received full intensive treatment for at least 48 h after CPR. At day three, after more than 48 h, SSEP and electroencephalography were performed. If N20 SSEPs were bilaterally absent and the patient remained unconscious (GCS <8 without any form of sedation) intensive treatment was considered futile and was withdrawn. Patients subsequently

died or were transferred comatose to a nursing ward. If N20 SSEPs were present or GCS was 8 or more, intensive treatment was continued. If GCS was still below 8 on the 6th day after CPR, treatment was withdrawn [2]. For the purpose of this study, we considered a patient to have regained consciousness if he/she was obviously awake or if he/she could obey simple commands at least once. At that time he/she would have a presumed GCS of 13, 14 or 15. Although an intermediate GCS of 8–12 would not lead us to withhold treatment, only a GCS of 13, 14 or 15 is considered to mean neurological recovery in terms of this study. Patients were followed up until hospital discharge.

Study protocol

Blood for NSE measurement was taken from routinely sampled arterial blood on admission and subsequently every 24 h for 5 days or until discharge from the ICU. NSE sampling was stopped when no more blood was sampled if a decision was made to withhold further treatment or if the patient regained consciousness and was discharged to the ward. Serum NSE was compared between patients regaining consciousness and those remaining unconscious and serum NSE was related to the results of somatosensory evoked potentials. The medical staff was blinded to the NSE results.

NSE measurements

Blood samples were taken from patients with an arterial line and collected in a plain tube (Vacutainer, Becton Dickinson, Plymouth, UK). The blood samples were clotted 30+/-15 min at room temperature. After clotting, the samples were centrifuged at room temperature for 10 min at 1,500 g. Subsequently, the serum samples were stored at 20 °C until the NSE concentration was measured. Serum NSE was established with a two-site fluoroimmuno-metric assay (Delfia, PerkinElmer Lifesciences, Wallac, Turku, Finland) with an interassay coefficient of variation of 9.6% (n =46) at 15.3 µg/l. Reference value <12.5 µg/l.

Data analysis

Data analysis was performed using SPSS 9.1. Values are presented as mean and 95% confidence interval (95% CI) or as median and interquartile range (IQ) for non-parametric data. Normality of distribution was explored by inspection of Q-Q plots. To compare NSE values between patients regaining consciousness and those who remained unconscious, logarithmic transformation was performed to obtain a normal distribution. To compare continuous variables between groups, one-way and repeated-measures ANOVA was performed. To evaluate the capability of different variables to predict neurological outcome, logistic regression was used.

RESULTS

Patient characteristics

From October 1st 1997 until January 1st 2001, 110 patients were enrolled in the study (Table 2.1, Figure 2.1). Thirty-four patients (31%) regained consciousness, 5 of whom died in hospital after regaining consciousness. Thirty-one out of the 34 patients regaining consciousness did so within the first 48 h after CPR, 33 out of 34 within the first 72 h. Seventy-six patients (69%) did not regain consciousness, four of whom were discharged comatose, and the other 72 died in hospital. Sixty-seven of these 72 patients died within one week after admission. At 48 h after CPR, 67 patients were still alive but comatose. Three of them eventually regained consciousness; only one of these three patients had GCS <8 at 48 h after CPR.

Table 2.1. Demographic data

Number of patients	110
Male/female	73/37
Median age (interquartile range)	62.3 (59.0–65.6)
range (yrs)	14–90
Number (%) of out-of-hospital arrest	85 (77.3%)
Glasgow Coma Score upon ICU admission (median, range)	3 (3–9)

Serum NSE levels in all 110 patients

In the 110 patients, a total of 271 NSE values were available. The first NSE sample was always taken within 6 h after CPR. Samples were missing due to death, withdrawal of intensive treatment, haemolysis, and miscellaneous reasons. In addition, NSE was not sampled any more if the patient regained consciousness and was discharged from the ICU. NSE results are presented for the patients regaining consciousness, and also if they died after regaining consciousness, and for those who remained comatose or died without regaining consciousness separately and for different sample times separately (Table 2.2). In the patients who regained consciousness, NSE was lower than in the patients remaining comatose. This difference was significant at 24 h ($P < 0.001$) and 48 h ($P = 0.001$) after admission. In addition, in the patients who remained comatose, NSE concentrations increased after admission with highest levels measured at 48 h after ICU admission. In contrast, in the patients who regained consciousness, NSE concentrations remained low. Finally, no NSE concentration higher than 25.0 µg/l was measured at any time in a patient eventually regaining consciousness. There were, however, several patients with NSE levels below 25.0 µg/l who remained comatose and died.

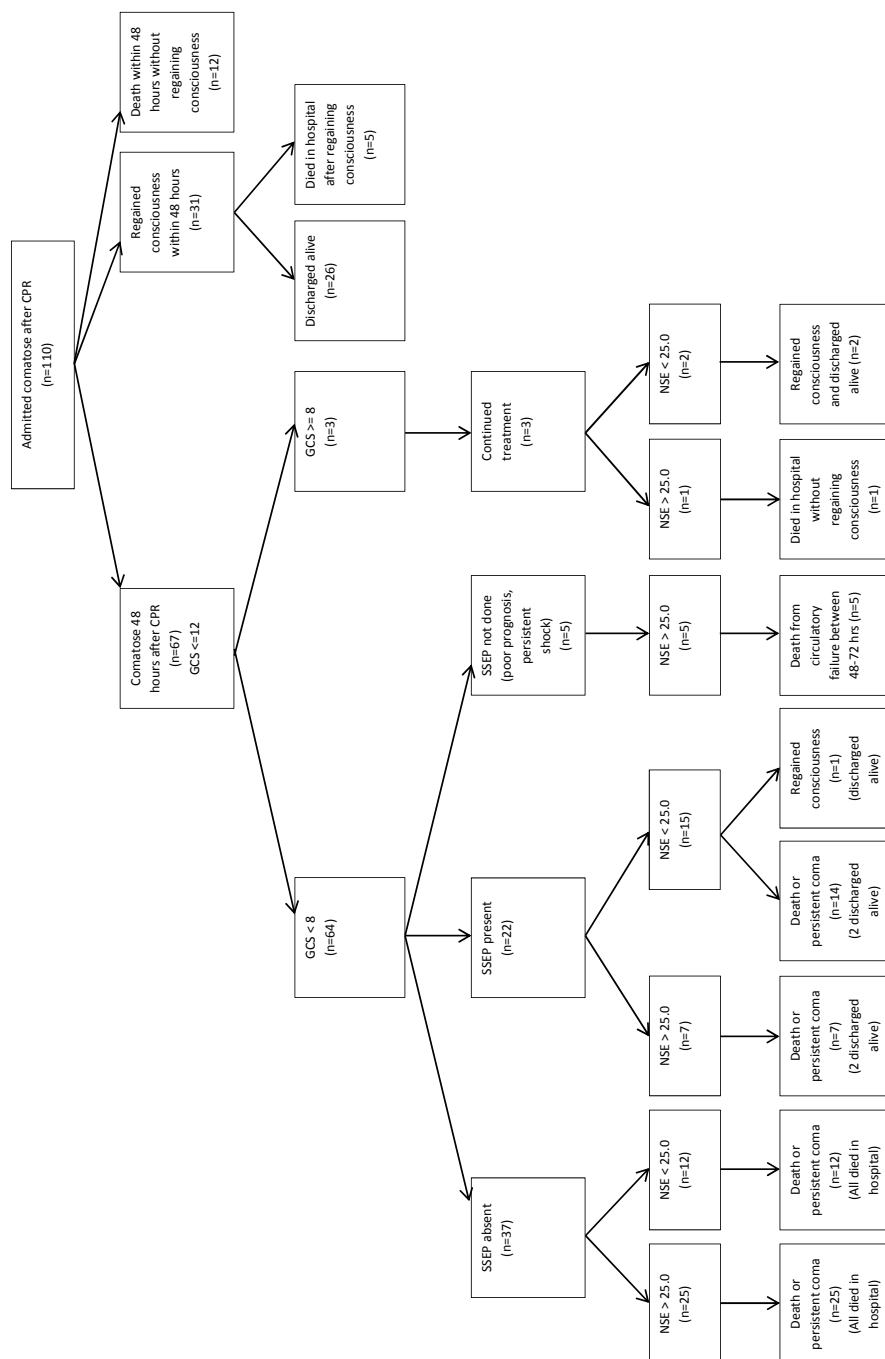


Figure 2.1. Outcome in all 110 patients admitted to the ICU comatose after CPR with regard to Glasgow Coma Scale (GCS), somatosensory evoked potentials (SSEP), and neuron-specific enolase (NSE).

Table 2.2. Relation between NSE levels ($\mu\text{g/l}$) in all 110 patients admitted comatose after CPR and neurological outcome. (NSE neuron specific enolase, CPR cardiopulmonary resuscitation).

Hours after CPR	Patients who eventually regained consciousness (n=34)		Patients who remained comatose or died without regaining consciousness (n=76)		p*	p**
	N***	Median NSE (IQR)	N***	Median NSE (IQR)		
0	34	11.4 (9.2-13.5)	76	12.5 (8.9-18.8)	0.108	
24	31	9.9 (6.3-14.1)	66	29.9 (11.5-52.3)	<0.001	<0.001 (24 and 48 hrs only)
48	16	9.5 (6.4-12.1)	51	37.8 (15.2-107.0)	0.001	
72	8	11.7 (6.5-18.5)	27	18.4 (13.4-41.2)	0.162	

*ANOVA after logarithmic conversion, ** ANOVA for repeated measurements, N*** is number of available NSE measurements

Results in comatose patients 48 h after CPR

Since the majority of patients who are alive but comatose 48 h after CPR do not regain consciousness, decisions regarding the continuation of treatment are most important in these patients. Forty-eight hours after CPR, 96 out of 110 patients were alive and 67 patients were comatose (Figure 2.1). Three of these 67 patients had GCSs of 10, 10, and 11, respectively. Treatment was continued in these patients and two out of the three regained consciousness and were discharged alive; one died without regaining consciousness. Sixty-four of these 67 patients had a GCS <8 48 hour after CPR. SSEP was not done in five patients with severe circulatory failure who all died between 48 h and 72 h after CPR. SSEP was done in the remaining 59 patients with GCS <8 48 h after CPR. In 37 out of 59 patients N20 cortical response to SSEPs was found bilaterally absent after which intensive treatment was withheld. None of these patients regained consciousness. In 22 out of five patients N20 cortical response to SSEPs was not bilaterally absent. Treatment was continued in these 22 patients. Only one of them eventually regained consciousness. NSE levels in 59 patients with GCS <8 48 h after CPR are shown in Table 2.3.

Table 2.3. Relation between NSE levels ($\mu\text{g/l}$) and cortical response to somatosensory evoked potentials (SSEP) 48 h or more after CPR in all 59 patients comatose (GCS <8) 48 h after CPR. (NSE neuron-specific enolase, CPR cardiopulmonary resuscitation, SSEP somatosensory evoked potentials).

Hours after CPR	Median NSE (IQR) in patients with present cortical response to SSEP (n=22)	Median NSE (IQR) in patients with absent cortical response to SSEP (n = 37)	p *
0	12.30 (9.10-17.07)	13.28 (5.53-121.6)	0.458
24	14.05 (8.65-25.60)	74.10 (62.93-326.0)	<0.001
48	15.20 (9.69-40.83)	385.0 (170.0-1133.4)	0.002
72	15.00 (9.41-39.20)	874.0 (874.0-874.0)	0.219

* ANOVA, after logarithmic conversion

Assuming a cut-off value of 25.0 µg/l for NSE

Not a single comatose patient after CPR with NSE above 25.0 µg/l regained consciousness. We therefore compared two groups of patients: comatose patients with NSE <25.0 µg/l and those with NSE >25.0 µg/l at 24 h or 48 h after CPR. This enables us to make a retrospective estimation of the possible value of a cut-off point of 25.0 to distinguish between those who will regain consciousness and those who will not, and to compare the usefulness of this cut-off point with other markers, such as SSEP. The bottom part of Figure 2.1 shows whether different groups of patients had NSE levels either above or below 25.0 µg/l. From Figure 2.1, sensitivity, specificity, and positive and negative predictive value can be estimated for the prediction of neurological outcome in comatose patients after CPR for SSEP, NSE, and the combination of both. These values are described in Table 2.4.

Multivariate analysis

To determine the predictability of good neurological outcome from available markers, GCS, somatosensory evoked potentials, (LN)NSE, and age were entered in a logistic regression model (Table 2.5). These variables were chosen since these are the clinically available factors known to influence outcome. This model shows that GCS and NSE at 24 h predict neurological outcome best. Somatosensory evoked potentials is a poor predictor of prognosis in this model. Similar results were obtained when GCS and NSE at 48 h were entered in the model.

Table 2.4. Evaluation of NSE (serum neuron-specific enolase 24 hr or 48 hr after CPR, either above or below 25.0 µg/l), cortical response to SSEP (somatosensory evoked potentials 48 h or more after CPR, either absent or present), and the combination of both for the prediction of neurological outcome in 67 comatose patients (GCS, Glasgow Coma Scale ≤12) 48 h after CPR. (SSEP absent = absent cortical response to somatosensory evoked potentials, SSEP present = present cortical response to somatosensory evoked potentials, NSE >25 NSE at 24 h or 48 h after CPR or both higher than 25.0 µg/l, NSE <25 NSE at 24 h and 48 h after CPR both below 25.0 µg/l)

	Test predicts patient will not regain consciousness		Test predicts patient will regain consciousness		Total number of patients	Sensitivity (TP/TP+FN)	Specificity (TN/TN+FP)	Positive predictive value (TP/TP+FP)	Negative predictive value (TN/TN+FN)
	Did not regain consciousness TP true positive	Regained consciousness FP false positive	Did not regain consciousness FN false negative	Did regain consciousness TN true negative					
NSE >25.0	38	0			67	59%	100%	100%	10%
NSE <25.0			26	3					
SSEP absent	37	0			59	64%	100%	100%	4%
SSEP present			21	1					
NSE > 25 or SSEP absent	50	0			67	78%	100%	100%	18%
NSE <25 and SSEP present			14	3					

Table 2.5. Logistic regression model for the prediction of good neurological outcome in patients who were admitted comatose after CPR. Hosmer-Lemeshow goodness-of-fit statistic chi-square = 0.421, df = 8, P = 1.000. (SSEP cortical response to somatosensory evoked potentials, LN(NSE) natural logarithm of serum neuron-specific enolase, GCS = Glasgow coma scale).

Variables entered	Odds ratio	95% CI	p
GCS 24 h after CPR	3.429	1.211–9.710	0.020
LN(NSE) 24 h after CPR	0.003	0.000–0.506	0.027
Age	0.901	0.806–1.007	0.066
Cortical response to SSEP	0.498	0.061–4.087	0.516

DISCUSSION

The aim of the present prospective observational cohort study was to determine whether serum NSE, in combination with GCS and somatosensory evoked potentials, can be used to predict outcome in comatose patients admitted to the ICU after CPR. In patients comatose after CPR, we found that serum NSE levels 24 h and 48 h after CPR were higher in patients who ultimately remained comatose than in patients who regained consciousness. Furthermore, NSE levels increased in the patients who remained comatose reaching a maximum at 48 h after CPR, whereas NSE remained low in the patients regaining consciousness. Most importantly, none of the patients with an NSE level above 25.0 µg/l regained consciousness. Therefore, measuring serum NSE at 24 h and 48 h may help to predict neurological outcome in patients remaining comatose after CPR. Most patients who are still comatose 48 h after CPR did not regain consciousness [1]. In the present study only three out of 67 patients who were still comatose 48 h after CPR eventually regained consciousness. Prediction of outcome is most relevant in the patients remaining comatose 2–3 days after CPR. Until now, somatosensory evoked potential is the most accurate predictor of prognosis in patients comatose after CPR. Absent cortical response to somatosensory evoked potentials predicts irreversible coma [1]. Specificity and positive predictive value reach 100%. The presence of cortical response to somatosensory evoked potentials, however, does not predict that consciousness will be regained. Indeed in the present study only one out of 22 patients comatose 48 h after CPR with present cortical response to somatosensory evoked potentials regained consciousness. Sensitivity and negative predictive value of somatosensory evoked potentials are low. The present study shows that NSE levels correlate well with somatosensory evoked potentials: comatose patients with absent N20 cortical response on the 3rd day after CPR have higher NSE levels than comatose patients with positive somatosensory evoked potentials. Indeed, 25 out of 58 patients comatose at 48 h after CPR who did not regain consciousness had both NSE levels above 25.0 µg/l and absent cortical response to somatosensory evoked potentials. Furthermore, multiple regression analysis showed that

the combination of GCS and NSE at 24 h proved to be the most accurate predictors of poor neurological outcome, while somatosensory evoked potentials were not accurate predictors if NSE and GCS were in the model. Thus, serum NSE may possibly replace somatosensory evoked potentials in situations where somatosensory evoked potentials are not available. We also found that 32% (12 out of 37) of the patients with absent somatosensory evoked potentials had low NSE levels, that is, below 25.0 µg/l. Therefore, in these patients irreversible coma was not predicted by their NSE level, but only by the absence of somatosensory evoked potentials. Most interesting is our finding that, in 19% (seven out of 37) of the comatose patients with somatosensory evoked potentials present, NSE was >25.0 µg/l. None of them regained consciousness. In these patients somatosensory evoked potentials did not predict irreversible coma whereas NSE, using a cut-off value of 25.0 µg/l, did. Therefore, by using the combination of somatosensory evoked potentials and serum NSE at 24 h and 48 h after CPR, sensitivity of the prediction of poor prognosis can be increased. This in turn might lead to fewer patients with little chance of regaining consciousness being treated in intensive care units.

This study confirms the results of other, smaller studies in which poor prognosis of post-resuscitation coma was found in patients with high NSE levels [7, 8, 9, 10, 11, 12, 13]. However, in some studies, a few patients with NSE levels above 25.0 µg/l have regained consciousness, but in none of the studies, have patients with NSE above 48.0 µg/l regained consciousness. Although data in this study were collected prospectively, the cutoff value of 25.0 µg/l for NSE was only applied retrospectively. The different cut-off values reported in the literature stress the importance of agreement in timing and biochemical technique, and of validation of a cut-off value in a large prospective population before a reliable serum NSE cut-off value can be used in clinical practice to decide that further intensive care treatment in patients remaining comatose after CPR is futile.

Up till now decisions regarding the continuation of treatment in comatose patients after CPR are based on clinical criteria, neurophysiologic data or the combination of both. The present study shows that the positive predictive value of high serum NSE for poor neurological outcome is high; none of the patients comatose 48 h after CPR with a single NSE level above 25.0 µg/l regained consciousness. Addition of serum NSE to the decision-making process on the continuation of treatment in comatose patients after CPR increased the predictability of poor neurological outcome. Confirmation of our data and the establishment of an exact cut-off value for serum NSE, however, require further studies.

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Chapter 3

Is cefazolin appropriate as the parenteral component in selective decontamination of the digestive tract in intensive care?

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ABSTRACT

Introduction

Selective decontamination of the digestive tract (SDD) in ICU patients is normally done using enteral antibiotics and intravenous cefotaxime, a third generation cephalosporin. On the introduction of SDD to our unit, we investigated if cefotaxime could be replaced by first generation cefazolin.

Patients and methods

The study was a prospective cohort study of before-and-after design. All patients expected to be ventilated for more than 48 hours were included. In total 113 admissions were studied. In the first six months no SDD was given, in the next six months SDD was administered using intravenous cefazolin in the first four days and enteral polymyxin, tobramycin and amphotericin B (PTA) throughout ICU treatment.

Results

On admission aerobic Gram negative bacilli (AGNB), excluding *P aeruginosa*, were cefazolin-resistant in 31 patients and cefotaxime-resistant in two patients, $p < 0.001$, RR 0.06 (95% CI 0.02-0.26). SDD patients had significantly less AGNB and fungi in late cultures. Antimicrobial resistance was reduced in the SDD group. *S aureus* or enterococcal carriage was not different.

Conclusions

SDD with enteral PTA combined with intravenous cefazolin during the first four days of ventilation reduces AGNB carriage, without antimicrobial resistance emerging. Thirty-one percent of patients however were admitted while carrying cefazolin-resistant AGNB. We conclude that cefazolin is not appropriate as the parenteral component in SDD.

INTRODUCTION

Selective decontamination of the digestive tract (SDD) using parenteral and enteral antibiotics reduces the incidence of severe infections such as lower airway and bloodstream infections as well as mortality in intensive care patients.¹⁻⁵ Usually a third generation cephalosporin, cefotaxime is given intravenously during the first four days in combination with enteral polymyxin, tobramycin and amphotericin (PTA) in throat and gut throughout ICU treatment. The concept behind the enteral component of SDD is to prevent secondary endogenous infections by the eradication of potentially pathogenic micro-organisms from throat and gut while preserving non-pathogenic micro-organisms thus maintaining colonization resistance.⁶⁻⁸ The parenteral antibiotic is given to prevent and treat primary endogenous or early infections, i.e. to treat the patient for potentially pathogenic micro-organisms that have succeeded in colonizing the patient, especially the airways, before ICU admission and cannot be reached by the enteral component.^{6,7,9} The choice of intravenous antibiotic depends on how well the spectrum of the antibiotic matches the carriage and colonization of patients on admission to ICU, but also on adequate excretion in the target organs, absence of side effects and lack of effect on the indigenous flora, and also on costs.⁷ Cefazolin is a first generation cephalosporin that is effective against community pathogens including *S aureus*, and *S pneumoniae* and susceptible aerobic gram negative bacteria (AGNB). Nosocomial pathogens such as *Klebsiella*, *Enterobacter*, *Morganella* and *Acinetobacter* are not usually covered by cefazolin. Cefotaxime, a third generation cephalosporin, is effective against the same community pathogens as cefazolin and also against the more resistant nosocomial pathogens *Klebsiella*, *Enterobacter*, *Morganella* and *Acinetobacter*. Neither cefazolin nor cefotaxime cover *Pseudomonas* species.⁷ The necessity of using a third generation cephalosporin as the parenteral component for SDD in our hospital was questioned, as third generation cephalosporins were not commonly required for the treatment of established infections because of the low local resistance rate. Therefore, it was thought that SDD using a first generation cephalosporin such as cefazolin would probably suffice in our ICU. The objective of this study was to see if a first generation cephalosporin such as cefazolin would suffice as the parenteral antibiotic in our SDD regime. On the introduction of SDD to our ICU we studied the carriage pattern with regard to AGNB of critically ill patients at the time of admission to the ICU and the effect of SDD with cefazolin and PTA on carriage and antimicrobial resistance amongst AGNB.

PATIENTS AND METHODS

The unit

The study was performed in the single mixed surgical medical intensive care unit of a 550 bed general hospital. The unit is a 10 bed closed format adult ICU.

Patients

All patients who were expected to be ventilated for more than 48 hours were included in the study. Subglottic suctioning was used on all endotracheal tubes. Cultures were taken from throat, rectum and tracheal aspirate on admission and then twice weekly until discharge. If a patient had been wrongly expected to be ventilated for less than 48 hours, the patient was included in the study as soon as this was recognized, but ultimately after 48 hours of mechanical ventilation. From February 1st 2003 until August 1st 2003, patients enrolled received what up to that time had been standard care - no SDD. This is the control group or the non-SDD group. From September 1st 2003 until March 1st 2004, patients enrolled in the study received SDD in addition to standard treatment.

Intravenous antibiotics

Patients in the non-SDD group received intravenous antibiotics only if clinically indicated. Patients in the SDD group were treated with cefazolin 1 gram 4 times daily intravenously for four days unless diagnosis required other antibiotics. Pneumonia was generally treated with cefuroxime with or without erythromycin, in which case cefazolin was not given. Abdominal sepsis was generally treated with cefuroxime and metronidazole in which case cefazolin was not given.

Enteral antibiotics

Patients in the non-SDD group received no enteral antibiotics. Patients in the SDD group were treated from inclusion until discharge from the ICU with polymyxin E 2%, tobramycin 2% and amphotericin B 2% oral paste 4 times a day and 10 ml of a polymyxin E 10 mg/ml, tobramycin 8 mg/ml and amphotericin B 50 mg/ml solution in the stomach 4 times a day. Patients with blind bowel loops were additionally treated with PTA suppositories 4 times a day.

Endpoints of the study

Primary outcome measures were three microbiological endpoints:

- (i) The carriage rate of AGNB on admission related to the adequacy of cefazolin (as compared with the more commonly used cefotaxime) with regards to AGNB cover;
- (ii) The impact of SDD with enteral PTA and intravenous cefazolin on carriage of AGNB, *S aureus* and enterococci.

- (iii) The impact of SDD with enteral PTA and intravenous cefazolin on antimicrobial resistance.

Sampling policy

Cultures were taken from throat, rectum and tracheal aspirate on admission or at the time the patient was recognized as needing mechanical ventilation for more than 48 hours and then every Monday and Thursday. Cultures taken on days 0, 1 and 2 after endotracheal intubation were defined as admission cultures and these were studied together as a single group assuming SDD treatment to have no effect on admission cultures. Cultures taken from day three onwards were defined as late cultures and these were compared between SDD and non-SDD patients. Carriage was defined as the presence of a micro-organism in at least one of the surveillance cultures.³

Microbiology

Surveillance samples

Three solid media – CLED, sheep blood agar (SBA) and CHOC-agar – were inoculated using the four-quadrant method. A semi-quantitative estimation was made by grading growth density on a scale of 1+ to 3+. Standard methods for identification, typing and sensitivity patterns were used for all micro-organisms.

Diagnostic samples

Tracheal aspirates were processed using standard microbiological methods. Macroscopically distinct colonies were isolated in pure culture. Standard methods for identification, typing and sensitivity patterns were used for all micro-organisms.

Statistics

Results were analysed using SPSS 12.1 (Chicago, Illinois, USA). Relative risks (RR) are given with 95% confidence intervals (95%CI) and with the risk for non-SDD patients as 1. P values were calculated using Chi-square, MannWhitney-U tests or independent sample t-Tests as appropriate.

RESULTS

Patients

A total of 113 patients were included in the study. At the time of admission 101 patients were expected to be ventilated for more than 48 hours. Only 68 patients were actually ventilated for 48 hours or more. Details on the 33 patients that were unexpectedly venti-

lated for less than 48 hours are given in Figure 3.1. Twelve patients were only recognized later, but ultimately after 48 hours, as needing mechanical ventilation for more than 48 hours. So in total 80 patients were ventilated for more than 48 hours. Patient characteristics are presented in Table 3.1 and Figure 3.1.

Table 3.1. Patient characteristics.

	Total	Non-SDD	SDD group	p
Number of patients	113=100%	39=100%	74=100%	
Age (mean-median-range)	66.1-70.0 17-92	65.7 – 70.0 17-92	66.2 – 68.0 21-90	p=0.85*
Male / female	66 / 47	24 / 15	42 / 32	p=0.62**
Days on ventilator (mean-median-range)	7.3 – 6.0 1-38	8.0 – 6.0 1-34	7.0 – 5.5 1-38	p=0.77***
Days in ICU (mean-median-range)	10.3 – 8.0 1-56	10.5 – 8.0 1-47	10.1 – 8.0 1-56	p=0.97***
Days in hospital (mean-median-range)	26.9 – 19.0 1-203	23.4 – 18.0 2-106	28.8 – 20.5 1-203	p=0.31***
Diagnosis				
Surgical	37 (32%)	10 (26%)	27 (36%)	p=0.24**
GI surgery	25 (22%)	4 (10%)	21 (28%)	p=0.03**
Vascular surgery	12 (11%)	6 (15%)	6 (8%)	
Medical	76 (67%)	29 (74%)	47 (63%)	p=0.24**
Sepsis/pneumonia	24 (21%)	10 (26%)	14 (19%)	
Post CPR	19 (17%)	8 (21%)	11 (15%)	p=0.45**
Other	33 (29%)	11 (28%)	22 (30%)	

*Independent sample t Test

**Chi-square test

***Mann-Whitney U test

Cultures

A total of 828 cultures, 245 from tracheal aspirate, 286 from the rectum and 297 from the throat were obtained (Figure 3.1).

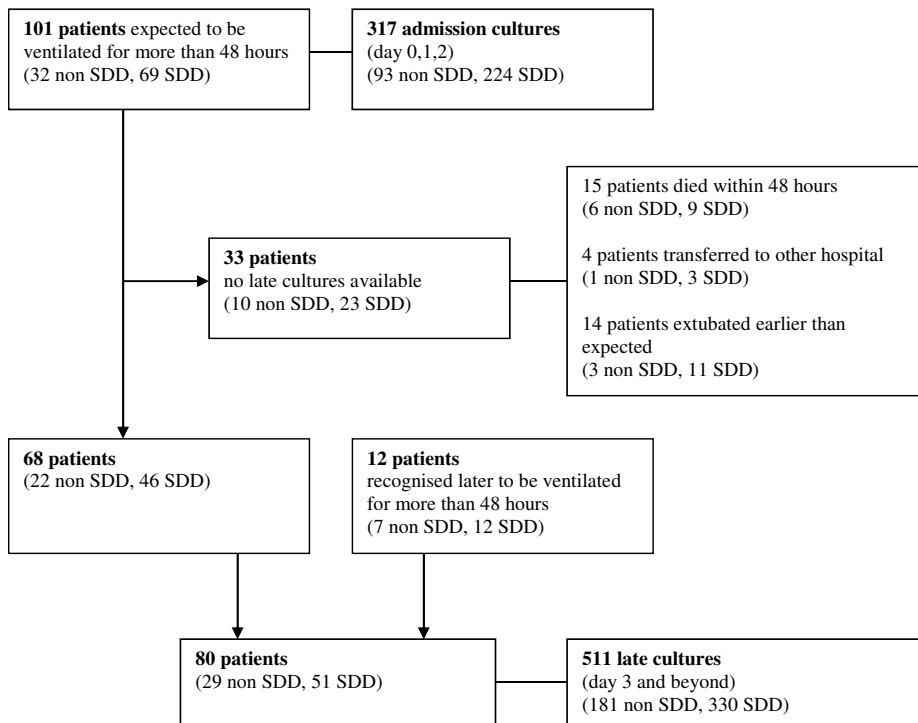


Figure 3.1. Cultures and patients.

Carriage on admission

Carriage on admission to ICU was studied in 101 patients with 317 admission cultures. SDD and non-SDD patients were studied as a single group. On admission, 25 out of 101 patients were carrying *S aureus*, none of which were methicillin-resistant *Staphylococcus aureus* (MRSA). On admission, enterococci were cultured from 54 out of 101 patients (54%), none were vancomycin-resistant enterococci (VRE). On admission 90 patients (90%) carried AGNB. Cefazolin-resistant AGNB were cultured from 31 patients (31%) and cefotaxime-resistant AGNB from two patients (2%), $p < 0.001$, RR 0.06 (95% CI 0.02-0.26). Cefuroxim-resistant AGNB were cultured from 14 patients (14%). Details on AGNB in admission cultures are presented in Table 3.2. On admission 57 (57%) patients were carrying *Candida* species.

Table 3.2a. Carriage of aerobic Gram-negative bacteria (AGNB) and antimicrobial resistance on ICU admission in the throat of 101 patients.

Micro-organism	Number of patients	Polymyxin resistant	Tobramycin resistant	Cefazolin resistant	Cefuroxime resistant	Cefotaxime resistant
<i>E coli</i>	22 (22%)	1	0	0	0	0
<i>P mirabilis</i>	6(6%)	0	0	1	1	0
<i>K pneumoniae</i>	11 (11%)	0	0	2	0	0
<i>P aeruginosa</i>	8 (8%)	0	0	*	*	*
<i>E cloacae</i>	8 (8%)	0	0	8	2	2
<i>C freundii</i>	4 (4%)	0	0	1	1	0
<i>M morganii</i>	2 (2%)	2	0	2	2	0

*Cultures not done, as *Pseudomonas* species all are considered to be resistant to the three cephalosporins

Table 3.2b. Carriage of aerobic Gram-negative bacteria (AGNB) and antimicrobial resistance on ICU admission from the rectum of 98 patients.

Micro-organism	Number of patients	Polymyxin resistant	Tobramycin resistant	Cefazolin resistant	Cefuroxime resistant	Cefotaxime resistant
<i>E coli</i>	71 (70%)	2	1	1	0	0
<i>P mirabilis</i>	20 (20%)	0	0	0	0	0
<i>K pneumoniae</i>	19 (19%)	2	0	4	0	0
<i>P aeruginosa</i>	10 (10%)	0	0	*	*	*
<i>E cloacae</i>	3 (3%)	0	0	1	0	0
<i>C freundii</i>	4 (4%)	0	0	4	1	0
<i>M morganii</i>	4 (4%)	4	0	4	3	0

*Cultures not done, as *Pseudomonas* species all are considered to be resistant to the three cephalosporins

Table 3.3a. Carriage in late cultures in the throat (3 days and more after ICU admission) with and without SDD.

Micro-organism	Number (%) of non-SDD patients (N=29)	Number (%) of SDD patients (N=51)	RR (95% CI)
<i>S aureus</i>	2 (7%)	3 (6%)	NS
MRSA	0	0	
Enterococci	12 (41%)	18 (35%)	NS
VRE	0	2 (4%)	
One or more AGNB	25 (86%)	12 (24%)	0.27 (0.16-0.46)
Tobramycin-resistant AGNB*	0	1	
Polymyxin E-resistant AGNB*	8 (28%)	5 (10%)	0.36 (0.13-0.99)
Cefazolin-resistant AGNB**	11 (38%)	5 (10%)	0.26 (0.10-0.67)
Cefuroxime-resistant AGNB**	10 (34%)	4 (8%)	0.23 (0.09-0.66)
Cefotaxime-resistant AGNB**	3 (10%)	0	
<i>Candida</i> species	22 (78%)	11 (22%)	0.28 (0.16-0.50)

* Including *Pseudomonas* species and *Enterobacter* species

** Excluding *Pseudomonas* species and including *Enterobacter* species

Table 3.3b. Carriage in late cultures in the rectum (3 days and more after ICU admission) with and without SDD.

Micro-organism	Number (%) of non-SDD patients (N=29)	Number (%) of SDD patients (N=51)	RR (95% CI)
<i>S aureus</i>	2 (7%)	3 (6%)	NS
MRSA	0	0	
Enterococci	19 (66%)	44 (86%)	NS
VRE	3 (10%)	4 (8%)	NS
One or more AGNB	27 (93%)	45 (88%)	NS
Tobramycin-resistant AGNB*	1 (3%)	1 (2%)	NS
Polymyxin E-resistant AGNB*	12 (41%)	20 (39%)	NS
Cefazolin-resistant AGNB**	11 (38%)	16 (31%)	NS
Cefuroxime-resistant AGNB**	12 (41%)	13 (25%)	NS
Cefotaxime-resistant AGNB**	4 (14%)	0	
<i>Candida</i> species	13 (45%)	11 (22%)	0.48 (0.25-0.93)

* Including *Pseudomonas* species and *Enterobacter* species

** Excluding *Pseudomonas* species and including *Enterobacter* species

Carriage during ICU treatment

Carriage during ICU treatment was studied in 80 ICU admissions (29 non-SDD and 51 SDD) and 511 cultures (181 non-SDD and 330 SDD) taken from day three onwards and presented in Table 3.3. There was no difference in either staphylococcal or enterococcal carriage between SDD and non-SDD patients. *Candida* and AGNB carriage was significantly reduced (Table 3.3).

DISCUSSION

Firstly this study shows that 90% of critically ill patients were carrying AGNB at the time of admission to the ICU. Thirty-one percent of patients carried AGNB resistant to cefazolin while only 2% of the patients carried cefotaxime resistant AGNB (excluding *Pseudomonas* species). Secondly, patients who received SDD with cefazolin and PTA had significantly fewer AGNB and *Candida* in late cultures than patients who were not treated with SDD. Thirdly, patients treated with SDD carried significantly fewer AGNB resistant to cefazolin, cefuroxime or cefotaxime in the throat, while resistance of AGNB to tobramycin and polymyxin was no different. There was no increase in VRE or MRSA.

In 1969 Johanson studied carriage on admission and showed that the higher the illness severity, the higher the carriage rate of AGNB.¹⁰ One third of our patients carried AGNB resistant to cefazolin - the parenteral agent used in the study. These findings add weight to the literature stating that first generation cephalosporins are inferior to

third generation cephalosporins as the parenteral component of SDD.⁸ Practically all cefazolin-resistant isolates were sensitive to cefotaxime, justifying the replacement of cefazolin by cefotaxime to cover early infections due to AGNB more appropriately.¹¹ Our findings that PTA significantly reduces carriage rates of AGNB, *Pseudomonas* species and yeasts are in line with all 56 RCTs and 10 meta-analyses.¹²

Kallet and Quinn, in their editorial,¹³ acknowledge that SDD is an evidence-based-medicine manoeuvre as SDD using parenteral and enteral antimicrobials, a prophylactic method that costs \$7 a day, reduces infectious morbidity by 65% and mortality by 22%. Yet they are not prepared to endorse SDD, as SDD increases antimicrobial resistance. These American authors ignore the de Jonge study that evaluated the impact of SDD on resistance amongst AGNB as primary endpoint.³ The Dutch study demonstrated that carriage of AGNB resistant to imipenem, ceftazidime, ciprofloxacin, tobramycin and polymyxins occurred in 16% of SDD-patients compared with 26% in control patients with a relative risk of 0.6, 95% CI 0.5 to 0.8. Our study is in line with the de Jonge study, in that SDD does not increase antimicrobial resistance but rather reduces the resistance problem. The Marseille group published the resistance data over a period of 6 years of using cefazolin and PTA in trauma patients.¹⁴ Their message that SDD moderately affects microbial ecology and resistance supports our data. There are four possible explanations why SDD reduces resistance amongst the target bacteria [i] in eradicating abnormal carriage and overgrowth, SDD prevents increased spontaneous mutation; [ii] very high topical bactericidal levels in throat and gut eradicate resistant mutants already present; [iii] polymyxin E and tobramycin are a synergistic mixture; [iv] the administration of parenteral antimicrobials is lower in successfully decontaminated patients.³

The present study has several limitations. First, the design of the study. This is not a formally designed multi-centre randomized controlled trial but a pragmatic single centre cohort study with a before-and-after design. Also, illness severity was not measured and cannot be compared. This limits the value of the comparison between the non-SDD and SDD groups' colonization, resistance and mortality but does not affect the significance of the pattern of colonization on admission. Furthermore, since resistance to cefazolin is mainly found in enterobacteriaceae with inducible betalactamase production (*Enterobacter* sp, *Citrobacter* sp, *Morganella* sp), these bacteria may be susceptible to cefotaxim *in vitro* but not *in vivo*. This may cause overestimation of the clinical importance of the difference between cefazolin resistance and cefotaxim resistance in the present study. Generalization of the results must be done cautiously because of the setting of this study in a general hospital ICU, not a specialized or referral ICU. Generalization is also restricted because no MRSA and very few VRE were found. In our study, the influence of SDD on the development of resistance was only measured for a short period of time. There are no data on resistance patterns of colonizing bacteria in individual patients after they are discharged from the ICU. Further studies are necessary to establish these

effects on the long term. Finally, there were far more patients enrolled in the SDD period of the study than in the non-SDD period mainly due to the development and expansion of our unit during the study.

In conclusion, this study supports the existing evidence that selective decontamination of the digestive tract in mechanically ventilated ICU patients is effective in reducing carriage with AGNB and yeasts without increasing short-term resistance. This study does not support the replacement of the traditionally used third generation cephalosporin cefotaxime by the first generation cefazolin as the intravenous antibiotic of choice.

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Chapter 4

Off hour admission to an intensivist-led ICU is not associated with increased mortality

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ABSTRACT

Introduction

Caring for the critically ill is a 24-hour-a-day responsibility, but not all resources and staff are available during off hours. We evaluated whether ICU admission during off hours affects hospital mortality.

Materials and methods

This retrospective multicentre cohort study was carried out in three non-academic teaching hospitals in the Netherlands. All consecutive patients admitted to the three ICU's between 2004 and 2007 were included in the study, except for patients who did not fulfil APACHE II criteria (readmissions, burns, cardiac surgery, younger than 16 years, length of stay less than 8 hours). Data were collected prospectively in the ICU databases. Hospital mortality was the primary endpoint of the study. Off hours was defined as the interval between 10 pm and 8 am during weekdays and between 6 pm and 9 am during weekends. Intensivists, with no responsibilities outside the ICU, were present in the ICU during daytime and available for either consultation or assistance on site during off hours. Residents were available 24/7 in two and fellows in one of the ICUs.

Results

A total of 6725 patients were included in the study, 4553 (67.7%) admitted during daytime and 2172 (32.3%) admitted during off hours. Baseline characteristics of patients admitted during daytime were significantly different from those of patients admitted during off hours. Hospital mortality was 767 (16.8%) in patients admitted during daytime and 469 (21.6%) in patients admitted during off hours ($p < 0.001$, unadjusted odds ratio 1.36, 95%CI 1.20-1.55). Standardized mortality ratios were similar for patients admitted during off hours and patients admitted during daytime. In a logistic regression model APACHE II expected mortality, age and admission type were all significant confounders but off hours admission was not significantly associated with a higher mortality ($p = 0.121$, adjusted odds ratio 1.125, 95%CI 0.969-1.306).

Conclusions

The increased mortality after ICU admission during off hours is explained by a higher illness severity in patients admitted during off hours.

INTRODUCTION

The first few hours after the initial insult are of major importance in treating critically ill patients. Adequate treatment in the first hours has a major impact on outcome. This has been shown for patients with trauma, sepsis, after major surgery as well as various other patient groups[1-4]. Patients can become critically ill 24 hours a day. Ideally, critical care services have to be organized in such a way that optimal treatment is available to all patients day and night. However, availability and quality of personnel and technology are often different during daytime hours as compared to off hours. Since the first hours of treatment are so crucially important, it is conceivable that outcome after intensive care admission depends at least partially on the time of the day the patient is admitted. This retrospective multicenter cohort study was done to evaluate whether outcome is different for patients admitted to the ICU during daytime hours as compared to admission during off hours.

MATERIALS AND METHODS

This retrospective multicenter cohort study was carried out in three intensivist-led ICUs in three different non academic teaching hospitals in the Netherlands: the 'Onze Lieve Vrouwe Gasthuis' in Amsterdam (OLVG), Gelre Hospitals in Apeldoorn (GH) and 'Reinier de Graaf Groep' in Delft (RDGG). The number of ICU beds in each unit is 16, 10 and 10 respectively. The local ethics committee waived the need for obtaining consent and the need for approval of the study.

Defining off hours

Daytime hours were defined as the hours between 8 am until 10 pm on weekdays and between 9 am and 6 pm during the weekend. Off hours were defined as the hours between 10 pm and 8 am on weekdays and between 6 pm and 9 am during the weekend.

Staffing

Intensivists are present in all three units during daytime and make rounds at the bedside at least two times a day. Each day, including weekends, a multidisciplinary meeting is held in which all patients are discussed. During off hours intensivists on duty are available for consultation 24/7 and have no other responsibilities apart from ICU-related patient care. During off hours, the intensivist on duty will see all unstable patients and will personally supervise all critical procedures including endotracheal intubation, but intensivists are not routinely present in the unit during off hours. In two hospitals, RDGG and GH, junior doctors are present in the hospital, available within 5 minutes and responsible for ICU

patients and airway management. During off hours they may also have responsibilities outside the ICU. In the OLVG, consultants in training to become intensivists, so called fellows, are available exclusively for the ICU around the clock. Nurse to patient ratio is around 1:1.5 during daytime in all three units. During the night, nurse to patient ratio is 1:2 or 1:2.5 at night in RDGG and GH. In the OLVG the nightly nurse to patient ratio on average is 1:1.5, never exceeding 1:2 ratio. Most nurses are registered ICU nurses but all three hospitals also have training programmes for registered nurses training to become ICU nurses. Throughout the study period there were no major changes in the composition of medical or nursing staff.

Patients

All consecutive patients admitted to the three units between January 1st, 2004 and December 31st, 2007 were included in the study. Patients were excluded if they were younger than 16 years of age, if they were admitted for less than 8 hours, if they were admitted after cardiac surgery or because of burns (APACHE II exclusion criteria)[5]. For patients who were readmitted to the ICU during a single hospital admission episode, only the first ICU admission was taken into account. A patient after elective surgery was defined as a patient admitted to the ICU within a seven day period after surgery according to the schedule of the operating room. A patient after urgent surgery was defined as a patient admitted to the ICU within seven days after unscheduled surgery. All other patients were defined as medical patients. These definitions are in accordance with the original APACHE II and SAPS II definitions and endorsed by the Dutch National Intensive Care Evaluation foundation (NICE) as described below [5;6].

Data collection

All three units have databases in which the minimal data set as defined by the NICE is collected prospectively for each patient[7]. Quality of these data is checked regularly[7]. Demographic data, APACHE II and SAPS II values, expected mortality and hospital discharge status (dead or alive) are among the data collected.

Study endpoints

Hospital mortality was the endpoint of the study. We calculated crude hospital mortality as well as standardized mortality ratios defined as observed mortality / expected mortality. Logistic regression was also performed analysing different models.

Statistical analysis

Data were collected prospectively in the ICU databases and analysed with SPSS 16.0 (Chicago, Illinois, USA). Normally distributed data were reported as means $\pm$ standard deviation (SD). Means were compared using Students t tests. Nonparametric data were

reported as median and interquartile range (IQR). Medians were compared using Mann Whitney U tests. Differences in proportions were compared using Chi square tests, odds ratios and 95% confidence intervals (95% CI) were also reported. P values below 0.05 were considered statistically significant.

RESULTS

A total of 6725 patients were included in the study, 4553 (67.7%) admitted during daytime and 2172 (32.3%) admitted during off hours. Baseline characteristics were not equal for both groups (Table 4.1). The difference was most marked in patients admitted after elective surgery, i.e. off hour patients after elective surgery were sicker than those admitted during daytime. The difference between the baseline characteristics of daytime and off hour patients after urgent surgery and medical patients was minimal. We found slight differences in the results between the three hospitals, but these results never conflicted with the overall results (Tables 4.2-4.4).

Hospital mortality is presented in Tables 4.1-4.4. We found no mortality difference in urgent surgery and in medical patients between patients admitted during daytime and patients admitted off hours. Standardized mortality ratios are no different for patients admitted during daytime as compared to those admitted during off hours (Tables 4.5 and 4.6). Logistic regression analysis confirmed that age, APACHE II expected mortality, as well as admission type were related to outcome but off hour admission was not (Tables 4.7 and 4.8). Results were similar with SAPS II expected mortality instead of APACHE II expected mortality (not shown).

Table 4.1. Basic characteristics

	All patients	Daytime	Off Hours	p
Number of patients	6725	4553	2172	
M/F	3937 / 2788	2676 / 1877	1261 / 911	ns
Mean age (SD)	65.1 (16.2)	65.9 (15.3)	63.5 (18.0)	<0.001
Mean APACHE II score at admission (SD)	16.8 (8.7)	16.3 (8.8)	17.9 (9.0)	<0.001
Mean SAPS II score at admission (SD)	37.3 (18.4)	35.7 (18.3)	40.6 (18.2)	<0.001
Mean APACHE II expected mortality	27.7%	25.8%	31.9%	<0.001
Mean SAPS II expected mortality (SD)	26.9%	24.8%	31.3%	<0.001
Median ICU LOS (IQR)	2 (1-4)	2 (1-4)	2 (1-5)	ns
Median ICU+Hospital LOS (IQR)	11 (6-21)	11 (7-21)	11 (5-21)	ns
Hospital mortality	1236(18.4%)	767 (16.8%)	469 (21.6%)	<0.001
Number of medical patients	3423	2068	1355	
Mean age (SD)	62.3 (17.1)	63.2 (16.4)	61.0 (18.0)	<0.001
Mean APACHE II (SD)	20.0 (9.5)	20.2 (9.4)	19.7 (9.7)	ns
Hospital mortality	880 (25.7%)	548 (26.5%)	332 (24.5%)	ns
Number of elective surgery patients	2338	1987	351	
Mean age (SD)	68.5 (13.5)	68.2 (13.3)	70.3 (14.9)	0.007
Mean APACHE II (SD)	12.3 (5.6)	12.0 (5.4)	14.0 (6.2)	0.013
Hospital mortality	186 (8.0%)	133 (6.7%)	53 (15.1%)	<0.001
Number of urgent surgery patients	964	498	466	
Mean age (SD)	66.6 (17.3)	67.5 (16.3)	65.7 (18.3)	ns
Mean APACHE II (SD)	16.1 (7.0)	16.6 (7.2)	15.5 (6.8)	ns
Hospital mortality	170 (17.6%)	86 (17.3%)	84 (18.0%)	ns

Table 4.2. Basic characteristics for the RDGG

	Day time	Off hours	p
Number of patients	2028	576	
M (%)	1119(55.2)	328 (56.9)	ns
Mean age (SD)	66.6 (15.3)	64.5(18.7)	0.014
Mean APACHE II (SD)	13.3 (7.4)	14.8 (8.2)	<0.001
Mean SAPS II (SD)	29.7 (15.9)	35.6(16.6)	<0.001
Mean APACHE II exp mort	17.9%	24.2%	<0.001
Mean SAPS II exp mort	16.7%	24.0%	<0.001
Median ICU LOS (IQR)	2 (2-4)	3 (2-5)	<0.001
Median Hospital LOS (IQR)	11 (8-19)	10 (5-18)	0.001
Hospital mortality	263(13.0%)	111(19.3%)	<0.001

Table 4.3. Basic characteristics for the Gelre Hospital

	Day time	Off hours	p
Number of patients	1267	754	
M (%)	781(61.6)	436(57.8)	ns
Mean age (SD)	66.5(14.6)	64.7(17.6)	0.014
Mean APACHE II (SD)	14.7 (6.9)	16.1 (8.0)	<0.001
Mean SAPS II (SD)	33.3(15.8)	37.9(17.5)	<0.001
Mean APACHE II exp mort	19.9%	23.3%	<0.001
Mean SAPS II exp mort	22.7%	26.1%	<0.001
Median ICU LOS (IQR)	1 (1-4)	2 (1-5)	ns
Median Hospital LOS (IQR)	12 (7-23)	12 (6-24)	ns
Hospital mortality	180(14.2%)	144(19.1%)	0.005

Table 4.4. Basic characteristics for the OLVG

	Day time	Off hours	p
Number of patients	1258	842	
M (%)	776(61.7)	495(61.7)	ns
Mean age (SD)	63.9(15.7)	61.8(17.7)	0.005
Mean APACHE II (SD)	22.5 (8.7)	21.6 (9.1)	0.018
Mean SAPS II (SD)	47.6(18.5)	46.5(18.1)	ns
Mean APACHE II exp mort	42.9%	41.4%	ns
Mean SAPS II exp mort	41.9%	40.0%	ns
Median ICU LOS (IQR)	2.3 (1-5)	1.8(0.7-4.3)	<0.001
Median Hospital LOS (IQR)	11 (5-21)	10 (5-20)	ns
Hospital mortality	324(25.8%)	214(25.4%)	ns

Table 4.5. Standardized mortality ratios and 95% confidence intervals.

	Daytime	Off Hours
APACHE II	0.65 (0.60-0.71)	0.68 (0.61-0.75)
SAPS II	0.68 (0.63-0.74)	0.69 (0.62-0.76)

Table 4.6. Standardized mortality ratios and 95% confidence intervals for each separate hospital

RdGG		
	Daytime	Off hours
SMR APACHE II	0.73 (0.63-0.84)	0.80 (0.64-0.99)
SMR SAPS II	0.78 (0.67-0.90)	0.80 (0.64-1.00)
GH		
	Daytime	Off hours
SMR APACHE II	0.66 (0.56-0.79)	0.71 (0.58-0.85)
SMR SAPS II	0.69 (0.58-0.82)	0.70 (0.58-0.85)
OLVG		
	Daytime	Off hours
SMR APACHE II	0.60 (0.54-0.67)	0.61 (0.53-0.71)
SMR SAPS II	0.61 (0.55-0.69)	0.64 (0.55-0.73)

Table 4.7. Logistic regression model

Parameters in the model	Wald	p	Adjusted Odds ratio (95% CI)
APACHE II expected mortality	755.9	<0.001	67.4 (50.0-91.1)
Age (per year)	118.0	<0.001	1.030 (1.024-1.035)
Admission type	14.8	0.001	
Admission type (1)	0.001	0.969	0.995 (0.772-1.283)
Admission type (2)	9.15	0.002	1.377 (1.119-1.695)
Off hours admission	1.89	0.121	1.125 (0.969-1.306)

Admission type (1): urgent surgery vs elective surgery = reference

Admission type (2): medical vs elective surgery = reference

Table 4.8. Logistic regression models for each separate hospital

RdGG		
Parameters in the model	p	Adjusted OR (95% CI)
APACHE II expected mortality	<0.001	202 (108-372)
Age (per year)	<0.001	1.04 (1.03-1.05)
Admission type	<0.001	
Admission type (1)	0.003	1.67 (1.19-2.34)
Admission type (2)	0.257	0.77 (0.50-1.21)
Off hours admission	0.266	1.19 (0.87-1.60)
GH		
Parameters in the model	p	Adjusted OR (95% CI)
APACHE II expected mortality	<0.001	70 (37-130)
Age (per year)	<0.001	1.03 (1.02-1.04)
Admission type	<0.001	
Admission type (1)	0.167	1.29 (0.90-1.84)
Admission type (2)	0.494	1.17 (0.75-1.83)
Off hours admission	0.508	1.10 (0.83-1.45)
OLVG		
Parameters in the model	p	Adjusted OR (95% CI)
APACHE II expected mortality	<0.001	51 (32-83)
Age (per year)	<0.001	1.02 (1.01-1.03)
Admission type	0.187	
Admission type (1)	0.590	1.12 (0.75-1.68)
Admission type (2)	0.391	0.81 (0.51-1.31)
Off hours admission	0.462	1.09 (0.87-1.37)

Admission type (1): urgent surgery vs elective surgery = reference

Admission type (2): medical vs elective surgery = reference

DISCUSSION

In this retrospective cohort study with prospectively collected data we found no difference in case-mix adjusted hospital mortality between ICU patients admitted during daytime as compared to those admitted during off hours. Differences in hospital mortality could entirely be explained by differences in disease severity.

Several authors have studied the difference in outcome between patients admitted during daytime hours as compared to off hours in ICU patients, all in retrospective cohort studies, all defining off hours differently[8-16]. No formal meta-analysis has been done, but the literature has been reviewed recently[8;12]. In three studies, an increased mortality was found for patients admitted during off hours even after adjustment for potential confounders[9;11;15]. In the remaining six studies no increased mortality was seen for patients admitted during off hours[8;10;12-14;16]. One author even found better outcome for patients admitted during off hours[12]. From looking at these studies one cannot judge the quality of off hour ICU care in general, but we can conclude that off hour care is not necessarily inadequate. For ICU managers it is important to know how to maintain adequate quality of care round the clock. In the present study, the off hour definition was based on the presence or absence of the intensivist in the ICU. Future studies should investigate whether the organisational model with intensivists present during the day and residents supervised by intensivist during off hours is adequate enough to avoid a 'quality gap' during off.

This study has several important limitations. Although data collection was prospective, the study hypothesis was formulated later, which makes this essentially a retrospective study. However, the division between the two groups is solely based on time and hardly the subject of subjective assessment or bias. Different definitions of the off hour interval showed similar results. If one assumes, as was done in the present study, that the first few hours of intensive care are more decisive than the time that follows, a difference in the quality of care between daytime and off hours may also be reflected in final outcome. If, however, the first few hours of critical illness are not so important and for instance off hour care is always suboptimal, most patients will experience this presumed suboptimal care during all off hour shifts in their intensive care episode. In this way the burden of suboptimal care will be divided equally among daytime admitted patients and off hour admitted patients and no difference in outcome will be found. Considering the very low standardized mortality ratios in the present study, in our opinion, this is unlikely. However we cannot prove that the quality of care does not differ between daytime and off hours. Excluding patients that were in the ICU for less than 8 hours may have excluded the most severely ill patients that died soon after admission. APACHE II expected mortality calculation is validated only after an 8-hour observation[5]. This is not so for SAPS II but it is conceivable that mortality prediction even by SAPS II will

be less correct after a short observation time[6]. The present study relies heavily on assessment of illness severity by APACHE II and SAPS II scoring. We felt that we needed at least two separate assessments of illness severity for all patients in the study and thus decided to exclude patients for whom only a probably imprecise SAPS II score was applicable. The higher mortality in the elective surgery group may be attributed to the classification of the admission type. Patients admitted within 7 days of surgery were classified according to their original type of surgery (elective/emergency). However, the reason for ICU admission (especially outside office hours) most probably does not correspond to the surgical indication. A patient admitted during daytime immediately after scheduled surgery is different from a patient admitted during off hours within seven days after previous scheduled surgery. So actually, we probably are looking at two different groups within the surgical group. The study was done in three ICU's with 24/7 intensivist availability. Concerns about off hour quality of care are mostly about ICUs without 24 hour intensivist coverage. The present study is not informative on this subject. Finally, hospital mortality is only a small part of quality of care. We did not study patient, family or nurse satisfaction, resource utilization, faults, (near) accidents or adverse events as related to off hours, all of which could be significantly different during off hours.

Conclusion

In conclusion, in this retrospective multicentre cohort study we found, after correction for illness severity, no difference in hospital mortality between patients admitted to the ICU during daytime hours as compared to patients admitted during off hours.

Key messages

- In this study in three intensivist led ICUs, daytime was defined by the time period in which intensivists are routinely present in the unit and off hours was defined by the time period in which intensivists are not routinely present in the ICU but available for consultation by telephone and present if necessary for critical procedures or unstable patients
- Unadjusted hospital mortality was higher after off hour ICU admission as compared to admission during daytime
- However, after adjustment for illness severity, hospital mortality for patients admitted during off hours and patients admitted during daytime were equal
- We speculate that if intensivists are continuously present in the unit during daytime and present when necessary during off hours this is sufficient to avoid a quality gap during off hours.

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Chapter 5

In critically ill patients serum procalcitonin is more useful in differentiating between sepsis and SIRS than CRP, IL-6 or LBP

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ABSTRACT

Introduction

We studied the usefulness of serum procalcitonin (PCT), interleukin-6 (IL-6), lipopolysaccharide binding protein (LBP) levels and C-reactive protein (CRP) levels, in differentiating between systemic inflammatory response syndrome (SIRS) and sepsis in critically ill patients.

Methods

In this single centre prospective observational study we included all consecutive patients admitted with SIRS or sepsis to the ICU. Blood samples for measuring CRP, PCT, IL-6 and LBP were taken every day until ICU discharge.

Results

A total of 76 patients were included, 32 with sepsis and 44 with SIRS. Patients with sepsis were sicker on admission and had a higher mortality. CRP, PCT, IL-6 and LBP levels were significantly higher in patients with sepsis as compared to SIRS. With PCT levels in the first 24 hours after ICU admission <2 ng/mL, sepsis was virtually excluded (negative predictive value 97%). With PCT >10 ng/mL, sepsis with bacterial infection was very likely (positive predictive value 88%). PCT was best at discriminating between SIRS and sepsis with the highest area under the ROC curve (0.95, 95% CI 0.90-0.99).

Discussion

This study showed that PCT is more useful than LBP, CRP and IL-6 in differentiating sepsis from SIRS.

INTRODUCTION

Critically ill patients often present with the systemic inflammation syndrome (SIRS) and these patients are treated with supportive therapy.¹ SIRS is commonly seen after major surgery, after trauma, with severe inflammation as with pancreatitis and with infection. If SIRS is due to infection the diagnosis is sepsis and supportive therapy alone is insufficient. The diagnosis of sepsis warrants specific and rapid therapy including early administration of antibiotics and control of the source of the sepsis.² In addition, sepsis has a worse prognosis than SIRS. Differentiating between sepsis and SIRS is of utmost importance and this is a common dilemma for the intensivist. Many biomarkers have been proposed and tested in a clinical setting but this search has not provided a test that is both widely accepted and enables the bedside clinician to confidently confirm or reject the diagnosis of sepsis.³ Serum levels of procalcitonin (PCT) are elevated in patients with sepsis and the usefulness of PCT in diagnosing sepsis has been studied extensively with conflicting results.⁴⁻⁷ The biological function of PCT is not known. Normal serum levels are below 0.5 ng/ml and patients with levels above 2 ng/ml are supposedly at risk for sepsis.⁸ Serum half time is 24-36 hours. In their meta-analysis of 33 studies including almost 4000 patients Uzzan *et al.* conclude that PCT is superior to CRP in differentiating between sepsis and SIRS and these authors favour the routine use of PCT to help differentiate between SIRS and sepsis.⁷ On the contrary Tang *et al.* review 18 studies including 2097 patients to conclude that PCT cannot reliably differentiate sepsis from other causes of SIRS and they argue against the routine use of PCT to aid in differentiating sepsis from SIRS.⁶ Interleukin-6 (IL-6) is an important mediator of the acute phase reaction in response to inflammation in sepsis. IL-6 is produced in response to TNF-alpha stimulation. In the liver IL-6 induces synthesis of acute phase proteins like CRP. The normal range of IL-6 serum concentration is < 5.9 pg/ml. Following inflammation serum levels of IL-6 have been shown to rise within one hour, before CRP levels do and even before the onset of fever. IL-6 values above 500 pg/ml were found in patients with sepsis.⁸ Lipopolysaccharide binding protein (LBP) is an acute-phase protein produced by the liver in response to circulating bacterial endotoxins or lipopolysaccharide (LPS). LPS is a constituent of the outer coat of Gram-negative bacteria. LBP facilitates the binding of LPS to the LPS receptor on monocytes, resulting in monocyte activation and cytokine production (eg. TNF alpha and IL-6). Elevated levels of serum LBP have been reported in Gram-negative, Gram-positive and fungal infections, but not in viral infections.⁹ The normal range of LBP serum concentration is 5 to 10 µg/ml.⁸ In patients with sepsis LBP levels rise to over 50 µg/ml in about 36 hours.^{8;10} CRP is produced by the liver in response to stimulation by several cytokines one of which is IL-6.⁸ CRP is measured routinely in hospitalized patients although it is generally recognized not to be specific for sepsis or

infection as it is elevated in infectious and non-infectious states.^{8,11} CRP in itself has pro and anti-inflammatory properties.

The objective of this prospective single centre cohort study was to see if PCT, IL-6 and LBP are useful in differentiating between sepsis and SIRS in critically ill patients.

METHODS

Study design and participants

This single centre prospective observational study was performed from February 1 through April 30, 2009, in the 10-bed mixed ICU of the Reinier de Graaf Hospital. The Reinier de Graaf Hospital is a 500-bed non-academic teaching hospital. All specialties except neurosurgery and cardiac surgery are available. The hospital has an ICU based medical emergency team. All consecutive patients admitted to the ICU were included if they were expected to be treated in the ICU for more than 24 hours. If a patient had neither SIRS nor sepsis, this patient was excluded from the study. If a patient had more than one ICU episode in the study period, only the first episode was included in the study.

Sepsis and SIRS

According to the standard definition patients with at least two of the following four criteria (1) fever ($>38.0^{\circ}\text{C}$) or hypothermia ($<36^{\circ}\text{C}$), (2) tachypnoea ($>20/\text{min}$) (3) tachycardia ($>90/\text{min}$) (4) leucopenia ($<4.0 \times 10^9/\text{L}$), leucocytosis ($>12.0 \times 10^9/\text{L}$ or a leftward shift ($>10\%$ immature granulocytes) were defined as having SIRS.¹ If SIRS was accompanied with bacterial infection as proven by cultures or on clinical grounds a patient was defined as having sepsis.¹ During treatment the doctors in charge were not blinded but did not use PCT, IL-6 or LBP results for clinical decision making. The final diagnosis of sepsis or SIRS was made at a later stage from the patients' records and blinded to PCT, LBP and IL-6 results. Due to the small numbers we did not differentiate between sepsis, severe sepsis or septic shock.

Data collection

On admission to the ICU patient characteristics and illness severity scores were documented. Blood samples for measuring CRP, PCT, IL-6 and LBP were taken on admission and subsequently at 6 am every morning until ICU discharge.

Laboratory measurements

PCT levels were measured using a time resolved amplified cryptate emission (TRACE) assay (Kryptor Compact; Brahms, Germany). Intra- and inter-assay coefficients of varia-

tion as determined in our laboratory were, depending on the sample concentration, between 2 and 5%. The best cutoff value of PCT in discriminating between septic and non-septic patients is still unclear, but most authors suggest a cut-off value of around 2 ng/ml. Additionally we arbitrarily chose a higher cut-off value of 10 ng/ml to see if we could increase the positive predictive value of PCT, that is, to find a cut-off value above which sepsis could be confirmed without doubt. LBP and IL-6 levels were measured using a solid phase, enzyme-labelled chemiluminescent immunometric assay (IMMULITE 2000; Siemens healthcare, The Netherlands). Inter-assay coefficients of variation as determined in our laboratory were, depending on the sample concentration, between 3.9 and 14.3% for IL-6 and between 5.9 and 6.2% for LBP. CRP levels were measured using an immunoturbidometric assay (Architect C16000, Abbott Laboratories). Inter-assay coefficients of variation, as determined by the manufacturer, ranged from 0.44% to 1.25%. A cut-off level of 50 mg/L is commonly used clinical practice.

Statistical analysis

For statistical analysis we used SPSS 18.0 (SPSS Inc., Chicago, IL). Comparisons between SIRS and sepsis patient characteristics were made using the Mann Whitney U test for continuous variables and Chi square test for categorical variables. To compare the usefulness of different markers in diagnosing sepsis we used the highest value of each marker in the first 24 hours of admission for each patient. Sensitivity, specificity, positive and negative predictive values and diagnostic odds ratios (DOR) were calculated and a receiver-operating characteristic (ROC) curve was made. The DOR can be used to represent test performance in one single figure. The DOR is defined as $[\text{sensitivity} / (1 - \text{sensitivity})] / [(1 - \text{specificity}) / \text{specificity}]$ and can be read as the ratio of the odds of disease with a positive test relative to the odds of disease with a negative test. DOR can range from 0 to infinity, with a higher value indicating a better performance of the test. A DOR of 1 means that the test is useless, a DOR >25 represents a useful test and a DOR > 100 represent a good test.^{6;12;13}

RESULTS

A total of 76 patients were included in the study; 32 with sepsis and 44 with SIRS. Patient characteristics are summarized in table 5.1. As expected, patients with sepsis had significantly higher illness severity scores on admission as compared to patients with SIRS. Patients with sepsis were more often ventilated and put on renal replacement therapy. Both mortality and length-of-stay in the ICU were higher in patients with sepsis.

Table 5.1. Patient characteristics

	All	Sepsis	SIRS	p**
Number	76	32	44	
Age*	66 (56-78)	68 (56-78)	65 (54-75)	ns
APACHE IV score*	57 (44-78)	70 (51-106)	53 (41-63)	<0.001
APACHE IV exp mort (median)	18%	25%	16%	<0.001
Medical	35	17	18	0.002
Planned surgery	25	4	21	
Emergency surgery	16	11	5	
Ventilated	51	24	27	ns
Days on ventilator*	4 (2-8)	6.5 (3.2-11)	2 (2-6)	0.018
Renal replacement therapy	10	9	1	0.001
Source of sepsis:				
Gastrointestinal		17		
Pulmonary		8		
Other		7		
ICU LOS***	3.3 (1.7-7.0)	6.4 (2.4-10.8)	2.7 (1.5-5.8)	0.024
Hospital LOS***	14 (7-30)	23 (8-36)	12 (7-21)	0.082
ICU mortality	7 (9%)	5 (16%)	2 (5%)	0.099
Hospital mortality	14 (18%)	9 (28%)	5 (11%)	0.063

* median, interquartile range

** for difference between sepsis and SIRS, Mann Whitney U test for continuous variables and Chi square test for categorical variables.

*** LOS = length of stay

To compare the usefulness of CRP, PCT, IL-6 and LBP in differentiating sepsis from SIRS we used the highest level of each in the first 24 hours of admission. On admission CRP, PCT, IL-6 and LBP levels were all significantly higher in patients with sepsis in comparison to patients with SIRS (Table 5.2). The differences were not equal: median CRP and LBP levels in sepsis were about 1.5 to 2 times higher in sepsis, whereas median PCT and IL-6 were about 10 times higher in sepsis as compared to SIRS. Interquartile ranges for IL-6 and PCT did not overlap, but they did overlap for CRP and LBP. With cut-off values of 2 and 10 ng/ml for PCT, 50 µg/mL for CRP, 50 pg/ml for IL-6 and 30 µg/ml for LBP sensitivity, specificity and predictive values are presented in tables 5.3 and 5.4. We found that PCT below 2 ng/ml makes sepsis highly unlikely (negative predictive value of 97%) and PCT above 10 ng/ml makes sepsis very likely (positive predictive value 88%). PCT has a diagnostic odds ratio of 120.6 with cut-off value of 2 ng/ml. Figure 5.1 shows ROC curves and areas under the curve for CRP, PCT, IL-6 and LBP for diagnosis of sepsis as opposed to SIRS. The area under the ROC curve is significantly higher for PCT as compared to IL-6, LBP and CRP.

In patients with sepsis maximum values for IL-6 were reached on day 0, for PCT and CRP on day 1 and for LBP on day 2 (Figure 5.2). IL-6 levels in patients with sepsis decline rapidly after day 1. The difference in PCT levels between sepsis and SIRS patients is maintained at least until day 3 or 4.

Table 5.2. The highest levels of CRP, PCT, IL-6 and LBP in the first 24 hours of ICU treatment.

	All	Sepsis	SIRS	p**
CRP* (µg/ml)	117 (56-194)	179 (88-297)	80 (52-152)	<0.001
PCT* (ng/ml)	2.2 (0.3-20.3)	24.3 (6.6-57.2)	0.5 (0.2-1.1)	<0.001
IL-6* (pg/ml)	153 (41-750)	1463 (243-12951)	54 (25-149)	<0.001
LBP* (µg/ml)	19.1 (12.6-31.7)	30.9 (14.7-41.5)	16.3 (10.8-22.2)	0.001

* median, interquartile range

** Mann Whitney U test for difference between sepsis and SIRS

Table 5.3. Test results using the highest value of the biomarkers within the first 24 hours of admission on the ICU.

		Sepsis	No sepsis	All
CRP (cut-off value 50 µg/mL)	Test +	28	34	62
	Test -	4	10	14
PCT (cut-off value 2 ng/ml)	Test +	31	9	40
	Test -	1	35	36
PCT (cut-off value 10 ng/ml)	Test +	21	3	24
	Test -	11	41	52
IL-6 (cut-off value 50 pg/ml)	Test +	29	26	55
	Test -	3	18	21
LBP (cut-off value 30 µg/ml)	Test +	17	4	21
	Test -	15	40	55
All patients		32	44	76

Test + : number of patients with marker-level equal to or above cut-off value

Test - : number of patients with marker-level below cut-off value

Table 5.4. Sensitivity, specificity, predictive values and diagnostic odds ratios using the highest values of all biomarkers within the first 24 hrs of ICU admission.

	Sensitivity	Specificity	PPV	NPV	DOR (95% CI)
CRP cut-off value 50 µg/mL	88%	23%	45%	71%	2.1 (0.6-7.3)
PCT cut-off value 2 ng/ml	97%	80%	78%	97%	120.6 (14.4-1006)
PCT cut-off value 10 ng/ml	66%	93%	88%	79%	26.1 (6.6-103.8)
IL-6 cut-off value 50 pg/ml	91%	41%	53%	86%	6.7 (1.8-25.4)
LBP cut-off value 30 µg/ml	53%	91%	81%	73%	11.3 (3.3-39.3)

Sensitivity = percentage of septic patients with positive test

Specificity = percentage of non-septic patients with negative test

PPV (positive predictive value) = percentage of test-positive patients with sepsis

NPV (negative predictive value) = percentage of test-negative patients without sepsis.

DOR (diagnostic odds ratio)= [sensitivity/(1-sensitivity)] / [(1-specificity)/specificity] = the ratio of the odds of disease with a positive test relative to the odds of disease with a negative test.

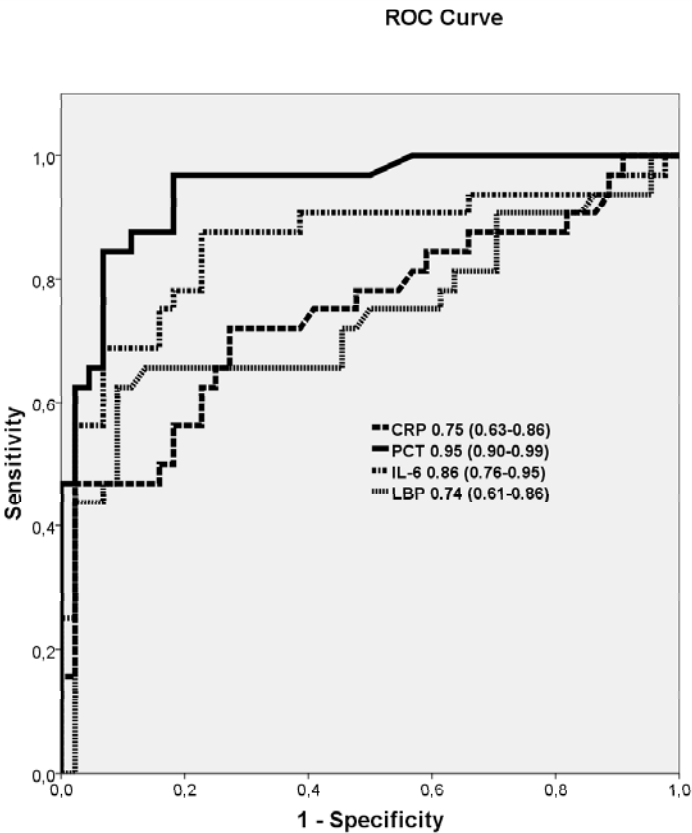


Figure 5.1. ROC curve and areas under the curve for diagnosing sepsis with the highest values in the first 24 hours after ICU admission for CRP, PCT, IL-6, and LBP.

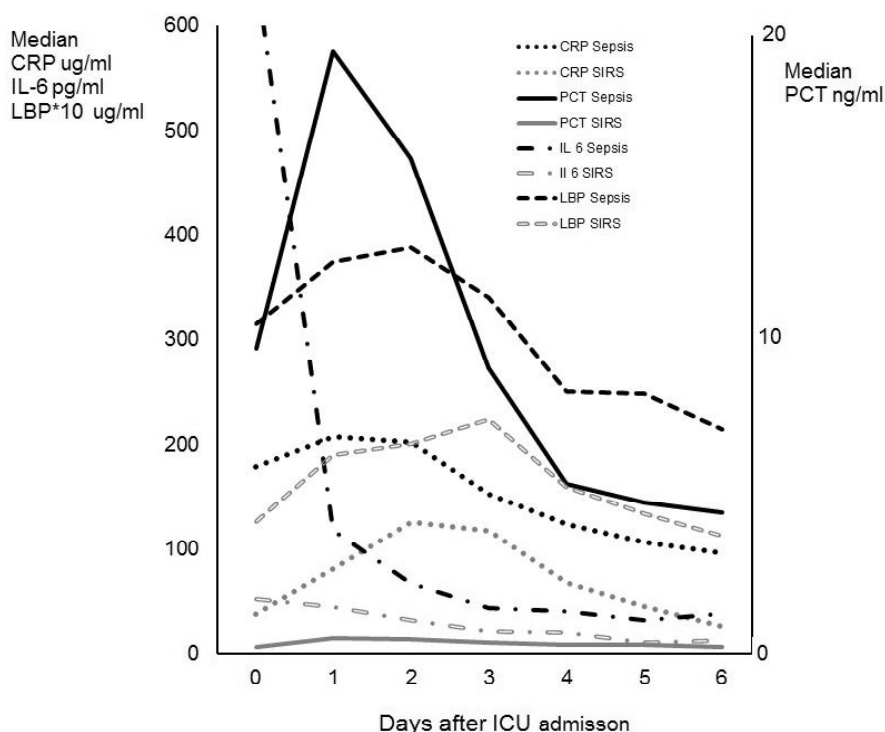


Figure 5.2. Median CRP, PCT, LBP, and IL-6 levels in patients with sepsis and SIRS during ICU admission.

DISCUSSION

This single centre prospective observational study showed that serum PCT levels are more valuable than serum CRP, LBP and IL-6 levels in discriminating sepsis from SIRS in critically ill patients. PCT has the highest area under the ROC curve and the highest diagnostic odds ratios. If PCT levels in the first 24 hours after ICU admission are below 2 ng/mL, sepsis with bacterial infection is virtually excluded (negative predictive value 97%). If PCT levels in the first 24 hours after ICU admission are above 10 ng/mL, sepsis with bacterial infection is very likely (positive predictive value 88%). Comparing positive and negative predictive values, PCT seems to be even more useful in excluding sepsis than in diagnosing sepsis. LBP, CRP and IL-6 had lower positive and negative predictive values. IL-6 is second best after PCT but the sharp decline of IL-6 levels after admission in patients with sepsis suggests that late sampling may easily cause false negative results.

A particular strength of this study is that it compares not only PCT but also LBP and IL-6 with standard CRP. The fact that this is a pragmatic real life study adds to its strength, but we recognize that this also induces serious limitations. The study is relatively small,

one of the smaller studies on this subject, and was performed in a single centre where no cardiac surgery or neurosurgery patients are treated. Also we found a rather high DOR for PCT (120.6 and 26.1 for cut-off values of 2 and 10 ng/ml respectively) as compared to the pooled DOR of 7.79 found by Tang *et al.* It is quite possible that due to the limitations of our study we have overestimated the diagnostic properties of PCT. Although PCT, IL-6 and LBP values were not used for treatment decisions, treating physicians were not blinded to the test results and this may have induced bias. The eventual diagnosis of sepsis versus SIRS was made by the physicians who were previously involved in treatment of the patients and this may have resulted in hindsight bias or information bias. Since patients with severe sepsis are more likely to be admitted to the ICU than patients with mild SIRS we may have missed patients with mild SIRS but with elevated PCT that went unnoticed, resulting in selection bias.

The real life value of an additional diagnostic tool is not easily estimated. The process of reaching a diagnosis is not entirely rational. In everyday practice clinicians use many clues (signs, symptoms, epidemiology, experience, etc) to reach a (differential) diagnosis. The value of a test depends on how probable the clinician thinks a certain diagnosis is beforehand (pretest probability). If the clinician is not in doubt any additional test is useless. If the doctor is in doubt and the additional test brings more certainty on rejecting or accepting a diagnosis (posttest probability) the test is useful in this case. In addition sometimes unlikely options are taken into account because of the grave consequences of neglecting such an option. The influence of an additional test on diagnosis and subsequent action depends not only on the pretest and posttest probability, but also on our willingness to act in accordance with the additional test result. In the context of this paper this would for instance mean: would we be willing to withhold a patient admitted for suspected sepsis antibiotics, if his PCT turned out to be low? The answer depends on our estimation of the likeliness of sepsis (pretest probability) but also on our willingness to accept the risk of not giving antibiotics. The point that we want to make is that the answer is not purely mathematical and cannot be given by just studying diagnostic properties of the test. We would therefore urge clinicians to see for themselves if PCT could be of value in differentiating SIRS from sepsis in their practice, as we have done. Incorporating PCT into clinical practice could improve decision making especially in patients with conflicting clues on the presence or absence of sepsis. PCT could also be valuable as a means to reduce the length of antibiotic treatment but that is outside the scope of this paper.¹⁴

CONCLUSION

This study showed that PCT levels are of value in differentiating between sepsis and SIRS in critically ill patients and more helpful than CRP, IL-6 or LBP levels. Especially during the first 24 hour of admission PCT levels can help determine the course of action to improve outcome, reduces mortality and prevent unnecessary diagnostic and therapeutic measures.

Although PCT is the best biomarker to distinguish sepsis from SIRS its diagnostic properties do not justify clinical decision making based on PCT alone. The diagnosis of sepsis still requires integration of multiple clinical data.

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Chapter 6

Spoedinterventiesysteem
bij vitale bedreiging:

5 jaar ervaring in een groot
algemeen ziekenhuis

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SAMENVATTING

Doel

Patiënten die in het ziekenhuis opgenomen zijn, lopen risico op ernstige complicaties zoals onverwachte hartstilstand of opname op een Intensive Care (IC). Bij deze patiënten zijn voorafgaand aan het incident vaak afwijkingen in de vitale functies die niet adequaat behandeld worden. Om deze vitaal bedreigde patiënten op te sporen en te behandelen is in ons ziekenhuis in 2004 een spoedinterventiesysteem opgezet (SIS). Doel van dit artikel is het beschrijven van implementatie en resultaten van het SIS.

Opzet

Prospectief cohortonderzoek.

Methode

Alle verpleegkundigen en artsen werden bij de implementatie van het SIS geïnstrueerd vitale parameters te scoren met een scorekaart. Bij een score van meer dan 3 punten moet eerst de behandelend arts de patiënt beoordelen en vervolgens – indien nodig – het spoedinterventieteam (SIT) inroepen, dat bestaat uit een IC-arts en een IC-verpleegkundige inroepen. Wij analyseerden alle consulten van het SIT in de periode januari 2005-december 2009.

Resultaten

Er werden 1058 SIT-consulten gedaan bij 981 patiënten. Bij 606 patiënten (57,3%) is besloten tot overplaatsing, meestal naar de IC. Bij 353 patiënten (33,4%) kon de patiënt op de verpleegafdeling behandeld worden. Bij 88 patiënten (8,4%) werd geconcludeerd dat zij niet zouden profiteren van IC-behandeling. Bij hen werden behandelgrenzen gesteld. Van de 981 patiënten overleden 255 (26,0%) in het ziekenhuis.

Conclusie

Het spoedinterventiesysteem heeft zich in ons ziekenhuis ontwikkeld tot een belangrijke voorziening om vitaal bedreigde patiënten vroegtijdig te herkennen en te behandelen. Met deze data is echter niet bewezen dat het SIS leidt tot een daling van de ziekenhuis-mortaliteit.

ABSTRACT

Objective

Hospitalized patients are at risk for adverse events like unexpected cardiac arrest or unexpected ICU admission. Prior to these adverse events patients often have derangements in vital signs that are not recognized and treated adequately. The concept of the Rapid Response System (RRS), Critical Care Outreach or Medical Emergency Teams was developed to identify and treat hospitalized patients at risk for unexpected ICU admission or unexpected cardiac arrest. Many, but not all clinical studies have shown improved outcome like reduced cardiac arrest rates. There is no overwhelming evidence that RRS save lives. Combining common sense and literature however, current consensus states that implementation of RRS is justified. RRS implementation is stimulated by the British National Health Service and National Institute for Clinical Excellence, by the American Institute for Health Care Improvement and by the Dutch Society for Critical Care. Nationwide implementation is mandated by the Dutch Safety Managements System programme. Our hospital implemented a RRS in 2004. The purpose of this paper is to describe implementation and results of our RRS. We did not attempt to prove efficacy in terms of lives saved.

Design

Prospective cohort study.

Method

The Reinier de Graaf Hospital is a 500 bed non-academic teaching hospital with a 10-bed intensivist-led ICU. All specialities except cardiac surgery and neurosurgery are available. On introduction of RRS in our hospital in 2004, all doctors and nurses were trained to score patients' vital signs using a modified early warnings system (MEWS) score card. If a patient has a score of 3 points or more, the treating physician is obliged to examine the patient and present a treatment strategy within 30 minutes. One of his options is to call the Medical Emergency Team (MET) consisting of an ICU doctor and an ICU nurse. The MET will immediately see the patient and compose a treatment plan in collaboration with the treating physician. Treatment options are to start intensive care treatment and transfer the patient to a higher dependency unit, most probably the ICU; to continue treatment on the ward, or to limit treatment and change the resuscitation code. All MET calls were logged in a special database by the MET coordinating nurse for evaluation purposes and for this prospective cohort study. Data were crosschecked with hospital and ICU databases. All consecutive MET calls between January 1st, 2005 and December 31st, 2009, were analyzed.

Results

A total of 1058 MET calls for 981 patients were analyzed. Median age was 70.8 years and mean MEWS score was 5.8. In 606 patients (57.3%) it was decided to transfer the patient to a higher dependency unit (HDU), in most cases the ICU. For 353 patients (33.4%) treatment was continued on the ward. In 88 patients (8.4%) it was decided that ICU treatment would not be beneficial and a limitation of treatment was installed. Hospital mortality of all 981 patients was 255 (26.0%). Hospital mortality was 139 (24.8%) for 560 patients who were transferred to a HDU, 47 (14.5%) for 325 patients who were treated on the ward and 58 (68%) for 85 patients who were too sick to benefit from transfer to a higher dependency unit. Eleven patients died on the ward during the RRT call with or without cardiopulmonary resuscitation.

Conclusion

In our hospital the rapid response system functions well to identify and treat patients at risk. We recognize several important limitations though. In our local RRS the doctor on call has to see the patient in whom the nurse finds a MEWS score of 3 or higher. Although this doctor has to act within 30 minutes this may still create unnecessary delay as compared to the system that is commonly reported in the literature where anyone can call the MET immediately. We choose to involve the patients' own doctors for several reasons: to be able to incorporate this doctors' knowledge about the patient in the decisions during the MET visit, to continuously educate non MET staff in the treatment of acutely ill patients, to minimize resistance against the MET and to reduce workload for the MET. Also due to this choice of system we have data only on the patients for whom the MET was indeed called and not on the patients with 3 point or more for whom the MET was not called.

Even despite these limitations we are confident that our RRS is an important tool to identify and treat acutely ill patients at an early stage and at the right place.

INLEIDING

Patiënten die zijn opgenomen in het ziekenhuis lopen het risico op ernstige complicaties zoals sepsis, ongeplande IC-opname, onverwachte hartstilstand en reanimatie. (1) Het is bekend dat deze patiënten in de voorafgaande uren tot dagen veranderingen vertonen in de vitale functies die echter niet altijd als bedreigend worden herkend en dus ook niet als zodanig worden behandeld. (2-5) Zelfs als een patiënt wél herkend is als vitaal bedreigd, maar de IC-opname wordt uitgesteld, is de prognose slechter. (6) Om deze vitaal bedreigde patiënten te identificeren en te behandelen zijn de zogenoemde 'Medical Emergency Teams' of 'Critical Care Outreach Services' bedacht, of – in het Nederlands – de spoedinterventieteam (SIT's). (4,7,8) Onder andere het Amerikaanse Institute for Healthcare Improvement, het Britse National Institute for Clinical Excellence en de Nederlandse Vereniging voor Intensive Care onderschrijven het belang van dergelijke teams (zie www.ihl.org/IHI/Topics/CriticalCare/IntensiveCare/changes/EstablishaRapidResponseTeam.htm en www.vmszorg.nl). (9,10) Introductie van een spoedinterventiesysteem (SIS) is tevens 1 van de 10 interventies in het VMS Veiligheidsprogramma. Dit betekent dat het SIS in alle Nederlandse ziekenhuizen ingevoerd moet worden (<http://www.vmszorg.nl/10-Themas/Vitaal-bedreigde-patiënt>). Uitgebreide uitleg over het SIS staat verderop in dit artikel.

Veel, maar niet alle, prospectieve cohortstudies die de effectiviteit van het SIS bestudeerden, laten positieve effecten zien in de zin van vermindering van onverwachte hartstilstand en onverwachte sterfte. (11-19) Prospectieve studies zijn relatief makkelijk uit te voeren. Er is echter een aanzienlijke kans dat een eventueel positief effect ten onrechte aan het SIS wordt toegeschreven, maar in werkelijkheid veroorzaakt wordt door miskende versturende factoren.

Er zijn slechts 2 gerandomiseerde studies: 1 studie waarbij binnen een ziekenhuis gerandomiseerd werd tussen afdelingen waar een SIT kon worden opgeroepen en afdelingen waar dat niet kon, toonde een vermindering van de ziekenhuissterfte door het SIT aan. (20) In een multicenter studie waarbij gerandomiseerd werd tussen ziekenhuizen die wel of geen SIT hadden werd geen verschil gevonden in het aantal onverwachte hartstilstanden of ongeplande IC-opnames. (21)

De meest recente van de 4 meta-analyses besluit dat het SIS het aantal patiënten met een onverwachte hartstilstand reduceert, maar geen effect heeft op de totale ziekenhuissterfte. (22-25) De algemene tendens in de literatuur is dat de voordelen van het spoedinterventiesysteem misschien niet overtuigend te bewijzen zijn in epidemiologisch onderzoek, maar dat de aanwezige data en het gezond verstand de invoering rechtvaardigen. (4,7,8,22) Er is in de literatuur slechts 1 Nederlandse studie, een retrospectief cohortonderzoek, van de hand van de SIS-pioniers in het Rijnstate Ziekenhuis in Arnhem, waarin een vermindering van het aantal reanimaties in het ziekenhuis wordt gezien sinds de introductie van het SIS. (12) De resultaten van een grote gerandomiseerde Nederlandse studie

(COMET-studie, 'Cost-effectiveness analysis of medical emergency teams') worden in 2012 verwacht (www.comet-studie.nl). In ons ziekenhuis is het SIS in 2004 geïmplementeerd. (26) De beslissing om tot invoer van een SIS over te gaan werd niet alleen genomen op grond van de toen beschikbare literatuur maar ook op grond van de ervaring dat patiënten soms pas na aanzienlijke verslechtering van hun klinische toestand werden gemeld bij de intensive care. In dit artikel beschrijven we de wijze waarop het spoed-interventiesysteem in ons ziekenhuis werd ingevoerd en wat er gebeurde met de patiënten voor wie de hulp van het SIT werd ingeroepen. We doen dit aan de hand van de procesindicatoren van het expertteam 'vitaal bedreigde patiënt' van het landelijke veiligheidsmanagement-systeem (www.vmszorg.nl/10-Themas/Vitaal-bedreigde-patient/Mijn-monitor).

Wij hebben nadrukkelijk niet geprobeerd om de effectiviteit van het SIS aan te tonen in termen van vermindering van onverwachte sterfte. Onze data zijn daarvoor ontoereikend en alleen een groot gerandomiseerd onderzoek kan nog bijdragen aan de bewijskracht van de bestaande literatuur. Gezien de actuele landelijke invoering van het SIS bestaat er volgens ons wel behoefte aan beschrijvende data over implementatie en de te verwachten werklast.

HET SPOEDINTERVENTIESYSTEEM

Het SIS, zoals beschreven door de internationale consensusgroep en door het expertteam van het veiligheidsmanagementsysteem, bestaat uit 3 componenten. (4,9,10) Het eerste deel wordt het 'afferente been' van het SIS genoemd: de vitaal bedreigde patiënt die op de huidige plek onvoldoende zorg krijgt moet eerst als zodanig geïdentificeerd worden. Het tweede deel is het 'efferente been': de juiste zorg moet naar de bedreigde patiënt toe. In de literatuur wordt onderscheid gemaakt tussen teams die bestaan uit verpleegkundigen en teams waar ook artsen aan toegevoegd zijn. Meestal wordt gesproken van 'critical care outreach' als het gaat om verpleegkundige teams en van 'medical emergency teams' als er artsen bij zijn. Deze teams moeten in staat zijn de toestand van de patiënt te beoordelen, behandeling te starten en vlot te beslissen over het verdere beleid. Het derde deel van het systeem, het 'borgingsbeen', bestaat uit scholing, onderhoud, organisatie en terugkoppeling. Dit derde deel moet resulteren in continue verbetering en aanscherping van procedures. Het belang van dit been wordt vaak onderschat, maar kan niet genoeg benadrukt worden. (4,9,10) Ter verheldering wijzen wij nog op het onderscheid tussen het spoedinterventiesysteem (SIS) en het spoedinterventie-team (SIT): met het team wordt slechts het efferente deel van het systeem bedoeld.

Implementatie in Delft

Op initiatief van de afdeling Intensive Care is eind 2004 in ons ziekenhuis de implementatie van het SIS gestart, na goedkeuring door het management en de medische

staf. Alle specialismen, met uitzondering van hartchirurgie en neurochirurgie, zijn in de Reinier de Graaf Groep aanwezig. Het ziekenhuis is lid van de vereniging 'Samenwerken-de topklinische ziekenhuizen' en beschikt over 500 operationele bedden. De Intensive Care is op 1 locatie en beschikt over 10 bedden. De afdeling voldoet aan de eisen voor een niveau 2-IC volgens de CBO-richtlijn. (27) De intensivist is hoofdbehandelaar en beslist over opname en ontslag. Jaarlijks worden 650-700 patiënten behandeld gedurende 3000-3500 behandeldagen. De SMR (de verhouding tussen werkelijke mortaliteit en de op grond van de ziekte-ernst verwachte mortaliteit) was van 2005-2009 0,64-0,78 voor het scoresysteem 'Acute Physiology and Chronic Health Evaluation II' (APACHE II), waarin naast de leeftijd, de indicatie voor IC-opname en de algehele gezondheidstoestand van de patiënt nog 12 fysiologische parameters worden gebruikt om de score te berekenen. Voor de 'Simplified Acute Physiological Scores' (SAPS II), was de SMR 0,72-0,86.

Bij de implementatie van het SIS zijn alle verpleegkundigen en artsen in het ziekenhuis geschoold in het scoren van patiënten met het zogenaamde SIT-kaartje (Figuur 6.1). Wanneer een verpleegkundige bij een patiënt 3 punten of meer scoort, wordt de behandelende arts gebeld. Deze dienstdoende specialist of arts-assistent dient de patiënt binnen 30 min te zien en een behandelplan in te stellen. Onderdeel van dat plan kan zijn het oproepen van het SIT, maar de behandelende arts kan ook besluiten dat hulp van het SIT niet of nog niet nodig is. Het SIT, bestaande uit een IC-verpleegkundige en een IC-arts (intensivist of arts-assistent IC) en uitgerust met alle middelen om IC-behandeling te starten, gaat desgewenst naar de patiënt toe. De behandelende arts is aanwezig voor overleg. Het SIT kan samen met de behandelende arts direct een behandeling instellen en besluiten dat de patiënt overgeplaatst moet worden, of dat overplaatsing de patiënt niet zal baten. Voor het borgingsbeen van het SIS heeft ons ziekenhuis een SIT-coördinator die samen met een commissie continue zorg draagt voor onderwijs, terugkoppeling en data-analyse.

Alle nieuwe verpleegkundigen en artsen krijgen bij hun introductie in het ziekenhuis onderwijs over het SIS. Het SIS in ons ziekenhuis is niet gelijk aan het systeem zoals dat in het buitenland, bijvoorbeeld in Australië, werkt. Bij ons wordt eerst de behandelende arts gewaarschuwd, daar wordt de behandelende arts overgeslagen. Deze aanpak, die ook ondersteund wordt door het expertteam 'vitaal bedreigde patiënt' van het VMS, is gekozen om (a) de kennis van de hoofdbehandelaar over de voorgeschiedenis, actuele problematiek en behandelwensen van de patiënt te behouden en te kunnen benutten bij beslissingen tijdens het SIT consult; (b) de kennis en vaardigheden van de hoofdbehandelaar over de zorg voor acuut zieke patiënten te behouden; (c) de weerstand tegen het SIS zo laag mogelijk te houden door de hoofdbehandelaar de vrijheid te geven om het SIT-consult al dan niet aan te vragen en de adviezen van het SIT al dan niet op te volgen, conform de bestaande werkwijze voor intercollegiale consulten; en (d) de werklust voor het SIT dragelijk te houden. Nadeel van deze aanpak is dat er mogelijk maximaal 30 minuten ongewenste vertraging optreedt doordat eerst de hoofdbehandelaar de patiënt moet beoordelen.

PATIËNTEN EN METHODE

De SIT-coördinator, die verantwoordelijk is voor implementatie, borging en terugkoppeling, administreerde alle SIT-consulten in de periode januari 2005-december 2009 op speciale consultformulieren. Deze informatie werd verwerkt in een database. In eerste instantie werden deze data verzameld voor kwaliteitsverbetering en terugkoppeling. In tweede instantie waren ze bedoeld voor dit prospectieve cohortonderzoek. Naast de personalia van de patiënt werden gegevens verzameld over de vitale functies, de SIT-score, de resultaten van het SIT-consult en de ontslagstatus van de patiënt. Met behulp van het ziekenhuisinformatiesysteem en de intensivacedatabase werden data aangevuld en gecontroleerd. Analyse vond plaats met behulp van SSPS 18.0 (Chicago, Illinois, USA.)

RESULTATEN

In de periode januari 2005-december 2009 werd het SIT 1058 keer geconsulteerd voor 981 patiënten (Tabel 6.1). Voor 63 patiënten werd het SIT gedurende de ziekenhuisopname 2 keer opgeroepen, voor 12 patiënten 3 keer en voor 2 patiënten 4 keer. Op zaterdag en zondag waren er minder SIT-oproepen dan op doordeweekse dagen (Figuur 6.2). Gedurende de nacht waren er minder oproepen dan overdag (Figuur 6.3).

Bij 606 patiënten (57,3% van de SIT-consulten) was de uitkomst van het SIT-consult dat de patiënt werd overgeplaatst naar een afdeling waar meer zorg kon worden geboden, meestal de IC. De situatie werd bij 88 patiënten (8,4%) zodanig ingeschat dat overplaatsing de patiënt niet zou baten: de patiënt bleef op de verpleegafdeling en er werd een behandelbeperking ingesteld, te weten: geen beademing, geen reanimatie en geen IC-opname. Bij 353 patiënten (33,4%) werd ingeschat dat de patiënt goed op de verpleegafdeling kon worden behandeld. Vaak werd een extra behandeladvies gegeven door het SIT (zie Tabel 6.1). Tot slot kon het gebeuren dat de patiënt tijdens het SIT-consult overleed met of zonder reanimatiepoging (zie Tabel 6.1). Van de 550 patiënten die binnen 24 uur na het SIT-consult werden opgenomen op de IC werd 52,4% beademd en had 36,7% 'sepsis' als opnamediagnose (Tabel 6.2).

Van de 981 patiënten bij wie een SIT-consult was gedaan, overleden er 255 (26,0%) tijdens de ziekenhuisopname. De sterfte was 68% bij de patiënten bij wie na het SIT-consult besloten was dat de patiënt niet zou profiteren van overplaatsing en waarbij vervolgens een behandelbeperking was ingesteld. De ziekenhuissterfte van de overgeplaatste patiënten was 24,8% en de ziekenhuissterfte van de patiënten die niet ziek genoeg waren voor overplaatsing was 14,5% (Tabel 6.3 en Figuur 6.4). De kans op overlijden was groter bij een hogere leeftijd en bij een hogere SIT-score (zie Tabel 6.3).

Tabel 6.1 Kenmerken van patiënten van in totaal 1058 consulten van een spoedinterventieteam (SIT) in een groot algemeen ziekenhuis in de periode 2005-2009.

	Totaal
Aantal SIT meldingen (1)	1058
Man	574 (54.3%)
Mediane leeftijd	70.8 (57.6-79.0)
Afdeling van herkomst	
Niet-chirurgische afdeling	379 (35.5%)
Chirurgische afdeling	354 (33.5%)
SEH	306 (28.9%)
Overig	19 (0.2%)
Gemiddelde SIT-score	5.9 (2.2)
0-4 punten (2)	290 (27.4%)
5 tot 7 punten	544 (51.4%)
Meer dan 7 punten	219 (20.7%)
Aantal verstoorde orgaansystemen	
0	33 (3.1%)
1	601 (56.8%)
2	352 (33.3%)
3	72 (6.8%)
Circulatie	357 (52.6%)
Ventilatie	669 (63.2%)
Bewustzijn	295 (27.9%)
Patiënt overlijdt tijdens SIT	11 (1%)
Ondanks CPR	7 (0.6%)
Zonder CPR	4 (0.4%)
Te ziek voor overplaatsing, behandelbeperking	88 (8.4%)
Overplaatsing (1)	606 (57.3%)
IC < 24 hr	550 (52.0%)
CCU	27 (2.6%)
OK	34 (3.2%)
Ander ziekenhuis	25 (2.4%)
Overplaatsing niet nodig	353 (33.4%)
Geen interventie	66 (6.2%)
Behandeladvies	287 (7.1%)

CPR = cardiopulmonale resuscitatie; IC = Intensive Care; CCU = 'coronary care unit', hartbewakingsafdeling; OK = operatiekamer

Tabel 6.2 Kenmerken van 550 patiënten die in aansluiting op het consult van een spoedinterventieteam (SIT) in een groot algemeen ziekenhuis naar de intensive care zijn overgeplaatst.

Aantal patiënten	550
Man; n (%)	310 (56.4%)
Leeftijd	69.3 (57.2-77.6)
Na reanimatie	5 (0.9%)
Na spoed OK (1)	30 (5.5%)
Heropname op IC	78 (14.2%)
Binnen 4 uur na SIT consult	482 (87.6%)
Binnen 4-24 uur na SIT consult	68 (12.4%)
Medisch	389 (70.7%)
Geplande chirurgie	83 (15.1%)
Spoed chirurgie	78 (14.2%)
Gemiddelde APACHE II score (SD) (2)	18.1 (8.0)
APACHE II verwachte mortaliteit (IQR) (2)	28% (14-49)
Gemiddelde SAPS II score (SD) (3)	39.8 (16.9)
SAPS II verwachte mortaliteit (IQR) (3)	20% (9-44)
IC opnameduur (dagen)	2.2 (1.0-5.8)
Ziekenhuis behandelduur (dagen)	15.3 (6.1-28.9)
Beademd	288 (52.4%)
Beademingsduur (dagen)	4 (2-8)
Nierfunctie vervangende therapie	67 (12.2%)
Sepsis als opname diagnose	202 (36.7%)
(1)	Inclusief de patiënten die na het SIT consult eerst op de IC zijn gestabiliseerd voor ze naar de OK gingen.
(2)	Bij de 430 patiënten die voldeden aan de APACHE II inclusie criteria.
(3)	Bij de 462 patiënten die voldeden aan de SAPS II inclusie criteria.

Tabel 6.3 Kenmerken van 981 patiënten die een consult van een spoedinterventieteam (SIT) hebben gehad, in een groot algemeen ziekenhuis, uitgesplitst naar patiënten die in het ziekenhuis overleden en patiënten die overleefden.

	Overleden ziekenhuis	Levend ontslagen	Totaal	p (1)
Aantal patiënten	255 (26.0%)	726 (74.0%)	981	
Man	145 (27.3%)	386 (72.7%)	531	
Gemiddelde leeftijd (SD)	73.7 (12.5)	63.5 (18.4)	66.1 (17.6)	<0.001
Afdeling van herkomst				
Chirurgische afdeling	71 (22.1%)	250 (79.9%)	321	
Niet-chirurgische afdeling	114 (33.9%)	222 (66.1%)	336	
SEH	68 (22.3%)	237 (78.0%)	305	<0.001
Overig	2 (10.5%)	17 (89.5%)	19	
Gemiddelde SIT-score (SD)	6.8 (2.3)	5.6 (2.1)	5.9 (2.2)	<0.001
0-4 punten	41 (14.9%)	234 (85.1%)	275	
5 tot 7 punten	128 (25.5%)	374 (74.5%)	502	<0.001
Meer dan 7 punten	84 (42.2%)	115 (57.8%)	199	
Aantal verstoorde systemen				
0	2 (6.5%)	29 (93.5%)	31	
1	136 (24.6%)	416 (75.4%)	552	
2	84 (25.5%)	245 (74.5%)	329	<0.001
3	33 (47.8%)	36 (52.2%)	69	
Circulatie	143 (27.2%)	383 (72.8%)	526	
Ventilatie	181 (29.6%)	431 (70.4%)	612	
Bewustzijn	79 (28.3%)	200 (71.7%)	279	
1 SIT melding tijdens opname	238 (25.9%)	680 (74.1%)	918	
2 SIT meldingen	13 (26%)	38 (74%)	51	ns
3 of 4 SIT meldingen	4 (33%)	8 (67%)	12	
Patiënt overlijdt tijdens SIT	11	0	11	
Ondanks CPR	7	0	7	
Zonder CPR	4	0	4	
Overplaatsing niet zinvol	58 (68%)	27 (32%)	85	
Overplaatsing	139 (24.8%)	421 (75.2%)	560	
Overplaatsing IC binnen 4 hr	119 (26.4%)	331 (73.6%)	450	
Overplaatsing IC 4-24 hr	16 (27%)	44 (73%)	60	
Overplaatsing CCU	4 (17%)	20 (83%)	24	
OK	9 (29%)	22 (71%)	31	
Ander ziekenhuis	0	23	23	
Na CPR tijdens SIT	5	2	7	
Overplaatsing niet nodig	47 (14.5%)	278 (85.5%)	325	
Geen interventie nodig	6 (10%)	54 (90%)	60	
Behandeladvies	41 (15.5%)	224 (84.5%)	265	

ns = niet-significant; CPR = cardiopulmonale resuscitatie; IC = Intensive Care; CCU = 'coronary care unit', hartbewakingsafdeling; OK = operatiekamer

(1) χ^2 -toets voor categorische variabelen, t-toets voor continue normaal verdeelde variabelen

Alarmsignalen bij vitaal bedreigde patiënt							
Score	3	2	1	0	1	2	3
Hartfrequentie		<40	40-50	51-100	101-110	111-130	>130
Bloeddruk (syst)	<70	70-80	81-100	101-200		>200	
Ademfrequentie		<9		9-14	15-20	21-30	>30
Temperatuur		<35,1	35,1-36,5	36,6-37,5	>37,5		
Bewustzijn				A	V	P	U
A = alert V = reactie op aanspreken P = reactie op pijn U = geen reactie							
Wanneer u ongerust bent over de conditie van de patiënt: 1 punt extra							
Wanneer de urineproductie < 75 ml gedurende de afgelopen 4 uur: 1 punt extra							
Indien de saturatie < 90 ondanks therapie: → 3 punten							

Patiënt scoort 3 punten of meer
→ Bel de arts-assistent



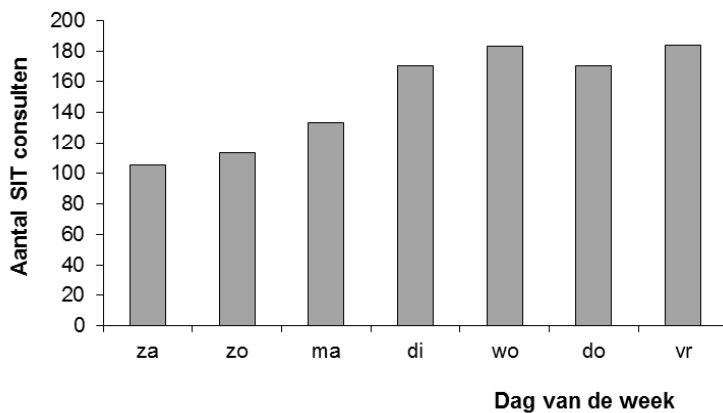
2/2008

Patiënt scoort 3 punten of meer
→ Bel de arts-assistent

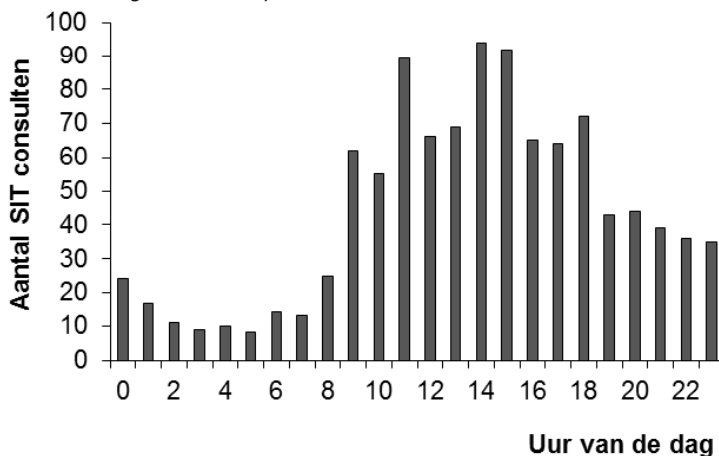
- De arts-assistent beoordeelt de patiënt en heeft, na overleg met de hoofdbehandelaar, binnen 30 minuten een behandelplan.
- De hoofdbehandelaar beoordeelt patiënt en neemt bij onvoldoende herstel contact op met intensivist. Toestel 3523 (7.30-17.30 u) of SIT-toestel 4124 (24 uur bereikbaar).
- In geval van sepsis **altijd** contact opnemen met de intensivist en start behandeling volgens richtlijn "surviving sepsis".
- Indien nodig komt het Spoed Interventie Team de patiënt beoordelen en wordt verder beleid bepaald.

IC - Spoed Interventie Team

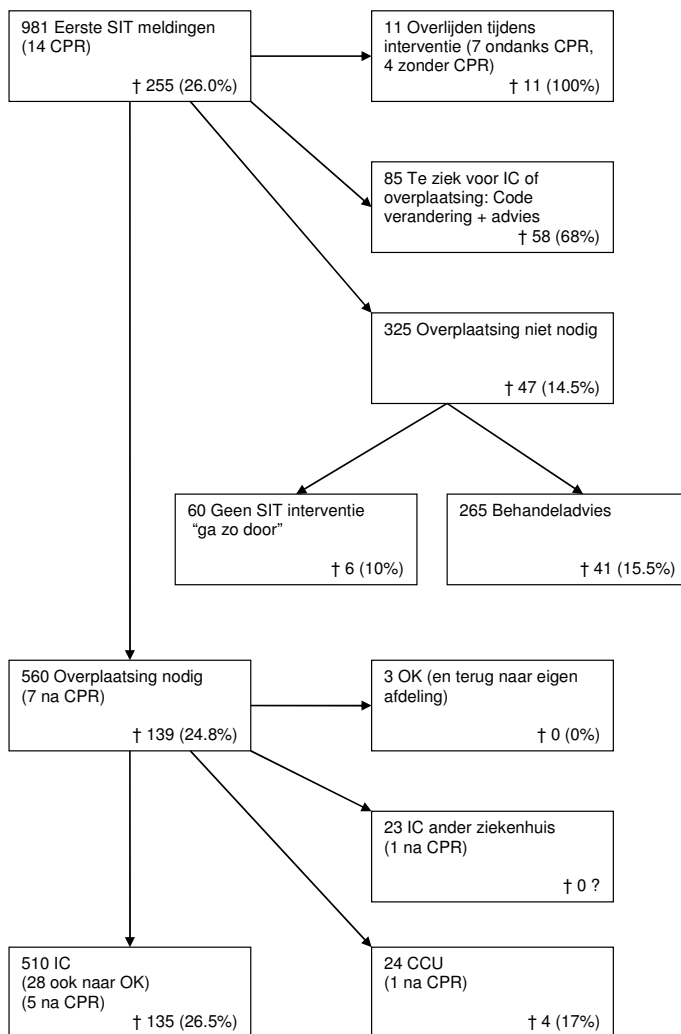
Figuur 6.1. De scorekaart van het spoedinterventieteam (SIT-scorekaart) van de Reinier de Graaf Groep.



Figuur 6.2. Spreiding van 1058 consulten van het spoedinterventieteam (SIT) van een groot algemeen ziekenhuis over de week, gemeten in de periode 2005-2009.



Figuur 6.3. Spreiding van 1058 consulten van het spoedinterventieteam (SIT) van een groot algemeen ziekenhuis over de dag, gemeten in de periode 2005-2009.



Figuur 6.4. Stroomdiagram van het verloop van de consulten van een spoedinterventieteam (SIT) in een groot algemeen ziekenhuis in de periode 2005-2009.

BESCHOUWING

Het is gebleken, ook in Nederlandse ziekenhuizen, dat patiënten die afstevnen op levensbedreigende complicaties zoals een hartstilstand, niet of pas laat herkend worden. (1-5) Dit was voor ons reden om in ons ziekenhuis het SIS op te zetten. Een groot voordeel van dit systeem is dat voor de herkenning van een mogelijk bedreigde patiënt geen speciale kennis nodig is: het enige wat nodig is, is het noteren van de vitale

parameters. Bij het overschrijden van een grenswaarde moet alarm worden geslagen. In ons SIS is eerst de behandelende arts en daarna ook het spoedinterventieteam met IC-arts, IC-verpleegkundige en de nodige apparatuur snel beschikbaar om de patiënt te beoordelen en te behandelen. Uit onze data blijkt dat een consult van het SIT in meer dan de helft van de gevallen leidt tot overplaatsing van de patiënt naar een afdeling waar meer zorg geleverd kan worden. Ongeveer een derde van de patiënten wordt op de verpleegafdeling verder behandeld, vaak met extra adviezen van de intensivist. Bij een belangrijke minderheid van de patiënten wordt besloten om geen IC-behandeling te starten en een groot deel van deze patiënten overlijdt in het ziekenhuis. Als we aannemen dat deze keuze terecht gemaakt is, betekent dat voor deze patiënten dat een ingrijpende en vergeefse IC-behandeling wordt vermeden ten gunste van een meer palliatief beleid.

Hoewel deze studie veel inzicht kan geven in de praktijk van het SIS kent de studie ook belangrijke beperkingen. Informatie over patiënten die wel vitaal bedreigd waren, maar voor wie het spoedinterventieteam niet werd opgeroepen, ontbreekt. De effectiviteit van het SIS is met de aanwezige data niet te beoordelen. Daarvoor zou gerandomiseerd onderzoek nodig zijn. Het is echter moeilijk om een gerandomiseerd onderzoek op te zetten om de effectiviteit van het SIS aan te tonen. Randomisatie kan misschien nog wel plaatsvinden op het niveau van de individuele patiënt, maar de artsen en hulpverleners kunnen om praktische en ethische redenen moeilijk geblindeerd worden voor, tijdens en na identificatie van een vitaal bedreigde patiënt. Het is immers niet verantwoord om een potentieel bedreigde patiënt te identificeren zonder daarna consequenties te trekken uit deze bevinding. Randomisatie moet daarom plaatsvinden op afdelingsniveau of op ziekenhuisniveau, maar hierdoor worden weer nieuwe mogelijk versturende factoren geïntroduceerd.

Cohortonderzoeken als het onze leiden voor zover het gaat om bewijs van effectiviteit van het SIS op zijn best tot zachte uitkomsten die zeer gevoelig zijn voor versturende factoren. Wij hebben daarom niet geprobeerd om de effectiviteit van het SIS aan te tonen doch slechts beschreven hoe het SIS geïmplementeerd werd en wat er gebeurde met de patiënten die daadwerkelijk zijn beoordeeld en behandeld door het SIT. Ook het model dat wij gekozen hebben voor het SIS kent beperkingen. Een veelgenoemd discussiepunt is de vraag of een SIS leidt tot vermindering van de expertise van anderen dan IC-artsen in de herkenning en behandeling van vitaal bedreigde patiënten. In onze ervaring is dat niet het geval. De scholing die gegeven wordt in het kader van het systeem, zowel algemeen als tijdens en na de behandeling van een bedreigde patiënt bij het SIT-consult, leidt in onze beleving tot een verbetering van kennis en handelsbekwaamheid bij de afdelingsartsen en verpleegkundigen. Dit is een direct gevolg van de keuze die wij gemaakt hebben om de behandelend arts te betrekken bij het SIT-consult. In de internationale literatuur wordt vaak gekozen voor een SIS waarbij iedereen op elk

willekeurig moment het SIT op kan roepen zonder dat de hoofdbehandelaar betrokken is bij het consult of zelfs maar op de hoogte gesteld wordt. Wij hebben bewust gekozen om alarmering alleen door artsen en verpleegkundigen te laten plaatsvinden en om de patiënt eerst door de hoofdbehandelaar te laten beoordelen. Driekwart van de beoordelingen worden door de hoofdbehandelaar afgehandeld zonder dat het SIT ingeroepen hoeft te worden. Zoals ook in de inleiding al beschreven, zijn de voordelen van deze aanpak dat de kennis van de hoofdbehandelaar over de voorgeschiedenis, behandelwensen en actuele situatie van de patiënt niet verloren gaan, dat de kennis en vaardigheden met betrekking tot acuut zieke patiënten in het algemeen bij de hoofdbehandelaar niet verloren gaat, dat de weerstand tegen het inroepen van het SIT minimaal is en dat de werklast voor het SIT dragelijk is. De vertraging tot het daadwerkelijk inroepen van het SIT (maximaal een half uur) kan echter in het nadeel van de patiënt zijn. Verder onderzoek hiernaar dient nog plaats te vinden. Uit onze data blijkt dat er minder SIT-consulten worden gedaan gedurende de nacht en in het weekend. Een verklaring hiervoor zou kunnen zijn dat er 's nachts en in het weekend minder ingrepen en dus minder verstoringen van vitale functies plaatsvinden. Het is echter ook mogelijk dat er onderrapportage of suboptimale zorg is gedurende de daluren.

Met dit artikel hebben wij beschreven hoe het SIS in ons ziekenhuis is geïmplementeerd en hoe het functioneert. Het SIS is in ons ziekenhuis een effectieve manier om tot een snelle triage voor IC-behandeling te komen. Daarmee kunnen we niet aantonen dat het SIS levens redt of dat het noodzakelijk is. Het is goed mogelijk dat de vitaal bedreigde patiënten ook zonder aanwezigheid van het SIS via een klassiek consult door de intensivist beoordeeld waren met een zelfde beloop als nu tot gevolg. Onze ervaring, die zoals bij veel organisatorische veranderingen niet in getallen is uit te drukken, is echter dat het SIS in ons ziekenhuis geleid heeft tot een verhoogd bewustzijn ten aanzien van mogelijk vitaal bedreigde patiënten, zowel bij artsen als verpleegkundigen. Dit betekent dat potentiële IC-behoefte patiënten eerder dan voorheen worden herkend en dat daardoor vaak meer tijd is om de juiste beslissingen te nemen. Patiënten die geen baat hebben bij IC-behandeling kunnen waardig afscheid nemen en patiënten die wel voor IC-behandeling in aanmerking komen, kunnen daar op worden voorbereid. We zijn ons ervan bewust dat deze voordelen niet blijken uit de gepresenteerde data, maar het geheel maakt dat wij in onze kliniek doorgaan met het SIS zoals hier beschreven.

CONCLUSIE

Wij zijn van mening dat het SIS zich in ons ziekenhuis heeft ontwikkeld tot een middel om te komen tot effectieve triage van vitaal bedreigde patiënten.

Leerpunten

- Het spoedinterventiesysteem identificeert en behandelt patiënten die het gevaar lopen ernstige complicaties te ontwikkelen, zoals een circulatie-of ademstilstand.
- De helft van de patiënten voor wie het spoedinterventieteam uitrukt, wordt overgeplaatst naar de IC.
- Bij een minderheid van de patiënten wordt ingeschat dat zij geen baat zullen hebben bij IC-behandeling en worden behandelgrenzen ingesteld.

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Chapter 7

Long-term survival after ICU treatment

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ABSTRACT

Background

To study long-term survival in patients treated in the ICU and who survive to hospital discharge.

Methods

Single center retrospective cohort study of patients admitted to a mixed intensivist-led 10 bed ICU in a teaching hospital between 2004 and 2009 and discharged alive from the hospital with complete follow-up until January 1st, 2011.

Results

A total of 3477 individual patients were admitted to the ICU, 491 (14.1%) of whom died in the hospital while 2986 survived to hospital discharge. In the first year after discharge 436 out of 2986 (14.6%) patients died. Mortality after hospital discharge was highest in the first three months. For patients discharged alive from the hospital the risk of dying during the first year increased significantly with age, APACHE II score at admission and being discharged to a place other than home. Sepsis on ICU admission, mechanical ventilation, renal replacement therapy during ICU treatment or admission type had no effect on one-year mortality rate.

Conclusions

Patients who survive ICU treatment have a high risk of dying during the next year. This risk is almost as great the risk of dying during ICU and hospital treatment and increases with age and illness severity on admission to the ICU.

INTRODUCTION

For critically ill patients survival is the outcome of greatest interest.^{1,2} Survival to ICU discharge or even to hospital discharge is only a short term goal though and data on long term outcome are necessary to appreciate the effectiveness of intensive treatment.^{1,3} In order to make informed and shared decisions regarding ICU care, patients and families alike may be more interested in prognosis after ICU treatment than in details of the treatment itself. Surviving intensive care to die shortly thereafter cannot be regarded as a good outcome but many studies and caregivers do not look beyond hospital or even ICU mortality. Awareness of risk factors for death shortly after intensive care treatment may help to prevent this unwanted outcome. Many recent studies focus on quality of life after intensive care treatment,^{4,5} but few studies focus on late mortality after intensive care treatment. Most studies date from the 1980's and these studies are difficult to interpret, not only because times have changed but also because of missing data including base line characteristics and analysis of risk factors for mortality.⁶ The purpose of this single center retrospective cohort study was to study long-term survival after ICU treatment and to study available patient and treatment related risk factors for mortality.

MATERIALS AND METHODS

Setting

The study was conducted in the single mixed medical and surgical adult intensive care unit of the Reinier de Graaf Hospital in Delft, the Netherlands. The hospital is a teaching hospital, has 500 beds and all specialities except cardiac surgery and neurosurgery are available. The closed format ICU has 10 beds and is supervised by a team of five intensivists who are available 24/7. The intensivists on call decide on admission to and discharge from the ICU. The nurse to patient ratio is between 1:2 and 1:3. During the study period APACHE II standardized mortality rate (SMR), the ratio between observed hospital mortality and expected hospital mortality according to APACHE II, was 0.73. The hospital has an ICU based medical emergency team. Starting in 2008, all patients who have been mechanically ventilated or have been treated in the ICU for more than 3 days are invited to visit the post ICU clinic.

Patients

All consecutive patients that were admitted between January 1st 2004 and December 31st 2009, who lived in the Netherlands (to enable long term follow-up), who fulfilled APACHE II inclusion criteria (16 years or older, no readmission to the ICU, no cardiac surgery and length-of stay of at least eight hours) and who were discharged alive from

the hospital after ICU treatment, were entered in the study. If a patient was admitted to the ICU more than once in the study period, only data from the first admission were used for the study. The need for ethical approval and informed consent was waived by the local ethical committee.

Data collection

Demographic data, APACHE II scores, expected mortality and outcome data (ICU and hospital mortality) were collected on admission as part of the routine and mandatory data collection that is demanded and monitored by the Dutch Intensive Care Registry (Nationale Intensive Care Evaluatie, NICE). All intensivists were trained on data collection. Physiological data and data about patient history were collected on paper by the intensivist on call, demographic data and laboratory data were collected electronically. All data were entered in a dedicated ICU database (Mediscore, Itemedical, Tiel, Netherlands) either electronically or by the unit's secretaries. In accordance with APACHE II and NICE definitions patients are defined as medical patients if they had not been in surgery in the preceding seven days and were not admitted to prepare them for surgery. Otherwise patients were either planned or elective surgical patients when the surgery took place according to the schedule, or emergency surgery patients when surgery had not been planned beforehand. Data quality is checked regularly by external officials from NICE.⁷ Data on ICU and hospital mortality are routinely entered in hospital and ICU databases and crosschecked. Data on mortality after hospital discharge were extracted from the hospital database and crosschecked with a national administrative database, Sectorale Voorziening Berichten in de Zorg, (SVZ-B) that allows local hospital data managers to check their patient data and keeps track of the date of death of all patients dying in the Netherlands. Patients who did not live in the Netherlands were excluded from the study. If no date of death was recorded on January 1st, 2011, the patient was presumed to be alive on that date.

Statistical analysis

The study endpoint was all cause mortality during follow up until January 1st 2011, so minimum follow-up after ICU admission was one year. We studied the association between mortality and risk factors as available in the database: age, illness severity as expressed by APACHE II score and expected mortality, the presence of sepsis on admission, treatment with mechanical ventilation, treatment with renal replacement therapy in the ICU, length of stay in the ICU, admission type and hospital discharge destination. The crude association between mortality and risk factors was studied for the cohort of patients that were discharged alive from the hospital. Data are presented in three overlapping analyses comparing one-year mortality, three-year mortality and Kaplan-Meier curves. Continuous data are reported as mean and standard deviation (SD) or as

median and interquartile range (IQR) as appropriate and compared using the t-test or Mann Whitney U test as appropriate. Normality was checked using histograms and Q-Q plots. Categorical data were compared using the Chi square test and by calculating odds ratios and 95% confidence intervals (CI). For comparing survival in the Kaplan-Meier curves the log rank test was used. Logistic regression analysis was used to study risk factors for one and three year survival. For logistic regression analysis age and APACHE II score and were entered as continuous variables and entered as categorical variables were sepsis on admission (yes/no), mechanical ventilation (yes/no), renal replacement therapy (yes/no), admission type (medical, planned surgery or emergency surgery), ICU length of stay (either seven days or less or more than seven days) and being discharged to a place other than the patient's own home (yes/no). Linearity was tested by using stratified analyses. Cox proportional hazard analysis was not used because the mortality risk declined significantly over time, violating the proportional hazard assumption. Multicollinearity was excluded by studying correlation between variables in the equation, R^2 was never more than 0.28, so overlap of information from variables was never more than 28%. Interaction was tested by studying product terms, no product term was found to be significant. Hosmer-Lemeshow statistic was reported for goodness-of-fit. Two sided comparisons with 95% confidence intervals (95% CI) were used and p values of less than 0.05 were considered statistically significant. Data were analysed with SPSS 18.0 (SPSS, Chicago, IL, USA).

RESULTS

From January 1st, 2004, until December 31st, 2009, 3665 individual patients had 4227 admissions to the ICU. After exclusion of patients not fulfilling APACHE II inclusion criteria and patients living outside the Netherlands and patients who died in the ICU or subsequently in the hospital, 2986 patients who survived to hospital discharge after ICU treatment remained as the study cohort (Figure 7.1). From this study cohort of 2986 individual patients who survived to hospital discharge, 436 (14.6%) patients died within one year after ICU treatment while 2550 patients (85.4%) were alive one year after ICU treatment. One year mortality increased with age from 3.4% in patients younger than 50 years to 44.7% in patients older than 90 years. Patient characteristics and one-year mortality are shown in Table 7.1. Three year follow up was complete for 1585 patients admitted between 2004 and 2007 and shown in Table 7.2. Mortality in patients that survived to hospital discharged after ICU treatment decreased from 14.6% of the patients at risk in the first year after discharge to 4.3% in the sixth year after discharge (Table 7.3). The highest mortality was seen in the first three months after discharge. Kaplan-Meier curves are shown in Figure 7.2. Mortality after hospital discharge was also associated

with APACHE II score on ICU admission and with being discharged not to the patient's own home. Sepsis on ICU admission, mechanical ventilation, renal failure requiring renal replacement therapy during ICU treatment and admission type (medical, planned surgery or emergency surgery) were not related to mortality (Tables 7.1, 7.2 and 7.4). Mechanical ventilation during ICU treatment was a risk factor for one year mortality in univariate analysis but not in multivariate analysis (Table 7.1 and 7.4).

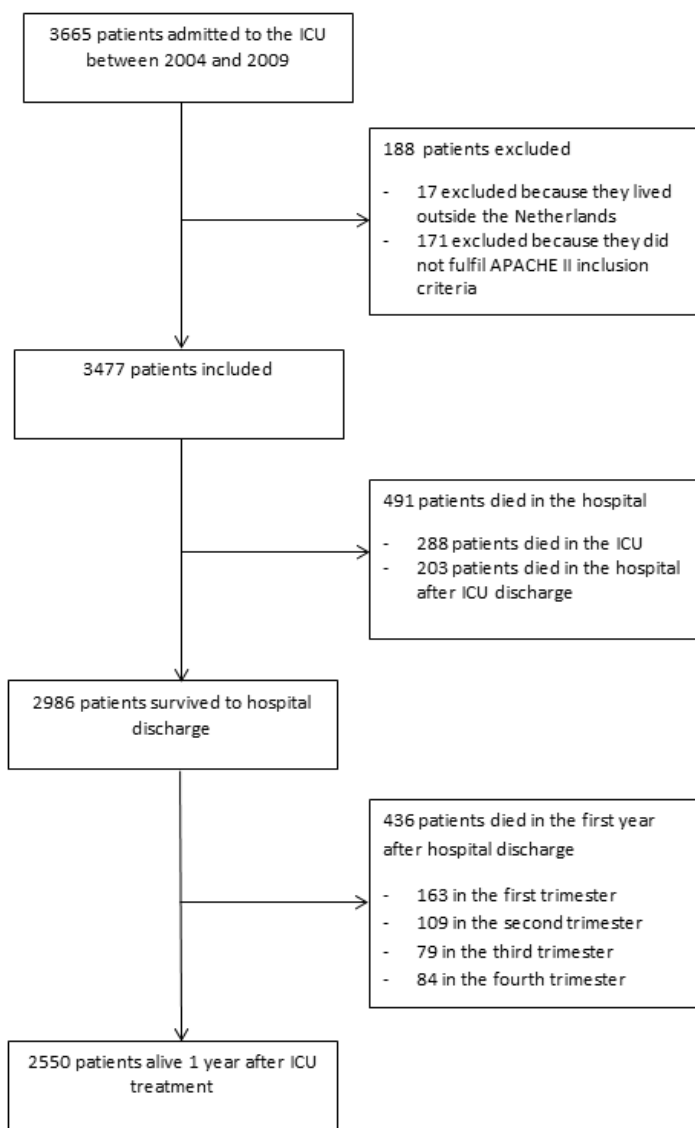


Figure 7.1. Patients.

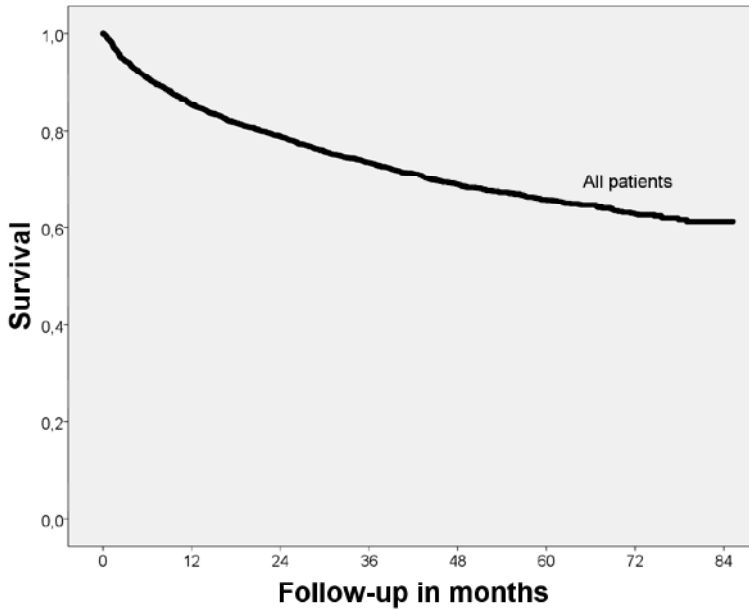


Figure 7.2a. Kaplan-Meier curve for all 2986 patients discharged alive from the hospital after ICU treatment.

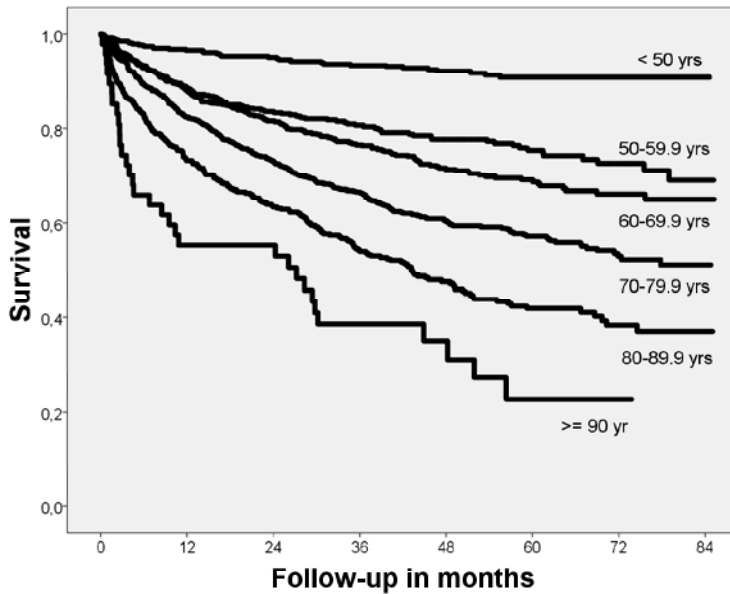


Figure 7.2b. Kaplan-Meier curve for all 2986 patients discharged alive from the hospital after ICU treatment with respect to age. $P < 0.001$, log rank test.

Table 7.1. One-year mortality in patients that were discharged from the hospital alive after ICU treatment. Normally distributed data presented as mean (SD), non-parametric data as median (interquartile range).

	Discharged alive from the hospital	Not alive 1 year after ICU admission	Alive 1 year after ICU admission	p (3)	OR (95% CI)
Number	2986 = 100%	436 (14.6%)	2550 (85.4%)		
Male	1677	245 (14.6%)	1432 (85.4%)	ns	
Age	64.5 (16.3)	72.6 (12.7)	63.1 (16.5)	<0.001	
Age <50	536	18 (3.4%)	518 (96.6%)		Ref = 1
Age 50-59	476	55 (11.6%)	421 (88.4%)		3.76 (2.17-6.50)
Age 60-69	654	79 (12.1%)	575 (87.9%)		3.95 (2.34-6.69)
Age 70-79	845	149 (17.6%)	696 (82.4%)	<0.001	6.16 (3.73-10.2)
Age 80-89	428	114 (26.6%)	314 (73.4%)		10.5 (6.23-17.5)
Age 90+	47	21 (44.7%)	26 (55.3%)		23.2 (11.1-48.9)
Medical	1049	157 (15.0%)	892 (85.0%)		
Planned surgery	1550	214 (13.8%)	1336 (86.2%)	ns	
Emergency surgery	387	65 (16.8%)	322 (83.2%)		
APACHE II score (1)	12.2 (6.2)	13.9 (5.9)	11.9 (6.2)	<0.001	
APACHE II exp mort	9% (4-19)	13% (7-17)	8% (4-18)	<0.001	
APACHE II score ≤10	1329	124 (9.3%)	1205 (90.7%)		Ref=1
APACHE II score 11-20	1354	255 (18.8%)	1099 (81.2%)	<0.001	2.26 (1.79-2.84)
APACHE II score 21-30	270	50 (18.5%)	220 (81.5%)		2.20 (1.54-3.16)
APACHE II score 30+	33	7 (21.2%)	26 (78.8%)		2.61 (1.11-6.15)
No sepsis (1)	2641	387 (14.7%)	2254 (85.3%)		
Sepsis	345	49 (14.2%)	296 (85.8%)	ns	
No mechanical ventilation (2)	2903	285 (13.6%)	1808 (86.4%)		Ref=1
Mechanical ventilation	893	151 (16.9%)	742 (83.1%)	0.023	1.29 (1.04-1.60)
No RRT (2)	2883	417 (14.5%)	2466 (85.5%)		
RRT	103	19 (18.4%)	84 (81.6%)	ns	
ICU LOS (days)	1.1 (0.8-2.9)	1.5 (0.8-3.5)	1.1 (0.8-2.9)	ns	
ICU LOS ≤ 7 days	2719	400 (14.7%)	2319 (85.3%)		
ICU LOS >7 days	267	36 (13.5%)	231 (86.5%)	ns	
Hospital LOS (days)	11 (7-19)	15 (9-27)	10 (7-18)	<0.001	
Cumulative TISS score	47 (31-100)	54 (35-113)	46 (30-98)	<0.001	
Discharge home	2296	284 (12.4%)	2012 (87.6%)		Ref=1
Discharge elsewhere	690	152 (22.0%)	538 (78.0%)	<0.001	2.00 (1.61-2.49)

(1) On admission to the ICU

(2) During ICU treatment

(3) Student's t test for normally distributed continuous variables, Mann Whitney U test for other continuous variables and Chi-square test for categorical variables; p values above 0.05 are given as ns=not significant.

Exp mort = expected hospital mortality. LOS = length of stay. RRT = renal replacement therapy. TISS = therapeutic intervention scoring system.

Table 7.2. Three-year mortality in 1585 patients that were discharged from the hospital alive after ICU treatment. Normally distributed data presented as mean (SD), non-parametric data as median (interquartile range).

	Discharged alive from the hospital	Not alive 3 years after ICU admission	Alive 3 years after ICU admission	p (1)	OR (95% CI)
Number	1585 = 100%	415 (26.2%)	1170 (73.8%)		
Male	908	249 (27.4%)	659 (72.6%)	ns	
Age	65.2 (16.3)	73.3 (12.1)	62.3 (16.6)	<0.001	
Age <50	260	16 (6.2%)	244 (93.8%)		Ref = 1
Age 50-59	255	39 (15.3%)	216 (84.7%)		2.75 (1.50-5.07)
Age 60-69	341	79 (23.2%)	262 (76.8%)		4.60 (2.61-8.09)
Age 70-79	452	147 (32.5%)	305 (67.5%)	<0.001	7.35 (4.27-12.7)
Age 80-89	250	117 (46.8%)	133 (53.2%)		13.4 (7.64-23.6)
Age 90+	27	17 (63.0%)	10 (37.0%)		25.9 (10.2-65.7)
Medical	566	140 (24.7%)	426 (75.3%)		
Planned surgery	834	231 (27.7%)	603 (72.3%)	ns	
Emergency surgery	185	44 (23.8%)	141 (76.2%)		
APACHE II score (1)	12.2 (6.1)	14.0 (5.7)	11.6 (6.2)	<0.001	
APACHE II exp mort	9 (4-19)	13 (7-26)	7 (4-16)	<0.001	
APACHE II score ≤10	702	116 (16.5%)	586 (83.5%)		Ref = 1
APACHE II score 11-20	722	242 (33.5%)	480 (66.5%)	<0.001	2.56 (1.98-3.28)
APACHE II score 21-30	148	53 (35.8%)	95 (64.2%)		2.82 (1.91-4.17)
APACHE II score 30+	13	4 (31%)	9 (69%)		2.25 (0.68-7.41)
No sepsis (1)	1455	378 (26.0%)	1077 (74.0%)		
Sepsis	130	37 (28.5%)	93 (71.5%)	ns	
No mechanical ventilation (2)	1178	298 (25.3%)	880 (74.7%)		
Mechanical ventilation	407	117 (28.7%)	290 (71.3%)	ns	
No RRT (2)	1543	404 (26.2%)	1139 (73.8%)		
RRT	42	11 (26.2%)	31 (73.8%)	ns	
ICU LOS (days)	1.1 (0.8-2.8)	1.6 (0.9-3.2)	1.0 (0.8-2.6)	<0.001	
ICU LOS ≤ 7 days	1468	382 (26.0%)	1086 (74.0%)		
ICU LOS >7 days	117	33 (28.2%)	84 (71.8%)	ns	
Hospital LOS (days)	11 (7-18)	14 (9-25)	10 (6-16)	<0.001	
Cumulative TISS score	43 (29-87)	54 (33-103)	41 (28-79)	<0.001	
Discharge home	1239	300 (24.2%)	939 (75.8%)		Ref = 1
Discharge elsewhere	346	115 (33.2%)	231 (66.8%)	<0.001	1.56 (1.20-2.02)

(1) On admission to the ICU

(2) During ICU treatment

(3) Student's t test for normally distributed continuous variables, Mann Whitney U test for other continuous variables and Chi-square test for categorical variables; p values above 0.05 are given as ns=not significant.

Exp mort = expected hospital mortality. LOS = length of stay. RRT = renal replacement therapy. TISS = therapeutic intervention scoring system.

Table 7.3a. Mortality following hospital discharge in patients that were discharged alive from the hospital after ICU treatment.

Time after ICU admission	Number at risk	Mortality	p (1)
0-3 months	2986	163 (5.5%)	<0.001
4-6 months	2823	109 (3.9%)	
7-9 months	2714	79 (2.9%)	
10-12 months	2635	84 (3.2%)	

(1) Chi square test In patients surviving to hospital discharge after ICU treatment, mortality is highest in the first three months after discharge.

Table 7.3b. Mortality following hospital discharge in patients that were discharged alive from the hospital after ICU treatment.

Time after ICU admission	Number at risk	Mortality	p (1)
0-12 months	2986	435 (14.6%)	<0.001
13-24 months	2383	183 (7.7%)	
25-36 months	1866	127 (6.8%)	
37-48 months	1391	88 (6.3%)	
49-60 months	954	44 (4.6%)	
61-72 months	557	24 (4.3%)	

(1) Chi square test In patients surviving to hospital discharge after ICU treatment, mortality is highest in the first year after discharge.

Table 7.4a. Logistic regression analysis for one-year mortality in 2986 patients admitted to the ICU that were discharged alive from the hospital.

	Adjusted OR	p
Age (per year)	1.04 (1.03-1.05)	<0.001
APACHE II score (per point)	1.02 (1.00-1.04)	0.011
Discharge not towards home	1.58 (1.26-1.99)	<0.001

Hosmer-Lemeshow goodness-of-fit statistic: 0.415. The model shows that one-year mortality in patients discharged alive from the hospital after ICU admission is independently associated and increases with older age, higher APACHE II score at ICU admission and being discharged not towards home. Sepsis, duration of ICU treatment, mechanical ventilation, renal replacement therapy and admission type were not independently associated with one-year mortality in this logistic regression model.

Table 7.4b. Logistic regression analysis for three-year mortality in 1585 patients admitted to the ICU that were discharged alive from the hospital.

	Adjusted OR	p
Age (per year)	1.05 (1.04-1.06)	<0.001
APACHE II score (per point)	1.03 (1.01-1.05)	0.001
Discharge not towards home	1.37 (1.08-1.74)	0.009

Hosmer-Lemeshow goodness-of-fit statistic: 0.444. The model shows that three-year mortality in patients discharged alive from the hospital after ICU admission is independently associated and increases with older age, higher APACHE II score at ICU admission, and being discharged not towards home. Sepsis, duration of ICU treatment, mechanical ventilation, renal replacement therapy and admission type were not independently associated with three-year mortality in this logistic regression model.

Table 7.5. Recent literature on long term survival in adult patients after intensive care treatment.

Publication	Design	Patients	Hospital mortality	Long term mortality in hospital survivors	Long term mortality including hospital mortality	Risk factors associated with long term mortality	Risk factors not associated with long term mortality
Williams 2005	Review 19 studies, most before 1990	mixed	11-64% (n=21203)		1-year 26-63% 2-year 20-72% 3-year 40-72% 5-year 40-58%	• Age • Comorbidity • Illness severity • Admission diagnosis • Admission type • LOS ICU	
Kaarkola 2006	single center	mixed (including cardiac surgery) >=65 year	36.5% (322 / 882)	3-year 29.6% (166 / 560)	3-year 55.3% (488 / 882)	• APACHE II • Admission diagnosis	
Williams 2008	single center	mixed (including cardiac surgery)	10.6% (2377 / 22298)	1-year 5.4% (1073 / 19921) 5-year 16.3%.	1-year 15.5% (3450 / 22298)	• Age • Comorbidity • Cancer • Admission diagnosis • APACHE II • LOS ICU >= 5 days	• Gender • Admission type (elective surgery / emergency surgery / medical)
Bihorac 2009	single center	surgical, with >=24 hrs ICU treatment		2-year 15.1% (1586 / 10516)		• Acute kidney injury • Age • Male sex • Type of surgery • Comorbidity • LOS-hospital • Discharge destination	• Sepsis
Roch 2011	single center	medical >=80 year	55.5% (166 / 299)	1-year 36.8% (49 / 133) 2-year 52.6% (70 / 133)	1-year 72.0% (215 / 299) 2-year 78.9% 236 / 299)	• SAPS II • Admission diagnosis	• Functional status (Kamofsky)
Kipphuth 2010	single center	non-surgical neurological	22.5% (165 / 733)	1-year 22.4% (127 / 568)	1-year 39.8% (292 / 733)		
Timmers 2011	single center	surgical (non-cardiac), with a single ICU admission	15.7% (286 / 1822)	1-year 10.8% (166 / 1536)	1-year 24.8% (452 / 1822)	• Male sex • Age • APACHE II • Dialysis • Type of surgery	• Comorbidity
Present study	single center	mixed, no cardiac or neuro surgery	14.1% (491 / 3477)	1-year 14.6% (436 / 2986)	1-year 26.7% (927 / 3477)	• Age • APACHE II • Discharge destination	• Sepsis on admission • Dialysis • Admission type • Mechanical ventilation • LOS-ICU

DISCUSSION

In this single center retrospective cohort study in patients discharged alive from the hospital after having been treated in the ICU we found that 14.6% of patients who were discharged alive from the hospital died in the first year after discharge which almost equals the total hospital mortality of 14.1%. For hospital survivors the mortality rate especially increased in the first months after discharge. The risk for mortality after hospital discharge increased independently with age, APACHE II score at ICU admission, ICU length of stay, with having been ventilated and with the patient being discharged to another place than home.

In the intensive care setting, treating patients with conditions that are an immediate threat to their lives, the focus tends to be on short term goals: the first few hours, ICU-, hospital- or 28-day survival. Most intensivists are likely to remember patients for whom the few hours or days that death was postponed were invaluable. Conversely, many patients and their families may think that postponing death for a short time does not justify the pain and suffering associated with many ICU interventions. Are we successfully treating patients who survive intensive care only to die a few weeks later? One could argue that this is unethical or a waste of resources. From our study it is clear that the patients' problems are not over when he or she leaves the ICU. Little is known about the reasons for high mortality in ICU survivors, but obviously there is much to be gained from increased understanding in this subject. A better understanding may also lead to more informed decision making when admitting critically ill patients to the ICU. It is important to understand the factors leading to the high mortality rate noted in ICU treated patients following hospital discharge, so that perhaps we may be able to improve outcome from ICU treatment. This has been acknowledged before but the problem has been far from solved.¹ We believe that this problem deserves more attention and resources from the critical care community.

Our study confirms some results found by others, but it is difficult to compare results from long term survival studies. Many authors choose to study special groups of patients. This has the advantage of reducing heterogeneity but reduces comparability. Results are not always reported in the same manner. Some report long term mortality including ICU and hospital mortality while others report long term mortality in hospital survivors. Different authors study different risk factors for mortality. Most studies date from the 1980's and have been reviewed by Williams *et al.*⁶. Data from this review and from the few more recent studies as well as from the present study are presented in Table 7.5.^{6,8-13} This table shows that in most studies long term mortality is associated with age, the severity of the acute illness, the severity of pre-existent comorbidities or the combination of the two latter as expressed by APACHE or SAPS scores. While age and illness severity on ICU admission are strong predictors for long term mortality both

in the present study and in the literature, these risk factors cannot be amended when the patient is discharged from the hospital. To improve long term mortality we will have to find amendable risk factors, but, as shown in Table 7.5, most if not all studied risk factors are not amendable and therefore will not enable us to change the long term mortality rate. Table 7.5 also shows that 1-year mortality varies between 5.4% and 36.8% in cohorts of hospital survivors or between 15.5% and 72% in cohorts that are studied from ICU admission. The huge variation is most probably related to case-mix. Cohorts with high ICU and hospital mortality also have a high long term mortality. In our opinion it is therefore more rational to compare long term mortality to hospital mortality within one cohort than to compare long term mortality in one cohort to another, but even then it is still not possible to say if long term mortality in a given cohort is inappropriately high or admirably low.

We recognize several limitations in this study. Firstly, ours was a single center study which may limit generalizability. Secondly, we did not record quality of life data, although it is widely recognized that quality of life can be greatly impaired after ICU treatment.^{4,5,14} Thirdly, we may have missed patients that were lost to follow-up because they have left the country. This would underestimate long-term mortality. Fourthly, we were not able to record the cause of death after ICU treatment. In particular we do not know how many patients were discharged with a treatment limitation or palliative care. Furthermore we have no information on organ failure scores during ICU treatment nor on organ failure at hospital discharge.

In conclusion, we found that one-year mortality in patients who were treated in the ICU and survived to hospital discharge was 14.1%. The mortality rate was higher in the first months after discharge. To improve survival of ICU-treated patients following hospital discharge, it is important to determine and understand the causes leading to the high post-discharge mortality rates noted in the present study. This knowledge may result in more rational ICU care and hopefully improved long-term outcome, especially if we find amendable risk factors for long term mortality.

Key messages

- The proportion of patients dying in the first year after ICU treatment is about the same as the proportion of patients who died during ICU and hospital treatment.
- Mortality in hospital survivors after ICU treatment is especially high in the first months after hospital discharge.
- Mortality in hospital survivors after ICU treatment is associated with age, illness severity and whether they are discharged home or not.

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Chapter 8

Introduction and evaluation of a computerised insulin protocol

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ABSTRACT

Objective

To lower glucose levels in all patients in the intensive care unit (ICU) to the target range of 4.5–7.5 mmol/l using a nurse-driven computerised insulin protocol in combination with bedside glucose measurement.

Design

Cohort study.

Setting

Mixed adult ICU.

Patients and participants

All 182 patients admitted to the ICU during a 3-month period were studied, except for 3 patients admitted for diabetic keto-acidosis.

Interventions

Five steps were taken to improve glucose regulation: (1) Nurses were authorised to adjust insulin dosage using a protocol. (2) Glucose was measured more often. (3) Glucose was measured at the bedside. (4) Consecutive protocols aimed for successively lower glucose levels; the final protocol had a target range of 4.5–7.5 mmol/l. (5) The protocol was computerised.

Measurements and result

Mean glucose decreased from 9.23 mmol/l without protocol to 7.68 mmol/l with the final protocol. This final protocol with the target of 4.5–7.5 mmol/l was evaluated more extensively. Glucose levels were measured a total of 1854 times in 179 ICU admissions during 552 ICU treatment days. The median glucose level was 7.0 mmol/l, and 53.1% of glucose measurements were within the target range of 4.5–7.5 mmol/l. One episode of hypoglycaemia (glucose $\leq$ 2.2 mmol/l) occurred, representing 0.5% of patients or 0.05% of glucose measurements.

Conclusions

The combined strategy of successively more ambitious nurse-driven (computerised) insulin protocols and bedside glucose measurement resulted in acceptably low glucose levels with very few episodes of hypoglycaemia.

INTRODUCTION

Evidence is accumulating that regulation of blood glucose around normal levels in critically ill patients reduces morbidity and mortality compared with accepting higher glucose levels [1, 2, 3, 4]. Several guidelines stress the necessity of strict glucose regulation in intensive care [5]. The exact glucose values one should aim for are currently a matter of discussion and probably depend on type of patient, time spent in intensive care and staffing [6, 7]. Enhanced glucose regulation requires intensive monitoring and frequent adjustments of insulin dose. Nurse-driven protocols and frequent glucose measurement are advocated to achieve this strict regulation of blood glucose. Several protocols have been published, some aiming for tight control (target 4.5–6.1 mmol/l), some aiming for less stringent control [3, 4, 8, 9, 10, 11, 12, 13, 14, 15].

In our unit insulin was traditionally prescribed by doctors based on their own personal rules, there was no uniform strategy. Glucose measurement was mostly done by sending the blood samples to the distant laboratory, with an average time of 60 min from sampling to result, and an even longer time interval until insulin administration. Mean glucose was 9.23 mmol/l and median glucose was 8.1 mmol/l.

We thought that enhanced glucose control could be achieved by taking insulin prescription away from the doctors and developing and implementing consecutive nurse-driven (computerised) insulin protocols, with each consecutive protocol aiming for lower glucose levels. We report here on the process of introduction of the protocols and on the effect of the protocol on the blood glucose levels of the patients in the unit.

PATIENTS AND METHODS

The unit is a closed-format 10-bed mixed adult ICU in a 550-bed general hospital. Two thirds of the ICU patients are surgical.

Introduction of the nurse-directed insulin protocol

Five organisational changes were made to arrive at the present situation. Traditionally, intensivists or internal medicine residents prescribed insulin as prompted by nurses and blood glucose levels. The first change was to eliminate delay, since the protocol enabled nurses to give insulin without having to contact a doctor. Previously glucose was measured at least once a day at 6 a.m., and when the patient was on insulin also at 11 a.m., 5 p.m. and 8 p.m. The second change was to have glucose measured more often during the day. Traditionally the glucose measurement was not done at the bedside but the blood had to be sent to the laboratory, so nurses had to wait 1 h on average for before the result of the measurement was available. The third change was to have glucose

measured at the bedside, with an instantaneous result. Traditionally every doctor had his own insulin-prescribing algorithm. The fourth change was the insulin-prescribing protocol itself. Four consecutive protocols were made with successively lower glucose goals. The first protocol, introduced in August 2003, consisted of one sheet of instructions for nurses on how much insulin to give depending on current glucose level, previous glucose level and previous insulin dose. As before, insulin was given either as an intravenous bolus or as a continuous intravenous infusion. The first protocol aimed for blood glucose between 6 and 11 mmol/l. This protocol was quickly replaced by the second, introduced in November 2003, aiming at glucose between 6 and 10 mmol/l. The third protocol, introduced in August 2004, aimed at glucose between 5 and 9 mmol/l and was no longer a paper sheet but a computer-based protocol. So, the fifth change was to computerise the protocol. From that moment on it was no longer necessary for the nurses to read along the various lines in the paper sheet. All they had to do now was to enter four variables (previous glucose, present glucose, present insulin dose per hour and the amount of feeding per hour) in the computerised form to receive new instructions. These instructions were also fourfold: the insulin bolus to give, the new hourly rate of the insulin pump, the next time to measure glucose and, in cases of hypoglycaemia, instructions for giving rescue dextrose. The fourth protocol, which is discussed and evaluated here, introduced in June 2005, aiming at glucose between 4.5 and 7.5 mmol/l is a computer-based protocol like the third and is described in detail below (Figure 8.1 and Table 8.1). Throughout the development of consecutive protocols, nurses were asked to actively participate in this development by constantly looking for possible mistakes or opportunities for improvement.

Invoer Geef <u>nieuwe</u> glucose 11.4 mmol/L Geef <u>oude</u> glucose (niet ouder dan 6 hr) 13.5 mmol/L Geef oude pompstand 0 E/hr Hoeveel voeding heeft de patient? > 25 ml/hr		- Dit programma geeft op grond van oude glucose, nieuwe glucose, pompstand, informatie over de voeding aan hoe de insuline verder gedoseerd moet worden. - Dit programma streeft naar glucoses tussen de 4,0 en de 8,0 mmol/L. - Het programma geldt voor alle IC patienten met 2 uitzonderingen: het geldt niet bij keto-acidose en het geldt niet bij voeding in porties, dus niet bij mensen die gewoon eten. Het programma geldt alleen bij glucoses tot 35. De toediening van insuline is altijd intraveneus. <u>Actrapid en novorapid</u> zijn beiden toegestaan. De bolus is maximaal 12 E, de pomp is maximaal 10 E/hr. - Glucoses worden meestal bepaald om de 4 uur (6, 10, 14, 18, 22, 02 hr), maar het programma geeft daar instructies over. Noteer steeds op de lijst wanneer er weer een glucose bepaald moet worden. - Gebruik bij voorkeur de AccuChek. De AccuChek <u>niet</u> gebruiken bij CAPD met isodextrine (gebruik bij CAPD patienten de AccuChek liever helemaal niet). - Als de oude glucose ouder is dan 6 uur, kies dan "niet bekend". - Bij TPN altijd glucose op zijn minst a 4 hr. - Als tussen door de voeding gestopt wordt moet de insuline pomp minstens worden gehalveerd. - Het is nadrukkelijk toegestaan om van het protocol af te wijken als je vanuit jouw kennis en ervaring een andere insuline dosering beter vindt. Bepaal dan eventueel een keer extra het glucose. - Meldt problemen aan mij (Iwan)
Bereken 		
Uitvoer Geef een bolus van 3 E De nieuwe pompstand wordt 1 E/hr Meet glucose opnieuw over 4 hr		

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Figure 8.1. The insulin protocol – computer interface.

Table 8.1 - The insulin protocol - algorithm The insulin protocol is computerised, the algorithm is given below. The nurse feeds 4 items to the interface: (1) the current amount of insulin per hour or OP (old pump), (2) the current blood glucose or NG (new glucose) (3) the previous blood glucose (no older than 6 hrs) or old glucose (OG) and (4) the amount of feeding, either ≤ 25 ml/hr or >25 ml/hr. Calculations are hidden from the user of the program. The interface returns 4 items: (1) new amount of insulin per hour (NP), (2) the amount of the intravenous insulin bolus (B), (3) timing of the next blood glucose measurement and (4) additional messages if any.

Table 8.1a Calculation of the new insulin dose per hour (NP)

OP	NG and OG		NP
If OP=0	and if NG<7.5	and if OG=known	Then NP=0
If OP=0	and if NG 7.5-9	and if OG=known	Then NP=0.5
If OP=0	and if NG <9	and if OG=unknown	Then NP=0
If OP=0	and if NG 9-12	and for any OG	Then NP=1
If OP=0	and if NG 12-15	and for any OG	Then NP=2
If OP=0	and if NG 15-20	and for any OG	Then NP=3
If OP=0	and if NG >20	and for any OG	Then NP=4
If OP>0	and for any NG	and if OG=unknown	Then NP=0 ("Call doctor")
If OP>0	and if NG 0-3	and for any OG	Then NP=0
If OP>0	and if NG 3-4.5	and if OG<3	Then NP=0
If OP>0	and if NG 3-4.5	and if OG 3-4.5	Then NP=NG*OP/4.5
If OP>0	and if NG 3-4.5	and if OG >4.5	Then NP=NG*OP/OG
If OP>0	and if NG 4.5-7.5	and if OG <4.5	Then NP=OP
If OP>0	and if NG 4.5-7.5	and if OG 4.5-7.5	Then NP=NG*OP/6
If OP>0	and if NG 4.5-7.5	and if OG >7.5	Then NP=NG*OP/OG
If OP>0	and if NG >7.5	and if NG<OG*0.9 and if 2NG-OG > 15	Then NP=OP*1.5
If OP>0	and if NG >7.5	and if NG<OG*0.9 and if 2NG-OG 9-15	Then NP=OP*1.2
If OP>0	and if NG >7.5	and if NG<OG*0.9 and if 2NG-OG 6-9	Then NP=OP
If OP>0	and if NG >7.5	and if NG<OG*0.9 and if 2NG-OG 3-6	Then NP=OP*0.7
If OP>0	and if NG >7.5	and if NG<OG*0.9 and if 2NG-OG <3	Then NP=OP*0.5
If OP>0	and if NG 7.5-10	and if NG>=OG*0.9	Then NP=MAX(OP*1.2,OP+0.4)
If OP>0	and if NG 10-15	and if NG>=OG*0.9	Then NP=MAX(OP*1.2,OP+1)
If OP>0	and if NG 15-20	and if NG>=OG*0.9	Then NP=MAX(OP*1.5,OP+1.5)
If OP>0	and if NG >20	and if NG>=OG*0.9	Then NP=MAX(OP*2,OP+2)

NP is maximised to MAX(4, OP+1) when feeding ≤ 25 ml/hr or to MAX(8, OP+1) if feeding > 25 ml/hr. NP is never higher than 10. NP is rounded to one decimal when <2 or to whole or halve units when >2 . Values between 0.1 and 0.4 are rounded to 0 or 0.5. (MAX(x,y) signifies the highest value of either x or y).

Table 8.b. Calculation of the intravenous insulin bolus (B)

OP	NG	OG	B
If OP =0	and if NG <9	and for any OG	Then B = 0
If OP =0	and if NG 9-12	and for any OG	Then B = 3
If OP =0	and if NG 12-15	and for any OG	Then B = 6
If OP =0	and if NG 15-20	and for any OG	Then B = 9
If OP =0	and if NG >20	and for any OG	Then B = 12
If OP >0	and for any NG	and if OG is unknown or older than 6hrs	Then B = 0 ("Call doctor")
If OP >0	and if NG ≤9	and if OG >0	Then B = 0
If OP >0	and if NG >9	and if OG >0	Then B = (2NG-OG)*OP/6

B is maximised to 8 when feeding is ≤25 ml/hr or 12 when feeding is >25 ml/hr.

B is rounded to whole units. Values between 0 and 2 are rounded to 0 or 2 units.

Table 8.1c. Timing of next glucose measurement

OP	NG	OG	Timing of next glucose measurement
If OP = 0	and if NG =4.5-7.5	and if OG =3-9	Then next glucose measurement is at 6 a.m.
For any OP	if NG<3	and for any OG	Then next glucose measurement is after 30 min
For any OP	if NG 3-4.5	and for any OG	Then next glucose measurement is after 2 hrs
For all other values of OP, NG and OG			Then next glucose measurement is after 4 hrs

Table 8.1d. Additional messages

If NG<3 display "give 50 ml dextrose 20%".

If OG=unknown and OP>0 display "Call doctor".

Glucose measurement

The central laboratory measured glucose in serum every day at 6 a.m. During the rest of the day glucose was preferably measured at the bedside with the Accu-Check Inform device (Roche Diagnostics). This device returns the glucose level instantly on instillation of a single drop of blood. The glucose results from the Accu-Check Inform are comparable with a hexokinase method (the reference technique) and deproteinised blood samples. The Accu-Check Inform was calibrated daily. All nurses had a single 30-min training session on the Accu-Check Inform device. Blood glucose and serum glucose measurements, glucose measurements from arterial lines, venous lines or finger-sticks were all considered equal. However, blood was drawn preferably from the arterial lines, and all patients with inotropic support, mechanical ventilation or hemodynamic instability had arterial lines in place.

Patients

All patients admitted to the ICU between 1 July 2005 and 30 September 2005 were entered in the study evaluating the fourth and present insulin protocol, except for patients admitted for keto-acidosis in diabetes mellitus.

Evaluation of the efficacy of the insulin protocol

Mean and median glucose levels for all patients admitted to the unit between 1 July 2005 and 30 September 2005 were calculated. Also mean and median glucose levels for the first five ICU treatment days were calculated, as well as the number of glucose measurements inside the target range (Table 8.2). Mortality and morbidity with respect to glucose level were not studied.

The fourth and present insulin protocol

The fourth and final protocol is described in detail in Figure 8.1 and Table 8.1. The insulin protocol was declared applicable for all ICU patients except for patients with keto-acidosis in diabetes mellitus and for patients who had normal meals. The protocol orders insulin to be started when a single glucose measurement above 9.0 mmol/l is recorded or when a second glucose level above 7.5 mmol/l is measured. Insulin is always given intravenously. Insulin is given by infusion pump with 50-ml syringes containing 1 unit of Actrapid insulin (Novo Nordisk) per millilitre. Rescue dextrose 20% 50 ml is given when glucose is below 3.0 mmol/l. The insulin protocol is computerised; the algorithm is given below. The nurse feeds four items to the form: (1) the current amount of insulin per hour, (2) the current blood glucose level, (3) the previous blood glucose level (no more than 6 h previously) and (4) the amount of feeding, either ≤ 25 ml/h or > 25 ml/h. Calculations are hidden from the user of the program. The software returns four items: (1) the new amount of insulin per hour, (2) the amount of the intravenous insulin bolus, (3) the timing of the next blood glucose measurement and (4) additional messages, if any.

Feeding and caloric intake

Patients were preferably fed enterally. If enteral feeding was not possible, parenteral feeding was given. Postoperative patients who were expected to eat again in 1 or 2 days were not fed, but were still treated with insulin if the protocol required this. No glucose infusion was given for the sole purpose of balancing insulin infusion, except as hypoglycaemia rescue therapy.

RESULTS

With the four consecutive protocols the mean of all measured glucose values in all patients decreased from 9.23 mmol/l without protocol to 7.68 mmol/l with the final computerised protocol. The median glucose value decreased from 8.1 mmol/l without protocol to 7.0 mmol/l.

Patients

Between 1 July 2005 and 30 September 2005, 182 ICU admissions were studied to evaluate the final computerised protocol. Three patients were excluded from the analysis because of an admission diagnosis of keto-acidosis in diabetes mellitus, leaving 179 patients to be studied. Characteristics of these patients are presented in Table 8.3.

Glucose measurements

Measured glucose values are presented in Table 8.2. This table illustrates that more than half of blood glucoses values were within the target range of 4.5–7.5 mmol/l and that mean blood glucose decreases from 8.16 mmol/l on day 1 to 6.74 mmol/l on day 5 of ICU treatment.

Table 8.2. Glucose measurements in 179 ICU admissions for the evaluation of the final protocol.

Total number of glucoses	1854
Range of glucose	1.8–29.8 mmol/L
Number of glucoses measurements per ICU treatment day	3.36
Number of glucose measurements per patient (mean / median / range)	11.0 / 4 / 0–129
Median of all glucose measurements	7.0 mmol/L
Mean of all glucose measurements	7.68 mmol/L
Number (%) of patients with hypoglycaemia (glucose $\leq$ 2.2 mmol/L)	1 (0.5%)
Number (%) of glucose $\leq$ 4.4 mmol/L	112 (6.0%)
Number (%) of glucose in target range 4.5–7.5 mmol/L	984 (53.1%)
Number (%) of glucose 7.6–9.9 mmol/L	469 (25.3%)
Number (%) of glucose $\geq$ 10 mmol/L	289 (15.6%)
Mean / median glucose on day 1 of ICU treatment	8.16 / 7.4 mmol/L
Mean / median glucose on day 2 of ICU treatment	8.06 / 7.0 mmol/L
Mean / median glucose on day 3 of ICU treatment	7.79 / 6.9 mmol/L
Mean / median glucose on day 4 of ICU treatment	6.69 / 6.3 mmol/L
Mean / median glucose on day 5 of ICU treatment	6.74 / 6.4 mmol/L

Table 8.3. Patient characteristics for the evaluation of the final computerized protocol

Number of patients	179
Age (years) (median, range)	67 (16-94)
Sex (M/F)	107 / 72
APACHE II at admission (median, range)	13 (2-38)
Medical / surgical	79 / 100
ICU mortality	14 (7.8%)
Number of ICU treatment days	552
Length of stay in the ICU (days) (median, range)	1 (0.03-51)

DISCUSSION

While many authors stress the necessity of strict glucose control in critically ill patients [2, 4, 5, 13] this is difficult to achieve. Many authors agree that insulin protocols should be used by nurses, not doctors, but the protocols themselves are seldom debated. No consensus exists on how these protocols should be evaluated or compared with each other [16, 17]. With our latest computerised insulin protocol we were able to achieve median blood glucose levels of 7.0 mmol/l and mean glucose levels of 7.68 mmol/l in our unit, counting all glucose measurements in all patients except for those admitted with keto-acidosis. There was only one episode of hypoglycaemia (glucose below 2.2 mmol/l) in 555 treatment days in 179 patients with 1854 glucose measurements. Before the implementation of the protocol, median glucose was 8.1 mmol/l and mean glucose was 9.23 mmol/l.

A computerised protocol has several advantages over a paper sheet. Nurses only have to be trained to use the interface, which is very simple, while the calculations of the protocol can be as intricate as needed. We agree with Taylor et al. [14] that protocols on paper sheets can be too complicated, resulting in mistakes or non-compliance. With a computerised protocol there is less chance of mistakes, since it is not necessary to read along lines or make calculations or comparisons by heart. Another advantage of a computerised protocol is that changes in the calculations are unseen by the users and do not require extra training or attention.

The results of this study must be interpreted with caution, and the generalisability of the results is limited due to the fact that this is a single-centre study without a control group. Compared with other studies [2, 13], fewer glucose measurements were done per ICU treatment day. This could mean on the one hand that variations in glucose levels were unnoticed in our study, but this is not very likely. On the other hand, frequent, say 2-hourly measurement of well-regulated patients increases the number of low glucose measurements and thus reduces the median and mean of the whole group, giving a false

impression of improvement of the protocol. Another drawback is that we did not study the effect of enhanced glucose control or lower glucose levels on outcome. The organisational changes we described took place in a 2- to 3-year period and were accompanied by several other changes. It would be wrong to ascribe changes in clinical endpoints like mortality or morbidity over this period solely to enhanced glucose control. But then, the object of this paper was not to study the effect of enhanced glucose control on outcome, but only to illustrate how enhanced glucose control can be achieved safely. One might also criticise this study for regarding all glucose measurements, whether from blood or serum, whether from arterial lines, venous lines or finger-sticks, whether from bedside or central laboratory, as being equal. We are aware that these measurements are not equal, and we are aware that especially in vasopressor-dependent and oedematous patients different measurements can disagree [18]. However, the more seriously ill our patients were, the more often they had arterial lines in place, eliminating the problem of incorrect measurements by finger-stick. Furthermore, we think that the variation from different methods of measurement is much less than the variation of blood glucose itself.

The present protocol targets glucose levels between 4.5 and 7.5 mmol/l. Tight glucose control is more or less defined by van den Berghe et al. [2] as glucose in the range of 4.5–6.1 mmol/l, so the present protocol does not aim for the same degree of control. However, the optimal glucose level for critically ill patients is not known. The landmark study by van den Berghe et al. suggests that glucose in the range of 4.5–6.1 mmol/l is associated with a much better outcome than glucose levels of around 10–11.1 mmol/l. This is largely accepted by the intensive care community although confirmatory studies of similar quality are lacking [2]. The study from the same group in the medical intensive care shows a better outcome only in the patients that received 3 days or more of intensive therapy [1]. The German SepNet group could not confirm the results of van den Berghe et al. [2] in terms of improved outcome, as stated in a preliminary report from the safety analysis of this multicenter trial in patients with severe sepsis and septic shock [19]. The danger of aiming for low glucose levels is hypoglycaemia, which can result, for instance, in permanent brain damage and death when hypoglycaemia goes unnoticed in sedated patients. Many clinicians eager to comply to the strict glucose control guidelines have experienced this. So the optimal glucose level in critically ill patients is apparently below 10 mmol/l and above 2.2 mmol/l, but it is not known if 6.0 mmol/l is better than 8.0 mmol/l. Even more difficult is the question whether it is worth taking the higher risk of hypoglycaemia when aiming for 6 mmol/l and not 8 mmol/l. While van den Berghe [2] suggests a target of 4.5–6.1 mmol/l, Finney [3] claims that glucose levels should be kept below 8.0 mmol/l based on his large retrospective analysis, the current sepsis guidelines advice blood glucose to be kept below 8.3 mmol/l after initial stabilisation [5]. Malhotra [6] advises to aim for glucose values below 8.3 mmol/l in the first days of intensive treat-

ment and suggests lower values after that. Watkinson [7] advises to apply strict glucose control only in selected patients. Hypoglycaemia defined as glucose ≤ 2.2 mmol/l was observed using intensive insulin therapy in 3.4–18.7% of patients in different studies [1, 2, 13, 14, 19]. These authors used more aggressive protocols, aiming at glucose of 4.5–6.1 mmol/l, than the present protocol, which aimed at 4.5–7.5 mmol/l but in which was found only one episode of hypoglycaemia, or 0.5% of patients. In our opinion the added risk of hypoglycaemia when aiming for lower glucose levels should be accepted only when extra benefit is proven. At the moment this is not the case.

Conclusion

In conclusion, we present a computerised insulin protocol to be used by nurses in combination with bedside glucose measurement by means of which we were able to achieve in our view very acceptably low glucose levels with very few episodes of hypoglycaemia.

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Chapter 9

Accuracy of AccuChek® glucose measurement in Intensive Care patients

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ABSTRACT

Objective

To evaluate the accuracy of the AccuChek Inform® point-of-care glucose measurement device as compared to central laboratory glucose measurement.

Design

Prospective, observational study

Setting

A 10-bed mixed closed format ICU in a 500-bed general hospital. The unit has a computerized insulin protocol aiming for 81-135 mg/dL.

Patients

All ICU patients were eligible.

Interventions

None

Measurements

Paired samples (AccuChek® glucose in whole blood calibrated to give whole blood results and central laboratory glucose in serum) were taken simultaneously.

Main results

In 32 critically ill patients, mean age 71.6 years (SD 11.9), mean APACHE II score at admission 17.8 (SD 6.7), 239 paired samples were taken from arterial lines. Mean AccuChek® whole blood glucose was 126 mg/dL (7.0 mmol/L), SD 36 mg/dL (2.0 mmol/L), mean central laboratory serum glucose was 137 mg/dL (7.6 mmol/L), SD 38 mg/dL (2.1 mmol/L). Mean difference was 11 mg/dL (0.61 mmol/L) (8%) (95%CI 9-13 mg/dL, $p < 0.001$). ISO 15197 guideline requires 95% of point-of-care measurements to be within 15 mg/dL margins with reference < 75 mg/dL or within 20% if reference is higher. 216 (90.4%) of AccuChek® measurements were within ISO 15197 margins. Since AccuChek® was calibrated to give whole blood results we calculated a correction factor of 1.086 from the two mean values to correct whole blood AccuChek® into serum like results. This is almost the same as the correction factor of 1.080 given by Roche Diagnostics. By multiplying AccuChek® whole blood results with 1.086, 225 (94.1%) of results were within the ISO 15197 margins. Hematocrit did not influence AccuChek results when in the 0.20-0.44 range. Beyond this range there were not enough data to draw conclusions.

Conclusions

In critically ill patients, the accuracy of AccuChek® glucose measurement calibrated to give serum-like results with blood samples derived from arterial lines is acceptable but falls short about 1% of complying with the ISO 15197 guideline.

INTRODUCTION

Since the landmark trial of van den Berghe¹ intensivists try to reduce morbidity and mortality by optimising glucose control in critically ill patients. How tight glucose control should be is a matter of debate, especially since tight control increases the risk of hypoglycaemia.²⁻⁴ The impact of hypoglycaemia on outcome is also a matter of debate.^{3,5-7} Van den Berghe argues for tight control, that is glucose levels between 80-110 mg/dL (4.4-6.1 mmol/L) and she and her co-workers were able to reach this in the treatment group with only 5 percent of patients experiencing hypoglycaemia.⁸ It has proven very difficult to reproduce this level of glucose control, even for the same group of researchers in another ICU in the same hospital.^{9,10} Intensive insulin therapy with a target range of 80-110 mg/dL has also been associated with increased mortality.¹¹ Our unit uses a computerised protocol that aims for glucose values between 81 and 135 mg/dL.¹² This is not as strict as proposed by van den Berghe.

Several difficulties prevent intensivists from reaching the target of tight glucose control, one of which is the reliability of the point-of-care glucose measurement that is essential in achieving glucose control. The accuracy of point-of-care glucose measurement in critically ill patients has been questioned.¹³⁻¹⁵ The AccuChek® Inform (Roche Diagnostics, Mannheim, Germany) is a point-of-care handheld device that returns glucose level instantly on instillation of a single drop of blood. The AccuChek® is designed for use in hospitals. Through its docking station the glucose result can be transferred to the laboratory database. Like many point-of-care devices the AccuChek® measures glucose in whole blood while the central laboratory reference is measurement of glucose in serum. Whole blood and serum results are not equal.¹⁶ The International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) recommends multiplying whole blood glucose values by 1.11 to estimate serum glucose values.¹⁷ Prior to the present study Roche diagnostics had announced to implement a correction factor of 1.08 to the AccuChek® whole blood result to represent serum glucose values more accurately.¹⁸

This prospective observational study was done to evaluate the accuracy of the AccuChek Inform point-of-care device in measuring whole blood glucose in critically ill patients and subsequently to see if serum glucose might indeed be estimated more accurately from AccuChek® whole blood glucose results by using a simple conversion factor as suggested by the manufacturer.

PATIENTS AND METHODS

The unit is a closed format 10-bed mixed adult ICU in a 500-bed general hospital. Two thirds of ICU patients are surgical. The study was done in February 2007. The local ethics committee waived the need for approval of the study. Of all patients admitted in the study, age, sex, and APACHE II score were recorded. All patients admitted to the ICU were eligible, except patients on peritoneal dialysis, as isodextrin in the dialysis fluids may result in faulty AccuChek® measurements. Glucose control was achieved by nurses, using a computerised protocol that has been described elsewhere.¹² The protocol aimed for glucose between 81 and 135 mg/dL (4.5-7.5 mmol/L). The protocol handles glucose measurements, be it arterial, capillary, venous samples, serum or whole blood samples, all in the same way, but in this study all samples were from arterial lines. According to this protocol glucose measurement was mostly done every 4 hours. Additional glucose measurements were done if necessary.

Glucose measurements

For the purpose of this study, two measures of glucose were used:

1. The AccuChek® Inform device. This is a point-of-care device that returns whole blood glucose level instantly on instillation of a single drop of blood on a dedicated test strip. The AccuChek® was calibrated every day. AccuChek® and test strips were calibrated to return whole blood glucose value. All nurses received a single 30-minute training on using the AccuChek® at the introduction of the device in the unit. The AccuChek® device has a docking station through which results are transferred to the laboratory database.

2. Glucose was also measured in serum by the central laboratory using the Abbott Architect CI 8200® (Abbott Laboratories, Irving, Texas, USA) using the hexokinase method. Precision was found to be 2.1 % at the 45 mg/dL level and 1.1% at the 300 mg/dL level on introduction of the CI8200 in our central laboratory.

We used paired samples, that is both serum send to the central laboratory, as well as blood instilled in the AccuChek®, drawn at the same time from a patient. The blood was always drawn from arterial lines. Laboratory handling was always as soon as possible and always within the hour.

Hematocrit measurements

Hematocrit was measured at least once daily in all patients routinely at 6 am on a Sysmex XE-2100 haematology analyser using the flow peak impedance technique. Hematocrit was measured additionally only if clinical circumstances made this necessary. We correlated hematocrit with the difference between central laboratory glucose and AccuChek results to see if hematocrit would influence the results. The most recent hematocrit value was used for the hematocrit analysis. This was never older than 24 hrs.

Statistical analysis

Data were prepared and analysed with Microsoft Excel. All statistical calculations were performed using SPSS 12.0 (Chicago, Illinois, USA). All values were expressed as mean and standard deviation (SD) for variables with a normal distribution. Normal distribution was confirmed using Q-Q plots and histograms. The association between the AccuChek® and laboratory values was determined by means of the Intraclass Correlation Coefficient (ICC). Because a series of glucose pairs from a single patient might not be considered independent, we also compared the mean of all AccuChek® glucose measurements of a single patient with the mean of all central laboratory glucose measurements of the same patient, resulting in one pair of mean glucose measurements for every single patient. The mean AccuChek and laboratory glucose values of all paired glucose measurements from all patients were compared by means of the paired t-test. The two means were used to calculate a correction factor: $(\text{mean AccuChek}^\circ \text{ whole blood glucose}) \times \text{correction factor} = (\text{mean central laboratory serum glucose})$. All the following methods of comparing central laboratory glucose and AccuChek® glucose were carried out for both the uncorrected and the corrected AccuChek® results.

Modified Error Grid Analysis

Several modifications to the original error grid^{19;20} have been proposed. Kanji et al. proposed a modification especially for tight control in the ICU setting.¹⁴ This error grid modification was a scatter diagram with the reference value on the X-axis and the difference between reference and point-of-care measurement on the Y-axis. In the diagram vertical lines were added at the lower and upper margins of the normoglycemic glucose range. Also two lines were drawn from the abscissa signifying the boundaries of the allowed 20% deviation of the point-of-care measurement from the reference. In this way the diagram clearly showed the accuracy of the point-of-care measurement as related to both the reference as well as related to the glucose values aimed for. We also added the margins of the ISO 15197 standard which differ only slightly from the 20% target zone as outlined below.

Locally-smoothed median absolute difference curves

The locally-smoothed median absolute difference curve (LS-MAD) was designed by Kost et al. to provide a visual and objective and non-forgiving assessment of the performance of point-of-care glucose measurement devices.²¹ The locally-smoothed curve provided a continuous representation of meter performance throughout the glucose range. It is calculated for integer values only. Its value at a point x is the median of the absolute difference of all paired meter and reference measurements where the reference results is within the specified bandwidth of x . These discrete median points are connected to generate a single curve. The absolute difference is the absolute value of the paired dif-

ference AccuChek® glucose minus central laboratory glucose.²¹ For the bandwidth we choose 27 mg/dL, because this is the bandwidth of the target range of our protocol (81-135 mg/dL).¹² An error tolerance of 5 mg/dL is advised and depicted in the diagrams by a dashed line.²¹

ISO 15197 guideline

The ISO 15197 guidelines stated that point-of-care values should deviate no more than 15mg/dL with reference values below 75 mg/dL and no more than 20% with reference values of 75 mg/dL or higher. Altogether 95% of point-of-care values should be within the desired range.²¹ The ISO guideline margins were added to the Modified Error Grid plots, because they differ only slightly.

RESULTS

During the study period 239 paired glucose measurements were done in 32 critically ill patients. The median number of glucose pairs per patient was 3, interquartile range 1.75-9.25. Patients had a mean age of 71.6 years (SD 11.9). Eighteen patients were male. The mean APACHE II score at ICU admission was 17.8 mean (SD 6.7). Twenty-five (78%) patients were ventilated, 16 (50%) patients had sepsis, 8 patients (25%) received renal replacement therapy, 17 patients (53%) were medical and 15 patients (47%) were surgical.

Results of the paired measurements are presented in Table 9.1. First, all 239 paired measurements were considered to be independent. The mean difference (central laboratory – AccuChek®) was 11 mg/dL (0.61 mmol/L) (95% confidence interval 9-13 mg/dL, $p < 0.001$), with the Intraclass Correlation Coefficient being 0.934. Results of the 32 pairs of mean glucose per patient are not significantly different from the analysis of the 239 pairs, with the intraclass correlation coefficient being 0.939, and the mean difference 13 mg/dL (Table 9.1).

From the mean difference of 11 mg/dL a factor of 1.086 (and a 95% confidence interval: 1.072-1.010) can be calculated to convert AccuChek® whole blood results to estimate central laboratory serum results more accurately. This corrected or serum like AccuChek® result is calculated by multiplying the original or uncorrected whole blood AccuChek® result by 1.086. Tables 9.2 and 9.3 and Figures 9.1 and 9.2 illustrate the difference between the corrected and uncorrected AccuChek® on the one hand and the central laboratory serum glucose on the other hand. The difference between the uncorrected AccuChek® and the central laboratory serum glucose is outside ISO 15197 limits in approximately 9% of cases. By applying the correction factor of 1.086 this is improved to approximately 6%.

Table 9.1. Results of 239 paired glucose measurements in 32 ICU patients.

	AccuChek® (whole blood)	Central laboratory (serum)	
Results on 244 paired glucose measurements in 32 patients			
Mean (SD)	126 (37)	137 (39)	Mean difference 11 (95%CI 9-13, p<0.001, t-Test)
Range	37-265	25-288	
ICC			0.934 (95%CI 0.915-0.948)
Results on the paired means of the glucose measurements in 32 patients			
Mean of the mean (SD)	127 (26)	139 (31)	Mean difference 13 (95%CI, 9-16, p<0.001, t-Test)
Range of the mean	31-176	25-185	
ICC			0.939 (95%CI 0.880-0.970)

SD= standard deviation, CI, confidence interval, ICC=Intraclass Correlation Coefficient, all glucose values in mg/dL

Table 9.2. Comparison of central laboratory serum glucose with AccuChek result with and without applying a correction factor of 1.086 to convert AccuChek whole blood result to "serum" glucose for 239 paired samples using the ISO 15197 standard.

	<u>Uncorrected</u> AccuChek	<u>Corrected</u> AccuChek*1.086	Number of paired measurements
LS ≤75 mg/dL and AC differs no more than 15mg/dL	9 (90.0%)	8 (80.0%)	10
LS >75 mg/dL and AC differs no more than 20%	207 (90.4%)	217 (94.8%)	229
Within ISO 15197 range	216 (90.4%)	225 (94.1%)	239 (100%)

AC= AccuChek result, LS= central laboratory serum glucose

Table 9.3. Comparison of central laboratory serum glucose with AccuChek result with and without applying a correction factor of 1.086 to convert AccuChek whole blood result to "serum" glucose for 239 paired samples as proposed by Kanji in his modification of the Error Grid Analysis. ¹⁴

	<u>Uncorrected</u> AccuChek	<u>Corrected</u> AccuChek*1.086
AC more than 20% higher than central lab	3 (1.3%)	8 (3.3%)
AC between 10 and 20% higher than central lab	5 (2.1%)	26 (10.9%)
Difference less than 10%	135 (56.5%)	168 (70.3%)
AC between 10 and 20% lower than central lab	77 (32.2%)	30 (12.6%)
AC more than 20% below lower than central lab	19 (7.9%)	7 (2.9%)

AC= AccuChek result, LS= central laboratory serum glucose

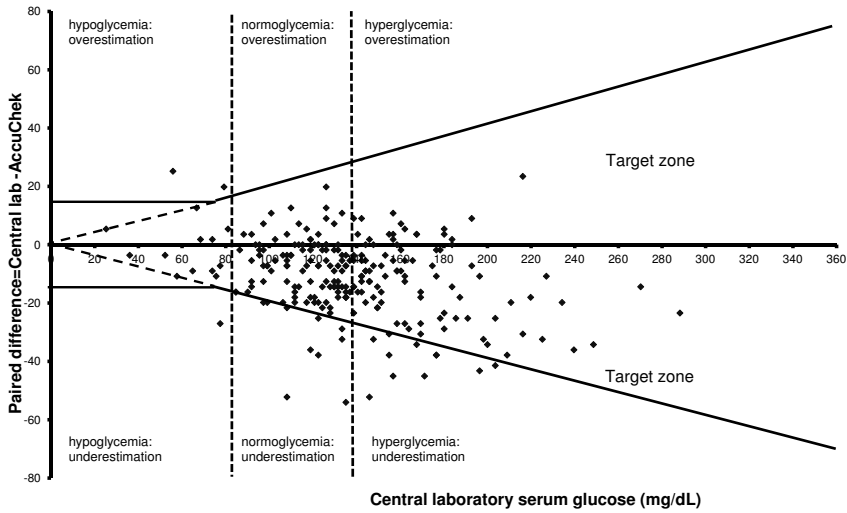


Figure 9.1a. Modified Error Grid Analysis as proposed by Kanji.¹⁴ Central laboratory serum glucose is displayed on the X-axis. The difference (central lab-AccuChek®) is on the Y-axis. The triangular target zone is the range in which the difference is within 20%. In addition the margins of the ISO 15197 guideline are given: point-of-care values should be within 20% when reference is 75 mg/dL or higher or within 15 mg/dL when reference is below 75 mg/dL. The vertical dashed lines depict the lower and upper margins of the target zone (81-135 mg/dL).

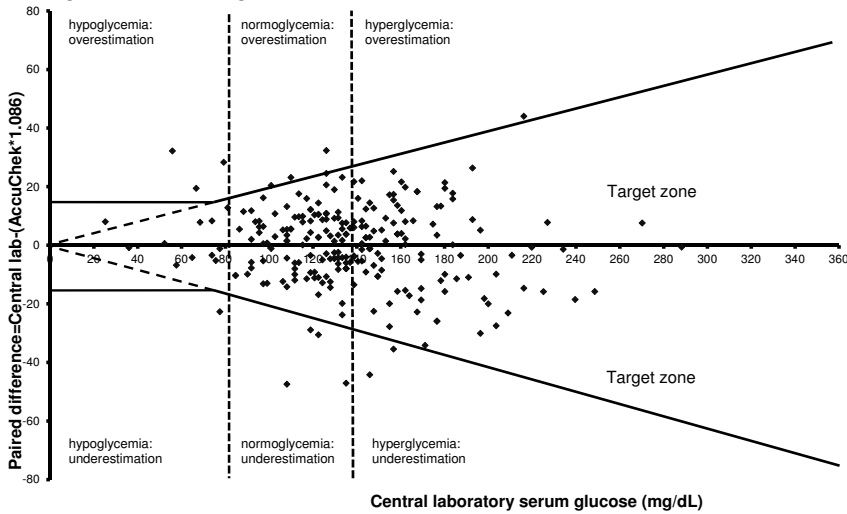


Figure 9.1b. Modified Error Grid Analysis as proposed by Kanji.¹⁴ Central laboratory serum glucose is displayed on the X-axis. The difference (central lab-AccuChek*1.086) is on the Y-axis. The triangular target zone is the range in which the difference is within 20%. In addition the margins of the ISO 15197 guideline are given: point-of-care values should be within 20% when reference is 75 mg/dL or higher or within 15 mg/dL when reference is below 75 mg/dL. The vertical dashed lines depict the lower and upper margins of the target zone (81-135 mg/dL).

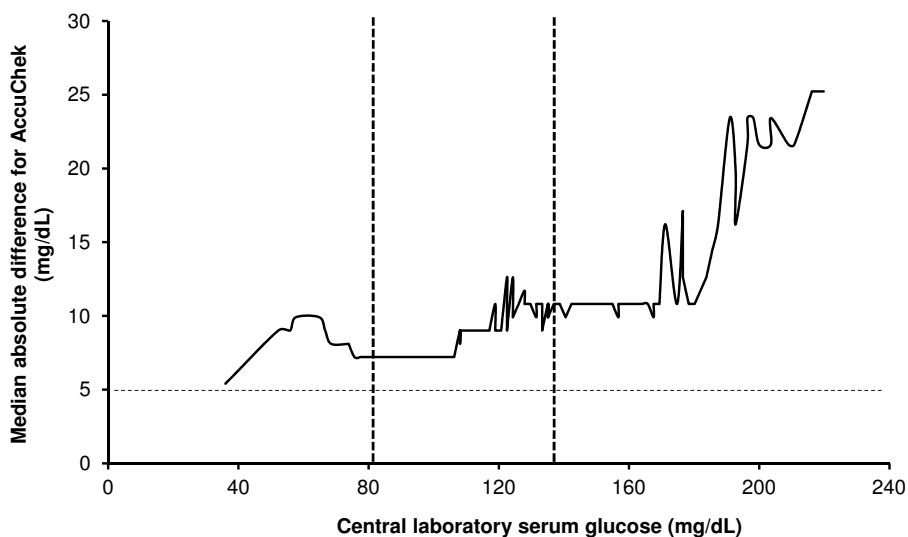


Figure 9.2a. Locally-smoothed median adjusted difference curve for AccuChek vs central laboratory glucose. See methods section for explanation. The closer the curve is to the x-axis, the more closely does AccuChek reflect the central laboratory glucose result. The vertical dashed lines depict the lower and upper margins of the target zone (81-135 mg/dL).

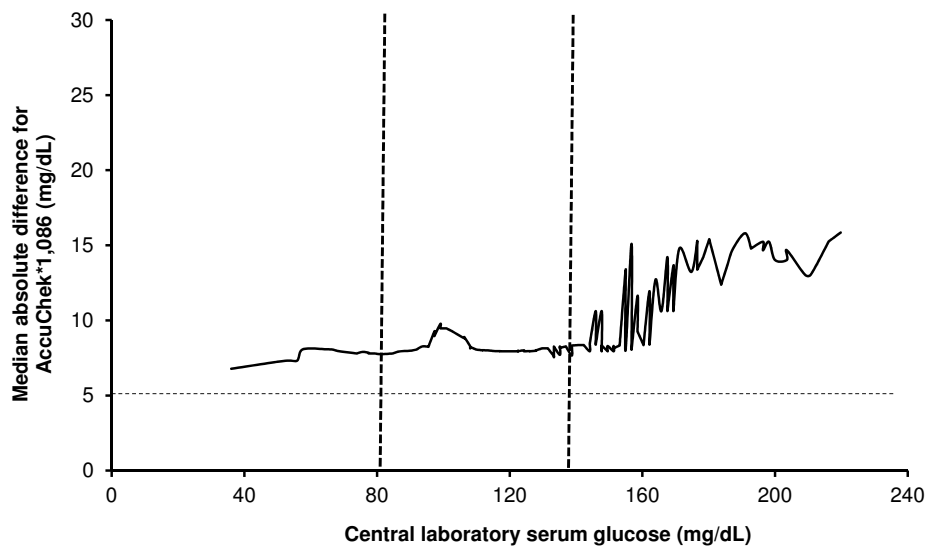


Figure 9.2b. Locally-smoothed median adjusted difference curve for AccuChek*1.086 vs central laboratory glucose. See methods section for explanation. The closer the curve is to the x-axis, the more closely does AccuChek*1.086 reflect the central laboratory glucose result. The vertical dashed lines depict the lower and upper margins of the target zone (81-135 mg/dL).

Mean hematocrit was 0.30, SD 0.05. The hematocrit did not systematically influence the corrected AccuChek result in the range from 0.20-0.45 (Table 9.4, Figure 9.3). Outside of this range there were insufficient data.

Table 9.4. The difference between the “corrected” AccuChek result (= $\text{AccuChek} \times 1.086$) and the central laboratory serum glucose as related to the hematocrit. In the 0.20-0.44 hematocrit range we did not find a significant influence of hematocrit on the corrected AccuChek result. Data outside this range are too scarce.

Hematocrit	Number of paired measurements	Mean difference (Central lab- AccuChek*1.086) in mg/dL (%)
0.15-0.19	4	9 (6%)
0.20-0.24	18	-2 (-2%)
0.25-0.29	102	-3 (-2%)
0.30-0.34	77	3 (1%)
0.35-0.39	25	-2 (-2%)
0.39-0.44	11	2 (1%)
0.45-0.49	2	30 (25%)
All	239	0

The number between parentheses is the mean difference (central laboratory serum glucose- $\text{AccuChek} \times 1.086$) expressed as percentage of the mean of the central laboratory glucose values in the respective hematocrit strata.

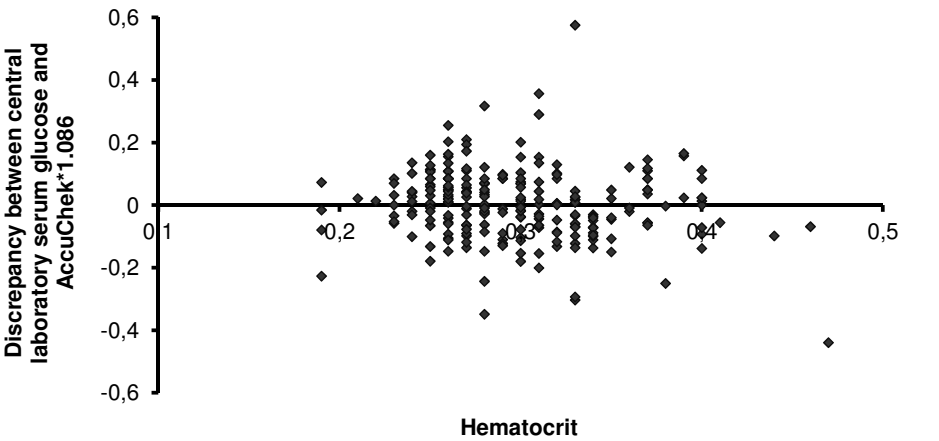


Figure 9.3. Correlation between the “corrected” $\text{AccuChek} \times 1.086$ and hematocrit. The accuracy of the AccuChek is independent from the hematocrit.

DISCUSSION

In this study including 239 paired glucose measurements in 32 critically ill patients, we found that the mean difference between serum glucose as measured by the central laboratory and whole blood glucose as measured by the AccuChek® was 11 mg/dL, the AccuChek® result being systematically lower than the central lab result. Approximately 91 percent of AccuChek® whole blood measurements were within ISO15197 limits. By applying a correction factor of 1.086 to the AccuChek® result this increased to approximately 94%. The AccuChek result was not influenced by hematocrit if the hematocrit was in the 0.20-0.44 range.

Before we can decide whether AccuChek® glucose measurements or any point-of-care device is accurate enough for use in intensive care we have to agree on how to evaluate accuracy. There is no consensus in the literature on this subject. This is reflected in the different methods of comparison we present in this manuscript. The subject has been discussed extensively by different authors some of which have added their own new methods.^{14;17;19-26} The more recent methods of comparison have given us more detailed insight but have made it more difficult to give a simple verdict in the sense of good or no good. The most simple, most comprehensive and probably because of that the most appealing way to judge the accuracy of the point-of-care device is the ISO 15197 standard, which is the same as the CLSI standard: In at least 95% of cases discrepancy between reference and point-of-care glucose should be below 15 mg/dL if the reference is below 75mg/dL or below 20% if the reference glucose is 75 mg/dL or higher.^{13;17;21}

So how should we judge the AccuChek® based on our results? Because we want the AccuChek® result to represent serum glucose we should not judge the AccuChek® whole blood calibration but the serum calibration instead. This means that we have to use the corrected AccuChek® result with our correction factor of 1.086 which is almost exactly the same as the correction factor of 1.080 given by Roche Diagnostics. Using this corrected or serum calibrated AccuChek® result 94% of measurements are within the desired ISO range which falls only 1% short of the desired ISO approval. We therefore nonetheless consider the accuracy of the corrected or serum calibrated AccuChek® result acceptable enough for use in intensive care.

AccuChek® accuracy in the intensive care setting has been evaluated by others. Critchell et al. compared AccuChek® capillary glucose measurements with serum glucose measurements in critically ill patients.¹³ Which calibration was used was not specified. In contrast to the present study they concluded that AccuChek® measurements *overestimate* glucose and thus may leave hypoglycaemia unnoticed in sedated patients. They warn against using the AccuChek®. We postulate that this may be caused by the sampling method used by Critchell et al who used fingerstick measurements,

while in the present study blood was derived from arterial lines or because of an inappropriate correction factor. Kanji et al. used serum calibrated AccuChek®. ¹⁴ They based their judgement on whether the difference influenced insulin dosage in their own protocol. This makes interpretation of their results by others difficult. They conclude that accuracy is better with arterial samples as compared to capillary samples. Karon et al. on the contrary found capillary glucose as measured with serum calibrated AccuChek® to be no different from serum glucose as measured by the central laboratory. Arterial and venous samples gave significantly higher results. ²⁷ They concluded that AccuChek® was accurate enough for use in the ICU. Meex et al. studied 20 paired samples from ICU patients with serum calibrated AccuChek® to conclude that there was no difference with the central laboratory result. ¹⁸

This study has several limitations. First, it is a single centre study. This could for instance imply that other centres need to do their own calibration of AccuChek® versus central laboratory. Second, all samples were derived from arterial lines. It has been shown that deriving samples from finger prick can result in faulty measurements, especially in patients with oedema, vasopressor medication or both. ¹⁴ This was not studied presently, mainly because in our unit patients on vasopressors or on a ventilator, have arterial lines in place. Third, we did not attempt tight glucose control as defined by van den Berghe. When aiming for glucose values between 80 and 110 mg/dL instead of what we do between 81 and 135 mg/dL it is conceivable that the measurements have to be more accurate than can be achieved with the AccuChek®. This was not studied presently. Fourth, influences of pO₂ and pH were not studied. There were very few extremes of hematocrit, pO₂ and pH. Hematocrits in the "normal" range of 0.20-0.44 did not influence AccuChek results. Fifth, samples sent to the central laboratory for measurement of glucose in serum were handled as soon as possible, but the short delay in handling may theoretically have induced error. This could have been ameliorated by using a plasma glucose comparison method immediately at the bedside, but this was not available. Finally, we had few extreme glucose values making it difficult to confidently assess accuracy of the AccuChek® in the extremely high or low glucose range.

Conclusion

In conclusion, we have found that the AccuChek® glucose measurement in whole blood with a correction factor to give serum like values narrowly fails to comply with the ISO 15197 guideline, but has acceptable accuracy for use in intensive care with a protocol that aims for glucose values between 81 and 135 mg/dL and with blood samples derived from arterial catheters. The hematocrit did not influence the AccuChek® result when in the 0.20-0.44 range.

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Chapter 10

Blood glucose amplitude variability
as predictor for mortality in surgical
and medical ICU patients

A multicenter cohort study

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ABSTRACT

Purpose

To aim of this study was to test the hypothesis that blood glucose amplitude variability (BGAV) is associated with mortality in critically ill patients.

Method

A prospectively collected multicenter dataset including all glucose measurements during ICU treatment and outcome was analyzed. We used logistic regression to assess the association between hospital mortality and standard deviation (SD), MAGE (mean amplitude of glycemic excursions), MAG (mean absolute glucose change per hour) and GLI (glycemic lability index). The analysis was adjusted for ICU, APACHE IV expected mortality, the presence of severe hypoglycemia, mean glucose, mean glucose measurement interval and interaction between the latter two.

Results

There were 855,032 glucose measurements included of 20,375 patients admitted to 37 Dutch ICUs in 2008 and 2009. Median APACHE IV predicted mortality was 14%, median glucose was 7.3 mmol/L. In all patients combined, adjusted hospital mortality was associated with SD and MAGE, but not with MAG and GLI. In surgical patients, adjusted hospital mortality was associated with SD, MAGE and MAG but not GLI. In medical patients, adjusted mortality was associated with SD but not with other BGAV measures.

Conclusion

Not all BGAV measures were associated with mortality. BGAV as quantified by SD was consistently independently associated with hospital mortality.

INTRODUCTION

In 2001 the single centre non-blinded randomized study by van den Berghe *et al.* showed improved survival in surgical intensive care patients when insulin and parenteral glucose were given to maintain serum glucose in the normal range (4.4-6.1 mmol/L) as opposed to conventional blood glucose control.⁽¹⁾ As a consequence, many ICUs implemented some form of glycemic control, although frequently the applied regimens tolerated higher blood glucose levels than those in tight glycemic control. However, subsequent studies did not confirm a survival benefit ^(2,3) and the largest and most recent randomized multicenter study even showed a worse outcome for patients with tight glycemic control (4.5-6.0 mmol/L) as opposed to patients who were treated with insulin only when glucose rose above 10.0 mmol/L (resulting in actual mean glucose of 8.0 ± 1.3 mmol/L).^(4,5) These conflicting results prompt us to reconsider our theories regarding glucose control in the ICU and several authors have focused on blood glucose amplitude variability (BGAV); hypothesizing that increased fluctuation of glucose levels would be associated with increased mortality. ^(6,7,8,9,10,11,12,13,14,15,16,17,18) Different measures of BGAV and their association with mortality have been reviewed recently. ⁽¹⁹⁾ When comparing different measures of BGAV the authors did not find one superior to another in term of association to mortality. Standard deviation (SD) was used in six out of 12 studies and five out of six reported a positive association with mortality. The second most commonly used BGAV measure was the presence of both hypo- and hyperglycemia, albeit used with different threshold values in three studies. Two out of three studies showed a positive association between mortality and BGAV as measured by the presence of both hypo and hyperglycemia. Each of the remaining 11 BGAV measures was used in only one study. These measures were conceived for instance to consider the order and/or timing of measurements. The authors found that although most studies used some correction for confounders, none of the studies corrected for all necessary variables namely mean or median glucose, glucose sampling interval (necessary if sampling intervals are not equal) and severity of illness.⁽¹⁹⁾ Hypoglycemia was corrected for in four out of 12 studies. ^(19,10,15,17,18) Most studies disregarded the nonlinear relation between, for instance, mean glucose and mortality and the authors suggested that the multivariate models could be improved by accounting for this nonlinearity.

In 2008 the Dutch National Intensive Care Evaluation (NICE) Registry introduced glucose regulation as one of eleven indicators of quality of care in the ICU. This means that for all ICUs participating in the quality indicator registration of the NICE, all glucose values of all admitted patients are collected prospectively in a database together with admission data including severity of illness scores and discharge data including survival discharge status (either dead or alive). This enables us to analyze the relationship between glucose BGAV and mortality in a large cohort of ICU patients. The aim of this study

was to test the hypothesis whether BGAV in glucose levels, and in which of its measures, is independently associated with hospital mortality in medical and surgical ICU patients.

METHODS

Data collection

The Dutch National Intensive Care Evaluation (NICE) registry contains among others demographic data, admission and discharge dates, diagnoses, severity of illness scores (APACHE II, SAPS II and APACHE IV) and ICU and hospital mortality for all admitted patient to 72 Dutch ICUs. Since 2008 a selected group of ICUs started to collect a set of eleven quality indicators among which that pertain to glucose regulation. A dataset from the NICE registry including patients admitted to all 37 Dutch ICUs that collect the glucose values of patients admitted from January 1, 2008 to December 31, 2009 was used in this study. Data collection takes place in a standardized manner according to strict definitions and is subject to stringent data quality checks. This has been shown to ensure that data are of high quality.(20) The data are encrypted in such a way that all patient-identifying information, including name and patient identification number, are removed. In the Netherlands there is no need to obtain consent to make use of registries that do not include patient-identifying information. Hence, there was no need for ethical approval. The NICE initiative is officially registered according to the Dutch Personal Data Protection Act.

Patient selection

To be able to reliably measure BGAV we only included patients with at least 24 hours of stay in ICU and having at least three glucose measurements. In analogy with the exclusion criteria commonly used in analyses based on the APACHE IV system, patients admitted with severe burns or for transplantation, patients younger than 16 years, patients admitted shorter than 4 hours or longer than 365 days, patients with missing APACHE IV diagnosis or admission type were excluded from the analyses. If a patient was admitted to the ICU more than once during a hospitalization period, only the first ICU admission was used. In the NICE registry patients are defined as surgical patients when they are admitted within 7 days after surgery or when they are admitted to the ICU before emergency surgery; all other patients are defined as medical patients. Medical and surgical patients were analyzed separately. All ICUs were free to use their own protocols and strategies for glucose sampling, insulin dosing and nutritional support. No information was collected on this matter. At the time of the study most Dutch ICUs used nurse directed insulin dosing regimes aiming at serum glucose targets between 4.4 and 8.0 mmol/L.(21)

Blood glucose amplitude variability (BGAV)

We are not aware of a formal consensus definition of BGAV or a consensus on the way that it should be measured. Based on a systematic review (19) on BGAV measures we selected for this study the standard deviation (SD), as it is the most frequently used measure. SD does not take the order or timing of glucose measurements into account. Therefore we also added BGAV measures that take the order of measurements or the timing or both into account. The mean amplitude of glycemic excursions (MAGE) was defined as the mean of the absolute values of any delta glucose from consecutive measurements that was higher than the SD of the entire set of glucose values.(6) The MAGE takes the order of measurements into account, but not the time that elapses between measurements. The MAG (mean absolute glucose change per hour) was defined as the sum of all absolute glucose changes divided by the time in hours.(10) The MAG takes order and time interval into account. In the original publication the glycemic lability index (GLI) was used in diabetic patients whose glucose values were continuously measured, it was not developed for intensive care use.(22,23) GLI was defined as the squared difference between consecutive glucose measures per unit of actual time between the samples per week.(6,22,23,24) As the median length of stay of ICU patients is only 3 days we changed the definition to samples per day. GLI depends on the order as well as the timing of the glucose measurements.

Statistical Analysis

The primary outcome measure was hospital mortality. We assessed the relationship between each separate BGAV measure and hospital mortality with multivariate logistic regression analysis. We used the ICU identifier (to correct for correlation of patients within one ICU), first level recalibrated APACHE IV probability (as done in all earlier studies on BGAV), mean glucose (as a spline function because of its non-linear relation and because of its demonstrated association with mortality), the presence or absence of at least one severe hypoglycemia event (<2.2 mmol/L) during ICU treatment, mean measurement intervals as suggested recently (25) and the interaction between ICU and mean glucose measurement interval as covariates to adjust for differences in case-mix and glycemic treatment strategy. In addition, in surgical patients we adjusted for elective or urgent surgery. Due to a quadratic relation demonstrated by smoothed plots for SD, MAGE and MAG, they have been included together with their squared terms in the logistic regression model. G-statistic (log likelihood ratio test) was used to compare models with and without BGAV related measures. If the difference in the log likelihood between models with and without a BGAV measure was statistically significant, then we considered that there was an association between the BGAV measure and hospital mortality (independent of the variables that were adjusted for). Statistical analyses were performed using the statistical environment R version 2.6.2.

RESULTS

A total of 855,032 glucose measurements of 20,375 patients admitted between January 1st, 2008 and December 31st, 2009 to 37 ICUs were available for analysis. Median age was 67 years (IQR 56-76), median APACHE IV expected mortality was 14% (IQR 5-33%), 52% of patients were medical, median glucose was 7.3 mmol/L (IQR 6.7-8.2), median SD was 1.73 mmol/L (IQR 1.2-2.4). Basic characteristics are summarized in Table 10.1.

In the combined cohort of all patients, adjusted hospital mortality (after correction for APACHE IV, mean glucose, presence of severe hypoglycemia (<2.2 mmol/L), mean of glucose measurement interval, ICU and interaction between ICU and mean glucose measurement interval) was associated with SD of glucose levels ($p<0.0001$) and MAGE ($p<0.0012$) but not with MAG and GLI (Table 10.2). In surgical patients, 85% of whom were admitted to the ICU immediately after surgery, adjusted hospital mortality was associated with the SD of glucose levels ($p<0.0001$), MAGE ($p<0.0001$) and MAG ($p=0.04$), but not with GLI. (Table 10.2). In medical patients adjusted mortality was associated with SD ($p<0.0001$), but not with MAGE, MAG and GLI (Table 10.2).

Table 10.1. Basic characteristics of all 20,375 patients (data presented as median (IQR)).

	Hospital survivors	Hospital non-survivors	All patients
<u>All patients</u>			
Number of patients	15962 (78%)	4413 (22%)	20375
Number of glucose tests	17 (9-40)	30 (14-70)	19 (9-46)
Age	65(54-74)	72(62-79)	67(56-76)
Expected APACHE IV mortality	.11(.04-.24)	.40(.22-.65)	.14(.05-.33)
ICU length-of-stay in days	3.0(1.8-6.6)	4.6(2.3-10.8)	3.2(1.9-7.3)
Hospital length of stay in days	16(9-31)	12(5-26)	15(8-30)
Mean glucose (mmol/L)	7.3(6.7-8.2)	7.4(6.7-8.3)	7.3(6.7-8.2)
SD(mmol/L)	1.66(1.2-2.4)	1.97(1.4-2.8)	1.73(1.2-2.4)
MAGE (mmol/L)	2.7(1.8-3.9)	3.2(2.3-4.4)	2.8(1.9-4.0)
MAG (mmol/L/hr)	0.32(0.18-0.51)	0.39(0.24-0.57)	0.33(0.19-0.53)
GLI (mmol/L) ² /hr/day	5.7(1.6-15.4)	8.7(3.2-20.7)	6.3(1.9-16.5)
BGL test interval in minutes	216(157-308)	197(145-263)	212(154-298)
<u>Surgical patients</u>			
Number of patients	8299 (86%)	1393 (14%)	9692
Elective surgical admissions	5247 (91%)	502 (9%)	5749
Urgent surgical admissions	3052 (77%)	891 (23%)	3943
Number of glucose tests	16 (9-33)	30 (13-78)	17 (9-38)

Age	67(57-75)	74(64-80)	68(58-76)
Expected APACHE IV mortality	.06(.30-.14)	.28(.14-.49)	.06(.03-.19)
ICU length-of-stay in days	2.6(1.7-5.2)	4.9(2.3-12.3)	2.8(1.8-5.9)
Hospital length of stay in days	15(9-29)	15(7-31)	15(9-29)
Mean glucose (mmol/L)	7.3(6.7-8.1)	7.3(6.6-8.1)	7.3(6.7-8.1)
SD(mmol/L)	1.63(1.2-2.3)	1.88(1.4-2.6)	1.70(1.2-2.3)
MAGE (mmol/L)	2.6(1.8-3.7)	3.0(2.2-4.2)	2.7(1.9-3.8)
MAG (mmol/L/hr)	0.32(0.18-0.50)	0.35(0.23-0.52)	0.33(0.19-0.51)
GLI (mmol/L) ² /hr/day	5.7(1.8-14.6)	7.4(2.9-17.1)	6.0(1.9-15.0)
BGL test interval in minutes	203(152-287)	202(150-265)	202(152-284)

Medical patients

Number of patients	7663 (72%)	3020 (28%)	10683
Number of glucose tests	20 (9-47)	30 (14-66)	23 (10-52)
Age	63(51-74)	70(60-78)	65(54-75)
Expected APACHE IV mortality	.18(.08-.34)	.46(.26-.69)	.23(.11-.46)
ICU length-of-stay in days	3.8(2.0-7.9)	4.3(2.3-10.2)	3.9(2.1-8.5)
Hospital length of stay in days	17(9-33)	10(4-24)	15(7-31)
Mean glucose (mmol/L)	7.3(6.3-8.3)	7.4(6.7-8.4)	7.3(6.7-8.3)
SD(mmol/L)	1.70(1.2-2.5)	2.02(1.5-2.8)	1.79(1.2-2.6)
MAGE (mmol/L)	2.8(1.9-4.1)	3.2(2.3-4.5)	2.9(2.0-4.2)
MAG (mmol/L/hr)	0.32(0.17-0.52)	0.40(0.25-0.59)	0.34(0.19-0.55)
GLI (mmol/L) ² /hr/day	5.7(1.4-16.4)	9.5(3.4-22.5)	6.7(1.8-18.1)
Glucose test interval in minutes	232(165-337)	194(143-261)	221(157-314)

MAGE: mean amplitude of glycemic excursions; MAG: mean absolute glucose change per; GLI: glycemic lability index.

Table 10.2. Association between hospital mortality and glycemic variability.

	Overall p*	Regression coefficient	p value
<u>Overall</u>			
SD	<0.0001	0.33×SD	<0.0001
		-0.04×SD ²	<0.0001
MAGE	<0.0012	0.05×MAGE	0.0004
		-0.0008×MAGE ²	0.06
MAG	0.92	**	
GLI	0.53	**	
<u>Surgical patients</u>			
SD	<0.0001	0.64×SD	<0.0001
		-0.08×SD ²	<0.0001
MAGE	<0.0001	0.24×MAGE	<0.0001
		-0.01×MAGE ²	<0.0001
MAG	0.04	0.82×MAG	0.01
		-0.32×MAG ²	0.04
GLI	0.17	**	
<u>Medical patients</u>			
SD	<0.0001	0.21×SD	<0.0001
		-0.03×SD ²	<0.0001
MAGE	0.61	**	
MAG	0.36	**	
GLI	0.77	**	

SD: standard deviation of glucose; MAGE: mean amplitude of glycemic excursions; MAG: mean absolute glucose change per; GLI: glycemic lability index

* p for the model adjusting for APACHE IV, mean glucose, the presence of severe hypoglycemia (<2.2 mmol/L), mean of glucose measurement interval, ICU and interaction between ICU and mean glucose measurement interval. Correlation between the presence of severe hypoglycemia (<2.2 mmol/L) and SD was below 40% allowing both to be included as independent covariates in the model.

** Regression coefficient is only presented when overall result of the model is significant (p<0.05)..

DISCUSSION

In this multicenter cohort study in over 20,000 patients that were treated for at least 24 hours in the ICU and with at least 3 glucose measurements we found that association between BGAV and mortality depends on the measure of BGAV and the patient population. SD was independently associated with hospital mortality in surgical and medical patients. MAGE and MAG were associated with adjusted hospital mortality in surgical patients but not in medical patients. GLI was not associated with mortality. This study confirms results of previous, mostly smaller studies on mortality and

BGAV; most of which found a positive relationship even though different measures of BGAV were sometimes used and correction for confounders was often less extensive. (6,7,8,10,11,12,13,15,16,17,18) These studies were reviewed recently. (19)

This study confirms the present understanding of the influence of glycemic control on outcome in critically ill patients as discussed in recent commentaries (26,27,28) and illustrated elegantly in a recent study by Mackenzie *et al* (14) that apart from central tendency and hypoglycemia, BGAV is to a certain extent associated with mortality. We found, as was shown before, (14) that these three measures influence each other in the analysis, which makes it difficult to correctly estimate each measures' contribution to outcome. We also found that the influence of BGAV is not as established in medical patients as compared to surgical patients. BGAV measures behaving differently in different patient groups was seen before by several authors. (1,4,29,30)

The fact that we found different results for different BGAV measures may relate to their distinct properties. GLI and MAG take both timing and sequence of glucose measurements into account, whereas MAGE only takes sequence into account and SD takes neither sequence nor timing into account. Some authors have used the presence of both hypo- and hyperglycemia (HH) during ICU stay as a BGAV measure, but this depends only on the two most extreme glucose measurements neglecting all other measurements as well as timing and sequence. We therefore refrained from presenting HH in our study but we found that HH was indeed associated with adjusted hospital mortality in surgical and in medical patients. SD is the BGAV measure that has been studied most extensively and, except for one study, all others found SD to be an independent predictor of mortality (19), just as we did. Interpreting these results is not straightforward even if one assumes that all theoretical confounders, collected or not, have been accounted for. On the one hand the increase in mortality may inherently be associated to increase in fluctuations of glucose levels. Subsequently, it might well be that decreasing glucose level fluctuations improves outcome. On the other hand, it could be the case that the absolute low and high values of blood glucose levels are a major contributor to the outcome. The high and low glucose values do of course affect variability but it is unclear to which extent (very) high and low glucose levels affect outcome. Subsequently, the goal here would be to avoid sharp deviations. Investigating the interplay between variability and absolute high and low BGL values merits more research. Closed loop glucose control would substantially help further investigation of this interplay and we eagerly await technological advances in this direction.

This study has several limitations. First, the study design is observational with data collected for quality enhancement purposes and not specifically for this research on BGAV. However, quality of data is checked regularly according to stringent rules and most glucose measures were validated and automatically derived from laboratory information systems.(20) Second, due to the design we could only investigate the as-

sociation between BGAV and hospital mortality and we could not confirm a cause-effect relationship. Subsequently we can only hypothesize that a glycemic treatment strategy with less BGAV could improve outcome. Third, we were not informed on insulin dosing regimen, nutritional strategies and glucose measurement and sampling strategies, all intensive care units were free to use their own protocols. To correct for this we included the identity of the ICU, mean glucose and mean glucose sampling interval as covariates in the multivariate model. Fourth, glucose control in this cohort is relatively tight as compared to for instance the control arms in the Leuven or NICE-SUGAR trials (although not as tight as the treatment arms) or compared to studies on BGAV in patients with a liberal glycemic strategy, if any, (9) and this may have affected our results. Fifth, as is common with this kind of studies, results depend heavily on correction for potential confounders. It is still possible that unidentified confounders were not corrected for. Particular strengths of the study are the use of sophisticated statistical techniques taking many potential confounders and the non-linear relation between glucose variability and (the log odds of) hospital mortality into account, the large prospectively collected dataset and the multicenter design. Also this is the first study to compare four different BGAV measures in a multicenter cohort.

Conclusions

In conclusion, in this multicenter retrospective cohort study with prospectively collected data we found that in surgical patients most measures of BGAV namely SD, MAGE, MAG but not GLI, were associated with adjusted mortality. In medical patients only SD was independently associated with mortality.

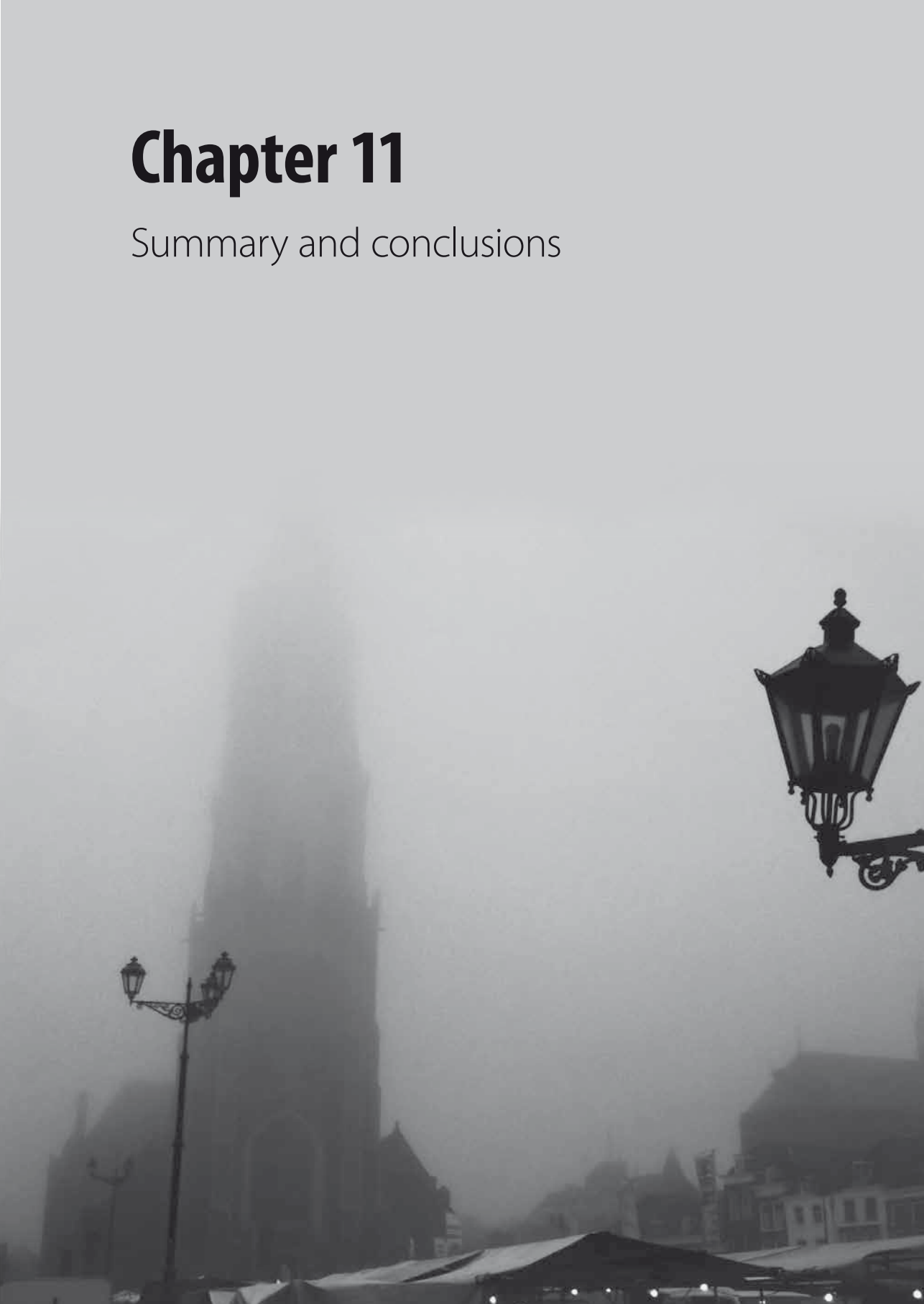
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Chapter 11

Summary and conclusions



How has the research presented in this thesis helped us improve decision making in critical care?

Neuron specific-enolase in post-anoxic coma

In Chapter 2 we studied whether the outcome of post anoxic coma could be predicted by serum neuron specific enolase (sNSE). Most professionals know and most laymen do not know that resuscitation attempts in people who suffer from cardiac arrest often fail. If however cardiopulmonary resuscitation (CPR) successfully returns spontaneous circulation and the patient reaches the intensive care unit, many patients will turn out to have irreversible brain damage due to post-anoxic encephalopathy. The damaged brain releases neuron specific enolase (NSE) into the circulation. In this study we hypothesized that based on an increased sNSE we would be able to identify patients who would not regain consciousness and for whom continuation of intensive treatment would be futile.

¹ Indeed we found that the patients with post-anoxic coma who eventually did not regain consciousness had significantly higher sNSE levels as compared to patients who did regain consciousness. We also found that no patient with post-anoxic coma and sNSE above 25 µg/L regained consciousness. This result suggested that sNSE might be used to make a decision on whether or not to continue treatment in comatose patients treated in the intensive care unit after cardiac arrest. Any test that is used in this situation has to be very accurate. If the test predicts that a comatose patient has no chance at all of regaining consciousness the decision will be made to stop intensive treatment and the comatose patient will often die in a short while. In other words the positive predictive value of the test should be (very close to) 100% and this has to be confirmed in other studies as well. In our study we found that sNSE above 25 µg/L had a positive predictive value of 100% for predicting that a comatose survivor of cardiac arrest would sadly not regain consciousness. The next thing to do before sNSE could be used to make decisions was to see if other studies would reveal the same threshold and results. Indeed several studies found similar results although cut-off values for sNSE were different. ²⁻¹⁰ But....at the same time the therapeutic use of hypothermia was introduced into the treatment of patients with post-anoxic coma. Two separate studies showed that applying hypothermia to 33°C for 24 hours to a patient comatose after cardiac arrest, improved prognosis. ^{11;12} While many centres around the world started cooling comatose survivors of CPR, the question arose if the old tools for establishing prognosis and deciding on continuation of treatment were still applicable. It was even more difficult to adequately appraise the newer tools like sNSE in the context of therapeutic hypothermia. Eventually it turned out that also in patients with post anoxic coma treated with hypothermia sNSE was indeed higher in non-survivors as compared to survivors ^{13;14} and in survivors a higher sNSE was associated with more brain damage¹⁵. However, some survivors were seen with high sNSE and this meant that the positive predictive value was not 100% ¹⁶. That is why sNSE

alone is not accurate enough to make the decision to stop or continue treatment in comatose patients after CPR and current guidelines do not advocate the use of sNSE as a single test to establish prognosis.¹⁷⁻¹⁹

Infection control in the ICU: SDD with cefazolin

Chapter 3 is about infection control in the intensive care unit. Patients who are treated in the ICU are at risk for infectious complications even if they have not been admitted to the ICU or the hospital with an infectious disease. It can be regarded as one of the main jobs of the ICU personnel to protect the patient from developing secondary or nosocomial infections. A patient may acquire secondary infections from two distinct sources; by bacteria that reach the patient from his surroundings or from the patient's own bacteria that he carries in the gut, on the skin or in the throat. In other words, secondary infections can be either exogenous or endogenous, depending on whether the source of the bacteria is the patients environment or the patient himself. Exogenous infections can be prevented by hygienic measures but endogenous infections cannot.²⁰ It has been postulated that endogenous infections arise from potentially pathogenic bacteria in the patients gut that had been relatively harmless until the patient developed critical illness. With critical illness these potentially pathogenic bacteria in the patients' gut are given the chance to multiply and to reach the lungs to give rise to ventilator associated pneumonia (VAP). If bacteria from the gut are indeed responsible for nosocomial infections like VAP, eradicating these bacteria might prevent VAP. The strategy of selective decontamination of the gut aims to eradicate potentially pathogenic bacteria from the gut while trying to preserve the really harmless bacteria. The mainstay of this strategy is to administer antibiotics topically in mouth and gut that are selective, meaning that these antibiotics kill potentially pathogenic bacteria but not the harmless bacteria. Along with the topical antibiotics, the patients also receive a short course of systemic antibiotics, mostly third generation cephalosporin cefotaxime is used.^{20;21} Hygienic measures and surveillance cultures of throat, sputa and rectum are the third and fourth pillar of SDD. As early as 1983, Stoutenbeek, van Saene and Zandstra were the first to show that this strategy of SDD reduces infectious complications in critically ill patients.²²⁻²⁵ Several authors found the same results in larger and methodologically better studies and even a Cochrane meta-analysis supported the use of SDD in critically ill patients to not only prevent secondary infections but also to reduce mortality.^{26;27} Nevertheless SDD is not used in many ICUs around the world. There are several reasons for this, one of which is the fear of antimicrobial resistance.^{28;29} Randomized trials found not an increase and sometimes even a decrease of microbiological resistance.^{30;31;31} Long term surveillance did not reveal increased resistance.^{32;33} When we wanted to introduce the strategy of SDD in our unit in 2003, our microbiologists objected against the use of third generation cefotaxime as prophylactic antibiotic, when most infections in the ICU could

be treated with second generation cephalosporins and first generation cephalosporins were used in prophylaxis. Could it be that in our hospital, first generation cefazolin would be good enough to use as the parenteral antibiotic? For our SDD study, in the first 6 months we only took cultures twice a week from throat and rectum of all patients eligible for SDD.³⁴ In the next 6 months we administered topical colistin, tobramycin and amphotericin in mouth and stomach 4 times daily as usual in SDD, but instead of 4 days of intravenous traditional cefotaxime we gave intravenous cefazolin. So essentially we compared microbiological differences between no SDD on the one hand and SDD with enteral tobramycin, colistin and amphotericin and intravenous cefazolin instead of cefotaxime on the other hand. As expected, with 80 patients the study was too small to show statistically significant differences in survival between the two groups. We found however that 31% of patients were admitted with cefazolin resistant anaerobic gram negative bacteria (AGNB) and only 2% with cefotaxime resistant AGNB. This made us decide to continue the use of SDD in our unit but with the 'original' cefotaxime instead of cefazolin. Also, we found not an increase of antimicrobial resistance in our patients on SDD but a decrease (although not significant in our small study). This study helped us decide in 2004 that cefazolin was not appropriate as the parenteral antibiotic in SDD in our unit and convinced opponents of SDD in our hospital that we should have no fear of increased microbiological resistance. In the Netherlands the debate on SDD has shifted around 2010 favouring the use of SDD in almost all Dutch hospitals after the large multicenter study by de Smet *et al.*³⁵ But the debate is not over, not in the Netherlands and certainly not outside of the Netherlands.³⁶

Mortality after off hours admission to the ICU

The outcome of treatment in the intensive care depends not only on individual decisions made for individual patients, but may be even more on adequate organization and staffing of the unit as a whole.³⁷⁻⁴⁰ For individual patients treatment in the first few hours of critical illness may be crucial and decisive for the eventual outcome.⁴¹⁻⁴³ Although intensive and emergency care is available around the clock it is evident that staffing, facilities and conditions in the hospital are not the same during office hours as compared to off hours. So both from a perspective of quality control as well as from a scientific point of view we might ask ourselves if outcome of patients admitted during off hours is different from outcome of patients admitted during office hours. Some authors found that patients admitted during off hours had a higher mortality even after correction for illness severity,^{41,44-46} while others did not find such a difference.⁴⁷⁻⁵² Our study, presented in chapter 4, was done together with colleagues of Gelre Hospital in Apeldoorn and the Onze Lieve Vrouwe Hospital in Amsterdam and of course the Reinier De Graaf Hospital combining data of these 3 hospitals.⁵³ We found that mortality was higher for patients admitted during off hours as compared to patients admitted during office hours, but this

difference was explained by the fact that patients admitted during off hours were sicker. We also participated in a larger study with the Dutch Intensive Care Registry (NICE), using data from all 70 participating Dutch hospitals. This study showed that for all the 70 hospitals combined, there was indeed a better outcome for patients admitted to the ICU during office hours and the difference could not be explained entirely by the difference in illness severity.⁵⁴ So in our three centre study we found that increased mortality of off hour admissions was explained by increased illness severity but the nationwide study concluded that off hours admissions fared worse simply because of the timing of admission. This might mean that there is no difference between office hours care and off hours care in the 3 hospitals from the 3 centres study or it might mean that the difference in outcome was too small to detect in this study but could indeed be detected in the larger 70 centres study. The debate on this issue continues, but in the meantime it is evident that every ICU and every hospital has to protect its patients from the quality gap that might occur during off hours. From our study we learned that in our hospital this quality gap if present was small. A recent development, also in the Netherlands is that more and more intensivists stay in the hospital during the night to increase quality of care during off hours, but the evidence for this costly intervention is conflicting.^{55;56}

Procalcitonin for diagnosing sepsis

Sepsis is one of the ICUs most life threatening illnesses and many resources are utilized in recognition and treatment of sepsis. Identifying patients with sepsis can be difficult because signs and symptoms are not specific: fever, high heart rate, fast breathing, low blood pressure may be seen and laboratory tests may show signs of inflammation. The same symptoms can be seen in the systemic inflammatory response syndrome (SIRS) and in fact for research purposes sepsis is defined as SIRS with infection.⁵⁷ To put it differently systemic inflammation can result from infection, but also from non-infectious causes like trauma or surgery. All patients with systemic inflammation response syndrome are treated with supportive therapy but patients with sepsis need additional treatment quickly.⁵⁸ It is not always difficult to distinguish between sepsis and SIRS. Every intensivist will recognize a patient with overt community acquired pneumonia and low blood pressure, fever, a high heart rate and leukocytosis to have sepsis. In patients after major abdominal surgery it is much more difficult to decide if they have just postoperative SIRS requiring inotropic support or fluids or if they have anastomotic leakage requiring antibiotics and reoperation. So it is important to differentiate sepsis from SIRS and in the fourth study we tested the hypothesis that serum procalcitonin might be useful in confirming or rejecting the diagnosis of sepsis in ICU patients and we compared procalcitonin (PCT) with C-reactive protein (CRP), interleukin 6 (IL6) and lipopolysaccharide binding protein (LBP).⁵⁹ The usefulness of PCT to diagnose sepsis had been studied extensively before⁶⁰⁻⁶⁴ but there were less data on IL6 and LBP in this

matter and furthermore the literature was not unanimous on the usefulness of PCT to diagnose sepsis. Two systematic reviews on the value of PCT to diagnose sepsis in critically ill patients had opposite results. Tang *et al.* reviewed 18 studies to conclude that PCT was not very helpful and should not be incorporated into daily practice.⁶⁴ On the other hand Uzzan *et al.* reviewed 33 studies to conclude that PCT is a good diagnostic marker for sepsis and that PCT should be incorporated into the guidelines.⁶³ We wanted to see for ourselves what PCT could do for us. We studied 76 patients with SIRS or sepsis and found that PCT was much better than LBP, CRP and IL6 in diagnosing sepsis. This study has taught us a lot about PCT and sepsis, PCT has been incorporated in our daily practice and we finished the discussion of this paper by urging clinicians to see for themselves what PCT could do for their patients. As has been stated above, sometimes it is clear that a patient has sepsis and we do not need additional the information from PCT at the moment the diagnosis is made. Daily PCT measurements may help us nonetheless though. If we see PCT decline we may conclude that the patient is doing better and that our treatment is adequate or that antibiotics can be stopped. A rising PCT on the other hand may prompt us to reconsider our diagnosis and therapy. In this manner PCT might give us improved monitoring of the patient with sepsis and allow for efficient and effective use of scarce resources in the ICU.⁶⁵⁻⁷⁰

The Medical Emergency Team in the Reinier the Graaf Hospital

It has been said that in every hospital there is at least one patient on the ward who should be treated not on the ward but in the ICU. This is a more or less philosophical approach but it has been shown that patients on the ward whose condition deteriorates into cardiac arrest have usually been giving warning signs in the hours before the arrest that went unnoticed or were inadequately treated.⁷¹⁻⁷⁴ Well, you might say, cardiac arrest will prompt a professional response involving basic and advanced life support from the hospital's cardiac arrest team. But CPR is always traumatic, often futile and sometimes unwanted. Had the patient been identified before, measures could have been taken to prevent cardiac arrest or a do not resuscitate order and adequate palliative care might have been given. It has also been shown that delayed admission to the ICU is associated with a worse outcome.⁷⁵ How to organize care in the hospital in such a way that this patient at risk is identified? One possible answer to this question is the Medical Emergency Team (MET) System, or Spoedinterventie Systeem as it is called in Dutch. The system consists of an afferent limb for detection of patients at risk and an efferent limb to treat these patients.⁷⁶⁻⁷⁸ For the detection of patients at risk all nurses and doctors have to be trained. Mostly, they are guided by an early warning system score card, which helps them identify patients at risk based on derangements of vital signs rather than diagnosis.^{79;80} The efferent limb requires a response team to evaluate and treat the patient that has been identified to be at risk. Finally the MET system needs control and constant

improvement in a plan-do-check-act cycle.^{76;78;81} Several authors have reported on their experiences with the MET system in before-and-after studies.⁸²⁻⁸⁷ However, there are two randomized trials only.^{88;89} Five systematic reviews conclude that the evidence that the MET system saves lives is not very strong.^{80;90-93} When we started the MET system in our hospital in 2004 we expected that proof of the effectiveness of the MET system would be delivered soon and besides we did not have sufficient resources to study the effectiveness of MET ourselves. Even with unlimited resources, from a methodological point of view it seems almost impossible to answer this question in a single centre study. Chapter 6 describes our experience with the MET system. About a 1000 MET calls were analyzed and we found that about half the patients were admitted to the ICU following the MET call, for about a third of the patients transfer was not necessary and for about one tenth of the patient it was decided that they were too sick to benefit from ICU treatment.⁹⁴ The paper was presented as a feature article in the *Nederlands Tijdschrift voor Geneeskunde* together with two commentaries questioning efficacy of the MET system.^{95;96} Although having a MET system has been made mandatory by the Dutch government, the debate continues.⁹⁷ We eagerly await the results of the COMET study, a Dutch nested multicenter trial evaluating the effectiveness of the MET system. In our hospital the MET system has proved itself to be a valuable service offered by the intensive care unit enabling timely and adequate triage of patients who might need intensive care. Many others have accepted the fact that the MET system is the sensible and logical way to go even when strong evidence of efficacy is lacking.⁹⁸ Recent studies show that care for patients at risk is suboptimal even today.⁹⁹ Of special interest considering this thesis is the study by Wunderink *et al.* who studied PCT levels in patients for whom the MET was activated.¹⁰⁰ They found that PCT levels were significantly higher in patients that were admitted to the ICU after a MET call as compared to patients who did not need intensive care treatment.

Long-term survival after ICU treatment

For many patients and their next of kin being treated in the ICU is about survival: will my beloved father, daughter, friend survive this live-threatening illness? Let us assume that this patient survives the ICU and subsequent treatment on the ward and is discharged alive from the hospital. Unfortunately this patient will most probably not be as healthy as he was before ICU admission. He may suffer from fatigue, general weakness, shortness of breath or post-traumatic stress disorder to name a few post ICU conditions.¹⁰¹⁻¹⁰⁶ Or even worse the patient whose life was saved at tremendous costs in the hospital may die shortly after being discharged from the hospital. While the literature focuses nowadays on morbidity after ICU treatment, we should not neglect mortality. We studied mortality in patients discharged alive from the hospital after ICU treatment by comparing our ICU database with a national social security database. This enabled us to confirm

either the date of demise or survival until January 1st, 2011 for all our patients living in the Netherlands. We found that mortality in the first year after ICU treatment was about as high as during ICU and hospital treatment combined. In other words, about 14% of patients admitted to the ICU died in the ICU or the hospital while mortality in patients who survived to hospital discharge was again 14% in the first year after discharge. As might be expected long-term mortality increases with age, illness severity on admission to the ICU and with being discharged not to the patient's own home. Unfortunately we were unable to study quality of life. This study has taught is that a patient who survives to hospital discharge is still at risk for increased mortality.

Introducing a computerized insulin dosing protocol

The second part of the thesis is about glycemic control in critically ill patients. In 2001 van den Berghe *et al.* published their randomized controlled trial which showed a remarkably increased survival in patients in whom serum glucose was maintained normal (4.4-6.1 mmol/L) using insulin combined with intravenous glucose as opposed to starting insulin only when glucose was above 12 mmol/L.¹⁰⁷ This was called intensive insulin treatment (IIT). Intensivists around the world hurried to implement this lifesaving strategy. One problem was how to give the right amount of insulin without causing hypo- or hyperglycemia. Van den Berghe could not supply us with a simple algorithm, she said that in her unit they did not use such an algorithm but relied on the team's experience to give the right amount of insulin. Many ICUs came up with insulin dosing protocols on paper and decided that nurses should give insulin according to these protocols instead of asking the doctors how much insulin should be given.¹⁰⁸⁻¹¹³ We developed and introduced a computerized insulin dosing protocol. For several reasons we thought that a computerized protocol would be better than a paper based one: a computerized protocol would be easier to comply with, avoiding mistakes by taking wrong turns or following wrong rules, a computerized protocol could be more intricate 'inside' without bothering the nurse with this intricacy, and changes in the algorithm could be applied without the necessity of re-training the nurses or having to retract an older protocol. Implementation and evaluation of this protocol is described in the seventh study.¹¹⁴ It turned out that nurses were quite satisfied with the protocol which empowered them to take care of glycemic control without having to consult the doctors and that mean glucose went down from 9.2 to 7.0 mmol/L with hypoglycemia occurring in only 0.05% of samples. Mean glucose was not as low as proposed by van den Berghe, but we did not dare aim as low as van den Bergh for fear of increasing the rate of hypoglycemia. A special editorial comment accompanied the paper.¹¹⁵ Many intensivists are still concerned about the hypoglycemia offsetting the advantages of glycemic control.¹¹⁶⁻¹²⁰ Although not many ICUs use computerized protocols, some authors find computerized protocols to be better than paper based protocol, especially when integrated into

the patient data management system.¹²¹⁻¹²⁵ Our insulin dosing program will shortly be available as an app.

Testing the accuracy of a bedside glucose measurement device

To achieve and maintain adequate glycemic control it became necessary to take blood samples from patients in intensive care more often. For intensive insulin treatment sampling frequency might increase from once a day to once every hour. This not only led to an increased workload, but it was also required that sampling results were readily available. It was no longer feasible to send the blood sample to the central laboratory where it would be processed and a result would be reported after 30-60 minutes. This would mean that the next sampling would be due almost before the clinicians could have reacted to the previous one. So to increase speed of reporting point of care devices were introduced in the ICU which had the advantage that they could report the glucose concentration of the blood sample within 1 or 2 minutes. But how accurate were these devices as compared to the results obtained from blood that was sent to the central laboratory? This was the question that we were trying to answer in chapter 9. We compared results from the central laboratory with results from our point of care device called AccuChek.¹²⁶ There is no consensus on how accurate the point of care measurement should be though. The ISO 15197 guideline requires that if the central laboratory value is below 4.2 mmol/L the point of care device should deviate no more than 0.8 mmol/L and if central lab glucose is above 4.2 mmol/L than the point of care device should deviate no more than 20%. Altogether 95% of measurements should be within set limits. We found the AccuChek to be within ISO limits in 94% of cases and concluded that its accuracy was just acceptable but that this inaccuracy was one of the main problems in achieving intensive insulin treatment. Many others came to this same conclusions.¹²⁷⁻¹³³

Not everyone was convinced that intensive insulin treatment was a good thing.¹³⁴ Subsequently several multicenter studies were reported that had tried to replicate the survival advantage for intensive insulin treatment that was first reported by van den Berge *et al.* and failed to do so.¹³⁵⁻¹³⁸ Two trials were stopped because of adverse events involving hypoglycemia.^{135;138} Van den Berghe even failed to repeat her own results in the study in the medical ICU (the first study was done in a surgical intensive care unit).¹³⁹ Only in the subgroup of medical patients that were in the unit for three days or more was mortality reduced by IIT, whereas mortality was increased in patients who were treated less than three days in the ICU. The NICE-SUGAR study revealed a worse outcome for patients on intensive insulin treatment.¹³⁷ These conflicting results have been heavily debated.^{139;140} Present guidelines favor a less strict glycemic control, trying

to have glucose not between 4.4 and 6.1 mmol/L but rather below 8.3 or even below 10 mmol/L while taking special care to avoid hypoglycemia.¹⁴¹⁻¹⁴⁴

Does it matter if glucose goes up and down?

Another subject in glycemic control that is studied in chapter 10 is variability: is it irrelevant if serum glucose goes up and down or is it better to have more steady glucose values? Several authors reported that increased fluctuation or variability is associated with increased mortality.^{116;120;145-149} One problem in studying glycemic variability is how to define and calculate variability. Different authors have used different variability measures to study the association with mortality. Standard deviation can be used to represent variability but standard deviation disregards timing and sequence of glucose measurements. Other variability measures were conceived that do take timing and sequence into account. This subject has been extensively reviewed by our coworkers in this project.¹⁵⁰ With them we studied glycemic variability in the large database of the Dutch Intensive Care Registry (NICE) resulting in one of the largest studies on the subject involving more than 20.000 patients. We found that the association between variability and mortality was stronger in surgical patients than in medical patients.¹⁵¹ We also found that depending on the variability measure chosen an association between variability and mortality could be proven or not. In other words, the association between variability and mortality depends on the variability measure chosen.

The future of glycemic control in the intensive care

There is consensus in the literature and studies in this thesis support that for good glycemic control in intensive care patients nurses should be empowered to decide on the insulin dose using protocol, experience or both and that accurate point of care devices should be used. There is less consensus on the range the serum glucose should be kept in, a minority advocating intensive insulin treatment aiming for 4.4-6.1 mmol/L, while others prefer a higher target zone.^{143;152;153} Hypoglycemia is to be avoided although there is no consensus in the literature on how deleterious hypoglycemia really is.¹¹⁹ And finally clinicians are advised to reduce variability as much as possible as mortality increases with variability as was shown in chapter 10 in this thesis.^{152;154;155} Although interest in glycemic control has lessened, the industry is currently developing devices for continuous glucose measurement and some even dream of integrating continuous measurement with automatic insulin infusion to have an artificial pancreas.¹⁵⁶ With such a device glycemic control might be more strict, targets achieved more easily and a new era will begin.

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Hoofdstuk 12

Samenvatting en conclusies



Hoe helpt dit onderzoek ons om betere beslissingen te nemen op de intensive care?

Serum neuron specifiek enolase als voorspeller van de prognose bij post-anoxisch coma

In hoofdstuk 2 is onderzocht of de uitkomst van post-anoxisch coma kan worden voorspeld door het serum neuron specifieke enolase (sNSE) in het bloed te meten. De meeste zorg professionals weten wat de meeste leken niet weten, namelijk dat reanimatie pogingen bij mensen die een hartstilstand krijgen vaak niet helpen en dat de patiënt ter plekke overlijdt. Als het echter wel lukt om het hart weer op gang te krijgen en de patiënt bereikt de intensive care, zal vaak blijken dat de patiënt onherstelbare hersenbeschadiging heeft als gevolg van post-anoxische encefalopathie: hersenschade door zuurstofgebrek. Door de hersenbeschadiging komt neuron specifieke enolase vrij in het bloedserum (sNSE). In deze studie hebben we onderzocht of we op basis van een verhoogd sNSE in het bloed, patiënten die niet meer bij bewustzijn komen, kunnen identificeren. (1) Dit is belangrijk omdat voortzetting van de intensive care behandeling geen zin heeft voor patiënten van wie zeker is dat ze niet zullen ontwaken uit hun coma.

Inderdaad vonden we dat de patiënten met een post-anoxisch coma die uiteindelijk niet meer bij bewustzijn kwamen, significant hogere sNSE niveaus hadden dan patiënten die wel weer bij bewustzijn kwamen. Dit suggereert dat sNSE zou kunnen worden gebruikt om een beslissing te nemen over het al dan staken van de behandeling van comateuze patiënten na reanimatie. Een test die tot zo een beslissing leidt moet wel zeer nauwkeurig zijn. Als de test voorspelt dat een comateuze patiënt geen kans meer heeft om bij bewustzijn te komen, zal besloten worden de intensieve behandeling te stoppen en zal de comateuze patiënt waarschijnlijk binnen korte tijd overlijden. Met andere woorden: de positief voorspellende waarde van de test moet bijna 100% zijn en dit moet worden bevestigd in andere studies. In onze studie vonden wij dat geen enkele patiënt met een post-anoxisch coma en een sNSE van boven de 25 µg/L nog bij bewustzijn kwam. En wat tonen vergelijkbare studies? Inderdaad toonde andere studies vergelijkbare resultaten, soms met iets andere grenswaarden (2-10).

Maar toen werd een nieuwe behandeling voor patiënten met een post-anoxisch coma geïntroduceerd: therapeutische hypothermie. Twee afzonderlijke studies hadden aangetoond dat bij de toepassing van onderkoeling tot 33 °C gedurende 24 uur van de patiënt in coma na een hartstilstand, de prognose verbeterde (11,12). Veel centra over de hele wereld begonnen met het koelen van deze comateuze patiënten na reanimatie. Toen rees de vraag of de bestaande middelen voor het vaststellen van de prognose en de beslissing over voortzetting van de behandeling nog steeds van toepassing waren. Uiteindelijk bleek dat ook bij patiënten met post-anoxische coma die waren behandeld met koeling, het sNSE hoger was bij patiënten die niet meer ontwaakten uit het post-anoxisch coma. (13, 14) Daarnaast was bij patiënten die wel ontwaakten een hoger

sNSE geassocieerd met meer hersenschade. (15) Er waren echter ook patiënten met een hoog sNSE die wel ontwaakten uit coma en dit betekende dat de positief voorspellende waarde niet 100% was. (16) Daarom is sNSE niet nauwkeurig genoeg om de beslissing te nemen om de behandeling van comateuze patiënten na reanimatie te stoppen of voort te zetten en adviseren de huidige richtlijnen om sNSE hiervoor niet te gebruiken. (17-19)

Infectie bestrijding op de intensive care: SDD met cefazoline

Hoofdstuk 3 gaat over de preventie van infecties op de intensive care. Patiënten die worden behandeld op de intensive care lopen het risico op infectieuze complicaties, zelfs als ze niet zijn opgenomen met een infectie. Het beschermen van de patiënten tegen zo een secundaire of nosocomiale infectie is één van de belangrijkste taken van het IC personeel. Een secundaire infectie kan ontstaan uit twee verschillende bronnen: door bacteriën uit de omgeving van de patiënt of door bacteriën die de patiënt zelf bij zich draagt in de darm, op de huid of in de keel. Met andere woorden, secundaire infecties kunnen exogeen of endogeen zijn, afhankelijk van de bron van de bacteriën. Exogene infecties kunnen worden voorkomen door hygiënische maatregelen, maar hygiënische maatregelen voorkomen endogene infecties niet. (20) Er wordt verondersteld dat endogene infecties het gevolg zijn van potentieel pathogene bacteriën in de darm bij patiënten die relatief onschuldig waren totdat de patiënt ernstig ziek werd. Bij een ernstige ziekte krijgen deze potentieel pathogene bacteriën in de darmen van de patiënt de kans om te delen en zich te verspreiden over het lichaam en om bijvoorbeeld in de longen een beademingsgerelateerde pneumonie te veroorzaken (ventilator acquired pneumonia - VAP).

Als bacteriën uit de darm inderdaad verantwoordelijk zijn voor secundaire of nosocomiale infectie zal de bestrijding van deze bacteriën helpen om secundaire infecties zoals VAP, te voorkomen. Selectieve darm decontaminatie (SDD) is bedoeld om potentieel pathogene bacteriën uit de darm te verwijderen en ondertussen te proberen de onschadelijke bacteriën in de darm te behouden. Dit wordt bereikt door de patiënt in de mond en de maag antibiotica te geven die selectief zijn, wat betekent dat deze antibiotica de potentieel pathogene bacteriën wel doden maar de onschadelijke bacteriën niet. Dit is de eerste pijler van SDD. Gedurende de eerste dagen van de intensive care behandeling wordt ook een systemisch antibioticum gegeven, meestal wordt daarvoor cefotaxim gebruikt, een derde generatie cefalosporine. (20, 21) Dit is de tweede pijler. Hygiënische maatregelen en het surveillance kweken van keel, sputum en rectum zijn de derde en vierde pijler.

Stoutenbeek, Van Saene en Zandstra waren in 1983 de eersten om aan te tonen dat SDD infectieuze complicaties vermindert bij intensive care patiënten. (22-25) Verschillende auteurs vonden dezelfde resultaten in grotere en methodologisch betere onderzoeken en een Cochrane meta-analyse bevestigde dat SDD bij intensive care patiënten

niet alleen secundaire infecties voorkomt, maar ook de sterfte vermindert. (26, 27) Toch wordt SDD wereldwijd niet veel gebruikt. Een belangrijke reden daarvoor is de angst voor antimicrobiële resistentie. (28, 29) Uit onderzoek is echter gebleken dat SDD geen toename maar eerder een afname van resistentie veroorzaakt. (30, 31) Ook bij langdurig gebruik is er niet meer resistentie. (32, 33)

Toen we in 2003 SDD op onze intensive care wilden introduceren, maakten onze microbiologen bezwaar tegen het gebruik van derde generatie cefotaxim als profylactisch antibioticum, aangezien de meeste infecties op de intensive care behandeld konden worden met tweede generatie cefalosporines en alleen eerste generatie cefalosporinen in ons ziekenhuis gebruikt werden voor profylaxe. Zou het kunnen dat in ons ziekenhuis een eerste generatie cefalosporine als cefazoline goed genoeg zou zijn? Voor onze SDD studie, hebben we in de eerste 6 maanden alleen twee keer per week kweken van de keel en rectum afgenomen bij alle patiënten die in aanmerking kwamen voor SDD. (34) In de volgende 6 maanden hebben we colistine, tobramycine en amfotericine 4 keer per dag in de mond en de maag toegediend zoals gebruikelijk bij SDD, maar in plaats van de gebruikelijke cefotaxim gaven we cefazoline intraveneus gedurende 4 dagen. Dus in wezen vergeleken we behandeling zonder SDD enerzijds met SDD met enterale tobramycine, colistine en amfotericine en intraveneuze cefazoline in plaats van cefotaxim anderzijds.

Met 80 geïncubeerde patiënten was het onderzoek te klein om statistisch significante verschillen in overleving tussen de twee groepen te laten zien. We vonden echter dat 31% van de patiënten werden opgenomen met cefazoline resistente anaërobe gram-negatieve bacteriën (AGNB) en slechts 2% met cefotaxim resistente AGNB. Dit heeft ons doen besluiten om het gebruik van SDD op onze intensive care voort te zetten maar met de 'originele' cefotaxim in plaats van cefazoline. Verder vonden we geen toename maar juist een afname van de antimicrobiële resistentie (hoewel niet significant in onze kleine studie).

Deze studie heeft ons geholpen om te besluiten dat cefazoline minder geschikt was als parenteraal antibioticum bij SDD op onze IC en dat we niet bang hoefden te zijn voor toename van resistentie met SDD. In Nederland is na de grote multicenter studie van de Smet *et al.* het debat over de SDD rond 2010 gekanteld ten gunste van het gebruik van SDD (of SOD, selectieve orale decontaminatie, waarbij alleen colistine, tobramycine en amphotericine B in de mond gegeven wordt). (35) Maar de discussie is nog niet voorbij, niet in Nederland en zeker niet daar buiten. (36)

Gaat het slechter met patiënten die tijdens diensturen worden opgenomen?

Het resultaat van behandeling op de intensive care is niet alleen afhankelijk van individuele beslissingen voor individuele patiënten, maar ook van een adequate organisatie en personeelsbezetting. (37-40) Met name de behandeling in de eerste uren van ern-

stige ziekte kan cruciaal en bepalend zijn voor de uiteindelijke uitkomst. (41-43) Hoewel intensieve en spoedeisende zorg in principe de hele dag beschikbaar zijn, is het evident dat expertise, faciliteiten en omstandigheden tijdens kantooruren niet gelijk zijn aan expertise, faciliteiten en omstandigheden tijdens de avond-, nacht- en weekenddiensten. Dus zowel vanuit het oogpunt van kwaliteitscontrole als vanuit wetenschappelijk oogpunt kunnen we ons afvragen of prognose van patiënten die buiten kantooruren worden opgenomen anders is dan de prognose van patiënten die tijdens kantooruren worden opgenomen. Sommige auteurs vonden dat patiënten die werden opgenomen buiten kantooruren een hogere mortaliteit hadden, zelfs na correctie voor ziekte-ernst, (41, 44-46) maar anderen vonden geen verschil. (47-52)

Voor onze studie, gepresenteerd in hoofdstuk 4, werden gegevens van het Gelre Ziekenhuis in Apeldoorn en het Onze Lieve Vrouwe Ziekenhuis in Amsterdam en natuurlijk het Reinier de Graaf Gasthuis in Delft samengevoegd. (53) We vonden dat patiënten die buiten kantooruren werden opgenomen een hogere sterfte hadden dan patiënten die tijdens kantooruren werden opgenomen, maar dat dit verschil te verklaren was door het feit dat de patiënten die waren opgenomen buiten kantooruren zieker waren.

We namen ook deel aan een groter onderzoek met de Nederlandse Intensive Care Registry (NICE), waarin gegevens van 70 Nederlandse ziekenhuizen werden samengevoegd. Deze studie toonde aan dat de mortaliteit van patiënten die op de intensive care worden opgenomen tijdens kantooruren lager is dan de mortaliteit van patiënten die buiten kantooruren worden opgenomen ook na correctie voor ziekte ernst. (54) Dus in onze studie met resultaten van 3 ziekenhuizen vonden we dat verhoogde mortaliteit van opnames buiten kantooruren werd verklaard doordat deze patiënten zieker waren, maar de grotere landelijke studie concludeerde dat dit verschil niet alleen verklaard werd doordat patiënten die buiten kantooruren werden opgenomen zieker waren. Dit kan betekenen dat er in de drie ziekenhuizen van ons eigen onderzoek geen verschil was tussen zorg binnen en buiten kantooruren, terwijl dat verschil er landelijk wel is. Het kan ook betekenen dat het verschil er in onze drie ziekenhuizen ook is, maar dat het verschil te klein was om te detecteren.

Het debat over deze kwestie gaat door, maar hoe dan ook is het duidelijk dat elke intensive care en elk ziekenhuis de plicht heeft om zijn patiënten te beschermen tegen kwaliteitsverlies dat kan ontstaan buiten kantooruren. Uit onze studie hebben we geleerd dat in dit kwaliteitsverlies op onze intensive care klein is. Een recente ontwikkeling, ook in Nederland, is dat meer en meer de dienstdoende intensivisten 's nachts in het ziekenhuis blijven om de kwaliteit van de zorg te verhogen buiten kantooruren. De literatuur om deze kostbare ingreep te rechtvaardigen is tegenstrijdig. (55, 56)

Kan bepaling van procalcitonine in het bloed de diagnose bloedvergiftiging helpen stellen?

Sepsis (bloedvergiftiging) is een van de meest levensbedreigende ziekten op de intensive care en er wordt veel moeite gedaan voor de herkenning en behandeling van sepsis. Het identificeren van patiënten met sepsis kan moeilijk zijn, omdat de symptomen niet erg specifiek zijn. Soms heeft de patiënt koorts, een snelle hartslag, een snelle ademhaling, of een lage bloeddruk en soms kunnen tekenen van ontsteking gezien worden in laboratoriumtests. Dezelfde symptomen kunnen worden gezien bij het syndroom van systemische ontsteking (SIRS) waarbij er geen infectie is, maar de patiënt wel een soortgelijke reactie vertoont. Sepsis is dan ook gedefinieerd als SIRS met daarbij een infectie. (57) Anders gezegd: systemische ontsteking (SIRS) kan het gevolg zijn van een infectie, maar ook van niet-infectieuze oorzaken zoals trauma of een operatie. Patiënten met SIRS worden behandeld met ondersteunende therapie, maar bij patiënten met sepsis moet er meer gedaan worden om de infectie te bestrijden en dat moet het liefst snel gebeuren. (58) Bij sepsis heeft de patiënt een veel grotere kans om dood te gaan dan bij SIRS.

Soms, maar niet altijd, is het moeilijk om onderscheid te maken tussen sepsis en SIRS. Elke intensivist herkent een patiënt met een longontsteking en lage bloeddruk, koorts, een hoge hartslag en een verhoogd aantal witte bloedcellen als een patiënt met sepsis. Bij patiënten na een grote buikoperatie is het veel moeilijker om te zien of ze een SIRS hebben die vraagt om ondersteuning met vocht of bloeddruk verhogende medicijnen of dat ze een sepsis hebben waarvoor ook nog antibiotica en misschien een her-operatie nodig zijn. Het is dus belangrijk om sepsis te onderscheiden van SIRS en in de vierde studie onderzochten we of bepaling van het procalcitonine (PCT) in het bloed hierbij beter kan helpen dan bepaling van C-reactive proteïne (CRP, de gebruikelijke routine), interleukine 6 (IL6) of lipopolysaccharide bindend eiwit (LBP). (59)

Over het nut van PCT bij het diagnosticeren van sepsis was eerder gerapporteerd (60-64), maar in de literatuur was hierover geen unanimititeit. Twee systematische reviews over de waarde van de PCT bij het diagnosticeren van sepsis hadden resultaten die lijnrecht tegenover elkaar stonden. Tang *et al.* beoordeelden 18 studies en kwamen tot de conclusie dat PCT niet erg behulpzaam is bij het diagnosticeren van sepsis en niet moet worden opgenomen in de dagelijkse praktijk. (64) Aan de andere kant beoordeelden Uzzan *et al.* 33 studies en concludeerden zij dat PCT een goede diagnostische marker voor sepsis is en dat PCT juist wel moeten worden opgenomen in de richtlijnen. (63)

Wij wilden nu zelf wel eens onderzoeken wat PCT zou kunnen betekenen in onze praktijk. We onderzochten 76 patiënten met SIRS of sepsis en vond dat PCT veel beter dan LBP, CRP en IL6 het onderscheid kon maken tussen SIRS en sepsis. Deze studie heeft ons veel geleerd over PCT en sepsis en de PCT bepaling is opgenomen in onze dagelijkse praktijk. Ons advies aan anderen was dan ook om PCT toch zelf te proberen.

Zoals gezegd, soms is duidelijk dat een patiënt sepsis heeft en hebben we aanvullende informatie van PCT niet nodig op het moment dat diagnose gesteld wordt. Misschien is er dan meer winst te verwachten van dagelijkse PCT metingen bij deze patiënt. Als we het PCT de volgende dag zien dalen, kunnen we concluderen dat deze patiënt aan de beterende hand is en dat onze behandeling voldoende is. Een stijgend PCT echter zou voor het behandelteam aanleiding kunnen zijn om diagnose en therapie te heroverwegen. Op deze manier zou PCT ons kunnen helpen om patiënten met sepsis beter te monitoren en om efficiënt en effectief om te gaan met de schaarse middelen op de intensive care. (65-70)

Het spoedinterventie systeem

Er wordt wel gezegd dat in er elk ziekenhuis ten minste één patiënt op de verpleegafdeling is, die eigenlijk op de intensive care zou moeten worden behandeld en hierover gaat hoofdstuk 6. Het is aangetoond dat patiënten op de verpleegafdeling bij wie de toestand zodanig verslechtert dat er een hartstilstand optreedt, in de uren daaraan voorafgaand meestal waarschuwingstekens hebben gegeven die niet werden opgemerkt. (71-74) Op het moment dat de hartstilstand optreedt wordt weliswaar een geoefend reanimatie team opgeroepen, dus je zou kunnen zeggen dat de juiste zorg dan geleverd wordt. Maar cardiopulmonale reanimatie is altijd traumatisch, vaak nutteloos en soms ongewenst. Als de slechte toestand van de patiënt eerder was (h)erkend, dan hadden maatregelen kunnen worden genomen om een hartstilstand te voorkomen. Of er was besloten tot een niet-reanimeer afspraak en adequate palliatieve zorg. Ook is gebleken dat uitgestelde opname op de intensive care van patiënten die wel behoefte hebben aan intensive zorg, leidt tot slechtere uitkomsten. (75)

Hoe moeten we de zorg in het ziekenhuis zodanig organiseren dat patiënten die risico lopen op een hartstilstand of die eigenlijk intensive care zorg nodig hebben, op tijd geïdentificeerd worden? Een mogelijk antwoord op deze vraag is het Spoedinterventie systeem (SIS) of Medical Emergency Team (MET) system, zoals het in het Engels heet. Het systeem vraagt om het tijdig opsporen van patiënten met een verhoogd risico (de afferente poot) en een manier om deze patiënten te behandelen (de efferente poot). (76-78) Voor de detectie van patiënten die een verhoogd risico lopen moeten betrokken verpleegkundigen en artsen worden geïnstrueerd. Meestal gebruikt men een 'early warning system score card', een puntensysteem dat helpt patiënten die gevaar lopen te identificeren op basis van stoornissen van de vitale functies (hartslag, ademhaling, bloeddruk, etc) en niet op basis van de diagnose. (79, 80) De efferente poot bestaat uit een behandelteam, het Spoedinterventie team (SIT), dat naar de patiënt toegaat als die met behulp van het punten systeem geïdentificeerd is als een patiënt met (risico op) een verslechtering van zijn klinische toestand. Een goed werkend SIS vereist tot slot controle en constante verbetering met een plan-do-check-act cyclus. (76, 78, 81)

Verschillende auteurs hebben gerapporteerd over hun ervaringen met het SIS in voor-en-na studies. (82-87) Er zijn maar twee gerandomiseerde studies. (88; 89) Vijf systematische reviews concludeerden dat het bewijs dat het SIS levens redt, niet erg sterk is. (80; 90-93) Toen we in 2004 in ons ziekenhuis met het SIS begonnen, hadden we verwacht dat het bewijs van de effectiviteit van de SIS al snel zou worden geleverd en hadden we zelf niet voldoende middelen om de effectiviteit te onderzoeken. Zelfs met onbeperkte middelen, is het vanuit methodologisch oogpunt bijna onmogelijk om hierover een vergelijkend onderzoek te doen in één enkel ziekenhuis.

Hoofdstuk 6 beschrijft onze ervaring met het SIS. Meer dan 1000 oproepen van het SIT zijn geanalyseerd. Ongeveer de helft van de patiënten werden opgenomen op de IC, voor ongeveer een derde van de patiënten was overplaatsing niet nodig en bij ongeveer een tiende van de patiënten werd geconstateerd dat zij te ziek waren om nog om te profiteren van intensive care behandeling. (94) Het manuscript werd gepresenteerd als een hoofdartikel in het Nederlands Tijdschrift voor Geneeskunde samen met twee commentaren waarin de effectiviteit van het Spoedinterventie systeem ter discussie werd gesteld. (95; 96)

Hoewel het hebben van een SIS verplicht is gesteld door de Nederlandse overheid, is de discussie over de effectiviteit nog gaande. (97) We zien uit naar de resultaten van de COMET studie, een Nederlandse multicenter onderzoek naar de effectiviteit van het Spoedinterventie systeem. In ons ziekenhuis heeft het SIS zich bewezen als een waardevolle dienstverlening van de intensive care aan het ziekenhuis. Het SIS zorgt voor tijdige en adequate triage van patiënten die mogelijk de intensive care nodig hebben. Vele anderen ondersteunen het SIS zelfs als het 'harde' bewijs ontbreekt. (98) Recente studies tonen aan dat ook vandaag de dag de zorg voor patiënten met een risico op verslechtering van hun toestand niet optimaal is. (99) Bijzonder interessant gezien dit proefschrift, is de studie van Wunderink *et al.* Zij bestudeerden PCT niveaus bij patiënten voor wie het spoedinterventie team werd opgeroepen. (100) Zij vonden dat PCT niveaus significant hoger waren bij patiënten die werden opgenomen op de intensive care na een SIT oproep in vergelijking met patiënten die geen intensive care behandeling nodig hadden.

Lange-termijnoverleving na intensive care behandeling

Voor veel patiënten die op de intensive care behandeld worden en voor hun naasten is de belangrijkste vraag zal ik, mijn geliefde, vader, dochter, vriend deze levensbedreigende ziekte overleven? En wat komt daarna? Laten we aannemen dat deze patiënt de intensive care en daaropvolgende behandeling op de verpleegafdeling overleeft en ontslagen wordt uit het ziekenhuis. De patiënt verdwijnt dan uit ons blikveld. Helaas is deze patiënt waarschijnlijk niet meer zo gezond als hij was voor de intensive care behandeling. Hij of zij kan last hebben van vermoeidheid, algemene zwakte, kortademigheid

of van een post-traumatische stress-stoornis om een paar vervelende gevolgen van het overleven van een levensbedreigende ziekte te noemen. (101-106) Of nog erger, de patiënt die met veel moeite levend is ontslagen, overlijdt kort na zijn ontslag. Terwijl de literatuur zich tegenwoordig meer richt op de morbiditeit na de intensive care behandeling, moeten we sterfte na intensive care behandeling niet over het hoofd zien.

Wij bestudeerden de mortaliteit bij patiënten die levend ontslagen werden uit ons het ziekenhuis na intensive care behandeling door onze database te vergelijken met de database van de Sectorale Voorzieningen Berichten in de Zorg (SVB-Z). Hierdoor konden we van al onze patiënten die in Nederland woonden de datum van overlijden of overleven tot 1 januari 2011 bevestigen. We vonden dat de sterfte in het eerste jaar na de ICU behandeling proportioneel even hoog was als tijdens de behandeling in intensive care en het ziekenhuis samen. Ongeveer 14% van de patiënten die waren opgenomen op de intensive care stierf tijdens verblijf in het ziekenhuis. Van de patiënten die overleefden tot ontslag uit het ziekenhuis overleed ook weer 14% in het eerste jaar na ontslag. De lange termijn mortaliteit neemt toe met het stijgen van de leeftijd, met toename van ziekte-ernst bij opname op de intensive care en als de patiënt bij ontslag uit het ziekenhuis niet naar zijn eigen huis terug gaat. Helaas hadden we geen gegevens over de kwaliteit van het leven. Deze studie heeft ons geleerd, dat een patiënt die na intensive care behandeling levend wordt ontslagen uit het ziekenhuis, nog steeds risico loopt.

Introductie van een gecomputeriseerd insuline doseringsprogramma

Het tweede deel van het proefschrift gaat over de glucose regulatie bij intensive care patiënten. Bij ernstig zieke patiënten wordt in het bloed vaak een verhoogd glucose gemeten en vroeger werd aan deze patiënten alleen insuline gegeven als het glucose erg hoog was. In 2001 publiceerden van den Berghe *et al.* hun gerandomiseerd onderzoek waaruit een betere overleving bleek bij patiënten bij wie het serum glucose met behulp van insuline werd gehandhaafd binnen de normale waarden (4.4-6.1 mmol/L) in vergelijking met patiënten bij wie pas insuline werd gegeven als het glucose tot boven de 12 mmol/L steeg. (107) Dit heet intensieve insuline behandeling. Intensivisten over de hele wereld namen deze strategie over.

Een probleem was hoe de juiste hoeveelheid insuline te geven zonder dat de patiënt een te laag glucose (hypoglycaemie) kreeg of toch een te hoog glucose (hyperglycaemie) hield. Vooral hypoglycaemie is schadelijk. De patiënt raakt in coma en als de hypoglycaemie lang duurt kan dat leiden tot onherstelbare schade. Van den Berghe kon ons echter geen simpel schema geven om insuline te doseren. Ze zei dat ze voor een juiste insuline dosis geen schema had maar vertrouwde op de ervaring van haar team. Op veel intensive care afdelingen maakte men toen eigen insuline doseringsschema's op papier. Daarbij werd besloten dat verpleegkundigen voortaan insuline moesten geven volgens deze protocollen, in plaats van aan de artsen te vragen de insuline te doseren. (108-113)

Wij hebben toen een gecomputeriseerd insuline dosering protocol gemaakt, ingevoerd en getest. Om verschillende redenen dachten we dat een gecomputeriseerd protocol beter zou werken dan een protocol op papier. Een computerprogramma leek ons minder foutgevoelig en makkelijker te veranderen zonder nieuwe scholing. Van ingewikkelde berekeningen zouden de gebruikers niets hoeven te merken. Invoering en evaluatie van dit protocol wordt beschreven in hoofdstuk 8. (114) Het bleek dat verpleegkundigen heel tevreden waren met het computerprotocol, dat hen instaat stelde om het glucose van hun patiënten te regelen zonder de artsen te raadplegen. Het gemiddelde glucose daalde van 9,2 tot 7,0 mmol/L met slechts in 0,05% van de monsters een ernstig verlaagd glucose (hypoglycaemie). Het gemiddelde glucose was niet zo laag als gepropageerd door van den Berghe, maar we durfden niet lager te gaan uit angst voor hypoglycaemie. Een speciale redactioneel commentaar vergezelde dit artikel. (115)

Veel intensivisten zijn nog steeds bezorgd dat de voordelen van de intensive insuline therapie teniet gedaan worden door het optreden van hypoglycaemie. (116-120) Hoewel niet veel IC's gebruik maken van gecomputeriseerde protocollen, vinden experts deze wel beter dan protocollen op papier. (121-125) Ons insuline protocol komt daarom binnenkort ook als app beschikbaar.

Is de glucose meter wel nauwkeurig genoeg?

Om een goede glucose regulatie te bereiken werd het noodzakelijk om veel vaker bloedmonsters te nemen van patiënten op de intensive care. Dit was niet alleen meer werk, maar er ontstond ook een noodzaak om de resultaten van de glucose meting sneller te weten. Het was niet langer acceptabel om het bloedmonster naar het ziekenhuis laboratorium op te sturen en een uur te wachten op het resultaat. Daarom werd overgestapt naar simpeler apparaten die binnen 1 of 2 minuten een uitslag konden geven op basis van een druppel bloed en die direct bij de patiënt konden worden gebruikt (point-of-care).

Maar hoe nauwkeurig waren deze apparaten in vergelijking met het ziekenhuislaboratorium? Dit was de vraag die we probeerden te beantwoorden in hoofdstuk 9. We vergeleken de resultaten van het ziekenhuislaboratorium met de resultaten van onze point-of-care AccuChek glucosemeter. (126) Er is echter geen consensus over hoe nauwkeurig een glucosemeter moet zijn. Het meest duidelijk is de ISO 15197-richtlijn. Die schrijft voor dat als de referentie waarde lager is dan 4,2 mmol/L de glucosemeter niet meer dan 0,8 mmol/L mag afwijken. Als de referentie waarde hoger is dan 4,2 mmol/L dan mag de glucosemeter niet meer dan 20% afwijken. In totaal moet 95% van de metingen binnen deze grenzen zijn. We vonden de AccuChek metingen in 94% van de gevallen binnen ISO grenzen waren en concludeerden dat de nauwkeurigheid net acceptabel was, maar dat deze onnauwkeurigheid één van de belangrijkste obstakels

was in het bereiken van goede glucose regulatie. Vele anderen kwamen tot dezelfde conclusies. (127-133)

Niet iedereen was na één studie overtuigd dat intensieve insuline therapie nuttig was. (134) Er volgden verschillende grote studies ter bevestiging van het nut van intensieve insuline therapie, maar het lukte niet om de resultaten van van den Berge *et al.* te herhalen. (135-138) Twee studies werden gestopt vanwege bijwerkingen (hypoglycaemie). (135; 138) Het lukte van den Berghe zelf niet om haar eigen resultaten te herhalen in de vervolg studie die gedaan werd in een niet-chirurgische intensive care in hetzelfde ziekenhuis (de eerste studie was gedaan in een chirurgische intensive care). (139) Alleen bij patiënten die drie dagen of meer op de intensive care behandeld werden was de sterfte verminderd met intensieve insuline therapie. Daarentegen was de sterfte verhoogd bij patiënten die minder dan drie dagen behandeld werden. De NICE-SUGAR studie toonde ook een slechtere uitkomst voor patiënten die intensieve insuline therapie kregen. (137)

Over deze tegenstrijdige resultaten is veel gesproken. (139; 140) De huidige richtlijnen schrijven een hogere streefwaarden voor dan van den Berghe suggereerde, niet tussen de 4.4 en 6.1 mmol/L, maar eerder onder de 8,3 of zelfs onder de 10 mmol/L en waarschuwen om hypoglycaemie ten koste van alles te voorkomen. (141-144)

Is het erg als de bloedsuikerwaarden veel variëren?

Een ander onderwerp in de glucose regulatie dat wordt bestudeerd in hoofdstuk 10 is variabiliteit: maakt het niet uit of het serum glucose op en neer gaat of is het beter om meer constante glucose waarden te hebben? Verschillende auteurs meldden dat een grotere fluctuatie of variabiliteit is geassocieerd met verhoogde mortaliteit. (116; 120; 145-149) Eén van de problemen bij het bestuderen van de glucose variabiliteit is hoe variabiliteit te definiëren. Verschillende auteurs hebben verschillende variabiliteitsmaten bedacht om de associatie met mortaliteit te bestuderen. De standaarddeviatie is een veel gebruikte maat om variatie weer te geven maar de standaarddeviatie houdt geen rekening met de tijd en met de volgorde van de glucose metingen. Men heeft andere variabiliteitsmaten bedacht die wel rekening houden met tijd en volgorde. De literatuur rond dit onderwerp is uitvoerig bestudeerd door onze collega's in dit project. (150) Met hen hebben we de glucose variabiliteit onderzocht in de grote database van de Nederlandse Intensive Care Registry (NICE), resulterend in een van de grootste studies over dit onderwerp met meer dan 20.000 patiënten. Wij vonden dat het verband tussen variabiliteit en mortaliteit sterker was bij chirurgische patiënten dan bij niet-chirurgische patiënten. Maar we vonden ook dat het van de gekozen variabiliteitsmaat afhing of er een verband werd gevonden tussen sterfte en variabiliteit. (151)

Hoe moet het verder met de glucose regulatie op de intensive care?

Er bestaat consensus in de literatuur dat voor een goede glucose regulatie op de intensive care verpleegkundigen bevoegd moeten zijn om de insulinedosis met behulp van het protocol, ervaring of beide te bepalen en dat accurate glucose meetapparatuur moet worden gebruikt. De onderzoeken in dit proefschrift ondersteunen dit ook. Er is minder consensus over welke glucose waarden moeten worden nagestreefd. Een minderheid pleit voor intensieve insuline therapie en streeft naar 4.4-6.1 mmol/L. De meerderheid geeft de voorkeur aan een hogere streefwaarde, om hypoglycaemie te voorkomen. (143; 152; 153) Hypoglycaemie dient te worden vermeden, hoewel er geen consensus in de literatuur is over hoe schadelijke hypoglycaemie werkelijk is. (119) En tenslotte wordt geadviseerd om de variabiliteit te beperken. (152; 154; 155)

Hoewel de belangstelling voor de glucose regulatie is afgenomen, werkt de industrie momenteel aan de ontwikkeling van apparaten voor continue glucose meting en dromen sommigen zelfs van de integratie van continue meting met automatische insuline-infusie tot een kunstmatige alveesklier. (156) Daarmee zou het misschien mogelijk zijn om het glucose van de intensive care patiënt laag te houden zonder hypoglycaemie te riskeren en zou een nieuw tijdperk beginnen.

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CURRICULUM VITAE

Iwan August Meynaar is geboren op 2 maart 1964 in Den Haag. Op de leeftijd van 6 jaar emigreerde hij met zijn ouders naar Suriname. Na het doorlopen van de Algemene Middelbare School in Paramaribo, begon hij aan de studie geneeskunde aan de Universiteit van Suriname. Toen de universiteit vanwege politieke verwikkelingen in 1982 gesloten werd zette hij de studie in Leiden voort. Na zijn afstuderen in 1990 verrichte hij onder leiding van Prof Dr R van Furth, Dr JW van 't Wout en Prof Dr JP Vandenbroucke onderzoek naar het gebruik van het vaccin tegen influenza. Na arts-assistentschappen in het Lange Land Ziekenhuis te Zoetermeer en in het Sint Clara Ziekenhuis te Rotterdam en na een reis van 8 maanden door Azië begon hij in 1995 aan de opleiding tot internist in het Rotterdamse cluster. Via het Reinier de Graaf Gasthuis Delft (opleiders Dr W Hart en Dr E Maartense), het Sint Clara ziekenhuis Rotterdam (opleider Dr AF Grootendorst) en het Dijkzigt Ziekenhuis Rotterdam (opleider Prof Dr H Pols) volgde subspecialisatie in de intensive care in het Leids Universitair Medisch Centrum (opleider Prof Dr P van de Berg) en het Onze Lieve Vrouwe Gasthuis Amsterdam (opleider Prof Dr DF Zandstra). Na een jaar als intensivist in het Dijkzigt Ziekenhuis gewerkt te hebben volgde benoeming tot intensivist in het Reinier de Graaf Gasthuis.

In het Reinier de Graaf Gasthuis werd vanaf 2002 samen met Ed Salm, Lilian Dawson en Fred van Tilborg en Peter Tangkau en later Steven Sleswijk Visser en Margot Verheijen de ontwikkeling van de intensive care ter hand genomen. Iwan deed daarnaast tot 2006 ook 2 dagen per week polikliniek en endoscopieën voor de vakgroep maag-darm-en-leverziekten. Vanaf 2005 tot 2011 was hij medisch manager van de intensive care. In 2009 completeerde hij de opleiding tot klinisch epidemioloog aan het VUMC in Amsterdam. Iwan woont samen met Tecla Aerts, samen hebben ze 2 dochters, Anne en Famke.

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Improving Decision Making in Intensive Care

In daily practice in intensive care many questions arise to which answers are not readily available. Sometimes the question has not been researched, sometimes the available data are inconclusive, sometimes the local situation is different from what was studied in the available literature. Intensivists (physicians who specialized in intensive care) and intensive care nurses have to act and decide even though they may not know all the answers.

This thesis tries to answer some of these questions using readily available data and resources: Will this particular patient benefit from intensive care treatment? Will this comatose patient regain consciousness? What is the cause of low blood pressure in this patient? How should we regulate glucose in intensive care patients? What will be the prognosis if a patient survives intensive care?

