VOLUME 16 - NO 6 - DECEMBER 2012

Bi-Monthly official Journal of the
Dutch Society of Intensive care (NVIC)

Netherlands Journal of Critical Care

Netherlands Journal of Critical Care is indexed in:

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bij

- **Invasieve candidiasis**[1]
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- **Empirische antifungale therapie**[3]

- **Bewezen effectiviteit**[1]
- **Gunstig veiligheidsprofiel**[4]
- **Bij volwassenen en kinderen**[5,6]

Referenties:
1. Mora-Duarte J.: Comparison of caspofungin and amphotericin B for invasive candidiasis. *N Eng J Med* 347;2020-9, 2002. **2.** Maertens J.: Efficacy and safety of caspofungin for treatment of invasive aspergillosis in patients refractory to or intolerant for conventional antifungal therapy. *CID* 2004;39:000-000. **3.** Walsh T.J.: Caspofungin versus Liposomal Amphotericin B for empirical antifungal therapy in patients with persistent fever and neutropenia. *N Eng J Med* 2004; 351:1391-402. **4.** David W. Denning: Echinocandin antifungal drugs. *The Lancet* 362: 1142-51, 2003. **5.** Walsh TJ: Pharmacokinetics, safety and tolerability of caspofungin in children and adolescents. *AAC* 49: 4536-4545, 2005. **6.** Zaoutis TE: A prospective, multicenter study of caspofungin for treatment of documented candida or aspergillus infections in pediatric patients. *Pediatrics* 123:877-884, 2009.

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NETHERLANDS JOURNAL OF CRITICAL CARE

Publisher
Netherlands Journal of Critical Care
ISSN: 1569-3511
NVIC
Horapark 9
6717 LZ Ede (Gld)
T.: +31-318-69 33 37
F.: +31-318-69 33 38
KvK Utrecht V30149527

Advress change Jan 1th 2013:
NVIC
PO Box 2124
3500 GC Utrecht
030-6868761

Production
Interactie, Ede

Design
SU Groep, Arnhem

Layout
Dimdim, The Hague

Printing
Multicopy, Ede

Advertising-exploitation/ Business contacts
Interactie, Ede
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As from Jan 1th 2013:
Van Zuiden Communications B.V.
www.vanzuidencommunications.nl
email:
info@vanzuidencommunications.nl
telephone: +31 (0)172-476191

Internet address
www.njcc.nl

Bankaccount
ABN AMRO Ede 52.45.61.893
IBAN NL 55ABNA0524561893
BIC ABNANL 2 A

NVIC membership and subscriptions
One year NVIC-membership costs € 300 (for registered intensivists) or € 130 (otherwise).
These costs include a subscrition for the Neth J Crit Care. Separate issues are available for € 17,50 excluding 6% VAT. Prices subject to change without notice.
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High quality reports of research related to any aspect of intensive care medicine, whether laboratory, clinical, or epidemiological, will be considered for publication in the Neth J Crit Care. This includes original articles, reviews, case reports, clinical images, book review, structured abstracts of papers from the literature, notes, correspondence etc. All manuscripts pass through an independent review process managed by the editorial board.

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Manuscripts should include an abstracts of no more than 300 words using the following headings: Background and objectives, Design, Methods and results and Conclusions.

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Describe the design of the study indicating, as appropriate, use of randomization, blinding, gold standards for diagnosis test and temporal direction (retrospective or prospective)

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Table of abbreviations

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

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From the editor-in-chief

At the end of 2012, we would like to thank all contributors to the Netherlands Journal of Critical Care in 2012. We are especially grateful to the below mentioned reviewers, who devoted their precious time in helping us to appraise potential contributions to the journal, during the peer-review process to which all papers are subjected.

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Received June 2012; accepted September 2012

EDITORIAL

Why is it so difficult to prove that rapid response systems improve patient outcome? Directions for further research

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Keywords - Patient outcome, rapid respons systems

Introduction

The implementation of rapid response systems (RRS) is based on the knowledge that deteriorating physiological processes are frequently present for hours or days before clear clinical deterioration is recognized [1,2]. It is assumed that this physiological deterioration is often treatable and that treatment will have greater effect when initiated early [3]. The RRS consists of an afferent limb, including "crisis detection" and "response triggering" and an efferent limb, the rapid response team (RRT) [4]. Even though robust evidence to support the effectiveness of the RRS is lacking [5-10] the system has been implemented worldwide. For example, Dutch hospitals are required to implement a patient safety programme including an RRS before 2013 [11]. This article explores the reasons why it is so difficult to prove the effectiveness of an RRS. We discuss the study designs that have been used and the various outcome measures in order to estimate the effects of an RRS. Finally, we make suggestions for future research.

Study design: how to find meaningful control groups?

Study designs used to estimate the effect of a treatment are the randomized controlled trial (RCT) and the non-randomized trial, the so-called quasi experiment [12]. The RCT usually has the most rigorous study design and the advantage of excluding potential bias due to heterogeneity and time trends. To date, the RCT design has been used only twice to estimate the effects of an RRS [13,14]. Both studies used cluster randomization at ward or hospital level, which of course has the disadvantage that e.g. bias due to heterogeneity in standard of care, patient groups, ward staffing ratios and ward staff expertise, cannot be fully eliminated. In addition, with randomization at hospital level, the heterogeneity of RRSs may also influence outcomes. These aspects make it extremely difficult to generalize the outcomes of both studies [13,14]. Due to heterogeneity, cluster randomization also requires the inclusion of a large number of wards or hospitals. The MERIT researchers estimated that over 100 hospitals were probably needed to show a 30% difference in the composite outcome cardiac arrest, unexpected death and unplanned ICU admissions [14]. Furthermore, since patient safety is an important topic in today's media, increased awareness of the staff to recognize critically ill patients in the control wards

Table 1. Overview of disadvantages of available study designs

DESIGN	DISADVANTAGES
RCT at patient level	Practically impossible
RCT at ward level	Heterogeneity in • standard care • patient groups • ward staff ratios • ward staff expertise Increased awareness of ward staff on control wards concerning patient safety
RCT at hospital level	Heterogeneity in • standard care • patient groups • ward staff ratios • ward staff expertise • Rapid response system procedures • Composition rapid response teams Increased awareness of ward staff on control wards concerning patient safety
Quasi experiment in general	See RCT at ward level
Quasi experiment with the use of historical controls	See RCT at ward level Organizational changes such as ward staff ratios, ward staff expertise Improvement of medical treatment
Meta-analyses and reviews	Heterogeneity

RCT=randomized controlled trial

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or hospitals might have influenced outcomes. While an RCT with randomization on a patient level would be the ideal design to solve these shortcomings, this is practically impossible to achieve.

Due to the aforementioned problems, the quasi experiment is a potential alternative. However, an important drawback of a quasi experiment is the non-randomized comparison of study groups [12]. The most frequently used quasi-experimental design to estimate the effects of an RRS is the one group before-after design, with the use of historical controls. Almost all those studies have been conducted in single hospitals. Several studies showed a positive effect on mortality [15-20] or incidence of cardiac arrest [15-17,19-23] whereas others found no effect on mortality [24-27] or cardiac arrest [25-28]. Although heterogeneity of patient categories can be partially controlled for, the use of historical control groups offers no way of controlling for other confounding factors, such as improvement in medical treatments and organizational changes [12]. One may therefore question whether the observed changes in outcome are actually due to the RRS.

Finally, systematic reviews and meta-analyses provide an objective method of integrating a number of study results and identifying patterns that otherwise might not have been detected [12]. The drawback of historical control groups was shown in a meta-analysis [9] of quasi-experimental studies as the magnitude of improvement in mortality, cardiac arrests and unplanned ICU admissions in the intervention groups was similar to the control group of the MERIT RCT study. Overall, to date, all reviews and meta-analyses found no or only weak support regarding the effectiveness of an RRS [5-10]. Table 1 shows an overview of the disadvantages of available study designs.

Outcome measures: how to find meaningful outcome measures?

Another reason why it may be difficult or even impossible to show the effectiveness of an RRS is that studies used a variety of outcome measures. The most frequently used outcome measures are the cardiac arrest rate, mortality rate, and number of (unplanned) intensive care unit (ICU) admissions. Unfortunately, the definition of cardiac arrest varies in regard to the type of arrest: cardiac arrest [21] and/or cardiopulmonary arrests [15,17,22,25,26] or cardiac arrest calls [19,28,29]. Also the location of cardiac arrest varies. Most studies used the hospital-wide cardiac arrest rate [7,16,17,19,20,25,26,28,29] thereby including places where the RRS is not active e.g. the operating theatre or the ICU. Others therefore used the out of ICU cardiac arrests [15,23], or cardiac arrests that occurred on the ward [14,22]. Several studies showed a reduction in cardiac arrest rate after the implementation of an RRS. However, this decreased incidence may also be the result of more patients being assigned a do not resuscitate order (DNR) [30-33]. A recent meta-analysis showed that a decline in cardiac arrest rates was not associated with lower hospital mortality [7].

Although the outcome measure mortality appears straight forward, definitions vary among studies. Most studies included all patients who died in the hospital [13,15-17,19,20,23-27,29,30]. Other studies excluded deaths in areas where the RRS was not active e.g. the operating theatre, the ICU or emergency areas [14,18]. However, ward patients may be referred to the ICU in a late stage of deterioration, and die in the ICU. This was the main reason why in our own study we did not exclude patients who died in the ICU following an unplanned IC admission from the ward [34].

Studies that did show a significant reduction in mortality had a high base line mortality incidence of 10 or more per 1000 admissions [13,16-18,23,25]. In the RCT by Priestley et al., baseline mortality was even 57 per 1000 admissions. It is obvious that a reduction in mortality is difficult to prove in settings with a lower baseline incidence. For example, since the baseline mortality rate in patients without a DNR order in our hospital was 3.6 per 1000, the observed decline of 50% of deaths without a DNR order was not statistically significant (Table 2) [34]. The third frequently used outcome measure is the incidence of unplanned ICU admissions. It was hypothesized that implementation of an RRS would decrease the incidence of unplanned ICU admissions due to timely detection and treatment of critically ill patients on the ward [4]. Unfortunately, definitions of ICU admission vary, as some studies included all (planned and unplanned) hospital ICU admissions [17,29] or ICU admissions only from general wards [21] whereas other studies limited inclusion to unplanned ICU admissions [18,35], or unplanned ICU admissions only from the general ward [14,26,36]. Overall, study results are inconclusive; both decreases, [17,21,26,36] no effect [14,28,35], and increases in ICU admissions [29,34] have been found. The hypothesis that the RRS decreases the number of unplanned ICU admissions is questionable, as more ward patients may be detected as

Table 2. Deaths before and after implementation of an RRS (per 1000 admissions)

	BEFORE N=1376		AFTER N=2410		OR	95% CI FOR OR	P-VALUE
		(%)		(%)			
Death without DNR	5	(0.36)	4	(0.17)	0.42	0.11–1.59	0.200
Death with DNR	9	(0.65)	19	(0.79)	1.05	0.46–2.40	0.900

ICU= Intensive care Unit IQR= inter-quartile range LOS=length of stay in days OR= odds ratio * Logistic regressions adjusted for age, gender and ASA
CI = confidence interval

critically ill and referred to the ICU. This could explain why we found an increased number of unplanned ICU admissions directly from the ward from 2.5% to 4.2% (OR 1.65, CI 1.07-2.55) after implementation of the RRS [34]. Table 3 shows an overview of what we know and do not know about the measured outcomes.

Remaining issues and future research

To reduce the incidence of cardiac arrests and unexpected mortality in ward patients, we need the timely detection and appropriate treatment of deteriorating patients. First, research is definitely needed on the accuracy and reliability of the 'track and trigger' systems, since the sensitivity of most current systems is low [32]. Pryterch et al. showed that using a ViEWS score of ≥5 as a trigger would result in a RRT call in 20% of all the observations, which implicates a substantial workload for the RRT team. However, this would only cover 82% of the deaths that would occur within 24 hours after the observation of the trigger [37]. Also the optimal monitoring frequency of the patient's vital signs should be explored in more detail [38].

Second, if treatment is started by the ward staff and/or RRT, it would be interesting to analyze if this treatment is appropriate [39]. For example, a study showed inappropriate treatment by the ward staff, despite an accurate diagnosis in 88% (CI 64%-97%) of all preventable adverse events prior to the RRT call [40]. Our own study showed that 20% of the patients, who were referred to the ICU by the RRT, were initially treated by the RRT on the ward for one or two days [34]. This may partly explain why we did not observe a decrease in the median APACHE II score for unplanned ICU admissions after introduction of an RRS. One other study also reported APACHE scores and found no decrease in scores after introduction of an RRS [29]. Apparently, doctors are reluctant to admit a deteriorating patient to the ICU if they feel that he or she does not fulfil obvious admission criteria, like the need for respiratory or inotropic support.

Third, it is important to define the necessary skills of ward personnel [41] and/or responding personnel [39] in different ward or hospital settings. Other solutions for prompt recognition and treatment of deteriorating patients, rather than implementing a rapid response team, may suffice in particular health care settings [14,42,43]. For example, the Denver Health Medical Centre introduced the afferent arm only, including "crisis detection" and "response triggering". A rapid response team was not introduced since shortage of qualified ward personnel was not a significant issue. Here the patients' designated house staff delivers the majority of care. Introduction of this system resulted in a significant decrease of cardiopulmonary arrests [44].

Fourth, cost-effectiveness studies, including different aspects of recognition and treatment of critically ill patients, would be helpful in choosing the best interventions. For example, if the main results of RRSs would be changes in circumstances of deaths, e.g. more deaths in patients with a DNR order versus deaths in patients without a DNR order, this raises the question whether other measures rather than implementing the complete RRS would suffice.

Finally, non-adherence of the ward staff to set procedures is of serious concern. Even when 'track and trigger systems' and

Table 3. Overview of what we know and not know about measured outcomes

OUTCOME	WHAT DO WE KNOW	WHAT DO WE NOT KNOW
Cardiac arrest	Unclear: several before-after studies found a positive effect, other studies, including one RCT at hospital level, found no effect.	Was the outcome influenced by • organizational changes and/or improvement of medical treatment • (some definitions) cardiac arrest calls without resuscitation • (some definitions) cardiac arrest in places where the RRS was not operating? • changes in DNR order policy
Mortality	Unclear: several before-after studies and one RCT on ward level one RCT on ward level and several before-after studies showed a positive effect, other studies, including an RCT at hospital level, found no effect.	Was the outcome influenced by • heterogeneity between wards? • organizational changes and/or improvement of medical treatment? • (some definitions) mortality in places where the RRS was not operating? • (when defined as deaths without a DNR order) an increase of deaths with a DNR order? Did the outcome • (some definitions) exclude patients who died on the ICU after an unplanned ICU admission?
ICU admissions	Unclear: several before-after studies showed a decrease, other studies, including one RCT at hospital level, found no effect, and some studies found an increase in ICU admissions.	Was the outcome influenced by • organizational changes and/or improvement of medical treatment? • (some definitions) unplanned ICU admissions from places where the RRS was not operating? • (some definitions) planned ICU admissions on which the RRS has no influence? Is the outcome reliable? • increase of unplanned ICU admissions could be positive as this may be the result of early detection of critically ill patients and prevent patients from dying

RRS=rapid response systems, DNR=do not resuscitate, ICU=intensive care unit

an RRT were implemented, suboptimal documentation of vital signs [14,45] and underuse of the RRT was a frequently reported problem [3,14,26,28,46]. Improvement of the implementation strategy will result in improvement of adherence of staff to procedures and studies on this subject are ongoing [47,48]. From the literature we know that in general, implementation strategies that are used most often target individual professionals (e.g. education, feedback, reminders), whereas strategies targeting social interaction in teams and leadership are very effective but used far less often [49].

Conclusion

Lack of adequate study designs and adequate outcome measures make it almost impossible to show the effectiveness of an RRS. Further research should therefore focus on the different aspects of the system, e.g. improvement of 'track and trigger systems' and treatment skills, ways to effectively and efficiently organize the care for critically ill patients in different organizational settings and the improvement of implementation strategies.

No financial support is declared for this study

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Received July 2012; accepted October 2012

REVIEW

Treatment of the delirious critically ill patient

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Abstract - Delirium is a commonly encountered disorder in critically ill patients. As delirium is associated with more adverse events and worse outcomes when compared to non-delirious patients, prevention and treatment of delirium in Intensive Care Unit (ICU) patients is of importance to intensivists. This article presents an overview of pharmacological (for example, prophylactic administration of antipsychotics) and non-pharmacological strategies (for example, early mobilisation and daily interruption of sedation) to prevent the occurrence of delirium and reduce its burden. Furthermore, an overview of pharmacological therapies (including α2-agonists and cholinesterase inhibitors) for treating delirium in ICU patients is presented. Finally, future directions for research are discussed.

Keywords - **Intensive Care Unit; delirium; treatment**

Introduction

Since the start of Intensive Care medicine in the second half of the last century, neuropsychiatric disorders in patients admitted to the Intensive Care Unit (ICU) have been commonly seen in critically ill patients. In the past, several names have been used for these symptoms, which include the ICU syndrome or ICU psychosis [1]. In recent years, however, the term delirium has been accepted as the underlying disorder. Since the landmark publication by Ely et al. [2] scientific interest has risen for this disorder, especially in the field of detecting delirium and identifying the risk factors [3]. Delirium is characterized by agitation (which can be severe) apathy or both. The *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV) defines delirium as a disturbance of consciousness with cognitive changes, which has developed over a short period of time, and is caused by a medical condition [4]. Several pathways have been suggested for the pathogenesis of delirium, although scientific evidence remains unavailable. Leading theories are the cholinergic deficiency hypothesis [5] and an excess of dopamine in delirious patients [6]. Other disorders may play a role as well, these include neuro-inflammation, microthrombosis and neurologic changes associated with sepsis (septic encephalopathy) [6,7].

Delirium in the ICU

Delirium is common in critically ill patients with reported frequencies ranging from 11% to 89%, depending on the method used for detection and case-mix [2, 8-15]. In a recent study among 282 critically ill patients admitted to ten Dutch ICUs, the point prevalence of delirium (e.g. the frequency of delirium in all admitted ICU patients at one point in time, including those deeply sedated) as diagnosed by an expert group (neurologists, geriatricians and psychiatrists) was 28% [16]. The ability of the ICU care-givers to recognize delirium, however, is low, as was shown in a 2009 study among 221 adult ICU patients. In this study, expert groups (as described above), evaluated the patients for the presence or absence of delirium and found a point prevalence of 19% (deeply sedated or comatose patients were also evaluated). As a secondary outcome, ICU physicians were asked to assess the patients (as part of their daily evaluation). The specificity of the ICU physician's evaluation was high (96%), the sensitivity, however, was surprisingly low (29%), indicating that the impression of the ICU physician is not sensitive enough to identify a delirious ICU patient [17].

Identifying delirium

In order to improve the identification of delirious patients, several easy-to-use screening methods have been developed for use in clinical practice. Most methods have been developed for use in the general population (e.g. hospital ward or care-home), but two methods were specially adapted for use in non-communicative (e.g. intubated) ICU patients; the Intensive Care Delirium Screening Checklist (ICDSC) and the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). The latter showed better test characteristics in a mixed-type, Dutch, ICU [17] and is now the most commonly used screening method in the Netherlands. The CAM-ICU showed remarkable good test characteristics in the original validation studies (range, 97% – 100%) and specificity (range, 89% – 100%) [2,18]. In these validation studies, the CAM-ICU was administered by specially trained and designated research nurses; in a recent study, sensitivity was shown to be much lower (47%) [16] when the test was administered by bedside nurses with only a basic training in the use of the CAM-ICU. Results, however, did improve with more extensive training. These results show that the CAM-ICU might not be as useful in identifying delirium in the daily, clinical situation as previously thought, although improved implementation strategies and training might enhance the quality of this instrument.

Consequences

The impact of delirium on critically ill patients is still a matter of debate. Earlier studies showed that patients admitted to the ICU suffering from delirium during their admission remained in the ICU longer, had a longer hospital stay, had a higher in-hospital mortality

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and showed more severe cognitive impairments after discharge [10-12,19,20]. Furthermore, persistent delirium was associated with worse outcomes, as each delirious day extra was associated with a 10% increased risk of death after 6 months [14]. Although these studies were performed with large cohorts and the data were adjusted for several key confounders (for example, age, severity of illness at admission and co-morbidities), an independent association between delirium and outcome is still uncertain.

Treatment

The first step of delirium treatment is management of the underlying illness [21]. In a septic patient, for example, the focus of the medical and nursing staff should be aimed on treatment of the infection and supportive measures to counteract the effects of the sepsis. However, there are several measures aimed directly at the symptoms and onset of delirium. In this article measures for preventing the occurrence of delirium are discussed along with non-pharmacological treatment of delirium. Finally, drug therapy and future perspectives on delirium treatment are discussed.

Non-pharmacological approach

There are numerous factors thought to play a role in the development of delirium, especially in patients who are critically ill. Not only the severity of the underlying disorder, or the critical condition of the patient, but also the treatment of ICU patients (for example, polypharmacy, sedation or analgesics) can cause and provoke delirium. Furthermore, the ICU environment, with noise and continuous light, can be a stimulus for a patient to develop delirium. Although the cornerstone of delirium treatment is focused on treating the underlying disorder, it is reasonable to assume that non-pharmacological measures might help to reduce the incidence, duration and adverse effects of delirium in critically ill patients.

Measures aimed at risk factors

One of the first studies to investigate a non-pharmacological approach to delirium was performed in 1999 by Inouye et al. and published in the *New England Journal of Medicine* [22]. The investigators developed a simple, multi-component intervention for preventing delirium, targeting six risk factors for the development of delirium (cognitive impairment; sleep deprivation; immobility; visual impairment; hearing impairment and dehydration). This intervention was compared with usual care in older patients with an increased risk of delirium. The incidence of delirium was significantly lower in the intervention group as compared to the usual care group (10% versus 15%; p-value 0.02), as was the duration of delirium. Although this study did not include patients admitted to the ICU, it is reasonable to assume that these measures might, in part, be useful in critically ill patients. This assumption is further substantiated by a more recent study by Schweickert et al. in 2009 [23]. In this study, the investigators targeted one of the six risk factors identified by Inouye: immobilization. 104 patients admitted to the ICU were randomized in two groups, one receiving usual care and one received early physical and occupational therapy. In the latter group, even deeply sedated patients on mechanical ventilation were visited by a therapist and underwent passive range of motion exercise. Delirium occurred significantly less in the intervention group; median duration of delirium days 2 versus 4 in the usual care group (p-value 0,03), indicating that early mobilisation can prevent delirium and non-pharmacological measures can be useful in the ICU.

Sedation and delirium

A unique feature of the ICU population is mechanical ventilation and prolonged sedation. In 2000 Kress et al. [24] showed that daily interruption of sedation reduced ICU stay by 3.5 days. Although delirium was not investigated it is reasonable to assume that shorter duration of sedation and mechanical ventilation can result in a lower incidence of delirium. For example, benzodiazepines were shown to be associated with a higher occurrence of delirium [25], thus, if fewer benzodiazepines are used, a decline in delirium is expected. Shorter duration of sedation and mechanical ventilation might be a promising way to prevent delirium from occurring.

Preventive pharmagological measures

A number of studies that investigate ways of preventing delirium in critically ill patients have been published (see table 1). As haloperidol (a first generation or typical antipsychotic drug) is the treatment of choice for delirium, several studies used this pharmacological approach to prevent delirium from occurring.

Prophylactic antipsychotics

Kalisvaart et al.[26] investigated the prophylactic administration of haloperidol to patients at risk of delirium who were scheduled for hip surgery. Although no effect on the incidence of delirium was shown, prophylactic haloperidol did shorten the duration of delirium. This important study, however, did not include critically ill patients. The first study to investigate prophylactic antipsychotics in critically ill patients was published in 2007 by Prakanrattanna et al. [27]. In this prospective study, 126 post cardio-thoracic surgery patients admitted to the ICU received either 1 mg. risperidone (an atypical antipsychotic) or placebo directly after regaining consciousness following surgery (not blinded). Using the CAM-ICU, delirium during admission was registered. Analysis showed that the incidence of post-operative delirium was reduced (11% in placebo group versus 32% in risperidone group, p 0.009). Although post-operative patients are not completely comparable to the general ICU population (e.g. septic patients), these results were promising. In 2010 Girard and others performed the Modifying the Incidence of Delirium (MIND) Trial [28]. In this prospective, randomized, double-blind trial, 101 mechanically ventilated surgical or medical ICU patients with an abnormal level of consciousness or who were on sedative medication, were randomized to receive either haloperidol (5 mg., n = 35); ziprasidone (an a-typical antipsychotic) (40 mg.; n = 30) or placebo (equivalent volume) four times a day, for up to 14 days. The main outcome in this study was delirium or coma free days; the secondary outcomes included mortality, use of antipsychotics (in addition to the study medication) and adverse events. The results of this small, but carefully executed study showed no differences in either the primary or secondary outcomes (number of delirium or coma free days: haloperidol: 14.0; ziprasidone: 15.0; placebo: 12.5; p-value: 0.66), which questions the use of antipsychotics as prevention for delirium. Wang et al.,

however, did find a significant difference in frequency of delirium when using haloperidol [29]. In this, double-blind, randomized, placebo controlled study with 475 older (age >65 yr) non-cardiac surgery ICU patients, 229 received haloperidol (0.5 mg. bolus followed by continous infusion of 0.1 mg./hr.) for 12 hours. The remaining 228 patients received an equivalent volume of placebo. The frequency of delirium was lower in the haloperidol group (15%) when compared to the placebo group (23%) (p-value: 0.03). These remarkable results were recently repeated by Van den Boogaard et al. [30]. In this prospective case-control study 177 ICU patients, with a high probability of developing delirium (identified using the PRE-DELIRIC [31] prediction model), received haloperidol 0.5-1 mg. every 8 hours of the ICU admission. The primary and secondary outcomes (including delirium incidence, number of delirium free days and 28-day mortality) were compared to 299 historical controls. The incidence of delirium was 75% in the control group and 65% in the haloperidol group (p-value 0.01), the number of delirium free days was also lower in the haloperidol group (13 (IQR 3-27) days in the control group versus 20 (IQR 8-27) days in the haloperidol group, p-value 0.003). Although the design of this study was not perfect, this study shows that preventing delirium by giving antipsychotic drugs might be feasible, especially in high risk patients.

Cholinesterase inhibitors

Another trial, performed by Gamberini et al., studied the cholinesterase inhibitor rivastigmine as a possible prophylactic drug for delirium in ICU patients [32]. 120 patients admitted to the ICU after an elective cardio-surgical procedure received either rivastigmine (1.5 mg; n = 59) or placebo (equivalent volume; n = 61) three times a day starting on the evening before surgery and throughout six days post-operatively. The primary outcome was the occurrence of delirium. Delirium was equally frequent in both groups (rivastigmine 30%; placebo 32%; p-value 0.80). The secondary outcomes (mortality, use of sedatives, side effects and others) did not differ between both groups. This study had

Table 1. Studies on pharmacological prevention of delirium in critically ill patients

STUDY	DESIGN	POPULATION	NUMBER OF PATIENTS	INTERVENTION	RESULT
Prakanrattanna et al. 2007[27]	Prospective, randomized	Cardio-surgical patients	126	Risperidone or placebo. Duration: one dose after regaining consciousness	Lower frequency of delirium in risperidone group
Pandharipande et al. 2007[35]	Prospective, randomized, double-blind	Mechanically ventilated medical and surgical patients	106	Dexmedetomidine or lorazepam. Duration: until extubation or maximum 120 hours.	More delirium/coma free days in dexmedetomidine group
Riker et al. 2009[36]	Prospective, randomized, double-blind	Mechanically ventilated medical and surgical patients	375	Dexmedetomidine or midazolam. Duration: until extubation or until maximal 30 days.	Lower frequency of delirium in dexmedetomidine group
Maldonado et al. 2009[37]	Prospective, randomized	Cardio-surgical patients	118	Dexmedetomidine; midazolam or Propofol sedation. Duration: from surgery until extubation in the ICU	Lower frequency of delirium in dexmedetomidine group
Shehabi et al. 2009[38]	Prospective, randomized, double-blind	Cardio-surgical patients	306	Dexmedetomidine or morphine. Duration: maximum 48 hours post-operatively	No difference on frequency of delirium. Shorter duration of delirium in dexmedetomidine group
Gamberinin et al. 2009[32]	Prospective, randomized, double-blind, placebo controlled	ICU patients, post cardio-thoracic surgery	120	Rivastigmine or placebo. Duration: 6 days post-operatively	No difference on frequency of delirium between interventions
Rubino et al. 2010[33]	Prospective, randomized, placebo controlled	Patients after acute type A aortic dissection	30	Clonidine or placebo. Duration: during weaning from mechanical ventilation	No difference on frequency of delirium. Lower severity of delirium in clonidine group
Girard et al. 2010[28]	Prospective, randomized, double-blind, placebo controlled	Mechanically ventilated medical and surgical patients	101	Haloperidol, ziprasidone or placebo Duration: 14 days	No difference on duration of delirium between interventions.
Wang et al. 2012[29]	Prospective, randomized, double-blind, placebo controlled	Non-cardiac surgical ICU patients (age >65yr)	475	Haloperidol or placebo. Duration: 12 hours	Lower frequency of delirium in haloperidol group
Van den Boogaard et al. 2012[30]	Prospective case-control study	ICU patients with a high estimated risk of delirium	177 (299 historical controls)	Haloperidol (historical controls: standard care). Duration: during ICU admission	Lower frequency of delirium in haloperidol group, increase of delirium free days in haloperidol group

ICU = Intensive Care Unit.

some design failures (the use of the CAM-ICU and the low dose of rivastigmine used) and these may have caused the negative results.

α -2 agonists

The α-2 agonist clonidine was used by Rubino et al. [33] to prevent delirium in 30 post aortic dissection surgery patients after weaning from mechanical ventilation. Patients included in this study received clonidine (0.5 µg./kg. followed by continuous infusion of 1-2 µg./kg./hr.; n = 15) or placebo (NaCl 0.9%; n = 15) throughout the weaning from mechanical ventilation. Although the primary outcome did not differ between both groups (frequency of delirium 40% in clonidine group and 33% in placebo group; p-value 0.70) and the study had several limitations (small population, method of diagnosing delirium uncertain) remarkably, the severity of delirium as measured with the Delirium Detection Score (DDS) [34], was lower in the clonidine group, indicating that clonidine might be successful in preventing severe delirium in ICU patients.

Dexmedetomidine

Another and newer α-2 agonist (dexmedetomidine) has been studied more extensively with regard to preventing delirium in ICU patients. Pandharipande et al. showed in the Maximizing Efficacy of Targeted Sedation and Reducing Neurological Dysfunction (MENDS) trial [35] that sedation with dexmedetomidine resulted in more delirium/coma free days when compared to sedation with the benzodiazepine lorazepam. In this prospective, randomized, double-blinded trial, 106 mechanically ventilated ICU patients were randomized to receive either dexmedetomidine (0.15-1.5 µg./kg./hr., titrated to the desired effect; n = 54) or lorazepam (1.0-10.0 mg./hr., , titrated to the desired effect; n = 52). The sedation was continued until extubation or for a maximum of 120 hours. Results showed that although the frequency of delirium was not different between groups (dexmedetomidine 79% versus lorazepam 82%; p-value 0.65), patients in the dexemedetomidine group experienced more delirium/coma free days (7.0 days in dexemedetomidine group versus 3.0 days in lorazepam group; p-value: 0.01). Following this trial several other trials showed the similar positive effects of dexmedetomidine. Riker et al. [36], Maldonado et al. [37] and Shehabi et al. [38] investigated dexemedetomide and compared it with other medication regimes (see table 1). In conclusion: dexmedetomidine seems to be successful in reducing the frequency of delirium in ICU patients when compared to other sedatives. A large meta-analysis by Tan et al. in 2010 [39], however, showed no beneficial effect on the occurrence of delirium when using dexmedetomidine. Several drugs have been studied in attempts to reduce the frequency of delirium. Although not all evidence is conclusive, it seems that some decline in the incidence of delirium can be achieved with either prophylactic use of antipsychotics or by choosing different sedatives to sedate ICU patients on mechanical ventilation.

Pharmacological treatment of delirium

Historically, antipsychotics have been the cornerstone of delirium treatment. Haloperidol is the most frequently used antipsychotic drug for treating delirium and is recommended by several international guidelines [21,40]. The recommended (based on expert opinion) dosage of haloperidol is 2 mg. intravenously in agitated, hyperactive patients followed by repeated doses every 20 minutes until agitation is under control, followed by scheduled doses four times a day [40]. In 2005, Millbrandt et al. showed in an observational study (single centre retrospective cohort analysis) that mechanically ventilated patients who received haloperidol during their ICU stay had lower in-hospital mortality when compared with patients who had not received haloperidol treatment [41]. However, even for haloperidol, evidence on efficacy of antipsychotics for delirium treatment in the ICU is scarce. Haloperidol is used by 75%-80% of intensivists in the United States of America [42] although haloperidol is not approved by the Food and Drugs Administration (FDA) for the treatment of delirium. Haloperidol is associated with several, serious, side effects, including prolongation of QT-interval, extrapyramidal symptoms and malignant neuroleptic syndrome. Atypical (or second generation) antipsychotics (for example, olanzapine, quetiapine and rispiredone) are associated with fewer side effects than typical antipsychotics and thus might be more suitable for treating delirium in ICU patients [43]. Evidence from randomized controlled trials on delirium treatment in the ICU is lacking. There are, however, several studies comparing haloperidol to other, atypical, antipsychotics.

Treatment with antipsychotics

Olanzapine was compared to haloperidol by Skrobik et al. in 2004 [43]. In this prospective, randomized trial, patients admitted to a surgical/medical ICU were screened for delirium using the Delirium Index (DI) [44], delirious patients were randomized to receive either haloperidol (n=45), 0.5 – 5 mg every 8 hours (based on age) or olanzapine (n=28) 2.5 – 5 mg. every 8 hours (based on age) for up to 5 days. Delirium associated outcomes (DI scores, use of escape medication and sedatives) were similar in both groups. Side effects, however, especially extrapyramidal symptoms, were more frequently reported in the haloperidol group. The authors conclude that olanzapine is a safe alternative when treating delirious ICU patients; the results of this trial, however, are hampered by its size, the diagnostic tool used and the lack of a placebo group. Another atypical antipsychotic (quetiapine) was studied prospectively in ICU patients by Devlin et al. in 2009 [45] In this trial 36 delirious ICU patients (diagnosed using the ICDSC) were randomized to receive quetiapine 50 mg twice a day (n=18) or placebo 50 mg. twice a day (n=18). Furthermore, all patients received haloperidol as needed, hampering the placebo controlled design of this study. Despite this limitation, patients receiving quetiapine had a shorter duration of delirium (36 hours (IQR 12 – 87) versus 120 hours (IQR 60 – 195); p-value 0.006) when compared to the placebo group. Although the results of this study are promising, apart from the previously mentioned design limitation, this study is limited by the small number of patients and the fact that quetiapine is only available as an oral tablet – which hampers its use in the majority of ICU patients. Current studies on typical or atypical antipsychotics for treating delirium in ICU patients are rare and those published [43,45] are small and have several other limitations.

Cholinesterase inhibitors

Another approach to the treatment of delirium in ICU patients is with cholinesterase inhibitors. Antipsychotic treatment mainly

focuses on dopaminergic neurotransmitters as pathogeneses of delirium. Several studies have shown that the cholinergic pathway may also play a role in the development of delirium [46-48]. This has resulted in the hypothesis that cholinesterase inhibitors might be successful in the treatment of delirium. As described in the preventive measures section of this article, Gamberinni et al. studied rivastigmine (a cholinesterase inhibitor) for the prevention of delirium, showing no benefit. Van Eijk et al. studied rivastgimine as treatment for delirium in ICU patients [49]. 104 delirious ICU patients (diagnosed using the CAM-ICU) were randomized to receive rivastgimine (n=54) up to 6 mg twice a day or a comparable dosage of placebo (n=50). The included patients also received standard care, with haloperidol, as deemed necessary by the, blinded, treating physician. This study was terminated prematurely due to an increased mortality rate in the rivastgimine group (22% versus 8% in the placebo group; p-value 0.07). This study showed no beneficial effect of rivastigmine on important delirium associated outcomes (among others duration of delirium, severity of delirium and use of escape medication). Although the hypothesis of cholinesterase inhibitors for the treatment of delirium seemed promising, studies have not shown any beneficial effect. Evidence (other than expert opinion) on delirium treatment in ICU patients is lacking. Some attempts have been made to find new or alternative therapies, but, to date, none have been shown to be superior to haloperidol. Interestingly, even the efficacy of haloperidol has not been studied in a large, placebo controlled trial.

Future prespectives

Delirium is commonly encountered in critically ill patients and is a stressful and frightening disorder for patients and their relatives. Delirium is also associated with adverse events, for example, auto-extubation and adverse outcomes. Delirium is therefore a serious problem in ICU patients and evidence for preventive and therapeutic measures is warranted. As shown above, the standard treatment of delirium is the typical antipsychotic haloperidol. Although several studies attempted to find alternative or other treatment options, haloperidol is still the drug of first choice. Future studies are hampered both by the lack of understanding of the exact pathogeneses of delirium (making it difficult to find a suitable new drug) and difficulties in designing a delirium treatment study. As antipsychotics are the drug of choice, it is unethical to withhold delirious patients this treatment, making it difficult, if not impossible to investigate an alternative drug in a placebo controlled matter. A third difficulty encountered when trying to investigate a new drug in the treatment of delirium is the ICU population. As the occurrence and maintenance of delirium is multifactorial, large populations are necessary to account for all confounders. Large trials in critically ill patients are scarce as they are labour intensive and difficult to manage. Large international and national collaborations are necessary if new drugs for the treatment of delirium are studied. One first step towards improved collaboration is the establishment of a collaboration of Dutch ICU delirium investigators (chaired by professor Pickkers).

Pharmacological prevention

In contrast to the treatment of delirium, pharmacological strategies to prevent its occurrence seem more promising. As shown above, the α2-agonist dexmedetomidine used as an alternative sedative, resulted in less delirium and a decline in its duration and severity. Not only the sedative used but also a different practice of sedation is a promising way of preventing delirium from occurring in critically ill patients. Daily interruption of sedation resulted in a shorter duration of sedation and mechanical ventilation [24] possibly reducing the incidence of delirium. Several studies investigated prophylactic treatment with antipsychotics in ICU patients, especially those at high risk of developing delirium. These studies showed promising results, future studies using this approach are under way or being planned and may help to reduce the burden of delirium in ICU patients.

Non-pharmacological prevention

Non-pharmacological approaches for preventing delirium are particularly promising. For example, the early mobilisation of patients resulted in shorter delirium and other 'simple' measures suggested by Inouye [22], for example, the use of spectacles in visually impaired patients or frequent orientation in place and time might contribute to the reduction of delirium. Of particular interest is the restoration of day-night rhythm in ICU patients. Pharmacological and non-pharmacological approaches aimed at a 'better' sleep pattern are promising new fields for studies, as sleep disturbance in ICU patients is still a relatively unknown problem. These, and other, non-pharmacological interventions are of particular interest as they are relatively simple and cheap to implement and have been shown to result in a reduction of delirium in other populations. Furthermore, because pharmacological treatment of delirium in ICU patients is difficult to study and may be undesirable in the, already multi-medicated, ICU patient, non-pharmacologic strategies are promising new directions for future ICU delirium studies.

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Received ; accepted

REVIEW

The consequences of treatment limitations on outcome

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Abstract - Cardiopulmonary resuscitation and mechanical ventilation have enabled us to prolong the life of patients, although this may not always be appropriate. To avoid patients experiencing a poor functional outcome or a long process of dying, Do-Not-Resuscitate (DNR) orders have been instituted. However, several studies suggest that DNR orders independently increase mortality.

DNR orders are based on the patient's own preferences or because resuscitation is judged to be futile by the medical team. This latter assumes that the prognosis of the patient concerned is known. However, an accurate prognosis is extremely difficult, and prognostic models only show good agreement for patients in aggregate, not for individuals. These difficulties in prognostication could partly explain a potential increase in mortality due to DNR orders. Another cause may be unintentional but unjustified broadening of DNR orders by health care workers in patients with DNR orders, with the withholding of other treatments besides CPR and suboptimal care.

Physicians should be aware of the unintentional impact of DNR orders. We recommend several precautions that can be taken to reduce the risk of increasing mortality due to DNR orders. Hospitals should develop clear guidelines, which describe indications for DNR orders and which emphasize that these orders have to be viewed in isolation from other treatment decisions. DNR orders should be made, if possible, at an early time, by combining prognostic models with the physician's own estimate of prognosis, jointly with other colleagues and in concordance with the patient's preferences. Because of the large differences between physicians and hospitals regarding the institution of DNR orders, together with the uncertainty of prognosis, and the self-fulfilling prophecy of treatment limitations, we need to be very cautious in recommending limitations of care.

Keywords - **Do-Not-Resuscitate order, treatment limitations, prognostic models, code order, prediction, critical care**

Introduction

The development of cardiopulmonary resuscitation (CPR), continuous veno-venous hemofiltration and mechanical ventilation have enabled us to extend the life of patients. However, inappropriate use of these life-sustaining procedures may prolong only the process of dying or result in a life with severe neurological damage. Therefore, treatment limitation policies, including do-not-resuscitate (DNR) orders are often prescribed to avoid treatment that would not positively affect the patient's condition and distribute medical resources to patients who are most likely to benefit. However, several studies have now suggested that DNR orders are associated with increased mortality [1,2].

Treatment limitations may be instituted based on a patient's own preference, or because treatment is judged to be futile by the medical team. The latter assumes that the prognosis of the patient concerned is known, which is questionable. For instance, predicted hospital mortality for an individual patient varies considerably among physicians. O'Brien et al. showed that mortality of simulated patients with septic shock, as estimated by two independent physicians, could differ by more than 50 percent [3]. This wide range in expected mortality may be explained by physicians' characteristics, such as differences in age, level of training, religion, country (strongest determinant in the study by Yaguchi et al. [4]) and the subjective component of the analysis of each individual situation [5,6,7] (figure 1).

To aid physicians in prognostication, models have been developed for several diseases. These models demonstrated good agreement for describing patients in aggregate, but their accuracy for individual patients is substantially lower [8]. Furthermore, these models appear to underestimate the probability of a favourable outcome in non-DNR patients. This pessimism may drive the decision towards a DNR order to an individual in whom a favourable outcome may have been possible [9]. In this overview we will discuss the negative impact that DNR orders may independently have on outcome.

History

Soon after the development of CPR in the early 1960s, it became evident that routine application of resuscitation efforts resulted in prolonged suffering for many patients. Accordingly, in terminally ill patients, medical staff often choose to abandon a full resuscitation attempt [10]. There was, however, no formal process for these important decisions and no documentation of the rationale in the medical record. In 1974 the American Medical Association became the first professional organization that recommended formally documenting and communicating decisions to forego resuscitation [11]. In 1983 the autonomy of the patient was acknowledged in the report of the "President's Commission" in Washington that concluded that it was permissible for competent patients to refuse life-sustaining treatment [12]. Ever since, an increasing number of guidelines have been developed concerning

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the use of DNR orders, although not adopted in all countries. There are important differences in decision making of DNR orders between North America and Europe. In North America, relatives by right, share this decision with physicians. In Europe, guidelines agree that proxies, whose preferences are to be taken into account, should be informed, but do not have the right and/or the responsibility for the final decision. European intensivists consider themselves the best decision makers, being better aware of the clinical situation and free from emotional involvement and interests [13]. Therefore, there is no international consensus with regard to DNR guidelines [13].

Epidemiology

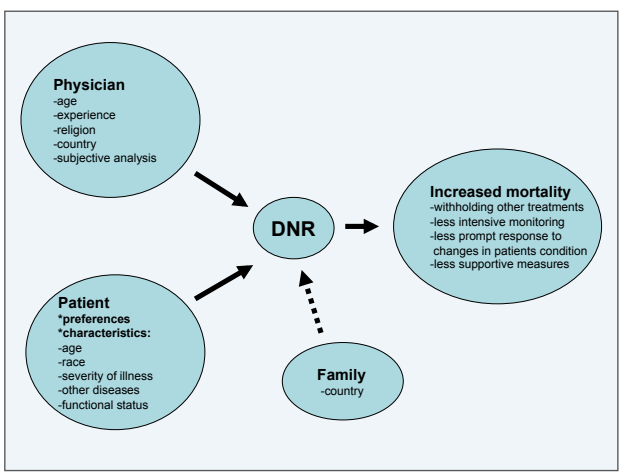
Between 18 and 28% of all hospitalized patients have a DNR order [14] and for Intensive Care Unit (ICU) patients this number varies between 1.5 and 34% [15]. Only 20% of patients who die in the ICU undergo CPR [15]. The assignment of DNR orders increases with severity of illness on admission, and most patients have experienced an acute episode of septic shock, cardiac arrest or intracranial haemorrhage before the assignment of DNR.

Certain patient characteristics are associated with higher incidence of DNR orders. For example, patients with Acquired ImmunoDeficiency Syndrome or cancer are more likely to have a DNR order than patients with cirrhosis or heart failure, despite similar prognoses [14]. Elderly patients are also more likely to have DNR orders. Furthermore, DNR orders are more frequently assigned to white Americans as compared to African Americans [14]. This may be related to the stronger spiritual belief with a reluctance for treatment limitations in African Americans [13]. Finally, educated respondents appeared to have a preference for comfort care [16].

Impact of DNR orders on mortality.

The association between DNR orders and mortality has been described in the literature since the nineteen-eighties. These earlier studies reported that mortality was 3 – 25 times higher in patients with DNR orders. However, those studies were limited to single hospitals and diadjust for severity of illness and other prognostic factors [17,18,19,20]. Later studies, also including withdrawal of vasopressors, mechanical ventilation and dialysis, showed a significantly increased mortality in patients with treatment limitations, even after adjustment for confounding variables, such as disease severity, functional impairment and comorbidities [6,21,22]. To demonstrate an independent relationship between DNR order and mortality, one would need to conduct a controlled clinical trial, randomizing patients either to receive DNR orders or full medical treatment. Ethical considerations obviously preclude such a trial. Shepardson used propensity scores to generate a matched cohort study simulating a randomized trial (1). This methodology first identifies factors related to the use of the intervention under investigation (i.e. DNR order). Then, based on these factors, estimates the likelihood (propensity) that each patient receives the DNR order. Outcomes are compared among patients with a similar propensity for the intervention. Her analysis showed, in line with earlier studies, an increased mortality in patients with a DNR order compared to patients without treatment limitations [1].

Figure 1. Factors with a potential impact on DNR decisions and possible consequences of DNR orders.



Variability in DNR policy between hospitals

The use of DNR orders varies among hospitals. Hospital rates of DNR usage range widely from 0% to 70% [23,24]. Academic medical centres appear to have lower rates of DNR orders than non-academic medical centres, even after adjusting for case mix [23]. However, even among the academic medical centres, a large variability in DNR rates (1.5 – 22%) is reported [16,25].
Mortality rates are higher in hospitals with more frequent use of DNR orders, even after adjustment for number of patients and hospital characteristics [26]. This implies that DNR is not restricted to patients with a particularly poor prognosis. The DNR rate of the hospital (case mix adjusted) may act as a proxy for overall aggressiveness of care [26]. A low threshold for the use of DNR orders may reflect an overall "nonaggressive" approach in that particular hospital. This variability in aggressiveness of care can influence patient outcome irrespective of code status (the ripple effect).

Prognostic models

To investigate the variability in hospital mortality between hospitals, prognostic models were developed to objectively quantify the risk and to evaluate the outcomes of care. These models were certainly not designed for prognostication of *individual* patients. Also, their accuracy for populations other than those used to develop the score is substantially lower [8], even after score customization [27]. A systematic review of studies comparing physician predictions of hospital survival of critically ill adults to objective scoring systems [28] did not demonstrate superiority of the scoring systems. Several explanations can be given for this unexpected finding. First, most of the prognostic models are based on data upon admission or soon thereafter. Physicians, however, will often use the clinical course in their prognostication, as the patient's prognosis becomes more evident during hospital stay. Second, physicians can use information beyond that

contained in severity of illness scores, especially factors that are difficult to quantify such as functional status and quality of life. Third, most prognostic models have been derived from cohorts that include both non-DNR and DNR patients. This results in predictions that appear to be pessimistic in patients without DNR orders, but optimistic in those with DNR orders [9]. Pessimism may result in a superfluous number of DNR orders. Fourth, when the decision is made to withdraw support this will make all previously identified clinical prognosticators of outcome worthless, because it becomes a self-fulfilling prophecy.

Prognostic models should be used to determine the prognosis of an individual patient with extreme prudence. They may have additional value in calibration, but limited value for a specific patient and should therefore not be used as a sole determinant for DNR decision making.

Patients with intracerebral haemorrhage

The effect of treatment limitations on outcome has been studied most thoroughly in patients with acute intracerebral haemorrhage (ICH). The effect of treatment limitations in this category of patients may serve as an example for other disorders.

Treatment limitation decisions are important in patients with acute stroke, since these patients may be prone to an outcome with a quality of life below patients' or relatives' expectations. However, in the last decade, both functional outcome and mortality after ICH have been improved by care in specialised neurologic ICUs, with 65% of subjects without DNR discharged home, and only 8% to a nursing home [22].

Shepardson et al. studied the use of DNR orders in 13,337 stroke patients. DNR orders were used in 22% and the mortality rate was 34 times higher in patients with DNR orders, as compared with patients without DNR orders after adjustment for propensity scores and based on nine demographic and clinical variables [1]. Hemphill et al. focused on the impact of DNR orders on outcome. In their study of 8233 patients with acute ICH, a hospital that used DNR orders 10% more often than another hospital with a similar case mix, had a 13% higher mortality rate ($p < 0.001$) [23].

The most important prognostic variables of ICH are the haematoma volume, the initial Glasgow Coma Score, the presence of intraventricular haemorrhage, hydrocephalus, an infratentorial location, age, active bleeding, the degree of midline shift, hyperglycaemia and marked hypertension [29]. Several prognostic models based on these factors have been developed. However, these models may be overly pessimistic in predicting outcome, since they have failed to account for care limitations such as DNR or withdrawal of technical support [29,9].

Most patients with ICH die soon after admission to the hospital when support is withdrawn because of presumed poor prognosis. Despite the uncertain ground on which it is based, the use of DNR orders within the first 24 hours after acute ICH is common and heterogeneous across different hospitals. Therefore, we agree with the guidelines of the American Stroke Association recommending aggressive guideline-concordant therapy in all ICH patients who do not have advanced directives. New DNR orders should be postponed until at least the second full day of hospitalization [30].

Reasons for increased mortality in DNR patients

The reasons for increased mortality in DNR patients is only partly understood; several hypothesis can, however, be formulated. First, DNR may reflect patients unwilling to undergo the burdensome care of life-sustaining interventions and have a lower "will to survive". Second, the propensity scores used to calculate the difference between the observed minus the expected mortality rate are inaccurate. More difficult to quantify covariates, such as quality of life and functional status, may be omitted from the propensity score, which may result in a too optimistic predicted survival for DNR patients. In contrast, in patients without a DNR order, prognostic models appear to be too pessimistic [31,9,29]. This may result in an inappropriate DNR order for this patient. There is no evidence what proportion of patients with a given condition will survive when support is not allowed to be withdrawn. Patients with an apparent poor prognosis would have to be randomized to continue or withdraw unrestricted treatment, which evidently would be unethical. Therefore, prognoses and prognostic models have to be made on the basis of the available evidence, derived from studies that have included patients with treatment limitations. This will certainly have an impact on outcome. In these predictions death despite treatment cannot be certain, and treatment limitations on this basis will therefore unavoidably increase mortality.

Finally and most worryingly, having a DNR order may affect that patient's penumbra of care. Although formally only interventions in the case of cardiac arrest should be withdrawn, these patients may face suboptimal care under other conditions as well. When, for example, more than one acutely ill patient needs attention at the same time, for instance during a nightshift, the doctor or nurse may give lower priority to a DNR patient. In his or her perception it may be acceptable to delay or to withhold treatments other than CPR (figure 1). This may cause a significant delay in doing diagnostic and therapeutic procedures, resulting in longer disturbance of functions of vital organs (hypotension, low urine output, deoxygenation et cetera), which may have a negative impact on the prognosis of that particular patient.

Practical recommendations

As shown earlier, several studies suggest that DNR orders are an independent risk factor for mortality. Despite this potential negative impact of DNR orders on mortality, using DNR orders is sometimes unavoidable. To completely refrain from using DNR orders may result in an increasing number of patients with a prolonged process of dying or survival with severe impairment [13].

So what can we do to decrease the risk of unwanted mortality due to the assignment of DNR orders? As explained earlier, in North America, relatives by right, share this decision with physicians, whereas in Europe, the preferences of proxies are to be taken into account, but the physician makes the final decision . We will focus on the situation in Europe.

Part of the enhanced mortality can be explained by patient preferences for limited therapy and this should be respected.

However, precautions should be taken into account when discussing DNR orders. As discussed earlier, prognostic models tend to underestimate the changes of survival in non-DNR patients. Although they may aid in calibration, they should not be used as a sole determinant for DNR decision making. Furthermore, it is important that treatment limitations are enforced only by experienced physicians, preferably intensivists [32] clinicians working in the ICU, as they are better in prognostication and can better overlook the effects of aggressive medical treatment. It is advisable to discuss treatment limitations early with the patient and family. During an emergency admission it is unlikely that there will be enough time to discuss the chances of a good functional outcome with the risk of resuscitation efforts being in vain. During evening and night shifts many senior staff members will not be available for this discussion and it turns out to be the – inexperienced house officer -- who has never seen the patient before -- who is confronted with this challenge. Whenever there is doubt about a code order, ICU attending physicians should be consulted.

When patients have already been admitted to the ICU without a code order, treatment limitations should be a multidisciplinary decision with the involvement of nurses and other colleagues.

Another important question here is how the broadening of DNR orders can be avoided? First, all hospitals should have clear guidelines about DNR orders, preferably based on national guidelines. These should state that DNR orders have to be viewed in isolation from other treatment decisions. Furthermore, treatment limitations should be specified and clearly written in the patient's medical record, by preference on specific code forms.

Conclusions

It should be remembered that having a DNR order does not only depend on patient characteristics, but on the attitude of individual doctors and the culture in a specific hospital as well. Therefore, it is extremely important that physicians are aware of the unintentional impact of DNR orders and avoid broadening the interpretations of DNR and withholding treatments other than CPR in DNR patients.

Competing interests

The authors declare that they have no competing interests.
Factors with a potential impact on DNR decisions and possible consequences of DNR orders

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Received October 2012, accepted October 2012

HOT TOPICS

Summary of hot topics session, European Society of Intensive Care Medicine

17 October 2012, Lisbon, Portugal

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Neurocognitive development of children 4 years after critical illness and treatment with tight glucose control

Mesotten D, et al. JAMA 2012:24;308(16):1641-50.

Background. In a previous study in paediatric critically ill patients, tight glucose control (TGC) improved acute mortality but there was concern about cognitive outcomes because of a major increase in the rate of hypoglycemia in the treatment arm (defined as a glucose<2.2 mmol/L, 24.9% versus 1.4% in standard care group).

Objective. To assess intelligence 4 years after randomisation to the TGC study.

Patients and Methods. All 700 children included in the previous RCT were approached for follow up. For comparison, 216 matched healthy children (102 siblings).

Main results. IQ 88.5 controls and 88.0 in TGC group versus 103 in matched healthy children (P=0.70). For more complex intellectual tasks, the children in the TGC group tended to have better outcomes, approaching those in the healthy controls. Subanalysis of children with hypoglycemia in TGC versus usual care group confirmed the absence of adverse cognitive consequences of TGC.

Clinical implications. Hypoglycemia during TGC in critically ill children, in spite of a 25% incidence, did not affect cognitive outcome in survivors, and even improved motor coordination and cognitive flexibility. It is argued that hyperglycemia may be more deleterious to the developing brain than brief hypoglycemia.

Daily sedation interruption in mechanically ventilated critically ill patients cared for with a sedation protocol. A randomized controlled trial. SLEAP investigators, and the Canadian Critical Care Trials Group.

Mehta S, et al. JAMA 2012;308(19):doi:10.1001/jama.2012.13872

Background. Minimisation of sedation in critically ill patients improves outcome. However, concerns exist about daily sedation interruption with regard to patient discomfort, device removal, and clinician workload.

Objective. To assess whether critically ill patients who were managed according to a nurse-driven analgesia/sedation (opioids and benzodiazepines only) protocol would benefit from daily interruption of analgesia/sedation.

Patients and Methods. Multicenter randomized controlled clinical trial (Canada/US) in adult patients anticipated to be mechanically ventilated ≥ 48 hours. Patients after cardiac arrest, with traumatic brain injury, those receiving neuromuscular blocking agents, with limitation of life support and with no informed consent were excluded. Primary outcome was the duration of mechanical ventilation from intubation to extubation, or tracheostomy mask for at least 48 h. The sedation goal in both groups was light sedation (comfortable and arousable) with an intent to wean sedation to zero when feasible. A weaning protocol including daily screen for unassisted breathing was used. Daily interruption of sedation was done in the intervention group.

Main results. More than 80% had a medical as opposed to surgical or traumatic condition (N=423). There were no differences in the primary outcomes between the two treatment groups. Patients in the intervention group received 102 mg of midazolam equivalent/day versus 82 mg in the control group (P=0.04) and 1780 mcg of fentanyl equivalent/day versus 1070 mcg (P<0.0001). Hospital mortality was similar in both groups (30%). Nurses found the workload higher in the intervention group.

Clinical implications. For critically ill mechanically ventilated patients managed according to a nurse-driven protocol aimed at light sedation, daily interruption of sedation did not reduce duration of mechanical ventilation.

The PROSEVA trial: Effect of prone positioning in patients with severe and persistent acute respiratory distress syndrome.

Guerin C, et al. Submitted.

Background. There is still uncertainty about the effect of prone positioning in acute respiratory distress syndrome (ARDS) on mortality.

Objective. To demonstrate that prone position (PP) can reduce mortality in patients with severe and persistent ARDS.

Patients and Methods. This trial included adult patients, intubated for <36 h, with ARDS according to the consensus criteria, which had to be confirmed 12-24 h later, and with the following criteria present: PaO2/FiO2 (PF) ratio<150, FiO2>0.6, PEEP≥5 cmH2O and tidal volume (Vt) of 6ml/kg ideal body weight. Exclusion criteria were increased intracranial pressure, massive hemoptysis, tracheal surgery, facial trauma, deep venous thrombosis, unstable bone fractures, mean arterial pressure<65 mmHg, pregnancy, chest tube with air leak, inhaled nitric oxygen, extracorporeal membrane oxygenation, lung transplant, non-invasive ventilation>24 h. PP

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had to be instituted for at least 16 h or until stopping rules including lower mechanical ventilatory support, serious complications during PP or PF ratio decrease>20%. Targets in both groups were pH>7.20, Vt 6ml/kg, plateau pressure≤30 cmH2O, SpO2≥88%. Sedation interruption and subsequent weaning were tried when in supine position PEEP was <10 cmH2O, PF ratio>150 and FiO2<0.6.

Main results. Baseline characteristics (N=466) were similar except for a lower Sequential Organ Failure Assessment (SOFA) score (10.4 vs 9.6, P=0.01) in the control group. Most patients had a primary ARDS due to pneumonia and aspiration. At inclusion both groups had a mean PEEP of 10 cmH2O with FiO2 0.8, pH 7.30, plateau pressure 24 cmH2O, lactate between 2 and 3. Mortality was 33% in the SP versus 16% in the PP group (P<0.0001), with a hazard ratio after adjustment for SOFA of 0.42 (0.26-0.66) at 28 days. More patients had a cardiac arrest in the SP group (13.5%, versus 6.4%).

Clinical implications. Prone positioning in severe and persistent ARDS in patients that fitted the inclusion criteria in this trial reduced mortality significantly. Baseline mortality seems lower than in previous trials. Reasons given by the presenting author for the large treatment effect found in this trial may include: long PP sessions, stopping rules for PP, lower PEEP (less hemodynamic worsening).

Albumin for volume replacement in severe sepsis. The ALBIOS trial, preliminary results.

Gattinoni L, et al. To be submitted

Background. Possible benefit of albumin on mortality was found in the SAFE study in septic patients.

Objective. Does resuscitation with albumin improve survival at 28 and 90 days in severe sepsis and septic shock compared with crystalloids.

Patients and Methods. Patients with severe sepsis and septic shock were included after a period of initial early goal directed therapy according to the Rivers protocol. Patients were randomised for crystalloids alone versus albumin and crystalloids as fluid for resuscitation targeted at >30g/L plasma albumin, both in the acute phase according to early goal directed therapy and until day 28. No other colloids were allowed during this period.

Main results. N=1815. Mortality was 35% in both groups at discharge. There was a trend towards less mortality in patients with severe septic shock.

Clinical implications. To be determined after publication of final results.

C.H.E.S.T.: Crystalloids Hydroxy-Ethyl Starch Trial.

Myburgh JA, et al. N Engl J Med 2012 Oct 17. [Epub ahead of print]

Background. Hydroxy-ethyl starches (HES) are widely used but there is concern with regard to risk of kidney injury and potential adverse effect on outcome in critical illness.

Objective. To assess safety and efficacy of 6% hydroxy-ethyl starch (130/0.4) as compared with 0.9% sodium chloride alone for fluid resuscitation in adult patients treated in the ICU.

Patients and Methods. Multicenter randomized controlled clinical trial across New Zealand and Australia. Patients received up to 50ml/kg of study fluid per day in accordance with maximum hydroxy-ethyl starch dose, followed by open-label 0.9% saline. Intervention was fluid resuscitation to correct hypovolemia at any time during ICU treatment according to the treating physician, and supported by one or more predefined criteria for hypovolemia. Patients with intracranial hemorrhage, dialysis dependent renal failure, burns, cardiac surgery, or liver transplant patients were excluded.

Main results. Relative risk for mortality was 1.06 in the HES group vs controls (NS, P=0.26, mortality 18% versus 17%). RR was 1.21 (P=0.04) for use of renal replacement therapy in the HES group (7.0% versus 5.8%). Pruritus and skin reactions were more prevalent in the HES group.

Clinical implications. The use of 6% HES (130/0.4) did not improve mortality as compared with normal saline for resuscitation in ICU patients, but was associated with a higher risk for RRT. HES did not confer any benefit in any subgroup over normal saline.

EuSOS: European Surgical Outcomes Study.

Pearse R, et al. Lancet. 2012 Sep 22;380(9847):1059-65.

Background. Surgical outcome data are generally of poor quality and not comparative across Europe.

Objective. To assess in hospital mortality across a wide range of surgical patients, and hospital and critical care stay in 28 European nations.

Patients and Methods. Observational 7 day cohort study with follow up until hospital discharge. All adult patients undergoing in-patient non-cardiac surgery during a 7 day period (April 2011) were included. Obstetric, neurosurgery and cardiac surgery patients were excluded.

Main results. Mortality rates after surgery were higher than expected from previous data (N=46 539, overall mortality 4%, range 1.2% for Iceland to 21.5% for Latvia). Evidence was found of international variation in mortality and critical care allocation to this population.

Clinical implications. Variations in mortality between countries suggest the need for national and international strategies to improve care for these patients.

Received September 2011; accepted March 2012

CASE REPORT

GHB withdrawal syndrome: a possible life threatening condition

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Abstract - Chronic use of gamma-hydroxybutyrate (GHB) can cause dependency. Subsequent acute cessation may lead to a variety of withdrawal symptoms. We present the case of a 22-year old man with a life-threatening GHB withdrawal syndrome, including delirium, autonomic dysfunction, rhabdomyolysis and renal failure. As high dosages of sedatives were ineffective, medical GHB was added to the treatment regimen. After 19 days of ICU treatment, he fully recovered. This case report describes the pathophysiology of the GHB withdrawal syndrome and discusses the options for treatment.

Keywords - **Gamma-hydroxybutyrate, withdrawal, rhabdomyolysis, renal failure, treatment, medical GHB**

Introduction

Gamma-hydroxybutyrate (GHB), an analogue of gamma aminobutyric acid (GABA), was originally synthesized as an anaesthetic. Due to associated side effects, its clinical use is currently limited to the treatment of narcolepsy and alcoholism. GHB is increasingly popular as a party drug for its euphoric and aphrodisiac effects, and is notorious as a 'rape drug'. Overdose occurs frequently in occasional users, but recovery is usually rapid and uneventful. Chronic use of GHB can cause severe dependence, and withdrawal symptoms may occur within hours after abrupt cessation [1]. In this case report, we describe the case of a patient with a life-threatening withdrawal syndrome after discontinuing chronic GHB use and we discuss the options for treatment.

Case report

A 22-year-old male had been using an increasing amount of GHB for two years, resulting in daily use of up to a litre and a half of self-made GHB of unknown concentration around-the-clock. He abruptly stopped taking GHB because he ran out of money. Within a couple of hours, he developed tremor, agitation, hallucinations and seizures. He was taken to the emergency department of another hospital and subsequently admitted to the emergency ward of a psychiatric hospital. Diazepam 10 mg orally 6 times daily was prescribed. Over the next few days, he was hypertensive, tachycardic, extremely agitated and suffering from severe hallucinations. Because of fever, laboratory abnormalities and ongoing delirium despite administration of several sedative agents (diazepam, haldol, cisordinol and GHB), he was transferred to the emergency department of our hospital on day three.

On arrival, we saw a confused, agitated and extremely combative man, who had to be restrained by a number of people. He was covered with bruises, crusts and scratch marks. Vital signs showed a heart rate of 120 bpm, blood pressure 125/75 mmHg, body temperature 37.8 ^{0}C, oxygen saturation 93% on room air. Laboratory results revealed elevated levels of serum creatinine 443 mmol/L, urea 29.4 mmol/L, creatine kinase (CK) 198798 U/L, aspartate aminotransferase (AST) 1688 U/L, alanine aminotransferase (ALT) 571 U/L, lactate dehydrogenase (LD) 5294 U/L. Urine drug screen was not performed, as he had already been hospitalised for three days. Ultrasonography of his kidneys and liver showed no abnormalities.

Repeated doses of midazolam i.v. did not yield any effect on the agitation or combativeness. To prevent any further deterioration, the patient was transferred to the intensive care unit (ICU) for sedation, tracheal intubation and mechanical ventilation. Infusion with a combination of normal saline and sodium bicarbonate was initiated for renal failure and severe rhabdomyolysis. His urinary output was 50 ml h^{-1}. Renal replacement therapy was not initiated.

Despite a combination of multiple sedative agents in high dosages (midazolam 25 mg h^{-1}, propofol 300 mg h^{-1}, remifentanil 8 ug kg^{-1} h^{-1}, clonidine 0.4 mg h^{-1} and haldol 3mg i.v. t.i.d.), the patient remained agitated and combative. After consultation of an expert in the treatment of GHB-withdrawal syndromes, we added medical GHB (Xyrem®), 1 gram 12 times daily to the treatment regime. After one week of ICU-treatment, self-extubation occurred. Because of ongoing extreme agitation accompanied with desaturations after lowering his sedatives, a percutaneous dilatation tracheostomy was performed.

In the following week, we could very slowly diminish the amount of sedatives. The GHB was gradually tapered to zero in twelve days. Renal function and serum CK, AST, ALT and LD normalised. On day 16, the patient was weaned from mechanical ventilation and the tracheostomy tube was removed. 19 days after admission, he was transferred to a psychiatric hospital for further treatment of his GHB dependence.

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Discussion

The most important clinical effect of exogenous GHB administration is inhibition of the central nervous system by mechanisms mediated by binding of GHB to the γ-aminobutyric acid (GABA)$_B$ receptor [1]. Chronic use of GHB can lead to tolerance due to down-regulation of GABA-receptors [2,3]. Subsequent withdrawal of GHB results in a boost of excitatory neurotransmitters as a result of decreased GABA-inhibition [2]. The withdrawal syndrome that follows often starts with mild symptoms like tremor, diaphoresis, restlessness, insomnia, nausea, vomiting and anxiety. After hours to days, this may progress to severe withdrawal syndrome with refractory agitation, hallucinations, tachycardia, hypertension, hyperthermia and delirium [1,2,4]. Rhabdomyolysis, seizures and death have been reported [2,3,5]. This case is one of the most severe cases of GHB withdrawal syndrome described in the literature. It is unique in the severity of the rhabdomyolysis and is one of the first reported cases of renal failure as part of the GHB withdrawal syndrome [6]. Despite the seriousness of the renal failure and rhabdomyolysis, we did not find hyperkalemia in this patient. Because of a steady urinary output on high fluid infusions and the absence of hyperkalemia, renal replacement therapy was not initiated.

Although the use and abuse of GHB have grown over the years, treatment of the withdrawal syndrome has not yet adequately been investigated and protocols are lacking [7]. Benzodiazepines, alone or in combination with other drugs, are frequently mentioned as agents of first choice, but are often ineffective [1-4,,8,9]. Benzodiazepines are indirect $GABA_A$ agonists, acting by increasing the receptor affinity for GABA, rather than by directly stimulating the receptor. They are thus less effective when central GABA stores are depleted or when receptors are down regulated [4]. Furthermore, benzodiazepines bind the $GABA_A$ receptor, whereas GHB mainly binds the $GABA_B$ receptor [5,7]. This might explain the extremely high dosages often required to control the withdrawal state.

Although considered ineffective and carrying the risk of substantial side effects such as dystonia and lowering the seizure threshold, antipsychotics are used regularly in the treatment of this withdrawal syndrome [4,8,10]. Some other treatments, such as pentobarbital or baclofen, have been suggested for benzodiazepine-resistant cases [4,5,11]. Based on the pharmacologic profile, treatment with the $GABA_B$ agonist baclofen seems argumentative [8]. However, only a few reports of one treatment with baclofen have been published so far [3,5]. Low dose baclofen (5 to 10 mg t.i.d.) has successfully been used in a patient with seizures as part of the GHB withdrawal syndrome [5]. Considering the lack of experience, we think baclofen should only be used when other options fail.

Currently, clinical detoxification with medical GHB in a gradually tapering dosage is being investigated in the Netherlands [12]. The results of a pilot study have recently been published. Twenty-three consecutive patients were transferred from illegal GHB to pharmaceutical GHB. After a titration period, they were placed on a 1-week taper. The results are promising: despite of the large amount of GHB the patients used to take, only mild withdrawal symptoms were reported. None of the patients had to be transferred to a medium or intensive care unit [6]. This pilot study has resulted in a *practice-based recommendation* which was presented at a conference for professionals in addiction medicine in December 2011. The proposed treatment protocol consists of two phases. During the first phase, the titration phase, the patient is stabilized on medical GHB. The starting dose is 60 to 70% of the self-administered dose. Every two hours, adjustment of the dose takes place based on the observed withdrawal symptoms. Due to the large variations in the amount of GHB patients are used to taking, the administered amount of medical GHB may vary from patient to patient. After the patient has been stabilized on medical GHB, the second phase, or detoxification phase, of gradually tapering the GHB follows. The GHB is administered every three hours and the dose is subsequently lowered to zero with 2-3 ml per gift per day (based on GHB with a concentration of 150 mg/ml) [13].

Treatment with medical GHB has also been proposed for cases refractory to other sedative agents [14]. When our patient was admitted, the previously mentioned pilot study was running [6]. The first results seemed positive which was the reason why we started treatment with medical GHB instead of a different none-evidence based treatment such as baclofen. In our case, adding medical GHB to the treatment regimen did not resolve the withdrawal symptoms and we still needed high dosages of other sedatives, but adding GHB did help in creating a manageable situation. Retrospectively, higher dosages of medical GHB might have been required considering the large amount of GHB the patient used to take.

In our opinion, detoxification and treatment of withdrawal symptoms with medical GHB deserve further investigation. Controlled prospective studies are necessary to develop and evaluate treatment protocols for this possible life-threatening condition.

We would like to thank Rama Kamal for her commentary on the manuscript.

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Received May 2011; accepted March 2012

CASE REPORT

"DRESSed" to kill: fatal case report of drug rash with eosinophilia and systemic symptoms

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Abstract - Multiorgan dysfunction syndrome (MODS) is a frequently encountered complication in patients who are admitted to the Intensive Care Unit with severe sepsis. Infrequently the same clinical syndrome can be caused by another pathophysiologic mechanism. We present a patient with possible Drug Rash, Eosinophilia and Systemic Symptoms (DRESS). This rare syndrome is caused by an allergic reaction to drugs. Treatment consists of discontinuation of the drug and supportive treatment. Early recognition of DRESS is vital to enable initiation of treatment at an early stage.

Keywords - **DRESS, eosinophilia, drug rash, fever, skin rash.**

Introduction

Multiorgan dysfunction syndrome (MODS) is a frequently encountered complication in patients who are admitted to the Intensive Care Unit with severe sepsis. According to the sepsis campaign guideline, treatment is aimed at a rapid identification of the source of infection, appropriate empiric antibiotics and early goal directed hemodynamic therapy [1]. Infrequently the same clinical syndrome can be caused by another pathophysiologic mechanism. In this case report we present a patient with possible Drug Rash, Eosinophilia and Systemic Symptoms (DRESS). This rare syndrome is caused by an allergic reaction to drugs. The clinical features and possible therapeutic options of this syndrome are described.

Case presentation

A 58-year old woman was admitted to the GI department of the hospital with abdominal colic and fever. Her medical history revealed a cholecystectomy, ERCP with papillotomy, ovariectomy and recently Aspergillosis of the sinuses. She was not known with immune disorders or pulmonary Aspergillosis. She reported to be allergic to a number of drugs (i.e. vancomycin, ciprofloxacin, lidocain and possibly penicillin). This had never been confirmed by skin tests. She was not using any medications on admission.

For a presumptive diagnosis of choledocholithiasis with cholangitis an ERCP was performed. This procedure was complicated by a perforation of the common bile duct and the development of a retroperitoneal abscess. The abscess was drained, and she was consecutively treated with a number of antibiotics: cefuroxime, metronidazole, ciprofloxacin, piperacillin/tazobactam, amoxicillin and vancomycin. On the 56th day after admission she developed a rash and fever while she was being given vancomycin and ciprofloxacin. She was thought to have an allergic reaction to vancomycin and/or ciprofloxacin and the antibiotics were discontinued. E. Coli en Enterococcus Faecium were cultured from the abscess. Prednisone, clemastine, linezolid and cotrimoxazole were started. On the 65th day after admission she developed high fever and a generalized rash (figure 1) accompanied by hypotension, oliguria, and hypoxic respiratory failure. The laboratory results showed a hemoglobin of 5.7 mmol/L, hematocrit 0.28 L/L, white-cell count 13.5 10^9/L, differentiation: eosinophils 3.59 10^9/L, basophils 0 10^9/L, metamyolcytes 0.22 10^9/L, neutrophils 13.01 10^9/L, lymphocytes 1.79 10^9/L, monocytes 0.22 10^9/L, normoblasts +. Platelets 194 x 10^9/L, BUN 10.8 mmol/L, creatinine 178 µmol/L, bilirubin 6 µmol/L, γ-GT 41 U/L, ASAT 51 U/L, Alkaline Phosphatase and ALAT were not elevated. Lactate of 4.7 mmol/l, C reactive protein of 69 mg/ml. Blood gas analysis showed a respiratory compensated metabolic acidosis and a severe hypoxia (pH 7.34, pCO2 33 mmHg [4.4 kPa], pO2 28 mmHg [3.7 kPa], HCO3 17.7 mmol/l, BE -6.9 mmol/l, O_2sat 44.6%). Blood cultures and cultures taken from drain fluid were negative. Tests for cellular immune response showed an absolute decrease of CD8 T-cells (0.13 x 10^9 [normal values 0.3-0.8]) with 1.183 x 10^9 CD4 cells and CD4/CD8 ratio 9.1 [normal values 1.0-3.6]). Chest/abdominal CT showed no focus of infection but signs of ARDS. She was transferred to the Intensive Care Unit where she was intubated. With the presumptive diagnosis of septic shock due to pneumonia, she was treated with cefuroxime, hydrocortisone, fluid resuscitation, and vasopressors. Because of renal failure, renal replacement therapy was started with continuous venovenous hemofiltration with unfractionated heparin as anticoagulant. Empiric antimycotic therapy with caspofungin was started to treat a presumptive invasive Aspergillosis. Meanwhile, the serum lactate and leucocytosis remained high and eosinophilia developed, which kept rising during the following days (see figure 3). Within five

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days after ICU admission the patient developed a maculopapular inflammatory rash starting on the trunk and spreading out to the extremities together with facial redness. Within days the lesions were confluating to erythroderma with sporadic vesicles and blisters with transient fluid mostly on the lower arms, wrists, and sporadically on the trunk. The hands were swollen with a livid-red discoloration. The redness on the lower legs was less intensive and showed a reticulate pattern like livedo reticularis as can be seen in small vessel vasculitis or as a sign of hypoperfusion.

Two days after ICU admission all antibiotics and antimycotics had been discontinued because DRESS syndrome was suspected as all bacterial and fungal cultures had remained negative. A skin biopsy of the rash revealed a mild, chronic dermatitis with eosinophilia (figure 2). No signs of vasculitis were seen. However, no skin biopsy was taken from skin affected by livedo reticularis. Serum ANA and ANCA were negative as was serum Galactomannan antigen. No tests were performed for viral hepatitis, EBV, CMV, HHV-6 infection or Chlamydia/Mycoplasma infection which have been described to be associated with DRESS. No bone marrow biopsy was performed to rule out a hypereosinophilic syndrome or a myeloproliferative disorder. She was not treated with intravenous immune globulin. On the 10th day after ICU admission she became unresponsive. Cortical and brainstem functions were absent and a large intracerebral haemorrhage was found on the CT scan. Lab results showed a prolonged coagulation time (APTT 58 seconds, PTT 28 seconds) associated with the use of heparin. She died after supportive care was discontinued. A post-mortem was not permitted by the family.

Discussion

A life-threatening severe adverse drug reaction characterized by skin rash, fever, lymph node enlargement and single or multiple organ involvement is called drug rash eosinophilia and systemic symptoms (DRESS). DRESS is a rare syndrome which may be life-threatening [4-6]. Systemic symptoms can present with skin rashes, fever, leucocytosis with eosinophilia or atypical lymphocytosis, lymph node enlargement, and liver or renal dysfunction [2-6]. In the literature, diagnostic criteria are described for this condition [5] (table 1). Hematologic abnormalities are a common feature, especially eosinophilia and mononucleosis-like atypical lymphocytosis [2-4]. The skin rash is characterized mostly by a generalized maculopapular erythematous rash which may extend to exfoliative dermatitis or erytrodermia. Less frequently blistering is reported. The severity of cutaneous changes does not necessarily reflect the severity of internal organ involvement [6].

The syndrome has a delayed onset of symptoms in relation to the introduction of the offending drug and worsening of the clinical symptoms after discontinuation of the responsible drug [7]. The syndrome typically starts within 8 weeks after initiation of the involved drug [2-4]. A number of drugs are associated with DRESS [2,4-6]. Drugs most commonly associated with DRESS are anticonvulsants, antidepressants, sulfonamides, Non-Steroidal Anti-Inflammatory Drugs, antibiotics, ACE-inhibitors and beta blockers.

A few laboratory tests can help differentiate DRESS syndrome from other severe drug reactions or severe sepsis. These tests include complete blood cell count, total eosinophils and leucocyte differentiation. Skin biopsy may help differentiating, but is usually not specific [2]. Histology may show a lymphocytic infiltrate, sometimes mimicking cutaneous lymphoma [7]. In this case skin biopsy was inconclusive. Confirming drug-induced allergic reactions by testing the drug is very difficult.

Epicutaneous tests are available but seldom positive. Intracutaneous tests with different concentrations of the causative drug are needed, but it can be a risk for the patient and those tests are mostly false positive [6,7]. Patch testing might be

Figure 1. Maculopapular erythematous generalized rash.

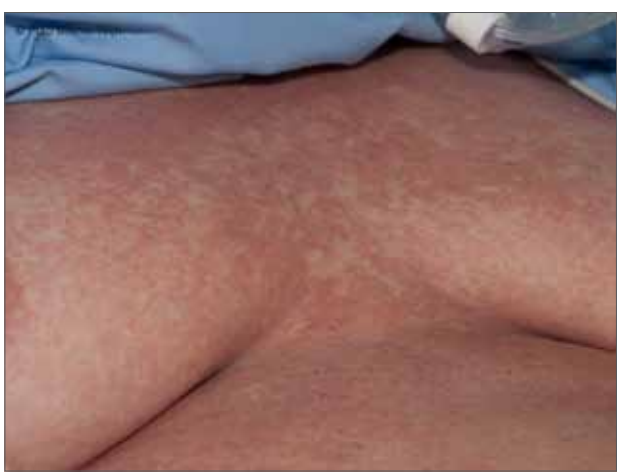
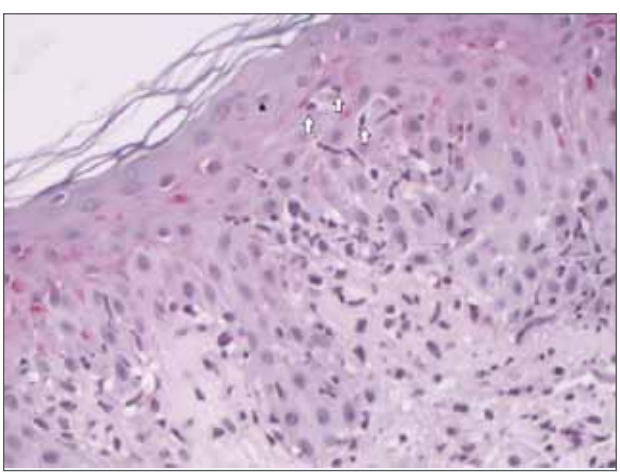


Figure 2. Skin biopsy showing lymphocytic infiltration of the epidermis with only sporadic eosinofilic granulocytes.



The asterix shows the epidermis and the arrows show lymphocytic infiltration of the epidermis.

useful in diagnosing anticonvulsant hypersensitivity syndrome; the usefulness of this test has yet to be determined. Moreover, during the acute phase of the reaction the patch test is not reliable. The advice is to apply patch testing 2 to 6 months after the reaction [9].

The differential diagnosis of DRESS syndrome includes Stevens-Johnson syndrome, toxic epidermal necrolysis, toxic shock syndrome, staphylococcal scalded skin syndrome, hypereosinophilic syndrome, Kawasaki disease, (adult) Still's disease and sepsis. The pathogenic mechanisms are not fully understood but are suggested to be multifactorial [2-4]. Most adverse effects of drugs, are due to the pharmacologic action of a drug, or are idiosyncratic and immune-mediated side effects, which are not predictable. Delayed hypersensitivity reactions are type IV reactions, mediated by T cells. Various T-cell–mediated immune mechanisms lead to clinically distinct diseases. MHC molecules present peptides of different origin (amongst them of drugs) and stimulate different T-cells. Stimulation of $CD8^+$ T-cells and $CD4^+$ T-cells causes secretion of cytokines and activation of other immune effector cells (among which eosinophils and monocytes), which may cause systemic reactions. A drug might not be chemically reactive itself, but become reactive during metabolism and result in an immune reaction. A third possibility is chemically inert drugs, unable to covalently bind to peptides or proteins, that may still activate certain T cells that happen to bear T-cell receptors that can interact with the drug [8]. Shiohara et al. [7] reported a coincidence between patients with DRESS syndrome and HHV-6 reactivation. The human herpesvirus remains latent in lymphocytes after the primary infection and may be reactivated in various conditions such as immunosuppression. HHV-6 DNA was detected in skin lesions of patients with drug hypersensitivity syndrome, but was negative in peripheral blood mononuclear cells.

The therapy of DRESS syndrome includes withdrawal of the offending drug. Supportive therapy includes antipyretics, systemic corticosteroids for reducing symptoms of delayed hypersensitivity reactions. N-acetylcysteine may inhibit the immune reactions involved in the pathogenesis of DRESS reactions and is a precursor of glutathione, which is involved in the detoxification pathway of several drugs [2-4]. Intravenous immune globulin should also be considered in the treatment of severe DRESS syndrome, but evidence for benefit from this treatment is lacking [4]. Family members of the patients should be informed of the diagnosis DRESS as it is inheritable.

In the case presented here, DRESS syndrome was the probable diagnosis by the combination of fever, eosinophilia, skin

Table 1. Diagnostic score for validation of DRESS/Hypersensitivity Syndrome (Kardaun et al. 2007)

ASSESSMENT/SCORE	-1	0	1	2	MIN	MAX
Fever ≥ 38.5	n	y			-1	0
Enlarged lymph nodes		n/u	y		0	1
Eosinophilia Eosinophilia Eosinophilia, if leucocyte count < 4000		n/u	700-1499/µl 10-19.9%	≥ 1500/µl ≥ 20%	0	2
Atypical lymphocytes		n/u	y		0	1
Skin involvement Skin rash extent (%BSA) Skin rash suggesting DRESS Histology suggesting DRESS	 n n	 n/u u y/u	 >50% y		-2	2
Organ involvement* Liver Kidney Lung Muscle/heart Pancreas Other organ		 n/u	 y y y y y y		0	2
Resolution ≥ 15 days	n	y			-1	0
Serology/PCR Hepatitis A, B, C EBV; CMV Mycoplasma/Chlamydia ANA Blood culture If none are positive and at least 3 negative			 y		0	1
Total					-4	9

y = yes, n = no, u = unknown

* After exclusion of other causes: 0 = no organ involvement, 1 = 1 organ, 2 = ≥ 2 organs

Final score: < 2: excluded, 2-3: possible, 4-5: probable, >5: definitive

involvement, and negative blood cultures (a score of five criteria according to the diagnostic score for validation of DRESS). The patient was treated by discontinuation of all possible disease associated medications and supportive treatment was started with corticosteroids, mechanical ventilation, and continuous renal replacement therapy. She did not receive treatment with immune globulins and no tests were performed for viral pathogens.

Tests for cellular immune response showed an absolute decrease of CD8 T-cells with normal CD4 cell count eliminating the possibility of immunodeficiency. Changes in CD4 and CD8 cell count have been described in patients with sepsis [10] and are associated with both the systemic inflammatory response syndrome and the compensatory anti-inflammatory response syndrome.

Intracerebral haemorrhage has not been previously described in DRESS syndrome, and seems to be unrelated.

Conclusion

A case of multiorgan dysfunction syndrome and rash is described here with an allergy for a drug without evidence for sepsis. DRESS is a rare syndrome which may be life-threatening. Early recognition of this syndrome is difficult but vital to enable initiation of treatment at an early stage. The most important features of this condition are rash, eosinophilia and high fever. Treatment consists of withdrawal of the offending drug, supportive therapy, antipyretics and systemic corticosteroids.

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Received November 2011; accepted April 2012

CASE REPORT

Fatal Neuroleptic Malignant-like Syndrome in a Patient with Severe Parkinson's Disease

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Abstract - ***Introduction*** The neuroleptic malignant syndrome and the serotonin syndrome are related and potentially fatal disorders. Their presentation can be similar and treatment is mainly supportive. ***Case*** A 63-year-old woman with a history of severe Parkinson's disease presented with an altered mental status, autonomic instability, severe hyperthermia and respiratory failure. There were no signs of infection and she developed a renal function impairment. Her comatose state was persistent and a magnetic resonance imaging scan finally showed bilateral thermal injury in the basal ganglia and cerebellum. She died twelve days after admission. ***Discussion*** The neuroleptic malignant syndrome and the serotonin syndrome can be hard to distinguish at clinical presentation. The neuroleptic malignant syndrome is mostly caused by the initiation of antidopaminergic agents but can also be due to an acute shortage of dopaminergic activity as seen in severe Parkinson patients. In these patients this syndrome is often caused by withdrawal of dopaminergic therapy but other triggers have also been described. The time of onset and a careful evaluation of the patient's medical and drug histories are the key to diagnosis and differentiation from related disorders. Causative agents should be abandoned in both syndromes and dopaminergic agonists should be initiated for the neuroleptic malignant syndrome. ***Conclusion*** Early recognition is important for the management of the neuroleptic malignant syndrome and the serotonin syndrome. In severe Parkinson patients a variant of the neuroleptic malignant syndrome known as the neuroleptic malignant-like syndrome or the parkinsonism hyperpyrexia syndrome may exist.

Keywords - **Neuroleptic Malignant Syndrome; Serotonin Syndrome; Parkinson Disease; Hyperthermia; Intensive Care; Magnetic Resonance Imaging**

Introduction

The Neuroleptic Malignant Syndrome (NMS) and the Serotonin Syndrome (SS) are related and potentially fatal entities. Both can present with severe hyperthermia, an altered mental status and autonomic instability. General treatment for both syndromes consists of supportive care and removal of the causative agent. Complications include aspiration pneumonia, respiratory failure, rhabdomyolysis, acute renal failure, disseminated intravascular coagulation (DIC) and thromboembolic events. [1-3]

A variation of the NMS is seen in patients with severe Parkinson's disease (PD). In the literature, different names for the condition such as the neuroleptic malignant-like syndrome (NMLS), the Parkinsonism Hyperpyrexia Syndrome (PHS) and the dopaminergic malignant syndrome are used. It is mostly seen after sudden withdrawal of levodopa therapy, but other known triggers include infection, dehydration, poor oral intake and excessively hot weather. [4]

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Case

A 63-year old woman with a history of severe PD was referred to the emergency department. In the few days prior to admission she had complained of agitation, restless movements, fever and dysphagia. Her drug therapy consisted of levodopa 250 milligrams (mg) 7 times daily, pramipexole 4.5 mg once daily, amantadine 100 mg twice daily, rivastigmine 9.5 mg once daily, selegiline 5 mg twice daily and tolcapone 100 mg three times daily. No recent changes had been made to this medication.

Table 1. Differences in Manifestation of the Neuroleptic Malignant Syndrome and the Serotonin Syndrome.

	NEUROLEPTIC MALIGNANT SYNDROME	SEROTONIN SYNDROME
Onset	Several days	Within 12-24 hours
Causative agents	Dopamine antagonist	Serotonin agonist
	Withdrawal of levodopa therapy	
Neuromuscular	Bradyreflexia	Hyperreflexia
Rigidity	Increased tone	
Resolution	Days to weeks	Within 24 hours

At presentation she was comatose (E1M4V1). Because of respiratory failure and hemodynamic instability she was intubated and mechanical ventilation and inotropic support were initiated in the intensive care unit (ICU). Her central body temperature rose as high as 43 degrees Celsius and active cooling measurements like ice packs, cold infusion and cold air were started. Peripheral motor reflexes were absent. There was no evident muscle rigidity. An abdominal, thoracic and cerebral computed tomography (CT) scan were performed and did not show any abnormalities. Infection parameters were negative and further laboratory evaluation showed a thrombopenia (10 .10^9 U/l) and an elevated creatine kinase (1200 U/l). Dantrolene therapy was considered but was not started because of the absence of muscular rigidity. The next day an electro-encephalogram (EEG) ruled out a non-convulsive status epilepticus. She was still comatose while no sedation was being used. Lumbar puncture was performed and cerebrospinal fluid tests were normal. Her infection parameters and all cultures stayed negative during the whole admission period. Despite cold air and cold infusion therapy her body temperature remained between 38 and 39.5 degrees Celsius. She developed a moderate renal function impairment (creatinine 300 µmol/l on day 4) which later showed spontaneous recovery. A clear diagnosis was still lacking and due to concerns for an SS or an NMS, all medication with possible serotonergic activity (selegiline) or antidopaminergic activity (amantadine and tolcapone) was stopped. Her other regular therapy was continued.

Because of her prolonged comatose state (E1M1V1) a second cerebral CT scan was performed three days after admission. This time bilateral hypodense areas were seen in the basal ganglia. A second EEG again ruled out a status epilepticus on day 6 and there were signs of a generalized encephalopathy. A magnetic resonance imaging (MRI) scan was performed on day 7 which showed symmetrical injury in the basal ganglia and cerebellum on both sides. (Figures 1 and 2) No sedative agent had been given since the second day of admission.

Based on her further persistent coma and the finding of a worsening severe encephalopathy on a third EEG performed on day 11, the decision to withdraw supportive care was made. The patient died after 12 days of ICU stay.

Discussion

The NMS and the SS are hard to distinguish at clinical presentation. The main clinical features like hyperthermia, an altered level of consciousness and autonomic instability are similar. Other findings such as muscle rigidity, rhabdomyolysis, respiratory failure, renal failure and DIC can be present in both conditions. Laboratory findings can include leucocytosis, metabolic acidosis, elevated creatine kinase, and liver or renal function impairment [1-3]. As well as the similarities described above, there are some important differences in the manifestation of these conditions. The time of onset and the patient's medical and drug history play a major role in a clinical differentiation being made, while other possible causes should be excluded (Tables 1 and 2).

The precise pathophysiological mechanisms in the NMS and the SS are unknown. While the primary mechanism in the NMS should be a sudden suppression of central dopamine pathways caused by antidopaminergic agents, the primary mechanism in the SS is an alteration in central serotonin metabolism due to serotonergic agents. Further pathologic mechanisms involved are sympathicoadrenal dysfunction and abnormal calcium availability in skeletal muscle cells. [1-3]

The first step in management for both the NMS and SS consists of abandoning the causative agent, concerning antidopaminergic agents in the NMS and serotonergic agents in the SS. Supportive care as ICU monitoring, intravenous fluid replacement, active cooling and hemodynamic and respiratory support should then be started. Sedation, mechanical ventilation, antibiotics and hemodialysis may be necessary. Dopaminergic therapy

Figure 1. Axial DWI; areas of restricted diffusion in the basal ganglia.

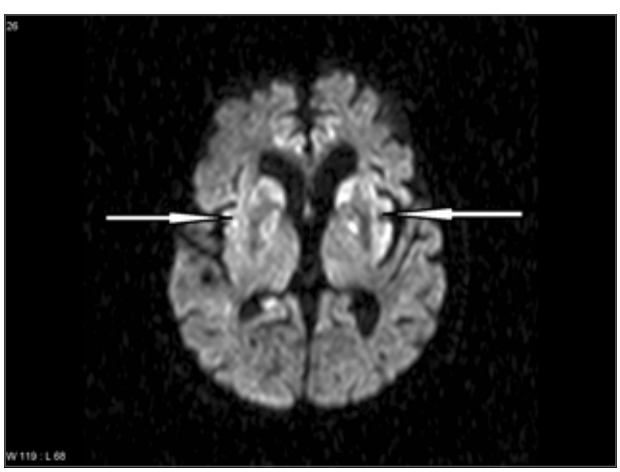
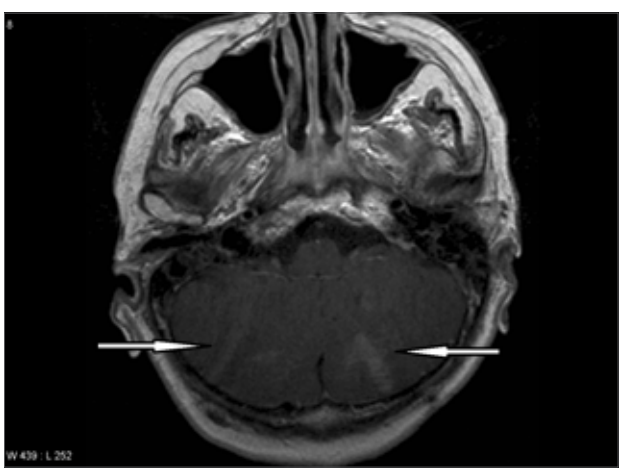


Figure 2. Axial postgadolinium T1-weighted image; bilateral cerebellar patchy enhancement.



with levodopa, bromocriptine, pramipexole or apomorphine is recommended for the NMS or the NMLS. Dantrolene is reserved for cases with severe muscle rigidity and rhabdomyolysis. [1-4]

The patient in our case probably suffered from a variant of the NMS – known as the NMLS or the PHS. This syndrome is seen in severe Parkinson patients without a necessary change in dopamine agonist therapy. Other triggers like infection, dehydration, hot weather or starvation, are thought to cause a sudden suppression in central dopaminergic activity. [4]

Severe hyperthermia, an altered mental status, autonomic instability, respiratory failure, renal function impairment and signs of rhabdomyolysis (elevated creatinine kinase) and DIC (thrombopenia) were all present in this case. Selective injury in the basal ganglia and cerebellum on an MRI scan as presented in our case has been described before and is thought to be direct thermal damage. Neuropathological studies show Purkinje cell necrosis and gliosis in these areas. The cerebellum especially is vulnerable to thermal damage although the exact mechanism of this is not fully understood. [5]

A diagnosis was made relatively late in our case and no clear differentiation was made between the NMS and the SS. All medication with possible serotonergic or antidopaminergic activity rarely reported was stopped. A better understanding of these disorders and the awareness of an entity like the NMLS in Parkinson patients would have made recognition more easy. Instead of stopping some of the patient's regular medication, it probably would have been more appropriate to start additive dopaminergic therapy in this perspective.

Conclusion

Early recognition is important for the treatment of the NMS and the SS as the causative agent should be abandoned and dopaminergic agonists should be initiated for the NMS. The time of onset and the patient's medical and drug history are the key to diagnosis, while other possible causes should be excluded. In severe Parkinson patients there is a variant of the NMS known as the NMLS or PHD that may exist. It is seen without a necessary change in dopamine agonist therapy.

Table 2. Differential diagnosis of the Neuroleptic Malignant Syndrome.

Infectious	Meningitis, Encephalitis, Brain abscess, Sepsis
Pharmacologic	Serotonin Syndrome, Anticholinergic Syndrome, Malignant Hyperthermia, Withdrawal of Dopaminergic Agents or Baclofen
Endocrine	Thyrotoxicosis, Pheochromocytoma

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Received ; accepted

CASE REPORT

Coughing after drinking

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Keywords - tracheo-oesophageal fistula, oesophagectomy, oesophageal stent.

A 60-year old man underwent a transthoracic subtotal oesophagectomy with gastric tube reconstruction after neo-adjuvant chemoradiotherapy for a distal T3N2M0 oesophageal adenocarcinoma. On the sixth postoperative day a contrast swallow study showed an intact oesophagogastric anastomosis. One week later the patient developed chest pain, fever and coughing after intake of fluids. A computer tomography (CT)-scan of the chest showed a fistula between the gastric tube and trachea, just above the carina, without signs of mediastinitis or abscess (Figure 1). The fistula was endoscopically confirmed on the ventral side of the oesophagogastric anastomosis. An oesophageal stent was inserted to cover the fistula and the patient was readmitted to the intensive care unit where he had an uneventful recovery (Figure 2). A follow-up CT-scan and contrast study did not show any leakage . The stent was removed after 6 weeks without any problems. A fistula between the trachea and gastric tube is a rare but serious complication of subtotal oesophagectomy. Anastomotic leakage with inflammatory involvement of the trachea is a well-known cause of benign tracheo-oesophageal fistulas.[1] Other causes are oesophageal dilation, ischemia or trauma of the trachea secondary to surgical dissection in the upper mediastinum and cuff-induced tracheal necrosis during prolonged endotracheal intubation. In our patient, the fistula most likely developed due to leakage of the anastomosis since the fistula tract was visible on the ventral side of the oesophagogastric anastomosis by endoscopy. Neo-adjuvant chemoradiotherapy has been associated with an increased risk of developing a benign tracheobronchial fistula after subtotal oesophagectomy[2] and may well have been a contributing factor in our patient. A typical symptom of a tracheo-oesophageal fistula is coughing associated with oral intake, but recurrent pneumonia and mediastinitis may also occur. The diagnosis is usually confirmed by contrast studies; endoscopy and bronchoscopy are optional. The management of benign tracheo-oesophageal fistulas used to be surgical.[1] Nowadays, endoscopic closure of the defect with a self-expandable stent, has become a viable alternative. It is a less invasive, safe and reliable alternative, although stent migration can occur.[3,4] Bronchoscopic closure of a tracheo-oesophageal fistula has recently been described as well.[5]

Figure 1. A CT scan of the chest showing the tracheo-oesophageal fistula.

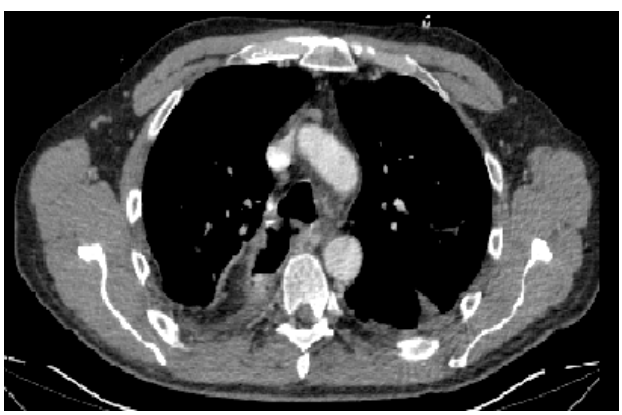
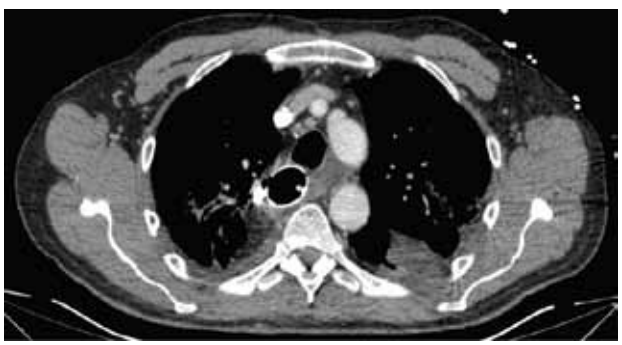


Figure 2. A CT scan of the chest with the stent covering the tracheo-oesophageal fistula in situ.



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Received January 2012; accepted June 2012

CLINICAL IMAGE

Traumatic pneumatoceles

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Keywords - trauma, CT, pneumatocele

Case history

A young motorist fell off his bike at 100 km/h. He landed on his right side before sliding to a full stop without hitting anything. This patient was rushed to the emergency department. On the initial physical examination, a dyspnoeic man was seen, with a normal blood pressure and mild sinus tachycardia without a need for fluid resuscitation. A CT scan was ordered because of the apparently multiple injuries. The CT scan showed an iliac crest fracture and fractures of ribs 9 and 10 with a concomitant right-sided pneumothorax. In addition, he had fractures of the spinous process of Th12 and L1 to L4, and the vertebral body of L5, all without neurological deficit. Finally, multiple pneumatoceles and a lung contusion in the inferior lobe of the right lung were present.

A chest tube was inserted which did not alleviate the patient's dyspnoea. After surgical repair of his iliac crest fracture, the patient was detubated on the second post-operative day and made an uneventful recovery. Clinical follow-up was unremarkable, additional chest imaging was not performed.

Discussion

A pneumatocele of traumatic origin may show as round radiolucent areas on a chest X-ray.

In general, pneumatoceles become apparent hours after trauma as multiple, cyst-like cavities, greater than 1 cm in diameter with a thin uniform wall [1,2]. However, most frequently pneumatoceles are not visible on a chest X-ray, in part because of the concomitant lung contusions. The most frequent clinical sign, not present in this patient, is haemoptysis [1]. Traumatic pneumatoceles are rare, most frequently found in young victims of high energetic blunt thoracic trauma. It is believed that pneumatoceles are created by compression-decompression trauma of the chest during (partial) airway closure, thus causing rupture of small airways [1]. Consequently, an air filled cavity may be created with a thin wall, within the lung parenchyma (intraparenchymal). It is possible that pneumatoceles are enlarged by a check-valve mechanism due to bronchiolar obstruction [3]. This mechanism allows air to pass during inspiration, but obstructing air flow during expiration. Pneumatoceles may secondarily be flooded with blood, thus creating an intrapulmonary haematoma.

In contrast, most pneumatoceles are caused by infection [4], for example, from staphylococcus aureus, streptococcus, or tuberculosis. Pneumatoceles following pulmonary infections may be caused by the drainage of necrotic lung parenchyma and/or local hyperinflation secondary to bronchial hyperinflation of the check-valve type [5]. Pneumatoceles in autoimmune diseases like SLE and rheumatoid arthritis may develop secondary to inflammation of the airway causing air to leak into the pulmonary parenchyma [3].

The treatment of traumatic pneumatoceles is conservative [6], focussing on sputum evacuation and thus prevention of secondary infections [1]. In contrast with lung contusions, which heal fast and completely, pneumatoceles heal in weeks to months, often with remaining tissue scarring.

However, specific treatment is required in secondary infected pneumatoceles, progressively growing pneumatoceles, in pneumatoceles rupturing into the pleural space, or if they are bleeding [6]. Prophylactic antibiotic therapy is not used for an uncomplicated pneumatocele, even though secondary infection is the most frequent complication (up-to 30%) [6]. Once a pneumatocele is infected, therapy is similar to that used for lung abscesses [6].

In summary, we have described a young man with traumatic pneumatoceles accompanying a pneumothorax and a lung contusion. As expected, he made a full and uneventful recovery.

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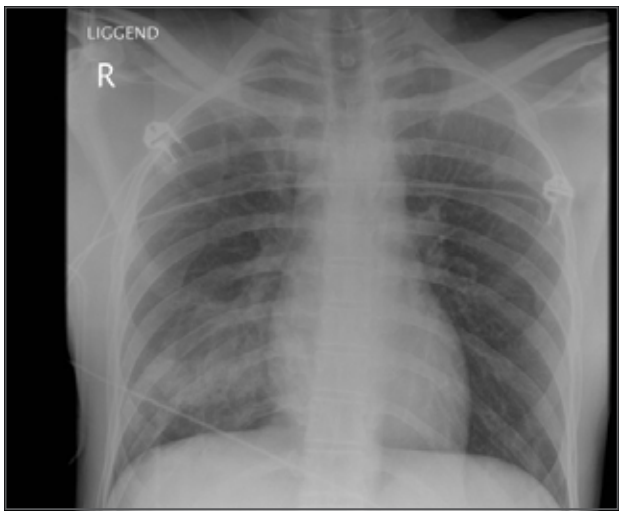
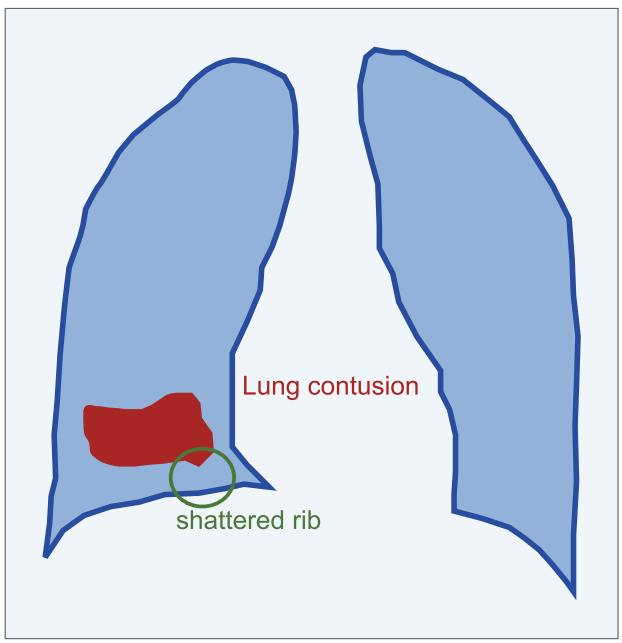
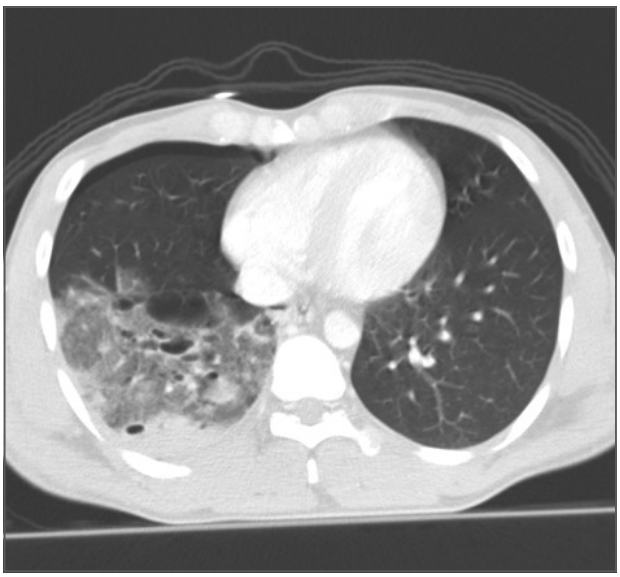
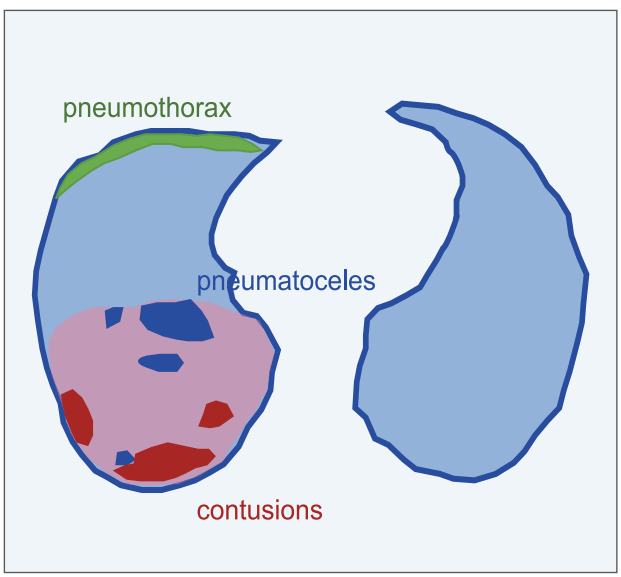
Figure 1. Chest X-ray. Right: Rib 10 shattered, lungcontusion, no obvious pneumothorax. Left: no obvious abnormalities.





Figuur 2. CT-Thorax. lung contusion, pneumatoceles and pneumothorax.





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Received May 2012; accepted September 2012

CLINICAL IMAGE

Pulmonary Cavities after High Energy Trauma

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Abstract - In this report, we describe a 21-year-old patient with pulmonary pseudocysts after a car accident. In our patient we found multiple, big Traumatic Pulmonary Pseudocysts (TPPC) on the CT scan. A chest radiograph did not show any radiologic sign matching TPPC. The size of the pseudocysts decreased during the admission period. In this case, mechanical ventilation had no influence on the size of the pseudocysts. With watchful waiting complete pulmonary recovery was attained.

Keywords - **Blunt chest trauma, Traumatic pulmonary pseudocysts, CT scan**

Case report

A 21-year-old male was admitted to hospital after a high energetic trauma. He had driven his car at high speed into a tree. On site, the patient was awake and he was haemodynamic and respiratory stable.

In the emergency department, his airway was clear and he had a Glasgow Coma Scale of 15. Oxygenation was adequate and breath sounds were normal. He had no haemoptysis and did not complain of chest pain. The patient's heart rate and blood pressure were normal. Examination of the abdomen did not reveal any abnormalities except for some tenderness in this area and in the pelvis. The patient had two open fractures of the femur on the right side and a swollen ankle. Because of increasing restlessness, he was intubated and sedated. His past medical history revealed no specific illness or substance abuse. Chest radiography on admission, before intubation, showed mediastinal and subcutaneous emphysema in the upper quadrants and consolidation of the right lower lobe.(Figure 1)

Computed Tomography (CT) of the thorax showed bilateral, basal consolidations in the lower lobes with cavitations, surrounded by lung parenchyma with patchy consolidations and a pneumothorax on the left. There were also similar cavities around the minor fissure. The largest cavity was found in the right lung and was 37 x 26 mm, no fluid levels were seen. Paraseptal emphysema on the anteromedial side of the right lower lobe and a left ventral pneumothorax was also seen (Figure 2). Because of oxygen desaturation combined with diminished breathing sounds on the left side, a chest tube was inserted on that side while the patient was still on the CT table.

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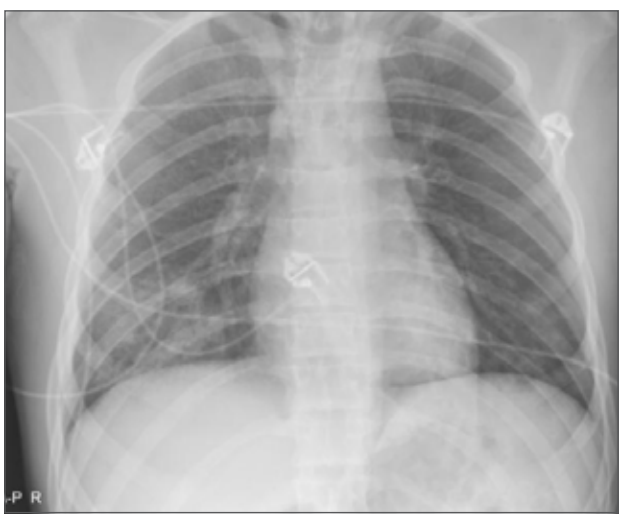
Complete examination of the patient revealed fractures of both femurs, and on the right side fractures of medial collum, os ilium, patella, forefoot, calcaneus, ankle and countenance. Furthermore, bilateral pulmonary contusion, ruptured spleen and devascularization of the right kidney were found. Due to decreased breath sounds on both sides and decreasing saturation after admission to the ICU, a chest tube on the right side was inserted. However, a pneumothorax on the right side was not confirmed by chest X-ray. External fixation of most fractures was performed. The pneumothoraxes required additional drains during the following days. Adequate gas exchange could be achieved with pressure supported volume controlled ventilation with low tidal volumes. The patient received antibiotics because of his open fractures. The damage to the abdominal parenchymatous organs was treated conservatively.

Figure 1. A-P Chest X-ray on admission before intubation



A repeated CT-thorax on day 4 showed that the pneumothorax on the left side had increased and new atelectasis of the left lower lobe was present. The cavities in the lower lobes had decreased in size (Figure 3). The cavitary lesions in the lung parenchyma were interpreted as TPPCs.

Discussion

Blunt trauma of the chest often leads to a pulmonary contusion or intrapulmonary haemorrhage. Development of pulmonary pseudocysts after blunt trauma is a rare complication, especially bilateral presentation of pseudocysts [1-3]. TPPCs are cavitary lesions, with a wall formed by interlobular interstitial connective tissue, without epithelial lining, that develop in the pulmonary parenchyma following chest trauma [2-4]. The incidence of TPPC is about 1-3% after a chest injury in adults [1,3,4]. With the increased use of CT scans in trauma screening, the incidence might very well increase in future. The incidence is higher among children and young adolescents, 85% of patients with TPPC are younger than 30 years [1,3,4]. The hypothesis is that the chest is more compliant in younger people and thus there is a greater transfer of kinetic energy to the lung parenchyma, compared with adults [3,4]. The rapid compression and decompression of the chest damages alveoli and interstitial lung tissue, retraction forces create small cavities filled with air and/or fluid [1,3,4]. If there is no connection between the lesion and the respiratory tract, the lesion will become a pulmonary hematoma [1,2,5]. Resolving pulmonary hematomas may develop into secondary pulmonary pseudocysts [5]. A primary pulmonary pseudocyst is a direct result of trauma itself [5]. In this case, however, no signs of intra-pulmonary hematomas were seen at any point and therefore the probable cause was direct laceration.

Another hypothesis for this condition is that when the glottis is closed or the bronchus is obstructed at the time of the trauma, the compressed air causes pressure cavities [4].

The role of mechanical ventilation in the development of pulmonary pseudocysts is unclear [1,3]. TPPC can be asymptomatic, but if there are symptoms they are variable and non-specific and include haemoptysis, dyspnoea, hypoxaemia, chest pain, coughing and sometimes hyperthermia [1-4]. However, these symptoms can also be attributed to the trauma itself [3]. Physical examination usually reveals little or no abnormalities; sometimes rales can be heard [2].

In the majority of cases the pseudocysts occur within 12 to 24 hours after trauma and can be oval or spherical, unilateral or bilateral and single or multiple [1,2,4]. The diameter of the pseudocysts varies from 1 to 14 cm and can quickly change in shape and size [2-5]. The lower lobes are those most commonly involved, the apices seem not to be affected by TPPC [3,4]. The location of pseudocysts can be central or subpleural, on the side of trauma impact, but they can also be located on the other side, due to the contre-coup effect [3]. In 50% cases the pseudocysts can be seen on chest radiography [2-4]. CT is the best diagnostic test for TPPC [1,2,4].

The diagnosis of TPPC is made by exclusion. Differential diagnoses for TPPC include rupture of the oesophagus, lung abscess, tuberculous cavity, mycosis, Wegener granulomatosis, bronchial carcinoma and bronchogenic cyst and substance abuse by inhalation [3-5]. Improvement of symptoms and the CT scan, without treatment, can confirm the diagnosis.

Figure 2. CT scan on day of trauma. In the right lower lobe multiple intraparenchymal cavities of variable sizes are present, one of which contains an air-fluid level. Surrounding ground glass opacity is noted. Ground opacities are also present in the left lower lobe. In both lower lobes, similar subpleural cavities in a paravertebral position can be seen. A pneumothorax is also noted on the left side.

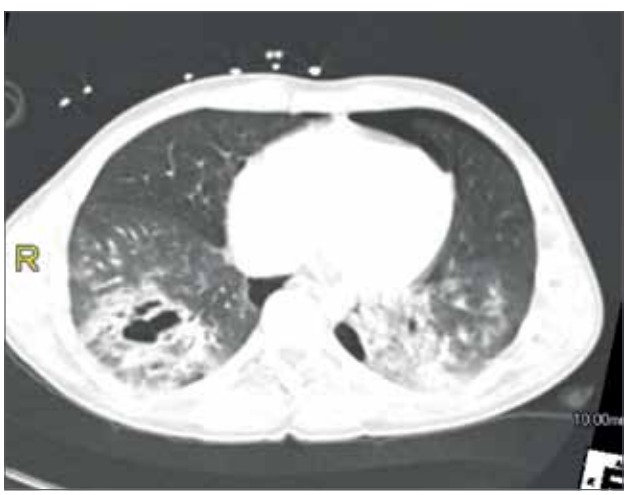
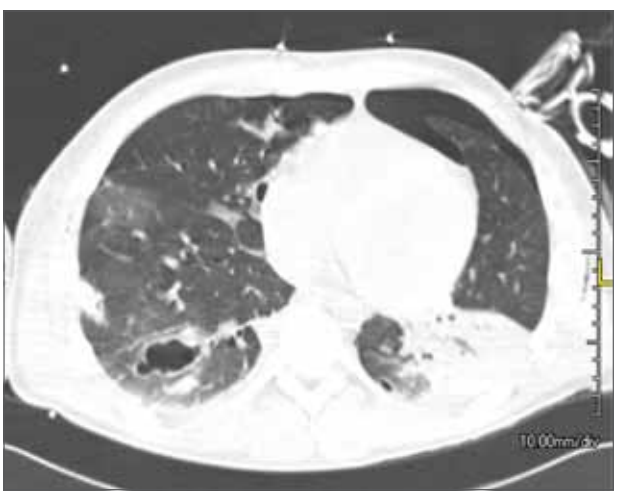


Figure 3. A follow-up CT on day 4 shows resolution of the ground glass opacities surrounding the cavities in the right lower lobe. There is atelectasis of the left lower lobe glass



Consolidation usually disappears within 7 to 10 days after the trauma [3]. The cysts will increase in size during the first 2 weeks and will slowly disappear within 2 to 3 months [1,2]. Given the spontaneous remission, only symptomatic therapy is indicated. Complications of TPPC are rare [2,3]. Rupturing of a pseudocyst can induce a secondary pneumothorax [1,3]. Pseudocysts can get infected [1-3]. After spontaneous remission, no residual radiographic abnormalities are usually present [2]. Indeed, our patient had a complete and uneventful pulmonary recovery.

Conclusion

TPPCs are cavitary lesions, with a wall formed by interlobular interstitial connective tissue, without epithelial lining, that develop in the pulmonary parenchyma after chest trauma with an incidence of 1-3%, possibly by damage to alveoli by the rapid compression and decompression of the chest during trauma. With the increase in use of CT scans in trauma screening, the incidence of this condition might very well increase in future. TPPC requires no special treatment and will resolve spontaneously.

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ABSTRACTS DUTCH ANNUAL INTENSIVE CARE MEETING 2013

Abstracts and Case Reports during the Dutch annual Intensive Care meeting

READING COMMITTEE

1.

Systemic inflammation decreases pain threshold in humans in vivo

M de Goeij[1,2,3], L van Eijk [2,3], P van Elderen [1], O Wilder-Smith[1] K Vissers [1], JG van der Hoeven [2,3], M Kox [1,2,3], GJ Scheffer [1], P Pickkers [2,3]

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Background: Hyperalgesia is a well recognized hallmark of disease and is frequently observed on the intensive care. Pro-inflammatory cytokines have been suggested to be mainly responsible, but human data are scarce. Quantitative sensory testing (QST) provides a standardized way of pain threshold quantification. This study aims to quantify the difference in pain perception caused by systemic inflammation during experimental endotoxemia.

Methods: Pressure pain thresholds (PPT), electrical pain thresholds (EPT) and resistance to the cold pressor test (CPT) were evaluated during systemic inflammation evoked by human endotoxemia. Pain thresholds were measured before and 2 hours after the intravenous administration of 2 ng/kg purified *E. Coli* endotoxin in 27 healthy volunteers. Another 20 subjects not exposed to endotoxemia served as controls.

Results: LPS administration caused a marked inflammatory response characterized by flu-like symptoms, fever and a marked rise in circulating cytokines in all 27 subjects. Peak levels were detected for TNF-α, IL-6, IL-10 and IL-1RA at 580±47, 1286±114, 435±67 and 6063±282 pg/ml respectively. In the endotoxin treated group a significant decrease in PPTs was noted at T=2hrs (-20±4%, figure 1), that was significantly more pronounced than in the control group (-7±3%, p=0.001). Electrical pain thresholds were significantly decreased in the endotoxin-treated group (-13±3%), while no significant changes were observed in control subjects. Two hrs after endotoxin administration, significantly more pain was reported in response to ice immersion (p<0.0001, figure 2A and 2B). Only 26% of the subjects completed the 90 second duration of the measurement during endotoxemia compared to 63% before LPS (p=0.001, figure 2C). The mean time to withdrawal from the ice was 76±4 seconds before endotoxin treatment and 54±5 seconds after (p=0.0001). In control subjects there was no difference between the two measurements (55% fulfilled the measurement at T=-1 hr versus 50% at T=2 h, p=1.00. Mean time to withdrawal was 77±4 seconds at T=-1 and 75±4 seconds at T=2 h, p=0.51, figure 2D).

Conclusion: This study shows that systemic inflammation elicited by the administration of endotoxin to humans results in lowering the pain threshold measured by 3 quantitative sensory testing techniques. The direct link between inflammation and pain sensation warrants further study.

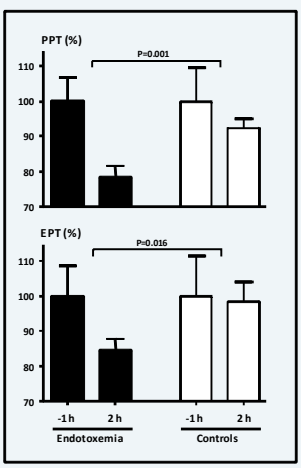

Figure 1.

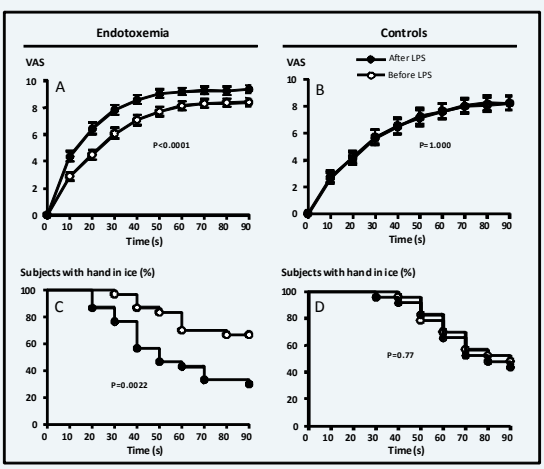

Figure 2.

2.

Use of CDC criteria to classify infections in critically ill patients: results from an interobserver agreement study

PMC Klein Klouwenberg[1,2], DSY Ong[1,2], LDJ Bos[3], FM de Beer[3], RTM van Hooijdonk[3], MA Huson[3], M Straat[3], LA van Vught[3], L Wieske[3], J Horn[3], MJ Schultz[3], T van der Poll[4], MJM Bonten[2,5],OL Cremer[1]

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Background: Correct classification of the source of infection is important in observational and interventional studies of sepsis. Centre for Disease Control (CDC) criteria are most commonly used for this purpose, but the robustness of these definitions in critically ill patients is not known. We determined the interobserver agreement for classifying infections according to CDC criteria in the intensive care unit (ICU).
Methods: Data were collected as part of a prospective cohort of 1214 critically ill patients admitted to two hospitals in The Netherlands between January 2011 and June 2011. Eight observers assessed a random sample of 168 out of 554 patients who had experienced at least one infectious episode in the ICU. Each patient was assessed by two randomly selected observers who independently scored the source of infection (by affected organ system or site), the plausibility of infection (rated as none, possible, probable, or definite), and the most likely causative pathogen. Assessments were based on a post hoc review of all available clinical, radiological and microbiological evidence. The observed diagnostic agreement for source of infection was classified as partial (i.e., matching on organ system or site) or complete (i.e., matching on specific diagnostic terms), for plausibility as partial (two-point scale) or complete (four-point scale), and for causative pathogens as an approximate or exact pathogen match. Interobserver agreement was expressed as a concordant percentage and as a kappa statistic.
Results: A total of 206 infectious episodes were observed. Agreement regarding the source of infection was 89% (183/206) and 69% (142/206) for a partial and complete diagnostic match, respectively (figure 1). This resulted in a kappa of 0.85 (95%CI 0.79-0.90). Agreement varied from 63-91% within major diagnostic categories, and from 35-97% within specific diagnostic subgroups. In the 142 episodes for which a complete match on source of infection was obtained, the interobserver agreement for plausibility of infection was 83% and 65% on a 2- and 4-point scale, respectively. For causative pathogen, agreement was 78% and 70% for an approximate and exact pathogen match, respectively.
Conclusions: Interobserver agreement for classifying infections using CDC criteria was excellent overall. However, full concordance on all aspects of the diagnosis between independent observers was rare for some types of infection.

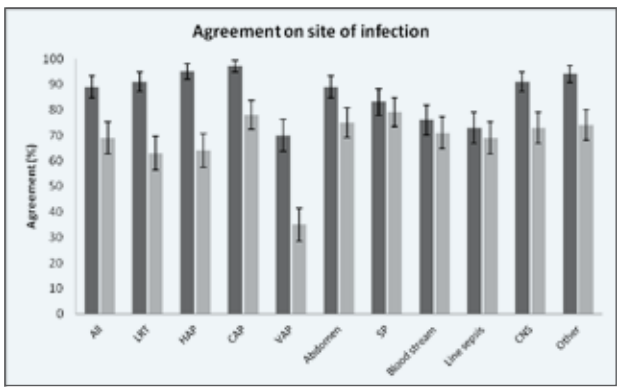

Figure 1. Interobserver agreement rates for source of infection within various diagnostic categories.

The observed diagnostic agreement was classified as complete (i.e., matching on specific diagnostic terms; light shaded bars) and partial (i.e., matching on organ system or site; dark shaded bars). LRT= lower respiratory tract, HAP=hospital acquired pneumonia, CAP= community acquired pneumonia, VAP=ventilator associated pneumonia, SP= secondary peritonitis, CNS= central nervous system.

3.

Randomized Double Blind Placebo Controlled PK/PD Study On the Effects of a Single Intravenous Dose of the Anti-Hepcidin Spiegelmer NOX-H94 On Serum Iron During Experimental Human Endotoxemia

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Background: Anemia is very frequently encountered on the intensive care unit. Nearly all critical care patients suffer from anemia during their hospital stay. Increased hepcidin production is one of the cornerstones of the pathophysiology of Anemia of Inflammation. The first-in-class hepcidin antagonist NOX-H94, a PEGylated anti-hepcidin L-RNA oligonucleotide, is in development for targeted treatment of anemia of inflammation. We investigated whether NOX-H94 prevents the inflammation-induced serum iron decrease during experimental human endotoxemia.
Methods: Randomized, double-blind, placebo-controlled trial in 24 healthy young men. At T=0 hr, 2 ng/kg *E. coli* endotoxin was administered

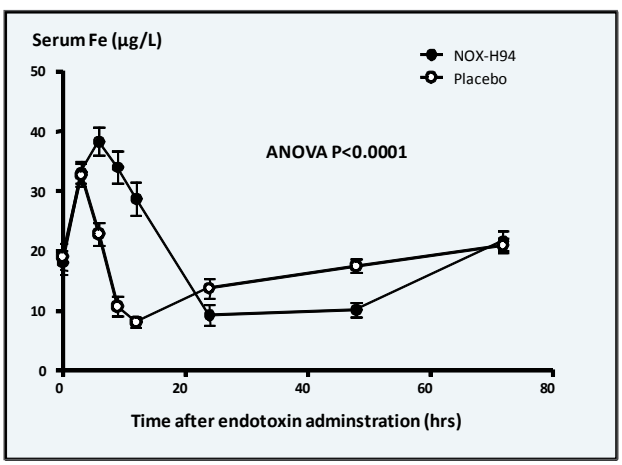

Figure 1. Mean serum iron concentrations (µg/L, ± SD) in subjects treated with LPS at T= 0h and with NOX-H94 or Placebo at T=0.5h

intravenously (i.v.), followed by 1.2 mg/kg NOX-H94 or placebo i.v. at T=0.5hrs. Blood was drawn serially for 24h and on day 3, 8 and 15 after endotoxin administration for measurements of inflammatory parameters, cytokines, NOX-H94 pharmacokinetics, total hepcidin-25, and iron parameters. The difference of serum iron change from baseline at T=9h was defined as primary endpoint. Data are expressed as mean±SD.

Results: Endotoxin administration led to flu-like symptoms peaking at T=1.5hrs, irrespective of the treatment group. Body temperature rose by 1.9±0.5 °C in both groups. Peak CRP at T=24hrs was also similar in NOX-H94 and placebo treated groups (34.3±18.0 vs. 36.8±8.7 mg/L) as was the rise in leucocytes at T=6 hrs (12.1±2.2 vs. 12.1±2.3 *10^9/L). Plasma levels of TNF-α, IL-6, IL-10, and IL-1RA peaked markedly and similarly in both treatment groups.

NOX-H94 was well tolerated. Plasma concentrations peaked at 0.7±0.4 hrs after the start of administration, after which they declined according to a two-compartment model, with rapid initial elimination followed by a slower elimination phase with a T½ of 22.5±4.28hrs.

Serum iron concentrations are shown figure 1. In the placebo group, serum iron increased from 19.0±7.6 µg/L at baseline to a peak at T=3hrs, returned close to baseline at T=6hrs and decreased under the baseline concentration at T=9hrs reaching its lowest point at T=12hrs. In the NOX-H94 group, serum iron concentrations rose until T=6hrs and then slowly declined until T=24hrs. From 6 to 12 hrs post LPS, the serum iron concentrations in NOX-H94-treated subjects were significantly higher than in placebo-treated subjects (P<0.0001, ANCOVA).

Conclusion: Experimental human endotoxemia induces a robust inflammatory response and a subsequent decrease in serum iron. Treatment with NOX-H94 had no effect on innate immunity, but effectively prevented the inflammation-induced drop in serum iron concentrations. These findings demonstrate the clinical potential of the anti-hepcidin drug NOX-H94 for further development to treat patients with anemia of inflammation.

4.

The value of serum procalcitonin and C-reactive protein monitoring in diagnosing bacterial ventriculitis

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Introduction: External catheters for cerebrospinal fluid (CSF) drainage are associated with a 10-20% incidence of bacterial ventriculitis. Early diagnosis is mainly based on CSF cell count, Gram stain and culture. These are non-specific or may be late. We assessed the hypothesis that serum procalcitonin (PCT) adds more to the diagnostic precision in bacterial ventriculitis than serum C-reactive protein (CRP).

Methods: To test this hypothesis we performed an open prospective observational study. We included patients who required temporary external CSF drainage on our neurosurgical ICU between April 2008 and September 2009. Patients with primary bacterial meningitis or other infections/sepsis were excluded. Both serum PCT and CRP were measured daily, CSF was obtained for gram staining, culture and cell count 3 times/week. The diagnosis bacterial ventriculitis was based on clinical signs and a positive CSF culture / Gram stain / catheter tip or CSF cell counts. The nonparametric Mann-Whitney U test was performed to compare the results of PCT and CRP. Best cut-off levels for both PCT and CRP were analyzed by the receiver operating characteristic curve (ROC). Sensitivity, specificity, positive and negative predictive values (PPV/NPV), positive and negative likelihood ratios (LR+/LR-) were calculated. A p-value of $< 0,05$ was considered statistically significant. Informed consent was obtained from each patient.

Results: A total of 54 patients were screened, 21 patients were excluded: 5 had no PCT data, 12 had other infections [primary bacterial meningitis, pneumonia, (uro)sepsis] and 4 were suspected of CSF contamination [no clinical signs but positive CSF culture]. Thus, 33 patients were included, 6 patients with bacterial ventriculitis and 27 controls. Characteristics are presented in table 1. Median peak PCT at time of diagnosis in ventriculitis group was 0,5 ng/mL (interquartile range 0,3-1,07) versus median PCT 0,07 ng/mL (0,05-0,09) for controls (p = 0,003) . Median peak CRP at time of diagnosis 174 mg/L (134-256) in ventriculitis group versus median CRP of 21 mg/L (11-60) for controls (p = 0,001). ROC analysis showed the best cut-off for PCT was ≥ 0,25 ng//mL with sensitivity 83%, specificity 96%, PPV 83%, NPV 96%, LR+ 20,75 and LR- 0,18. A cut-off level ≥ 10 mg/L for CRP is commonly used and revealed sensitivity 100%, specificity 18,5%, PPV 21%, NPV 100%, LR+ 1,23 and LR- 0. ROC analysis showed that the best cut-off level for CRP in diagnosing bacterial ventriculitis would be ≥ 122 mg/L (sensitivity 83%, specificity 100%).

Conclusion: In this study, we demonstrated that in patients who required temporary external CSF drainage both serum PCT and CRP were significant higher in patients with bacterial ventriculitis. At a cut-off level ≥ 0,25 ng/mL PCT was better in ruling in bacterial ventriculitis compared to CRP with a cut-off level ≥ 10 mg/L. (figure 1.).

	BACTERIAL VENTRICULITS	CONTROLS
Number	6	27
Gender	3 male / 3 female	14 male / 13 female
Age (mean +/- sd)	50 +/- 12,5	52 +/- 17,4
Neurological disorder	2 SAH	14 SAH
	2 intracranial hemorrhage	4 intracranial hemorrhage
	2 intracranial tumor	6 intracranial tumor
		1 cerebellar infarction / 2 brain trauma
Type of catheter	6 EVDs	17 EVD / 10 ELD
No drain days median (range)	15 (10-21)	7 (5-10)
Bacteriology		negative
CSF culture:	Ecoli,	
	enterobacter aerogens	
	enetrobacter cloacae	
	CNS	
Catheter tip:	CNS	
CSF Gram stain:	gram - rods	

Table 1.

5.

Is hemoglobineconcentration effected by sepsis in the acute phase?

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Introduction: In the acute phase of sepsis several potential mechanisms may change the hemoglobin (Hb) concentration. On the one hand endothelial activation may lead to increased vascular permeability and fluid sequestration to the interstitium, leading to hemoconcentration. On the other hand degradation of the glycocalix has been reported (1). Shedding of this carbohydrate-rich layer with an estimated thickness of 0,2 – 0,5 µm measured in rats, may lead to a substantial increase of the intravascular space, and thus to decrease of Hb concentration (2). Aim of this study is to determine whether there is a decrease in hemoglobin (Hb) in the acute phase of sepsis.
Patients and Methods: In this single-center retrospective analysis we identified patients with sepsis, as the primary reason for non-elective ICU-admission from a standard patient database. Patients who fulfilled the international criteria of sepsis and organ failure during ICU-admission, were included in the sepsis group (S-group). The control group was formed by patients with other non-elective reasons for ICU-admission (C-group). Exclusion criteria were (recent) bleeding, surgery in the last 6 weeks, chronic renal failure (creat > 177 umol/L, or hemodialysis), untreated chronic anemia, pregnancy, polytrauma, age < 18, hematologic or metastasized malignancies, cardiac arrest, use of bone marrow suppressive drugs. Laboratory data were collected from bloodsamples, prior to in-hospital iv fluid therapy. In order to detect a difference in Hb concentration of 0.2 mmol/L , we anticipated a sample size of 283 per group, based on a standard deviation (SD) of 1.2, an α=0.05 and a β =0.8. Data are expressed as mean ± SD.
Results: We included 296 patients in the S-group and 320 in the C-group. Baseline characteristics are summerized in Table 1.The difference in Hb between the S- and C-group was not significant (8,76 ± 1,18 mmol/l versus 8,93 ± 1,16 mmol/l, p=.07). After correcting for a number of confounders, using a multivariate regression analysis, we observed a significant difference in Hb of - 0,23 mmol/l in the S-group in comparison to the C-group (p= .01).
Conclusion: At first presentation, prior to in-hospital iv fluid therapy, Hb concentration in patients with sepsis is significantly lower in comparison to a controls; however, the difference is very small, without the existence of anemia.

VARIABLE	S-GROUP (N = 296)	C-GROUP (N = 320)	P-VALUE
Age (years)	64 (50-76)	57 (41-70)	.00
Sex (man, %)	167 (56,4%)	180 (56,3%)	.97
Category control group Respiratory Neurologic Endocrine Emergency surgery Auto-intoxication Cardiac Remaining		58 (18,1%) 56 (17,5%) 26 (8,1%) 18 (5,6%) 77 (24,1) 55 (17,2) 30 (9,4%)	
Diabetes mellitus	60 (20,3%)	57 (17,8%)	.44
Hypertension	70 (23,6%)	66 (20,6%)	.37
Hypercholesterolemia	19 (6,4%)	23 (7,2%)	.71
COPD	32 (10,8%)	38 (11,9%)	.68
Alcohol abuse	35 (11,8%)	25 (7,8%)	.09
Carcinoma	7 (2,4%)	7 (2,2%)	.88
APACHE-II score	22 (16-27)	19 (12-24)	.00

Table 1. Baseline characteristics
Data are presented as median with 25th and 75th percentile at a significant non normal distribution or number with percentage for categorical variable.

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6.

GRIP-COMPASS-trial: Computer guided low-normal versus high-normal potassium control and its effect on potassium, atrial fibrillation and mortality in 1225 thoracic ICU patients

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Background: Potassium management is a standard component of clinical care in the intensive care unit (ICU). Extreme potassium levels can cause fatal conditions such as cardiac arrhythmia. In contrast to many glucose control studies, the desired potassium target level in terms of the incidence of arrhythmias and mortality has not been studied. In

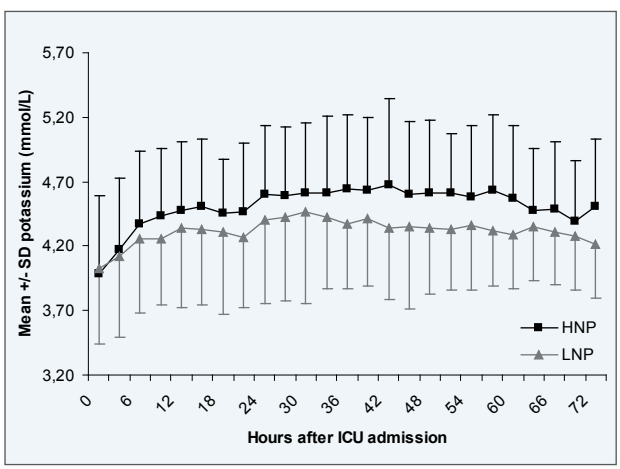

Figure 1. Potassium trend during the first 72 hours after ICU admission.

cardiosurgical patients supraventricular arrhythmias in the post-operative period have been associated with adverse outcome. The GRIP-COMPASS trial examined two different potassium targets that were both within the normal range. The incidence of atrial fibrillation or flutter (AFF) was the main outcome measure. Secondary endpoints were potassium control, metabolic parameters and outcome [1].
Methods: The GRIP-COMPASS study was a prospective study performed at the thoracic ICU of a university hospital. Potassium regulation of both trial arms was performed by the validated GRIP-II computer-assisted decision support system. Potassium chloride was continuously administered by syringe pump. At ICU admission, consecutive patients were assigned to either a low-normal (LNP) target of 4.0 mmol/L or high-normal potassium (HNP) target of 4.5 mmol/L in blocks of 50 patients, until 1200 consecutive patients were included. Excluded were patients who did not require potassium control, as determined by the attending physician. For the primary endpoint, the occurrence of post-operative AFF during ICU admission or within 5 days after ICU discharge was determined
Results: During the study period, 1253 consecutive patients were admitted to the thoracic ICU. Final analysis was performed on 1225 patients, with 610 patients in the LNP group and 615 patients in the HNP group. The majority of patients were admitted after cardiac surgery (77%). There were no differences in baseline characteristics. Over a total of 27,929 potassium measurements, the mean ± SD potassium was 4.20 ± 0.53 mmol/L versus 4.39 ± 0.55 mmol/L in the LNP and HNP groups respectively (P<0.001). The potassium trend for both groups over the first 3 admission days is demonstrated in figure 1. The mean daily administered dose of potassium chloride was 70% higher in the HNP group compared to the LNP group. The incidence of AFF was similar in both groups: 35% in the LNP group and 38% in the HNP group (P=0.26). In multivariate analysis independent predictors of post-operative AFF (PO-AFF) were older age, prior AFF and valvular surgery (P<0.001). In patients with post-operative PO-AFF, 79% occurred within the first 3 days after surgery, with the highest incidence on the second day (26%). PO-AFF was associated with a longer ICU and hospital admission, a higher incidence of myocardial infarction, cerebral vascular accidents (CVA), delirium and hospital mortality. Between LNP and HNP no differences were found in ICU-, hospital, and 90-day mortality.
Conclusion: In this first prospective trial on potassium regulation in the ICU, the achieved target values for the two groups were closer than expected, despite a 70% higher potassium dose in the HNP group. In this study, neither univariate nor multivariate analysis showed a different incidence of AFF or mortality between these two close potassium targets.
NCT 01085071 at ClinicalTrials.gov

Reference

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7.

Improving outcomes of patients requiring intensive care support within 100 days of an allogeneic haematopoietic stem cell transplantation

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Background: It is thought that better recognition of those in need of intensive care support and improvements in intensive care treatment have contributed to the decrease in transplant-related mortality (TRM) after allogeneic haematopoietic stem cell transplantation (HSCT). However, while an increasing number of haematological patients are admitted to the intensive care during the last decade, the effects of intensive care treatment on outcome has not been determined in this specific group of patients. This study was conducted to determine trends in outcome of HSCT-recipients transferred to the intensive care unit (ICU) in a tertiary care hospital.
Methods: All patients treated with HSCT between 2004 and 2009 were analyzed. Comparisons of the baseline and outcome characteristics were made and risk factors for ICU admission and survival were identified.
Results: Of 325 consecutive HSCT's, 49 patients (15%) were transferred to the ICU. On multivariate analysis transplantation from an unrelated donor was a significant risk factor for ICU-admission (OR 1.9; CI 1.0-3.6, P=0.048). Main cause for ICU admission were infectious complications (n=42, 86%) mostly presenting with respiratory insufficiency as the main symptom (n=33, 67%). Male gender (P=0.03) prolonged ICU-length of stay (P=0.02), the need for invasive ventilation (P=0.03), and use of vasopressors (P<0.01) were predictors for ICU-mortality. During the years, APACHE-II scores on ICU admission remained the same (mean 20.7, sd ±6.1), while a decrease was found in the 100 day mortality of patients who had been transferred to the ICU (figure 1) .
Conclusions: ICU admission has become an integral part of HSCT-treatment. Over the years, more HSCT patients have been admitted to the ICU and while their severity of illness on ICU admission did not change, their survival improved. This improvement might be related to more adequately timed transfers and improved intensive care treatment and emphasizes that ICU treatment of haematological patients is not futile.

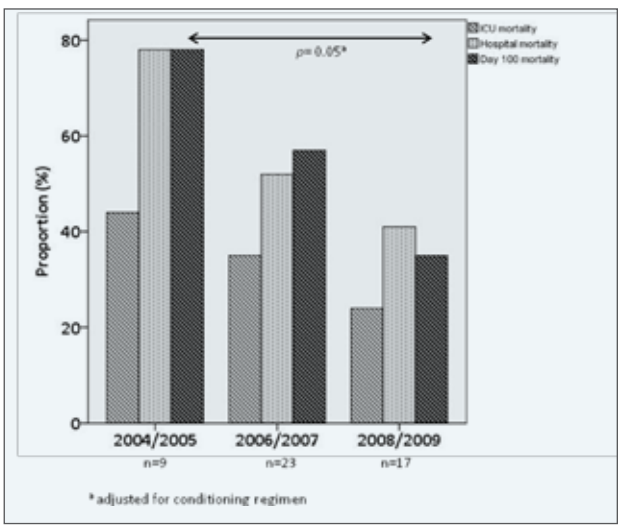

Figure 1. Mortality rates in time

8.

Diaphragm dysfunction induced by mechanical ventilation: role for titin?

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Rationale: Diaphragm weakness induced by prolonged mechanical ventilation contributes to difficult weaning from the ventilator. The elastic protein titin is indispensible for optimal structure and function of skeletal muscles. We have previously shown in COPD patients that structural modifications of titin are associated with reduced passive tension generation of diaphragm fibers upon stretch (1). The present study investigated if controlled mechanical ventilation affects titin structure and function in peripheral and respiratory muscles.
Methods: Male Wistar rats were either assigned to a control group (n=10) or submitted to 18 hours of controlled mechanical ventilation (MV, n=10). After mechanical ventilation diaphragm and soleus muscle were excised for functional and biochemical analysis. Passive force generation of skinned single fibers, isolated from the diaphragm and soleus muscle, was determined after 7 subsequent stretches from a sacrome length of 2.4 µm.
Results: Passive force generation upon stretch was significantly reduced in diaphragm fibers from MV rats by ~35% (figure 1). Diaphragm titin content and titin's mobility on gel were not significantly different between control and MV. Also, immunohistochemical staining intensities of antibodies directed against the titin epitopes T12 (Z-line) and T51 (M-line) were comparable between MV and control diaphragm, confirming that loss of titin did not occur. In-vitro pre-incubation with phosphatase-1 decreased passive force generation upon stretch in diaphragm fibers from control rats, but not from MV rats (Figure 2). This implicates that a low phosphorylation status of titin in the diaphragm of MV rats is responsible for decreased passive tension generation upon stretch.

Since hypercapnia is known to modulate activity of protein kinases, we additionally investigated titin function in diaphragm fibers from hypercapnic ventilated animals (Pco2 level of 75 mmHg) (2). Accordingly, passive force-length relations of diaphragm fibers from MV+H rats were similar to CON (Figure 1). Mechanical ventilation did not significantly affect passive force generation of muscle fibers from the soleus muscle.
Conclusion: The data of the present study provide the following new and important insights in the effects of controlled mechanical ventilation on diaphragm muscle function;

1. Mechanical ventilation significantly reduces passive force generation of diaphragm muscle fibers.
2. The effects of mechanical ventilation on passive force can be mimicked by dephosphorylating the elastic protein titin.
3. Hypercapnia during MV prevents reduction in passive force generation.
4. The effect of mechanical ventilation on passive force does not occur in the soleus muscle within 18 hours.

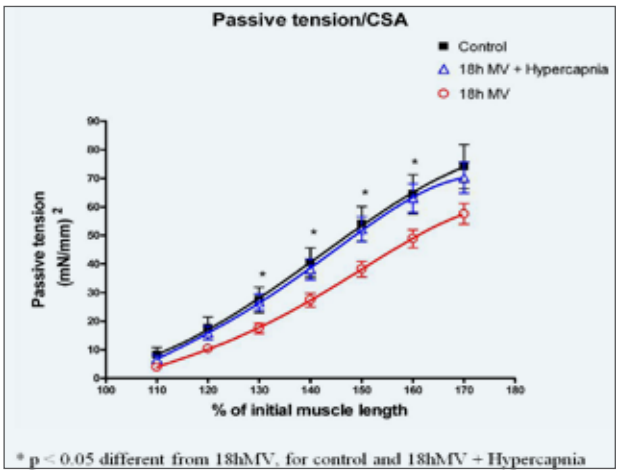

Figure 1.

* p < 0.05 different from 18h MV, for control and 18MV + Hypercapnia

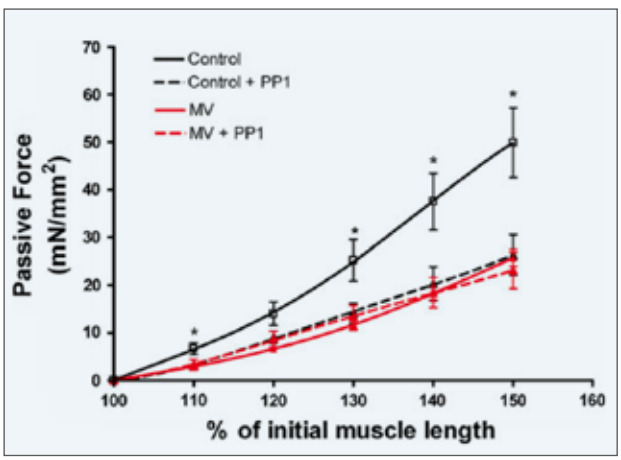

Figure 2.

* p < 0.05 different from 18h MV, for control

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9.

Silence in the intensive care unit?

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Background: Delirium in the intensive care unit (ICU) leads to a longer stay and increased mortality. Patients are exposed to various delirium provoking factors such as medication, illness, pain, light and sound exposure. Studies have shown that noise has a negative impact on patient physiology and health. [1] Therefore, it is hypothesized that reduction of noise will lead to less sleep deprivation and thus better patient outcome and shorter ICU stay. We set up a study to map the sound surrounding the patient in the ICU.
Methods: To map noise, we performed sound level and frequency measurements near the ICU bed using a microphone and sound analysis software. As a baseline measurement, we recorded the sound levels and frequencies of individual medical devices and their alarms in an empty ICU room without external sound interference. The results were analyzed and displayed in a sound level-frequency graph. This measurement was performed for a number of medical devices that are common in the ICU such as infusion pumps, ventilators, heaters and vital signs monitors. Next, we investigated sounds in the actual ICU setting, near an ICU patient. In this setup we automatically include noise due to human voices, people movement, equipment handling and patient treatment. We compared our findings to international recommendations for hospital noise levels.
Results: The baseline measurements showed that running medical devices without alarm signals produce sound levels ranging from 40 to 45dBA. These findings agree with other studies.[1, 2] In alarm the medical devices produced averaged sound levels ranging from 45 to 57dBA. The alarm sound frequencies ranged from 2 to 8 kHz. We were able to identify each individual medical device and its alarm by analyzing the sound level-frequency graph. For comparison, international organizations such as the World Health Organization and the International Noise Council recommend night time noise level limits of 20dBA and day time limits of 45dBA.
Conclusions: Our results show that during daytime even without alarms, several medical devices, e.g. respiratory ventilators and heaters exceed the recommended daytime limits surrounding the ICU patient. Moreover, all devices exceed the recommended night time noise limits. Regarding the adverse effects of noise on patient health, our results indicate that overall sound reduction is recommended for both daytime and nighttime situation. Currently, we are defining measurement parameters to follow the patient's health and a protocol to reduce noise.

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10.

The Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score has prognostic value in predicting mortality in necrotizing fasciitis patients

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Background: Necrotizing fasciitis (NF) is a life threatening soft tissue infection that progresses rapidly and has a high mortality. Early recognition and adequate treatment by a multidisciplinary team is essential. The Laboratory Risk Indicator for Necrotizing Fasciitis score (LRINEC)[1] is a validated diagnostic tool for detecting patients with NF. However, little is known about the prognostic value of the LRINEC score. We therefore hypothesized that the LRINEC score is also a useful tool in predicting mortality in NF patients.
Methods: The study was designed as a retrospective cohort study. All consecutive patients diagnosed with NF in the Gelderse Vallei Hospital, Ede and the Radboud University Medical Centre, Nijmegen between January 2003 en May 2012 were included. Vital parameters and laboratory results at presentation as well as all demographic data were collected from the patient charts. For all patients the LRINEC score was calculated. Data were analyzed using logistic regression analysis and Classification and Regression Tree (CART) analysis.
Results
Twenty-nine NF patients (11 GVH, 18 RUMC) were included. Characteristics of the cohort are presented in table 1. During admission all patients stayed at least one day at an intensive care unit and/or medium care unit. The mortality rate was 34% (10/29). Multivariate logistic regression revealed an odds ratio for mortality of the LRINEC score of 3.57 per point increase (95% CI 1.41–18.92, *p*-value 0.04). CART analysis showed similar results, identifying a LRINEC-cutoff point for maximal discrimination between surviving and mortality of 7.5 (figure 1).
Conclusion: Despite the limited study size, the current study suggests the LRINEC score to be a useful prognostic tool for predicting mortality in necrotizing fasciitis patients.

Reference

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	TOTAL COHORT	SURVIVORS	DEATHS	
Variable	(n = 29)	(n = 19)	(n = 10)	p-value*
Mean age (SD)	54.4 (14.1)	52.2 (15.3)	58.7 (11.0)	0.20a
Male gender	18 (62.1)	13 (68.4)	5 (50)	0.43b
Comorbidity				
Diabetes Mellitus	4 (13.8)	2 (10.5)	2 (20.0)	0.59b
Immune deficiency	6 (20.7)	2 (10.5)	4 (40.0)	0.14b
Renal insufficiency	3 (10.3)	0 (0.0)	3 (30.0)	0.03b
Cardiovascular disease	8 (27.6)	4 (21,1)	4 (40.0)	0.39b
Chronic liver disease	2 (6.9)	0 (0.0)	2 (20.0)	0.11b
Malignancy	4 (13.8)	2 (10.5)	2 (20.0)	0.59b
Cause of necrotizing fasciitis				
Minimal trauma	12 (41.4)	6 (31.6)	6 (60.0)	0.13b
Surgery	9 (31.0)	8 (42.1)	1 (10.0)	
Other	7 (24.1)	5 (26.3)	2 (20.0)	
Unknown	1 (3.4)	0 (0.0)	1 (10.0)	
Median laboratory values at admittance (IQR)				
Hb	8.7 (6.4–9.0)	8.7 (7.0–9.1)	6.7 (6.1–8.6)	0.18c
Leucocytes	10.6 (3.7–16.4)	13.7 (9.6–17.1)	3.6 (1.7–11.0)	0.03c
CRP	335 (214–443)	320 (184–439)	345 (329–453)	0.41c
Creatinine	182 (120–236)	128 (80–189)	229 (178–338)	0.01c
Sodium	135 (131–137)	136 (133–138)	133 (130–136)	0.28c
Potassium	3.9 (3.6–4.5)	3.8 (3.5–4.2)	4.6 (3.6–5.3)	0.11c
pH	7.36 (7.29–7.41)	7.37 (7.32–7.41)	7.28 (7.21–7.42)	0.14c
Creatine kinase	172 (53–1190)	172 (56–979)	297 (44–2045)	0.97c
Lactate	3.5 (2.3–4.7)	3.3 (2.1–5.0)	3.9 (3.4–4.7)	0.30c
Albumin	17 (12–22.5)	19 (14–33.5)	13 (11–15.5)	0.02a
Median vital parameters at admittance (IQR)				
Temperature	38.1 (37.5–39.1)	38.1 (37.5–38.9)	38.4 (36.8–39.8)	0.80c
SBP	110 (92–120)	110 (99–125)	101 (79–110)	0.28c
DBP	55 (47–70)	56 (49–77)	50 (46–59)	0.23c
Mean HF (SD)	108 (24.7)	107 (20.5)	110 (32.4)	0.78a
LRINEC score	7 (5–8)	6 (5–8)	8 (8–9)	< 0.05c

Table 1. Characteristics of the cohort (n = 29). Values are numbers (%) unless otherwise indicated.

* P-values were derived with a: Student's t-test; b: Fisher Exact Test; c: Mann-Whitney U test.

DBP = diastolic blood pressure; HF = heart frequency; IQR = interquartile range; LRINEC = laboratory risk indicator for necrotizing fasciitis; SBP = systolic blood pressure; SD = standard deviation.

11.

Autonomic dysregulation in infants with RSV infection

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Background: Respiratory Synctial Virus (RSV) infection is the most frequent cause of acute lower respiratory tract illness, accounting for up to 90% of the reported cases of bronchiolitis in infancy. Apnea can be the presenting sign of this infection, and its incidence varies between 16 and 25% of RSV infected infants, with a particularly high risk associated with young age (<3 mo) and prematurity. The pathophysiology of apnea associated with RSV infection remains to be elucidated. Polysomnographic recordings point to a failure of central origin. Apnea may be a presenting symptom in early infection when RSV is still confined to the upper airways, suggesting inflammatory response induced autonomic dysfunction.
Objective: The purpose of this pilot study is to assess autonomous dysfunction, as indexed by Heart Rate Variability and baroreflex in RSV infection necessitating PICU admission, and its correlation with inflammatory profiles.
Methods: Prospective observational pilot study in infants with viral RTI. Controls were age matched infants without any sign of infection. Autonomic function was evaluated by heart rate variability (HRV) registration, monitoring low frequency (LF) and high frequency (HF) indices.
Results: LF, total HRV and LF/HF ratio were significant lower in patients (fig 1).

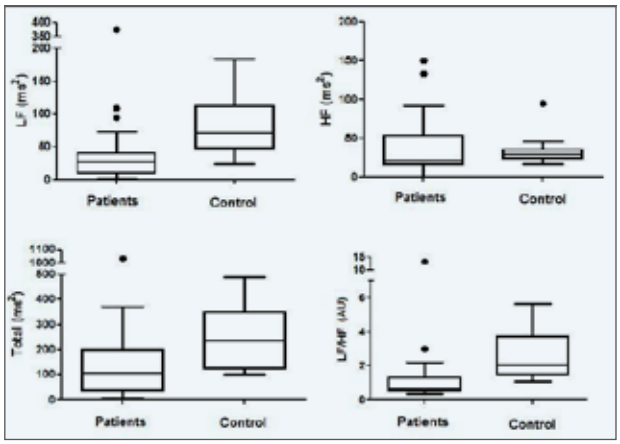

Figure 1.

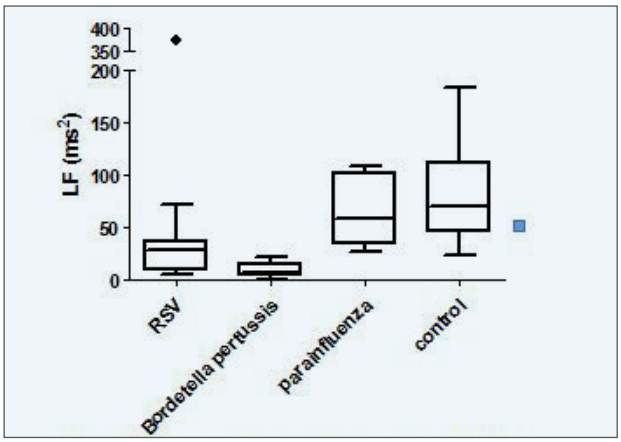

Figure 2. Low frequency between different kinds of infection
These results suggesting a decrease in sympathetic activity and total autonomic function.

LF recordings were significant lower in RSV patients (28.3 (9.3-37.4) N=24) and patients with Bordetella co-infection versus controls (P=0.0002) and (7.4 (3.5-14.9) N=5) (P=0.0141). Patients with parainfluenza RTI (58.3 (34.2-101.6) N=5) showed no difference in HRV versus controls (P=06221) (fig2).

Conclusion: Preliminary data of this pilot study suggests that viral respiratory tract infection in infants is associated with autonomic dysfunction of central origin. This may result in an increased risk for serious apnea or ALTE, for which prolonged cardio respiratory monitoring may be indicated.

12.

Effects of 24 and 72 hours of mild hypothermia on the inflammatory response after cardiac arrest

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Funding: The authors have no financial interests to disclose.
Introduction: The post-cardiac arrest syndrome partly results from generalized ischemia-reperfusion with systemic activation of the innate immune system. We previously demonstrated a strong temporal relationship between several inflammatory parameters and hypothermia and rewarming. Whether temperature had a causal effect on inflammation in these patients could not be established. Aim of our study was to analyze the effect of hypothermia and rewarming on the inflammatory response after cardiac arrest by comparing 24hrs versus 72hrs of hypothermia treatment.
Methods: We performed an observational study in 20 comatose patients resuscitated from an out-of-hospital cardiac arrest. Ten patients were treated with hypothermia for 72hrs following asystole, PEA or resistant ventricular fibrillation and compared with ten patients treated with hypothermia for 24hrs. Concentrations of cytokines and adhesion molecules were measured at admission, and at 12, 24, 48, and 72hrs.
Results: Upon admission, patients treated with 72hrs of hypothermia had a longer interval between collapse and ROSC and higher lactate concentrations, APACHE II and SAPS-scores, indicating prolonged cardiorespiratory arrest. The proinflammatory cytokine IL-6, anti-inflammatory cytokine IL-10 and the chemokines IL-8 and MCP-1 were significantly higher at admission in the patients treated with prolonged hypothermia. The concentrations of adhesion molecules ICAM-1 and VCAM-1 were comparable. During treatment with hypothermia and subsequent rewarming, no significant differences in the inflammatory response was found between the two groups. In contrast to the patients treated with hypothermia for 24hrs IL-6 did not increase significantly during rewarming in the patients treated with prolonged hypothermia.
Conclusions: Patients after prolonged cardiac arrest have a higher inflammatory response to ischemia-reperfusion compared to patients with a shorter cardiorespiratory arrest. Hypothermia did not seem to modify the inflammatory response in the first 72hrs after cardiac arrest. After a prolonged period of hypothermia rewarming did not increase proinflammatory IL-6 levels, therefore prolonged hypothermia may be necessary to prevent a secondary proinflammatory response.

13.

Accuracy of body weight estimation in an Intensive Care Unit

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Introduction: Body weight is mandatory for correct dosage of drugs, nutrition, and correct interpretation of hemodynamic data. However, in critically ill patients, the exact body weight is often unavailable. Therefore, it is common practice to estimate the patient's weight just by looking at the patient. The purpose of this study was to establish the accuracy of visual body weight estimation by intensive care nurses.
Methods: The study was performed in the 10-bed mixed intensive care unit of the Reinier de Graaf Hospital between May 2012 and July, 2012. Since new intensive care beds (Hill-Rom Total Care) including an incorporated weighing module became available, the comparison between an actual and estimated body weight became feasible. For each patient that was given such a bed on admission to the ICU one ICU nurse estimated the patient's body weight. Immediately thereafter a second ICU nurse, the one who would take care of the patient, measured the patient's body weight using the bed-incorporated weighing module.
Results: During the study period complete data were collected of 76 individual patients (figure 1). The mean measured weight was 84,3 kg (SD 20,3, range 45-143) and the mean estimated weight was 80,8 kg (SD 17,5, range 50-140). The mean difference between measured body weight and estimated body weight was +3,5 kg (SD 9,3, range -25 - +30). The error (the difference between measured body weight and estimated body weight) was less than 10% in 50 patients (66%), between 10 and 20% in 20 patients and more than 20% in 6 patients.
Conclusion: Our study suggests that the error in estimating body weight in critically ill patients is more than 10 % in about one third of the patients. Measuring body weight instead of estimating body weight may prevent therapeutic errors.

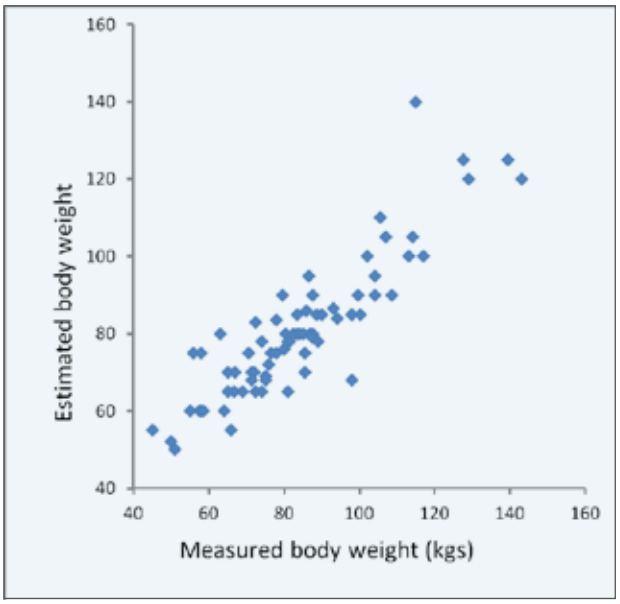

Figure 1. Measured body weight versus estimated body weight in 76 critically ill patients.

14.

Asynchrony in ventilator support: NAVA vs PSV in patients without COPD

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Introduction: Neurally Adjusted Ventilatory Assist (NAVA) is considered to be associated with less patient-ventilator asynchrony than the conventional pressure support ventilation (PSV). However, NAVA and PSV have been compared predominantly in COPD-patients, with a high prevalence of asynchrony during PSV. Moreover, for both ventilator modes asynchrony events have been defined according to criteria established for PSV, not taken into account the different nature of asynchrony in NAVA. We studied asynchrony in patients without COPD on NAVA and PSV to assess the hypothesis that in NAVA asynchrony events occur as frequently as in PSV.
Methods: 10 mechanically ventilated patients without COPD were studied. Respiratory mechanics and the electric activity of the diaphragm (Eadi) were obtained during NAVA and PSV for two consecutive 20-min periods. Asynchrony was defined according to criteria primary based on the flow signal, correlated with pressure and Eadi signals. Asynchrony events were separately defined for NAVA and PSV and were pooled in two categories: ineffective efforts and double triggering. All measurements were obtained with the Servo tracker (Maquet, Netherlands) and the NICO-computer (Respironics Novametrix, inc.).The measurements were analyzed using Matlab® and the Analysis Plus program (Respironics Novametrix, inc.)
Results: The patient group studied included both patients with and without pulmonary diseases. The total number of asynchrony events was significantly higher in NAVA. The most frequently encountered asynchrony event in NAVA was the interruption of the expiratory flow due to an inspiratory effort related to a minimal Eadi peak. In PSV premature cycling from inspiration to expiration leading to an early expiratory flow decrease was most frequently observed, which was labeled as double triggering.

MEAN ± SD	PSV	NAVA	P-VALUE
No of asynchronies / 20min	5 ± 8	15 ± 12	< 0,05
Ineffective efforts / 20min	1 ± 2	8 ± 12	< 0,05
Double triggering / 20min	4 ± 7	5 ± 3	n.s.

Conclusion: In this mixed group of patients without COPD and with a low prevalence of asynchrony, NAVA was associated with more asynchrony events than PSV. However, comparing asynchrony between NAVA and PSV is hampered by the different nature of the various asynchrony events, detected in NAVA and PSV.

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Grant acknowledgment: None

15.

Effects of viscosity on cerebral blood flow after cardiac arrest

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Introduction: After CA, microcirculatory reperfusion disorders develop despite adequate cerebral perfusion pressure. Increased blood viscosity strongly hampers the microcirculation resulting in plugging of the capillary bed, arteriovenous shunting and diminished tissue perfusion. The rheologic properties of blood depend on hematocrit and plasma constituents, mainly acute phase proteins. The aim of the present study was to assess blood viscosity in relation to cerebral blood flow in patients after a cardiac arrest.
Methods: We performed an observational study in 10 comatose patients after cardiac arrest. Patients were treated with mild therapeutic hypothermia for 24 hours and passively rewarmed to normothermia. Blood viscosity was measured ex-vivo at 0, 6, 12, 24, 36, 48 and 72 hours after admission using a Contraves LS300 viscometer. Mean flow velocity in the middle cerebral artery (MFV_{MCA}) was measured by Transcranial Doppler (TCD) at the same time points.
Results: The median viscosity on admission was 9.12(8.19-11.19)mPa.s, remained stable at 9.13(7.57-10.51)mPa s and 9.70(8.50-11.42)mPa s at 3 and 6 hrs respectively (p=0.47). From 6 hrs after admission viscosity decreased significantly to 3.66(3.12-4.04)mPa s (p<0.001). Median MFV_{MCA} was low (27.0(23.8-30.5)cm/s) on admission, and significantly increased to 63.0(51.0-80.0) cm/s at 72 hrs (p <0.001). There was a significant association between the viscosity and the MFV_{MCA} (p=0.0019). Median hematocrite was 0.41 (0.36-0.44)l/l on admission and subsequently significantly decreased to 0.32 (0.27-0.35) l/l at 72 hrs (p < 0.001) In contrast, acute phase proteins such as CRP and fibrinogen increased during admission (from 2.5(2.5-6.5)mg/l to 101(65-113.3)mg/l and 2795 (2503-3565)mg/l to 6195(5843-7368)mg/l respectively (p < 0.001).
Conclusion: Viscosity decreases in the first 3 days after cardiac arrest and is strongly associated (correlated) with an increase in cerebral blood flow. Since viscosity is a major determinant of cerebral blood flow, repeated measurements may guide therapy to restore cerebral oxygenation after cardiac arrest.

16.

Relation between hypernatremia and non-inflammatory hyperthermia in critically ill patients

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Background: Hypernatremia is a frequent complication in patients who have a prolonged ICU-stay. Elevated sodium levels may interfere with perspiration and thus with thermoregulation. We hypothesized that hypernatremia may lead to hyperthermia in ICU patients, independent of systemic inflammation.

Thus we analyzed the relation of sodium levels with body temperature in critically ill patients known to have an elevated risk for hypernatremia.
Patients and methods: From a cohort of consecutive ICU patients admitted between June 2009 and October 2010 we first identified patients who stayed for at least 5 days at the ICU. Patients with organ transplants, or on chronic dialysis requirement or new renal replacement therapy during the ICU stay were excluded. Hypernatremia was defined as a serum sodium level of ≥150 mmol/L. C-reactive protein and leukocyte count were considered objective measures of systemic inflammation. Temperature was continuously measured with a bladder catheter or rectal probe. For each ICU day, the CRP-level, leukocyte count, the sodium concentration, the maximal and minimal temperature were determined. The first admission day, or ICU-days when active cooling was performed were excluded. To assess their relation with temperature, leukocyte count, CRP, sodium level and ICU-day were entered as independent variables in multivariate linear regression analysis with minimal and maximal temperature as the dependent variables.
Results: During the study period, 1260 patients were admitted to our ICU, of whom 175 (14%) stayed for more than 5 days at the ICU. After excluding patients with renal replacement or organ transplantation, 58 patients were further studied. From these patients, 30 (52%) developed hypernatremia. Hospital mortality was 7 (23%) in the hypernatremia group and 4 (14%) in the other patients. For 843 ICU-days complete data on serum sodium CRP, leukocyte count and body temperature were available for the selected patients. Mean ±SD minimal and maximal daily body temperatures were 37.0 ±0.8 38.0 ±1.0 respectively. Multivariate analysis with minimal temperature as the dependent variable showed a correlation coefficient of 0.47 (R^2 =0.22) and the following coefficients**:**

VARIABLE	UNIT	COEFFICIENT	(95% CI)	P
constant		29.9	(28.5 - 31.4)	<0.00001
CRP	mg/L	0.002	(0.001 - 0.003)	<0.00001
leukocyte count	10^9/L	0.020	(0.011 - 0.029)	<0.00005
serum sodium	mmol/L	0.048	(0.038 – 0.059)	<0.00001
ICU day	day	-0.012	(-0.015 - -0.009)	<0.00001

Conclusion: A comparatively straightforward regression model showed a satisfactory predictive power for body temperature. Moreover we observed that sodium levels were independently related with body temperature. When patients develop fever under hypernatremia with low levels of inflammatory markers such as CRP, hypernatremia itself should be considered as a direct cause. The mechanisms underlying this potential association deserve further study.

17.

Human endotoxemia improves diaphragm function in its early phase

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Background: Respiratory muscle weakness frequently occurs in the critically ill and is associated with prolonged weaning from mechanical ventilation. Studies utilizing animal models of inflammation have shown that endotoxin administration induces injury and reduces force-generating capacity of the diaphragm. In contrast, human endotoxemia-induced increases in plasma catecholamines might improve diaphragm function. To know whether endotoxin administration improves or attenuates diaphragm function is of great interest, because this could provide valuable information as to whether human endotoxemia can serve as a model for early sepsis-induced diaphragm dysfunction. Such a model would allow controlled *in vivo* studies of new therapeutic agents aimed to improve respiratory muscle function in critically ill patients. Thus, the objective of this explorative study is to investigate the effects of human endotoxemia on the function of the diaphragm *in vivo*.
Methods: In this study, 12 healthy male volunteers received an intravenous bolus of 2 ng/kg of *E.coli* lipopolysaccharide (LPS). Prior to LPS infusion, subjects were instrumented with an esophageal catheter equipped with gastric and esophageal balloons. Twitch transdiaphragmatic pressure (Pdi,tw) elicited by cervical magnetic stimulation of the phrenic nerves, was obtained before and after LPS infusion. In addition, plasma cytokines were measured before and after LPS infusion. Data are presented as mean±SEM.
Results: LPS infusion resulted in flu-like symptoms and an increase in pro-inflammatory cytokines TNF-α and IL-6 (Figure 1A). Also, Pdi,tw increased within one hour and gradually decreased afterwards, being not significantly different from baseline from 2 hours after LPS (Figure 1B). There were no correlations found between plasma cytokines and Pdi,tw.
Conclusion: In conclusion, this explorative study shows that *in vivo* diaphragm contractility improves in the early phase following endotoxin administration in humans. The exact mechanism behind these findings is unknown, but may be related to increased plasma catecholamine levels or potentiation of the diaphragm.

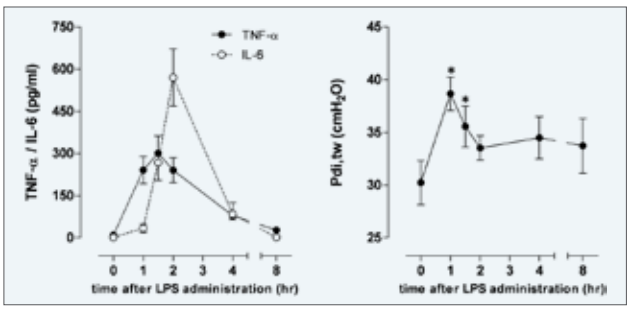

Figure 1. A) Production of pro-inflammatory cytokines TNF-α and IL-6 after LPS infusion. B) Pdi,tw after LPS infusion. Pdi,tw at t=1 and t=1.5 hours after LPS infusion are significantly higher compared to before LPS infusion (P<0.05). Data are presented as mean ± SEM. Pdi,tw = twitch transdiaphragmatic pressure.

18.

Risk of severe hypernatremia depends on underlying cause in critically ill patients

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Background: Hypernatremia is a common problem in critical care patients and is associated with increased duration of hospital stay and increased morbidity and mortality.[1] Mechanisms of hypernatremia include sodium gain, loss of free water or renal concentrating defects and can be discriminated by clinical assessment and urine electrolyte analysis. We sought to investigate the mechanisms of severe hypernatremia (sodium >160 mmol/l) in a very large unselected cohort of adult patients in a large tertiary Intensive Care Unit (ICU). We also tried to establish the impact of severe hypernatremia on outcome for the various underlying causes.
Methods: We included all consecutive patients with severe hypernatremia admitted to the ICU from 2002 through 2011. Patients <16 years (n=6), referred from another hospital (n=9) with severe hypernatremia, missing archived data (n=7) were excluded. The mechanisms of hypernatremia were classified according to established causes by two independent specialists. Intensive care and hospital length of stay and survival till September 2012 were determined.
Results: A total of 273 (1%) patients with severe hypernatremia were identified among 25,807 admissions to the ICU over the 10 year study period. The main causes of severe hypernatremia were central diabetes insipidus (n=61), renal sodium retention (n=50), loop diuretics (n=45), osmotic diuresis (n=44), and sodium rich fluid administration (n=41) (table 1). One-year mortality was 57% (n=156). The highest mortality rate was observed in patients with high or persisting fever (83%), central diabetes insipidus (79%), osmotic diuresis (68%) and renal sodium retention (64%) (table 1.). One-year mortality was relatively low in patients on sodium rich fluid (37%).
Conclusion: In this largest cohort study published so far, severe hypernatremia in critically ill patients has a number of underlying causes, mainly related to treatment. Severe hypernatremia was associated with a high mortality, especially in patients with central diabetes insipidus, osmotic diuresis and renal sodium retention. Although a retrospective study cannot prove causality, specialists should understand that their treatment is strongly related to disorders of sodium and water balance in critically ill patients that carry a poor prognosis.

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CAUSE OF HYPERNATREMIA	NUMBER	MORTALITY (%)
Excessive sodium gain		
- Sodium chloride 0.9% / 5% / sodium bicarbonate	41	14 (37%)
- Renal sodium retention, secondary to steroids	50	32 (64%)
Excessive free water losses		
- From gastro-intestinal tract	10	2 (20%)
- Resulting from high or persisting fever	6	5 (83%)
Renal concentrating defect		
- Central diabetes insipidus	61	48 (79%)
- Nephrogenic diabetes insipidus	3	1 (33%)
- Loop diuretics	45	21 (47%)
- Tubular dysfunction	13	2 (15%)
- Osmotic diuresis (hyperglycemia, mannitol)	44	30 (68%)

Table 1. Causes of severe hypernatremia

19.

Assessing the Quality of Interdisciplinary Rounds in the Intensive Care Unit

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Background: Interdisciplinary rounds (IDRs) in the intensive care unit (ICU) are increasingly recommended to support quality improvement and to reduce preventable patient harm and conflicts, but uncertainty exists about assessing the quality of IDRs. We developed, tested, and applied a scoring instrument to assess the quality of IDRs in ICUs.
Methods: A literature search was performed to identify criteria for instruments about assessing team processes in the ICU. Then, 10 videotaped patient presentations led by different intensivists in 2 ICU for adults were analyzed by Delphi rounds. Appropriate and inappropriate behaviors were highlighted. The IDR-Assessment Scale was developed and statistically tested. The interrater reliability was evaluated by rating 9 randomly selected videotaped patient presentations by 3 raters including 1 intensivist, 1 ICU nurse, and 1 author (E.T.H.). Finally, the scale was applied to 98 videotaped patient presentations during 22 IDRs in 3 ICUs for adults in 2 hospitals in Groningen.
Results: The IDR-Assessment Scale had 19 quality indicators, subdivided in 2 domains: "patient plan of care" and "process." The domain "patient plan of care" reflects the technical performance from the initial identification of a goal to the evaluative phase, such as "main problem discussed", "provisional goal formulated" and "long-term therapeutic items (≥ 16 h) discussed". The domain "process" reflects the team processes that are important to ensure that the appropriate plan of care is agreed, understood, and executed as planned by all care providers, such as "it is clear who is responsible for performing tasks", "summary given" and "input of nurses encouraged". Indicators were "essential" or "supportive." The interrater reliability of 9 videotaped patient presentations among 3 raters was satisfactory (kappa, 0.85). The overall item score correlations between 3 raters were excellent (r, 0.80 to 0.94). Internal consistency in 98 videotaped patient presentations was acceptable (α, 0.78). Application to 22 IDRs lead by 14 different intensivists in 3 ICUs in 2 hospitals, demonstrated that indicators could be unambiguously rated.
Conclusions: This study showed that the quality of IDRs can be reliably assessed for patient plan of care and process. The IDR Assessment Scale had satisfactory interrater reliability, excellent overall item score correlations, and acceptable internal consistency. Our instrument may provide feedback for ICU professionals and managers to develop adjustments in quality of care. Testing the IDR- Assessment Scale in other ICUs may be required to establish general applicability.

20.

A novel method to evaluate upper airway patency during noninvasive ventilation

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Background: Noninvasive ventilation (NIV) has assumed an important role in managing patients with acute respiratory failure, in particular in patients with chronic obstructive pulmonary disease (COPD). NIV avoids important complications related to endotracheal intubation, such as pneumonia and ventilator-induced lung injury. Furthermore, lower levels or even no sedation is feasible. However, NIV frequently fails and endotracheal intubation is still needed. To improve care for patients with acute respiratory failure it is important to understand why patients fail during NIV. A major determinant of poor NIV tolerance is asynchrony between the patient's neural drive (respiratory effort) and the response of the ventilator, known as patient-ventilator asynchrony. A possible explanation for this asynchrony is the response of the upper airway to positive pressure. Studies in newborn lambs observed that NIV induces inspiratory glottis closure [1]. Remarkable is the fact that increasing pressure support results in decreased glottic dilator activity. Although the response might be appropriate from an evolutionary point to protect lungs against barotraumas, glottal narrowing negatively affects the efficiency of ventilator support by increasing airway resistance. In this methodological study, a set-up is described to enable analysis of the synchrony between diaphragm and glottic activity during NIV.
Methods: A novel experimental set-up has been designed that allows simultaneous recording of diaphragm electrical activity (EAdi), airway flow, mouth pressure, and glottic movement. An esophageal catheter with multiple electrodes is positioned to measure EAdi. NIV is performed with a Servo-i ventilator (Maquet Critical Care, Solna, Sweden). To evaluate glottis behaviour a fiberoptic flexible bronchoscope is passed through the facemask through the nare and is placed 2 cm above the vocal cords. Glottic opening is evaluated by calculating the angle of the anterior commissure of the vocal cords (Figure 1).
Results: The developed experimental set-up enables synchronous measurement of EAdi, airway flow, mouth pressure and glottic aperture. Figure 2 shows a representative recording of signals. It is nicely shown that the glottis opens before activity of the diaphragm with inspiration.
Conclusion: A unique experimental set-up has been developed to enable analysis of upper airway behaviour in respiratory failure patients during NIV. This new method gives the possibility to investigate the kinematics of the glottis during different ventilator settings. Understanding of the consequences of ventilator settings on upper airway patency may lead to a better synchrony between ventilator and patient which improves success of NIV.

Literature

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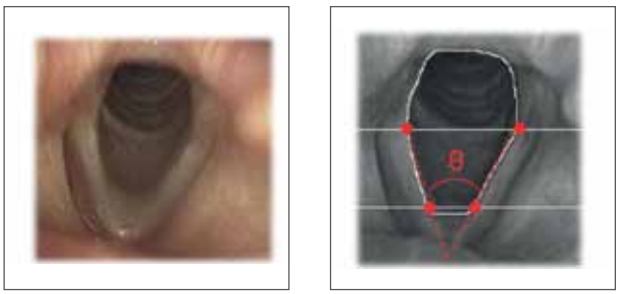

Figure 1. A) Example of a full color image. B) Calculation of angle of the anterior commissure of the vocal cords.

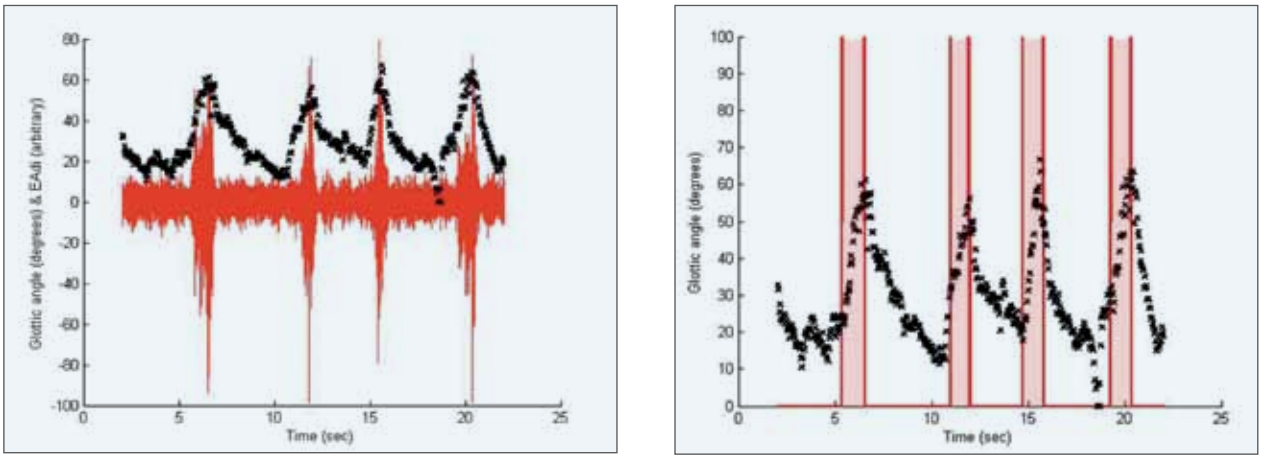

Figure 2: A) Tracings of vocal cord angle (black) and diaphragm activity (red). B) Tracings of vocal cord angle (black) and respiratory phase (red strokes).

21.

Intestinal- fatty acid binding protein represents a possible new plasma biomarker for the early diagnosis of mesenteric ischemia

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Background: Mesenteric ischemia is a rare disease, but it is associated with high mortality. Because diagnosis is difficult, patients are already severely ill at the moment of diagnosis, which contributes to the high mortality observed. There is still lack of (a) suitable biomarker(s) that is/are detectable in an early disease stage. Intestinal-fatty acid binding protein (I-FABP) is an intracellular protein appearing only in the mucosa of the small intestine which has been shown to increase as a result of cellular damage. It therefore could represent a suitable biomarker for the early detection of mesenteric ischemia. Furthermore, it has been speculated that the hypoperfusion-induced inflammatory reaction plays a central role in the intestinal cell damage observed in mesenteric ischemia.

The aims of the present study were to investigate whether I-FABP is an early marker for mesenteric ischemia and whether it is correlated with inflammatory cytokines in heart valve surgery patients. We chose this group of patients because numerous studies have indicated that this type of surgery is associated with intestinal hypoperfusion and the development of mesenteric ischemia.

Methods: Plasma samples from 37 patients undergoing heart valve surgery were collected on various time points before, during and after surgery. Samples were analysed for I-FABP and cytokines (TNF-α, IL-6, IL-8 and IL-10).

Results: During surgery, I-FABP levels increased significantly, peaking at the moment after administration of protamine, after which they decreased to lower levels than those found preoperatively (Figure 1). There was a significant correlation between the length of extracorporeal circulation and aortic clamp time, and peak I-FABP levels (r=0,44, p=0,006 and r=0,35, p=0,036, respectively). None of the patients studied developed mesenteric ischemia. Nevertheless, there was a significant positive correlation between I-FABP levels and time to first postoperative defecation (r=0,67, p=0,001). All measured cytokines showed a significant rise during surgery (Figure 2), but no correlation between I-FABP and cytokine levels was found.

Conclusion: I-FABP levels significantly increase during a period of intestinal hypoperfusion during heart valve surgery and are positively correlated with time to first postoperative defecation. These results suggests I-FABP is an early marker for mesenteric ischemia.

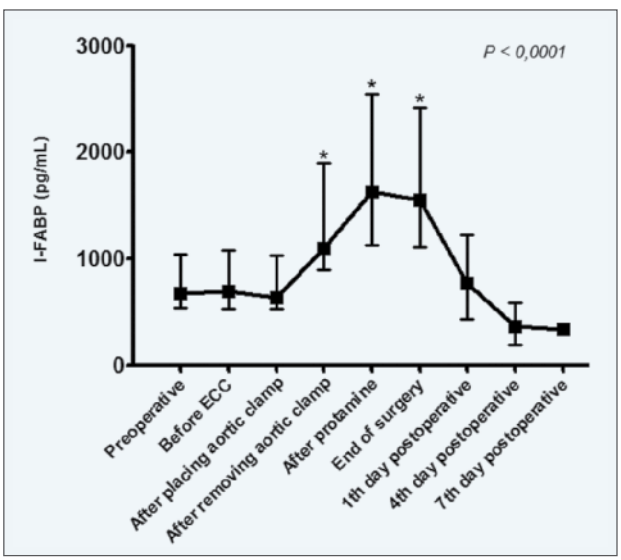

Figure 1. Plasma I-FABP levels in patients undergoing heart valve surgery (n = 37). Data are represented as median with interquartile range. P-values calculated by Friedman test; * indicates P <0,05 compared to pre-operative value (Dunn's post-hoc test).

22.

Observed changes in intracellular volume as a function of sodium levels in ICU patients

Classical clinical assumptions versus laboratory observations

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Background: The current clinical doctrine with regard to changes in extracellular volume (ECV) and intracellular volume (ICV) rests on three main determinants (i) sodium, (ii) potassium and (iii) water bound by two principles. Firstly changes in ECV and ICV occur after changes in total sodium and potassium respectively, resulting from the selective homing of these cations. Secondly, ECV and ICV must be equiosmotic implying that ECV and ICV change proportionally to changes in total body water. Although conceptually elegant, these basic principles are neither compatible with careful anecdotal clinical observations nor with fundamental observations on the intrinsic stability of the ICV in vertebrates [1]. More exact knowledge on the effect of changes in water, sodium and potassium on ICV and ECV has clinical relevance as it may directly influence the choice of infusion fluids.

We hypothesized that if the conventional doctrine holds true, the mean corpuscular volume of erytrocytes (MCV) *in vivo* would increase/decrease under conditions of hypo/hypernatremia. However, automated blood cell analyzers will report virtually no change of *in vitro* measured red cell volume since blood samples are diluted in a medium of constant osmolarity [2]. Consequently, *in vitro* mean cell hemoglobin concentration (MCHC) measurements will also remain constant. Therefore, we assessed the relation between serum sodium and MCHC expecting to find a positive or no correlation if the conventional doctrine is in fact true.

Methods: This retrospective study was performed in a cohort of anonymized ICU patients admitted between 2000 and 2011 to our adult 45-bed tertiary ICU. Since the erytrocyte hemoglobin content is virtually constant during the lifespan of erythrocytes, osmotically induced changes in erythrocyte volume lead to proportional and reciprocal changes in MCHC. MCHC was calculated from independent hematocrit (Ht) and hemoglobin (Hb) measurements as MCHC=Hb·Ht-1 and expressed as mmol·L-1 (reference range 19.6 – 22.0 mmol·L-1). Serum sodium levels were compared with MCHC with linear regression analysis.

Results: In 35,159 patients 197,736 triple measurements of sodium, Hb and Ht were available.

Mean ±SD sodium was 138.7 ±5.3 mmol·L^{-1},mean Hb was 6.5 ±1.4 mmol·L^{-1},mean Ht was 0.313 ± 0.064 and mean MCHC was 20.6 ±0.9 mmol·L^{-1}. The corresponding coefficients of variation for sodium, Hb, Ht and MCHC were 4%, 21%, 20% and 4% respectively. MCHC showed a significant negative correlation with sodium levels:

MCHC=25.51 - 0.04·sodium mmol·L^{-1} (R^2=0.05; P<0.0001).

Conclusion: In a large cohort of ICU patients we could demonstrate a small but significant negative correlation between *in vitro* measured MCHC levels and serum sodium. Consequently, there is an *in vitro* increase in MCV. These findings thus support an *in vivo* stabilization of erythrocyte volume in response to hyperosmolar stress, probably by generation of osmolytes. Since there are strong indications that other intracellular compartments are osmolyte-stabilized as well [1], long standing clinical assumptions regarding the distribution of infused fluid over ECV and ICV may not be valid.

References

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23.

The Effect of Dexamethasone on Cerebral Edema After Cardiac Surgery: a Randomized Trial

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Trial Registry Number: NCT00293592

Funding: This study was supported by grants from the Society of Cardiovascular Anesthesiologists Foundation, The Dutch Heart Foundation and ZonMW.

Introduction: Early postoperative magnetic resonance imaging (MRI) studies in cardiac surgical patients have demonstrated transient cerebral edema. Cerebral edema is a potential etiologic factor in postoperative cognitive dysfunction after cardiac surgery. The influence of corticosteroids on cerebral edema following cardiac surgery has not been studied. We hypothesized that high-dose intraoperative dexamethasone attenuates the development of cerebral edema after cardiac surgery.

Methods: After institutional review board approval, early postoperative cerebral MRI-scans were obtained from a subset of patients from the randomized, double-blind, placebo controlled, DExamethasone for Cardiac Surgery (DECS) trial, who received either dexamethasone 1mg/kg or placebo at induction of anesthesia. All patients underwent coronary artery bypass grafting (CABG). Outcomes observed were severity and incidence of cerebral edema.

Results: 20 patients were included. In each study group, 9 patients could be analyzed. Patients were on average 66 years old [range 43 - 79], and spent 87 minutes [range 27 - 194] on cardiopulmonary bypass. The average delay between end of surgery and MRI-scanning was 80 minutes [range 37 - 129 min]. Only one patient in the dexamethasone group had slight cerebral edema.

Conclusion: In the 18 CABG patients included in this study, we could not detect relevant degrees of cerebral edema. Because we were unable to replicate older studies showing cerebral edema early after cardiac surgery, it seems unlikely that cerebral edema plays a role in the pathogenesis of postoperative cognitive dysfunction. The large difference in incidence of cerebral edema in our sample, compared to previous studies, is likely due to medical and technological advances that were made in the last two decades.

24.

Leadership Training and Quality Improvement of Interdisciplinary Rounds in the Intensive Care Unit

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Background: The introduction of interdisciplinary teams in the intensive care unit (ICU) to provide patient-centered care, has focused attention to the relevance of leadership behaviour. Leadership behaviour of the intensivists is important during IDRs in the ICUs where an interdisciplinary team communicates and makes decisions about patient plans of care. Recent studies demonstrates that this leadership behaviour can be trained to improve subsequent team performance during resuscitation. In addition to these results, we conducted a study to critically assess the effect of a leadership training course on the quality of Interdisciplinary Rounds (IDR) in the ICU, measured with the IDR-Assessment Scale.
Methods: A non-randomized intervention study. Study participants included intensive care medicine-fellows, who practically finished their education and a control group of experienced though untrained intensivists. The intervention was participation in leadership training which was consistent with principles of adult learning and behavioral modeling. The IDRs led by participants of both the intervention and control groups were videotaped and the quality of the IDR was measured in reference to the IDR-Assessment Scale. This scale had 19 quality indicators, subdivided in 2 domains: "patient plan of care" and "process." The domain "patient plan of care" reflects the technical performance from the initial identification of a goal to the evaluative phase, such as "main problem discussed", "provisional goal formulated" and "long-term therapeutic items (≥ 16 h) discussed". The domain "process" reflects the team processes that are important to ensure that the appropriate plan of care is agreed, understood, and executed as planned by all care providers, such as "it is clear who is responsible for performing tasks", "summary given" and "input of nurses encouraged". Indicators were "essential" or "supportive."
Results: The leadership training improved the quality of 99 patient presentations led by the participants of the intervention group compared with 99 patient presentations led by the participants of the control group, with improvement in both "patient plan of care" and "process" domains of the IDR-Assessment Scale. Significant increase was noted in 12 of the 19 quality indicators and significant decrease was noted in 1 quality indicator, namely "secondary problems discussed".
Conclusion: The results from this study demonstrate that the quality of leadership will be reliably trained and measured in the context of IDRs in ICUs. Training in a simulation environment, with real-life IDR scenarios including conflicting situations, and workplace-based feedback in the preparation and feedback phases, appears to be effective to train leadership behaviour.
This study provides a basis for further work on training leadership within the ICUs. The authors aim to develop and test a leadership training program and also measure the effect of the training with a quantitative system, in support of the ultimate goal of improved safety of patient care.

25.

Evaluation of white blood cell scans on an Intensive Care Unit in a regional hospital

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Aim of the study: To evaluate the use of white blood cell scans on an Intensive Care Unit in a regional hospital.
Case history: A 66 yr old patient received an endoprosthesis for an acute abdominal aortic aneurysm. After the procedure the patient remained febrile without an obvious focus. Repeated CT scans and bloodcultures remained negative or were inconclusive. 27 days after the initial procedure a Tc-99m HMPAO white blood cell scans (WBCS) was preformed which showed uptake in the region of the sigmoid. The patient underwent a Hartmann procedure for a perforation of the sigmoid which was complicated by a duodenal perforation. The patient was discharged in reasonable health with a prolonged course of antibiotics for an infected haematoma surrounding the endoprosthesis.
Introduction: To elucidate the cause of fever in patients both Positron Emission Tomography CT (PET/CT) scans and WBCS can be used. Although only PET/CT can detect tumours, both can detect sources of inflammation or infection. PET/CT scans are not available in every hospital, for instance only WBCS is available in our hospital. Increasingly PET/CT scans are used for critically ill patients[1]. However, there is a paucity of literature regarding the use of WBCS in critically ill patients. We have therefore compared the results of WBCS on the ICU and on the regular wards of the Westfriesgasthuis (WFG).
Results: During a 7.5 yr period, WBCS was used in a total of 48 patients. 13 patients were admitted on the ICU when the WBCS was performed. The final diagnosis on discharge was used to evaluate the results of the WBCS.

	REGULAR WARD	ICU
Sensitivity	73%	80%
Specificity	87%	75%

Conclusions: Results of WBCS on the ICU and regular wards are comparable. WBCS can be helpful to establish the cause of fever in ICU patients. However, recent data[2] suggest PET/CT scan is more sensitive and specific then WBCS.

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26.

Non-invasive ventilation with neurally adjusted ventilatory assist improves patient-ventilator synchrony

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Background: Non-invasive ventilation (NIV) has assumed an important role in managing patients with acute respiratory failure in the intensive care unit (ICU), in particular in patients with chronic obstructive pulmonary disease (COPD). Relief of dyspnea and reduce the work of breathing are important goals of NIV to avoid endotracheal intubation. This is important as invasive ventilation frequently requires sedation and is associated with increased morbidity and mortality. However, NIV frequently fails and endotracheal intubation inevitable. A major determinant of poor NIV tolerance is asynchrony between the patient's neural drive (respiratory effort) and the response of the ventilator, known as patient-ventilator asynchrony. Neurally adjusted ventilatory assist (NAVA) is a relatively new ventilatory mode that improves patient-ventilator asynchrony in invasive mechanical ventilation. NAVA triggers the ventilator using electrical activity of the diaphragm instead of flow/pressure. The main objective of this study is to compare patient-ventilator asynchrony during non-invasive ventilation between NAVA and pressure support ventilation (PSV). In addition, a dedicated NIV ventilator is compared to an ICU ventilator with NIV module in delivering PSV.

Methods: Ten COPD patients (male/female 9/1; age 65±4 yrs) with a clinical indication for NIV were recruited. After obtaining informed consent, patients were ventilated for 30 minutes in three different modes: 1) PSV with the BiPAP vision (dedicated NIV ventilator); 2) PSV with the Servo-i; and 3) NAVA with the Servo-i. Patients were ventilated using their individual clinical settings. During each ventilatory mode, tidal volume, diaphragm electrical activity (Edi), and mouth pressure were recorded simultaneously. Patient-ventilator asynchrony was analyzed using a computer algorithm to detect wasted efforts, double triggering, auto-triggering and dyssynchrony (trigger delay and cycling off errors). After each ventilator mode an arterial blood gas was taken and patients were asked to score dyspnea on a visual analog scale.

Results: Patients were ventilated with PS-level 7±0.7 cmH_2O or NAVA-level 0.7±0.4 $cmH_2O/\mu V$; positive end-expiratory pressure 6.0±0.4 cmH_2O; and fiO_2 = 0.5±0.04. Ventilation parameters and blood gas analysis are shown in Table 2. Patient-ventilator asynchrony is presented in Figure 1. Dyssynchrony during NAVA was lower compared to PSV-BiPAP (P<0.05), and there were significantly less wasted efforts during NAVA compared to PSV-BiPAP (P<0.05) and PSV-Servo-i (P<0.05). Furthermore, there were no differences in dyspnea score.

Conclusion: In conclusion, our preliminary data show that non-invasive ventilation with NAVA improves patient-ventilator synchrony. In this study improved synchrony does not result in changes in blood gases and dyspnea sensation. Furthermore, the dedicated NIV ventilator and the ICU ventilator with NIV module are equally effective in PSV mode.

	PSV-BIPAP	PSV-BIPAP	NAVA-BIPAP
Respiratory rate	22±8	23±2	26±3*
Tidal volume	-	557±50	488±66
Edimax	24±7*	32±10	29±10
SpO2	97±1	96±1	96±1
P/F	225±24	202±13	202±20
pH	7.39±0.02	7.38±0.02	7.38±0.02
PaO2	14.5±2.2	12.9±0.9	12.6±1.0
PaCO2	6.4±0.8	6.3±1.0	6.5±1.0
HCO3-	27±2	26±3	27±3

Table 1: Ventilation parameters and blood gas analysis in three different ventilatory modes.

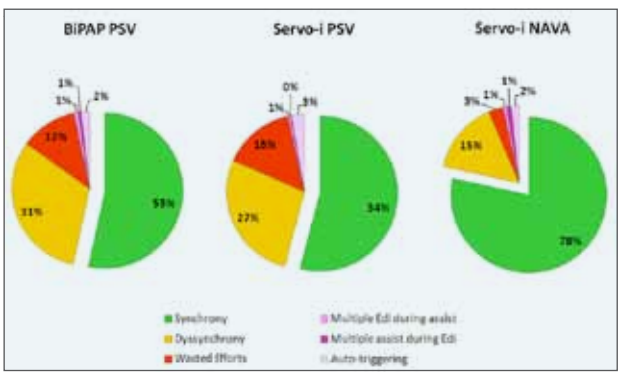

Figure 1. Pie diagrams representing patient-ventilator asynchrony in three different ventilatory modes.

27.

The effect of high-dose dexamethasone on transfusion of blood products in cardiac surgical patients

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Background: During cardiac surgery, prophylactic corticosteroids are often administered to attenuate the inflammatory response to cardiopulmonary bypass and surgical trauma. The main aim is to stabilize the postoperative hemodynamic status, thereby reducing the need for intravenous fluid therapy (including autologous blood products), vasopressor and inotropic therapy.
Objective: To study the effects of high-dose dexamethasone on the specific need for transfusion of blood products in the perioperative period.
Methods: Between 2006 and 2011, 4,494 adult patients undergoing cardiac surgery with cardiopulmonary bypass were enrolled in a multicenter, double-blind randomized trial studying the effects of prophylactic dexamethasone on major adverse outcomes (DECS study[1]). Of the 4,482 patients who could finally be analyzed, 2,235 patients received a single dose of dexamethasone 1 mg/kg after induction of anesthesia, and 2,247 received placebo treatment.
In this sub study, the primary outcome measure was the proportion of patients free of transfusion of any blood products. Secondary outcome measures included the proportion of patients receiving packed red blood cells (pRBC), fresh frozen plasma (FFP) or thrombocytes (Thr), in both the operating theatre (OR) and the intensive care unit (ICU). For the comparison of the proportions of patients with primary and secondary outcomes, we used the chi-square test.
Results: Baseline patient characteristics were well balanced between the 2 groups. In the dexamethasone group, 1,364/2,235 patients (61.0%) remained free of transfusion of blood products, as compared to 1,301/2,247 patients (57.9%) in the placebo group (absolute risk reduction [ARR] 3.1%; 95% confidence interval [CI] 0.3 to 6.0%; p=0.03). Less patients in the dexamethasone group received pRBC in the OR, but not in the ICU (table 1). There was no statistically significant effect on the transfusion rates of the other types of blood products in either the OR or the ICU.
Conclusion: High-dose dexamethasone increased the proportion of cardiac surgical patients remaining free of transfusion of autologous blood products. This increase was mainly caused by less transfusion of red blood cells during the operation itself. As dexamethasone administration is a low-cost and relatively safe[2] intervention, its prophylactic administration in cardiac surgery might be a cost-effective intervention to decrease the number of patients exposed to autologous blood product transfusion.

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% FREE OF :	DEXA-METHASONE	PLACEBO	ABSOLUTE RISK REDUCTION (%)	95% CI	P-VALUE
Any transfusion	61.0	57.9	3.1	0.3 to 6.0	0.03
Any pRBC	68.2	66.0	2.2	-0.6 to 4.9	0.13
pRBC in OR	83.9	80.8	3.1	0.9 to 5.4	<0.01
pRBC in ICU	77.2	77.0	0.2	-2.3 to 2.6	0.92
Any FFP	80.6	79.6	1.0	-1.3 to 3.4	0.40
FFP in OR	89.0	88.3	0.7	-1.3 to 2.5	0.49
FFP in ICU	87.6	86.9	0.7	-1.3 to 2.7	0.49
Any Thr	83.9	82.3	1.6	-0.5 to 3.8	0.15
Thr in OR	90.5	90.4	0.1	-1.6 to 1.8	0.92
Thr in ICU	91.2	89.7	1.4	-0.3 to 3.2	0.10

Table 1. Patients remaining free of transfusion

pRBC = packed red blood cells; FFP = fresh frozen plasma; Thr = thrombocytes; OR = operating room; ICU = intensive care unit; 95% CI = 95% confidence interval

28.

Immune paralysis in trauma patients; implications for pre-hospital intervention

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Background: Multi-trauma is one of the major indications for intensive care admission. Recovery is frequently complicated by post-injury immunological complications, caused by a dysfunctional immune system. This hyporeactive state of the immune system, known as immune paralysis, renders patients increased vulnerable for secondary infections. In order to treat or prevent this immune paralysis, knowledge on the time course of immune paralysis *in vivo* and the pathophysiological mechanisms of immune paralysis is essential. The aim of this study is to determine the time course of post-injury immune paralysis and factors that could predict and/or induce this phenomenon to ultimately find a suitable target and timeframe for intervention.
Methods: Blood was drawn from adult multitrauma patients (n=94) admitted to the emergency room (ER) of the Radboud University Nijmegen Medical Center. Blood was drawn at the trauma scene by the helicopter emergency medical services (HEMS), at arrival at the ER, and at days 1, 3, 5, 7, 10, and 14 after trauma. Plasma concentrations of TNFα, IL-6, IL-10, IFN-γ, IL-8 and MCP-1 were determined by Luminex. *Ex vivo* 24h whole blood stimulations with the TLR4 ligand LPS and the TLR2 ligand Pam3Cys were performed and production of TNFα, IL-6 and IL-10 was measured using ELISA to analyze immune paralysis. Clinical data, e.g. Injury Severity Scores, trauma mechanism, medication and survival were collected from electronic patient files.
Results: As depicted in figure 1, plasma levels of the anti-inflammatory cytokine IL-10 at the ER were 16.5-fold increased in comparison to time point HEMS (p<0.01). Similar, but much less pronounced effects were found for the pro-inflammatory mediators IL-8 and MCP-1. A significant correlation (r=0.53, p=0.03,) was found between injury severity scores and IL-10 plasma concentrations at time-point ER.
Time-courses of *ex vivo* produced cytokines revealed that LPS-induced pro-inflammatory IL-6 and TNFα production is already decreased in the first few hours after trauma and recovered from day 5 onwards, while *ex vivo* IL-10 production showed an inverse pattern.

Conclusions: Immune paralysis appears to develop within hours after trauma. Excessive production of the anti-inflammatory cytokine IL-10 in the pre-hospital phase could play a crucial role in generation of this refractory state of the immune system. Furthermore, a higher injury severity score is associated with more IL-10 production in this phase. Immune stimulatory strategies applied by the HEMS or early after hospital admission could represent a potential future approach to prevent immune paralysis in multi-trauma patients.

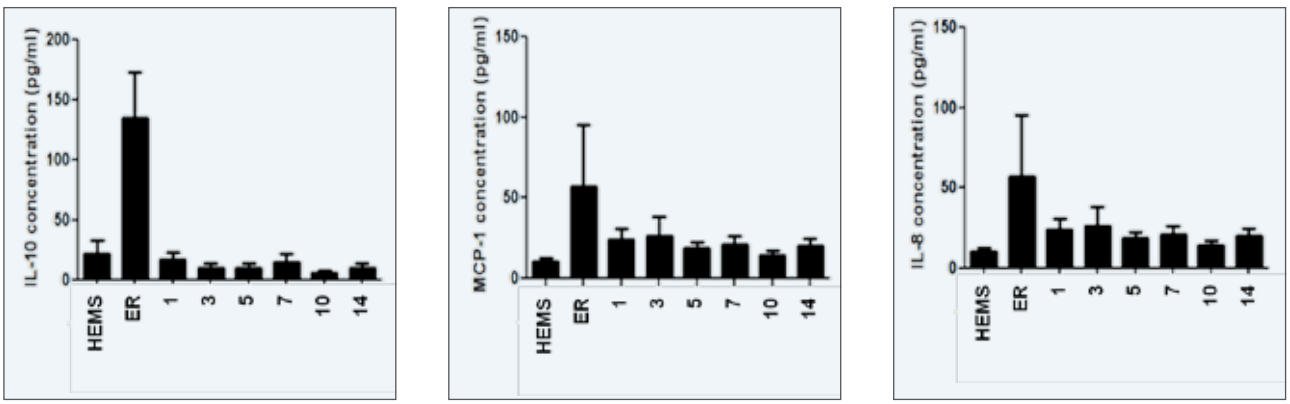

Figure 1. Anti-inflammatory (IL-10) and anti-inflammatory (IL-8 and MCP-1) plasma cytokine levels in multi-trauma patients

29.

Dysnatremia incidence in the ICU over two decades: hypernatremia increases, hyponatremia decreases

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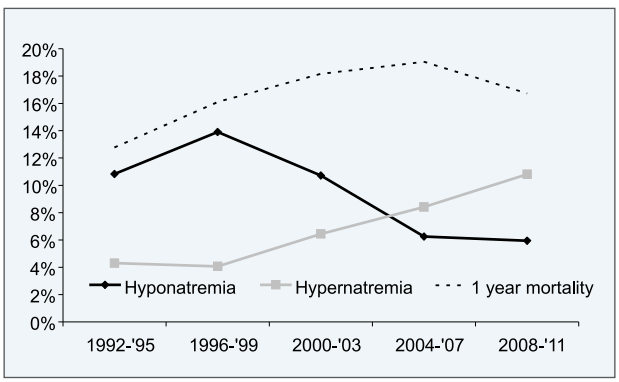
Background: Dysnatremias (hyponatremia and hypernatremia) are common findings on admission of patients to the intensive care unit (ICU). Historically most attention has been focused on hyponatremia, as it was more common. In the largest cohort study so far the prevalence of hyponatremia ([Na^+]<130 mmol·L^{-1}) on ICU admission was 3.9% and 1.8% for hypernatremia ([Na^+]>150 mmol·L^{-1}).[1] Patients in the ICU are at high risk of developing dysnatremia during ICU stay because of the incapacitation, lack of free access to water and the treatment given for their critical illness. Both admission and ICU-acquired dysnatremia are associated with increased in-hospital mortality[1,2]. We studied the temporal changes in the incidence of admission or ICU-acquired dysnatremia because of our impression that hypernatremia has become more prevalent than hyponatremia. We also studied the association between dysnatremia and mortality..

Methods: This retrospective study was performed in a cohort of mixed ICU patients admitted between 1992 and 2011 to our adult 45-bed tertiary ICU. Age <15 years was the only exclusion criterium. All sodium measurements during ICU admission were collected. Hyponatremia was defined as [Na^+]<130 mmol·L^{-1} and hypernatremia as [Na^+]>150 mmol·L^{-1}. Survival was determined at 1 year after ICU-admission.

Results



During the 20 year study period more than 46.000 consecutively admitted ICU patients were included.

In this cohort of ICU patients we observed a clear shift in the incidence of ICU-acquired dysnatremias (Figure). The incidence of hyponatremia nearly halved over the study period whereas the incidence of hypernatremia doubled. Most patients had ICU-acquired dysnatremia. Dysnatremia was strongly associated with mortality.

Conclusion: The shift from hyponatremia to hypernatremia may be due to changes in therapy, especially because dysnatremia is usually ICU-acquired. Possible iatrogenic causes include the increased use of isotonic IV-fluids, which are often hypertonic to the urine, and increased use of hydrocortisone. Our results should be compared to those of other centers. We also propose an interventional trial to evaluate the effect of a therapeutic strategy that aims to prevent dysnatremia.

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30.

The value of central venous-arterial pco_2-gap in patients admitted to icu with severe sepsis or septic shock

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Background: Severe sepsis and septic shock are major causes of mortality; identification of prognostic and therapeutic targets is therefore of particular importance. In this respect venous saturation (S(c)v02) is only of partial value since many septic patients appear to have a S(c) v02 above 70%.(1) The venous-to-arterial pCO2 difference (pCO2-gap) is proposed as an alternative prognostic marker in sepsis. However, the origin of the venous blood samples, i.e. mixed venous (v) versus central venous (cv), is different in various studies. The pCO2-gap has also been used as surrogate for cardiac index in ICU patients.(2) It has also been suggested that in septic patients the origin of the pCO2-gap may be due to alterations in microcirculatory blood flow, and therefore cannot be used a predictor for cardiac index.The aim of this study was to establish the relationship between pCO2-gap between central and mixed venous blood and to elaborate the relationship between the cardiac index and pCO2-gap in patients with severe sepsis or septic shock.
Methods: This post-hoc analysis of a prospective observational study was performed in 54 patients from 2 Dutch hospitals, with severe sepsis or septic shock according to international criteria. Arterial, central and mixed venous blood samples were collected every 6 hours during the first 24 hours after admission to the ICU. The interchangeability between mixed and central venous pCO2-gap was assessed by the mean bias and 95% limits of agreement (mean bias ± 1,96 SD) described by Bland and Altman. The correlation between pCO2-gap and cardiac index was assessed with Pearson's correlation coefficient. Data are presented as mean ± SD.
Results: A total of 265 paired blood samples were obtained. The pv-aCO2 underestimated the pcv-aCO2 by a mean bias of 0.03kPa ± 0.32kPa. The 95% limits of agreement ranged from -0.62kPa to 0.58kPa. In literature a cut-off > 0.8kPa has been associated with adverse outcome. Cardiac index and pCO2-gap correlated significantly at ICU admission, but this relation was clinically irrelevant (p<0.0001; R2=0,07).
Conclusions: In conclusion pv-aCO2 reliably predicts pcv-aCO2, However the limits of agreement are in the range of the suggested cut-off value, complicating interchange ability. Furthermore, due to the significant, but weak correlation with cardiac index, the pCO2-gap cannot be used as a surrogate for cardiac index in septic patients. This suggests alternative causes for the origin of the pCO2-gap.

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31.

Use of physical restraint in Dutch Intensive Care Units: prevalence and motives

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Introduction: Physical restraint is a widely known tool to facilitate essential care and prevent secondary injuries. Over the years, more consideration has been given to the effect of physical restraint on patient autonomy and the possible harmfulness of restraint. However, research on physical restraint in hospitals is scarce and studies on the use in Dutch Intensive Care Units (ICUs) are absent. The aim of this study is to determine the scope of physical restraint use, hereby promoting the discussion on the subject and preventing inappropriate use or overuse of physical restraint in the ICU.
Objectives: To quantify the use of physical restraint in Dutch ICUs and the conditions under which restraint is applied.
Methods: Twenty-one ICUs ranging from local hospitals to academic centres participated in this study and each ICU was visited twice by a researcher. We included 327 patients, who were admitted to the ICUs during researchers' visit. Among others, we recorded the Confusion Assessment Method adapted for the ICU (CAM-ICU) score, medication use over the last 24 hours and the possibility of verbal communication. The following outcome parameters were collected: use and methods of physical restraint, motives for applying the restraint, the acquaintance of the medical personnel with a protocol concerning physical restraint and the physicians' awareness of their patient's physical restraint status.
Results
Physical restraint was applied in 74 (23%) patients, ranging from 0 to 54% for different hospitals. The physical restraint consisted mostly of bilateral upper limb restraint (87%). In all cases, professional restraint materials were used. Frequent motives for restraint use were 'possible threat to airway' (36%) and 'pulling lines/probes' (31%). Restrained subjects had, compared to non-restrained patients, more often a positive CAM-ICU (34% versus 16%, p<0.001), could less frequently verbally communicate (14% versus 49%, p<0.001), and received more often antipsychotics (49% versus 28%, p<0.001), or benzodiazepines (55% versus 36%, p=0.003). The use of physical restraint was registered in the patient's record in 48% of cases. The included ICUs used a physical restraint protocol in 88%, of which 23% was specific for the ICU. Of the total of 310 interviewed nurses, 290 worked in an ICU that provided a protocol. Of these, 258 (89%) were familiar with the protocol and 89 (31%) used it in any situation. Thirty percent of the 60 questioned physicians were aware of the physical restraint status of their patients.
Conclusions: Physical restraint is frequently used in Dutch ICUs. Physically restrained patients showed more often a positive CAM-ICU, were more often treated with antipsychotics or benzodiazepines and were more often unable to verbally communicate (e.g. intubated). Important motives for the use of physical restraint were 'possible threat to airway' and 'pulling on lines or tubes'.
The majority of physical restraint protocols are not ICU-specific and attending physicians are often not aware of physical restraint use.

References

not applicable

32.

Validation of non-invasive pulse contour cardiac output using finger arterial pressure in cardiac surgery patients requiring fluid therapy

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Introduction: Nexfin™ allows for the non-invasive continuous monitoring of blood pressure and cardiac output by measuring finger arterial pressure (FAP) using a finger cuff.To evaluate the accuracy of FAP in measuring blood pressure (ABP_{NI}) and cardiac output (CO_{NI}) as well as the adequacy of detecting changes in blood pressure and cardiac output, we compared FAP to intra-arterially measured blood pressure (ABP_{IA}) and transpulmonary thermodilution (CO_{TD}) in post cardiac surgery patients before and after fluid expansion.
Methods: We included mechanically ventilated post-cardiac surgery patients admitted to the critical care unit. Fluid challenges were performed according to local practice if a mean arterial pressure below 70 mmHg occurred. We collected simultaneous blood pressure and cardiac output measurements using Nexfin, intra-arterial blood pressure measurement and transpulmonary thermodilution before and after fluid expansion. We compared CO and systolic, diastolic and mean arterial pressure.
Results: 20 Post cardiac surgery patients were included with a mean age of 67 years. We performed 28 fluid challenges, 40% of all patients required norepinephrine. A sufficient quality non-invasive finger signal was obtainable in all patients and complications were not observed. When comparing ABP_{NI} to ABP_{IA}, the bias was 2.7 mmHg (LOA ± 22.2), 4.9 mmHg (LOA ± 13.6) and 3.1 mmHg (LOA ± 13.4) for systolic, diastolic and mean arterial pressure, respectively. The four quadrant plot analysis showed concordance between changes in ABP_{NI} and ABP_{IA} of 100% using a 5% exclusion zone. Mean bias between CO_{NI} and CO_{TD} was -0.26 (LOA ± 2.2) with a percentage error of 38.9% (Figure 1). Concordance between changes in CO_{NI} and CO_{TD} before and after a fluid challenge was 100% using a 5% exclusion zone (Figure 2).
Conclusion: FAP reliably measures blood pressure as well as changes in blood pressure. Although FAP is not interchangeable with transpulmonary thermodilution although it follows changes in cardiac output closely.

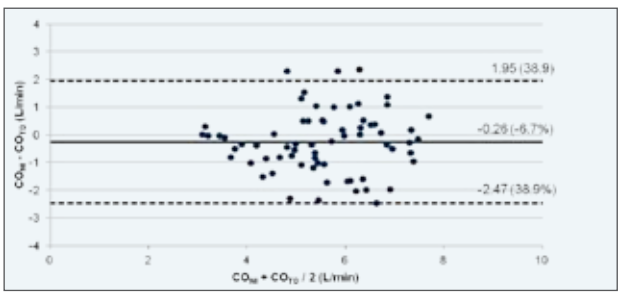

Figure 1. Agreement between COTD and CONI depicted in a Bland-Altman analysis.

33.

Let the sunshine in? The influence of pre-admission daylight exposure on the incidence of ICU acquired delirium

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Background: Light exposure before and during acute illness appears to have contradictory affects on outcome. Recent data suggest that shorter pre-hospital daylight exposure is associated with improved survival in critically ill patients[1]. While ICU-acquired delirium is an independent predictor of mortality and its incidence is associated with environmental factors[2], the influence of pre-hospital sunlight exposure on the incidence of ICU-acquired delirium is unknown. Aim of the present study was to determine the effect of pre-hospital light exposure on the incidence of ICU-acquired delirium.
Methods: In this retrospective cohort study, data of three ICU's (Radboud University Nijmegen Medical Centre, University Medical Centre Utrecht, and Jeroen Bosch Hospital, 's-Hertogenbosch) from the period 2007-2012, were analysed. Delirium was assessed using the CAM-ICU. Daily photoperiod data were obtained from meteorological stations in the vicinity of the three hospitals. Cumulative photoperiod was calculated for each patient for 7, 28 and 60 days prior to hospital admission. The association between light and delirium incidence was analyzed using a multivariate analysis adjusting for diagnosis, APACHE II score, infection and sedation.
Results: Data of 3384 patients, aged 61.9±15.3 and APACHE II score 16.3±6.8 were analysed. The mean delirium incidence was 31.7% and did not vary significantly during the year (figure 1). Pre-admission photoperiod was clearly associated with the season of the year, however, the 28-day pre-admission photoperiod was not associated with the delirium incidence (OR 1.000; 95% CI 0.997-1.002, p=0.72). Furthermore delirium was significantly associated with age, infection, use of sedatives, APACHE II score and diagnosis of neurological disease or trauma, but not with any season (table 1)
Conclusion: Prior sunlight exposure does not play a role in the development of ICU-acquired delirium. Age, infection, sedation, APACHE II score and diagnosis of neurological disease or trauma were found to be independent risk factors for delirium. In addition, this is the first study to demonstrate that ICU-acquired delirium is independent of the season.

References

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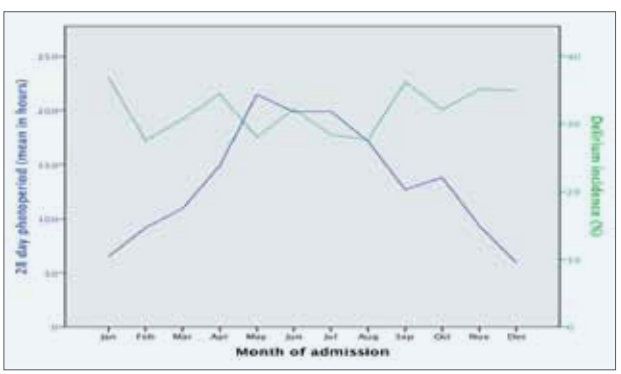

Figure 1. Monthly 28-day photoperiod and delirium incidence

	OR	95% C.I.		P-VALUE
		Lower	Upper	
Gender	1.022	0.857	1.218	0.812
Age	1.017	1.010	1.023	<0.001
APACHE II	1.096	1.080	1.113	<0.001
Infection	3.207	2.630	3.911	<0.001
Sedation	3.705	3.094	4.437	<0.001
Season				
Spring (referent)				
Summer	1.005	0.801	1.261	0.969
Autumn	1.076	0.798	1.452	0.631
Winter	0.901	0.641	1.268	0.550
Diagnostic category				
Surgical (referent)	1.0			
Medical	0.881	0.710	1.094	0.252
Trauma	2.923	1.727	4.947	<0.001
Neurological	3.724	2.761	5.024	<0.001
Unknown	0.847	0.201	3.564	0.821
28 day photoperiod	1.000	0.997	1.002	0.721

Table 1. Multivariate logistic regression analysis for delirium

34.

Skin conductance monitoring and its ability to detect discomfort during a painful stimulus in an Intensive Care Unit population

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Introduction: Usually the assessment of pain intensity depends on a patient's self-evaluation, but is often impossible during intensive care unit (ICU) stay. Sympathetically mediated palmar skin conductance variability is related to emotionally induced perspiration, correlates with pain levels in the perioperative setting but has not been studied in ICU patients. We therefore evaluated whether noninvasive pain assessment could provide beneficial information during a painful stimulus.
Material and Methods: We prospectively included 51 General ICU patients in this observational study. Patients were monitored with the MED-STORM Stress Detector®. The number of skin conductance fluctuations per second (NSCF) is reflected in microsiemens per second (µS) and was measured before (BL), during (T1), and 30 seconds after (T2) a noninvasive constant nociceptive stimulus for 15 seconds at the nailbed of the index finger. Data were analyzed using repeated measures ANOVA with a Bonferroni correction for multiple comparisons and are presented as mean (±SE).
Results: In non-sedated patients (n=24), NSCF increased significantly during the nociceptive stimulus and decreased thereafter from respectively 0.08 (0.02) µS at BL to 0.19 (0.03) µS at T1 (P=0.02). At T2 NSCF decreased towards baseline values, although this was not significant 0.11 (0,03). In sedated patients (n=27) NSCF increased significantly during the nociceptive stimulus from 0.07 (0.02) µS at BL to 0.23 (0.03) µS at T1(P <0.001) and accordingly decreased towards baseline values 0.14 (0.02) (p= 0.059).
Conclusion: In critically ill patients, NSCF increases during a nociceptive stimulus in both non-sedated and sedated patients. The measurement of NFSC may therefore provide an additional tool
for pain assessment in this group of patients. Further study of skin conductance variability for monitoring distress or pain in ICU patients is warranted.

35.

Early complications of percutaneous dilatational tracheostomy in critically ill patients

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Introduction: Percutaneous dilatational tracheostomy (PDT) placements are gaining in popularity in critically ill ICU patients. With a complication rate comparable to open surgical tracheostomy, PDT has several other benefits. It is easy to perform at the bedside, no logistic problems in planning the procedure, less wound infections, cost effective and less unfavourable scarring.

We evaluated our experience of PDT's in 54 patients in our intensive care unit.

The purpose of our study is to examine the short-term complications of PDT.
Methods: We evaluated the PDT in 54 patients respectively from August 2009 till November 2011. We used the PDT- technique, first described by Ciaglia(1). The kit we used was the Portex® Percutaneous Dilatation Tracheostomy Kit with a single-stage dilator. The procedure was performed under fiberoptic guidance to minimize the risk of a false route or posterior trachea-wall injury.
Results: Study population consisted of 54 patients (34 men and 20 women), mean age 53 (18-80), mean APACHE II score 22 (8-35), mean SAPS-II score 50 (15-82). Indications for performing PDT are listed in table 1. Complications were divided into minor, intermediate and serious according earlier report (2). Data are shown in table 2. No serious complications were seen. Initially we performed PDT's in low risk patients i.e. easy airway and favourable neck anatomy. With growing experience

complication rate decreased and we could perform PDT's in more complex patients with significant reduction in surgical tracheostomies.
Conclusion: PDT using the Portex PDT kit was feasible in our ICU. Although in 24 patients minor to intermediate complications were encountered no serious adverse events occurred. With growing experience in our staff members, complication rate decreased with a significant reduction in surgical tracheostomy procedures.

Indication for PDT	N=54 (%)
One or more failed detubations	4 (7.4)
Anticipated prolonged weaning	22 (40.7)
Airway clearance difficulty	12 (22.2)
Low EMV-score	13 (24.1)
Dysfagia	3 (5.6)

Table 1. Indications for PDT

COMPLICATIONS	N=24 (%)
Minor	
Haemorrhage	10 (19)
Tube displacement	5 (9.3)
False route	0 (0)
Intermediate	
Desaturation	2 (3.7)
Hypotension	2 (3.7)
Tracheal wall injury	2 (3.7)
Malposition cannula	1 (1.9)
Serious	
Death, Arrest, pneumothorax, pneumomediastinum	0 (0)

Table 2. Complications of PDT's

References

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36.

Continuous intra-arterial fluorescent glucose monitoring in post-operative cardiac surgery patients in the ICU: initial experience in The Netherlands

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Background: Continuous glucose monitoring (CGM) in ICUs has the potential to improve glycaemic control and thereby enhance patient safety and outcomes. The GluCath Intravascular CGM System uses a novel quenched chemical fluorescence sensing mechanism to measure blood glucose in arterial blood. The aim of this non-randomized open-label study was to evaluate the performance and safety of the GluCath CGM system in post-operative cardiac surgery patients admitted to the ICU.
Methods: This is an ongoing clinical study and data of the five lead-in subjects (of 20 intended) are reported. GluCath sensors were inserted shortly after ICU admission via a secondary 20 gauge radial arterial study catheter. GluCath glucose values were recorded each minute for 24 hours and were blinded for the clinical staff. Reference blood samples were collected from the study catheter every 1–2 hours and analyzed on a Radiometer ABL Blood Gas Analyzer. The routine glucose protocol was maintained.

Ultrasound measurements were performed to assess the vessel's reaction to the sensor.
Results: The sensor was successfully inserted in all five subjects and did not interfere with clinical care or blood sampling. In all subjects the sensor operated without interruption for 24 hours. No thrombus formation, serious adverse events, or unanticipated adverse device effects were observed. Ninety-four reference samples were collected; 69/94 (73.0%) of the GluCath measurements met ISO 15197 glucometer criteria (within ± 20% of reference) across a 4.4-14.7 mmol/L range (figure 1). Several sensors were negatively affected by patient motion and device securement. Four out of five sensors had a mean absolute relative difference in the 12–15% range.
Conclusion: The GluCath CGM system safely and continuously measured with acceptable accuracy arterial blood glucose for 24 hours in post-operative cardiac surgery patients. The system will be modified based on these results to improve accuracy and ensure reliable performance for use in clinical practice.

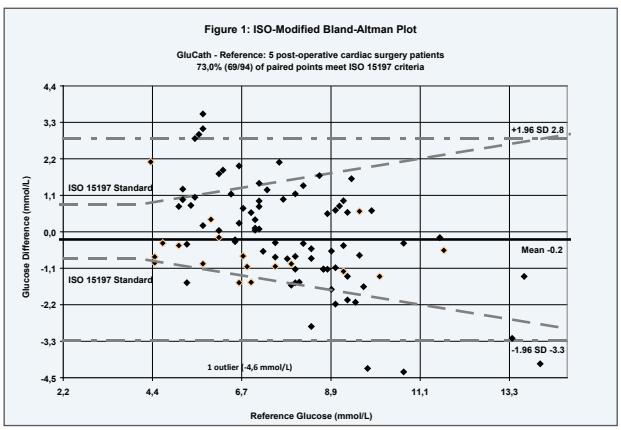

Figure 1.

37.

Sevoflurane therapy for life threatening asthma in children

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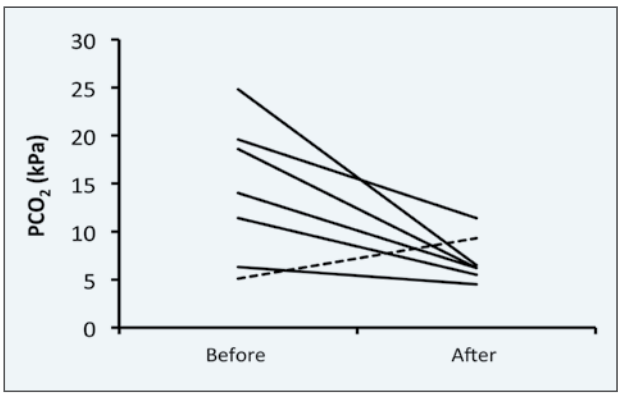
Background: Severe asthma is treated with bronchodilators like salbutamol, corticosteroids, magnesium sulphate, and if necessary mechanical ventilation. If these options fail, volatile anesthetic agents can be used. This is the first multicentre case series that describes the effectiveness of sevoflurane therapy in children with life-threatening asthma.
Methods: Pediatric patients admitted to the pediatric intensive care unit (PICU) with severe asthma and sevoflurane treatment were included. A retrospective review of demographic, medical, laboratory and ventilation parameters was performed.
Results: 7 children from two PICU's in The Netherlands with age ranging from 4 to 13 years were included. The mean length of PICU stay was 6.7 days (range 3-10). Mean (range) dose of sevoflurane and duration of treatment were 2.2% (1-4%) and 24h (0.5-90h). Median (range) pH at the beginning and at the end of sevoflurane treatment were 7,02 (6,97-7,36) and 7,43 (7,15-7,47) ($p < 0.01$). Median (range) pCO_2 were respectively 14 (5,1-24,8) and 6,2 (4,5-11,4)kPa ($p < 0.05$). Median (range) peak pressure declined from 30 (23-56) to 20,4 (14-33) cmH_2O ($p < 0.03$). Four patients developed hypotension, which was successfully treated with norepinephrine. One patient (dotted line figure), was afterwards judged to suffer from ARDS and indeed failed to respond to sevoflurane therapy.
Conclusion: Mechanical ventilation with sevoflurane inhalation is a safe and effective treatment for children with life-threatening asthma.



38.

Dysnatremia incidence in the ICU over two decades: hypernatremia increases, hyponatremia decreases

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Background: Dysnatremias (hyponatremia and hypernatremia) are common findings on admission of patients to the intensive care unit (ICU). Historically most attention has been focused on hyponatremia, as it was more common. In the largest cohort study so far the prevalence of hyponatremia ($[Na^+]<130$ mmol·L^{-1}) on ICU admission was 3.9% and 1.8% for hypernatremia ($[Na^+]>150$ mmol·L^{-1}).[1] Patients in the ICU are at high risk of developing dysnatremia during ICU stay because of the incapacitation, lack of free access to water and the treatment given for their critical illness. Both admission and ICU-acquired dysnatremia are associated with increased in-hospital mortality[1,2]. We studied the temporal changes in the incidence of admission or ICU-acquired dysnatremia because of our impression that hypernatremia has become more prevalent than hyponatremia. We also studied the association between dysnatremia and mortality..
Methods: This retrospective study was performed in a cohort of mixed ICU patients admitted between 1992 and 2011 to our adult 45-bed tertiary ICU. Age <15 years was the only exclusion criterium. All sodium measurements during ICU admission were collected. Hyponatremia was defined as $[Na^+]<130$ mmol·L^{-1} and hypernatremia as $[Na^+]>150$ mmol·L^{-1}. Survival was determined at 1 year after ICU-admission.
Results: During the 20 year study period more than 46.000 consecutively admitted ICU patients were included.
In this cohort of ICU patients we observed a clear shift in the incidence of ICU-acquired dysnatremias (Figure). The incidence of hyponatremia nearly halved over the study period whereas the incidence of hypernatremia doubled. Most patients had ICU-acquired dysnatremia. Dysnatremia was strongly associated with mortality.
Conclusion: The shift from hyponatremia to hypernatremia may be due to changes in therapy, especially because dysnatremia is usually ICU-acquired. Possible iatrogenic causes include the increased use of isotonic IV-fluids, which are often hypertonic to the urine, and increased use of hydrocortisone. Our results should be compared to those of other centers. We also propose an interventional trial to evaluate the effect of a therapeutic strategy that aims to prevent dysnatremia.

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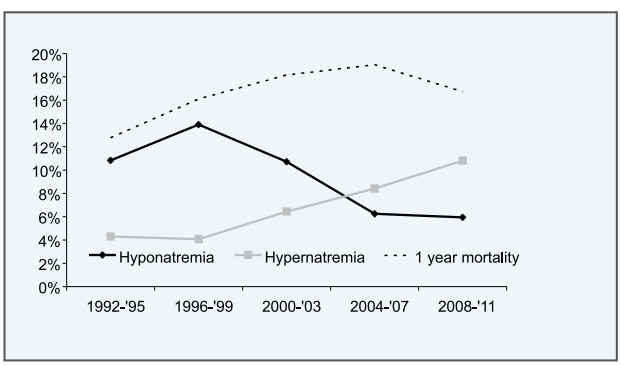

39.

Guideline 'Control of Nasogastric tube by measurement of the pH' is not suitable for ICU patients

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Background: A national guideline regarding the procedure of nasogastric tube positioning was authorized in November 2011 and implemented on our ICU. The guideline states that the auscultation method is unreliable for the determination of adequate nasogastric tube positioning (grade B). Instead, measurement of pH in the aspirate was proposed for nurses to determine at the bedside whether the nasogastric tube is placed in the stomach and not in the airways (grade A1). In 15 % of all patients the pH of gastric aspirate is higher than 6.0 (grade A2). The aim of our study was to asses the usefulness of pH measurements in gastric aspirate to determine the correct position of the nasogastric tube in the ICU setting..
Methods: We performed a prospective, observational study in both medical and surgical patients. In these patients the pH was measured in the first aspirate that was collected after ICU admittance or after placement of the nasogastric tube on the ICU. In all patients a routine X-ray of the thorax was performed. The X-ray was considered the gold standard. Data are expressed as mean ± SD.
Results: We collected data of 50 consecutive patients after elective cardiac surgery and 50 medical and non-cardiac surgery patients. In one patient no aspirate was obtained and the position of the nasogastric tube was confirmed with X-ray. Mean pH was 4.7 (± 1.93) after elective cardiac surgery and 4.6 (± 1.87) in medical and non-cardiac surgery patients. In 13 of 49 patients after cardiac surgery the pH was higher then 5.5 (26 %). In 16 of 50 non-cardiac admissions the pH was higher then 5.5 (32 %). In patients after elective cardiac surgery the tube was replaced after measuring a high pH. In non of these patients the nasogastric tube was misplaced.
Conclusion: In this study, the percentage of patients with a pH above 5.5 seems to be higher when compared with the literature. In the hands of our experienced nursing staff, the auscultation method in combination with a macroscopic evaluation of the aspirate appeared to be a reliable method. Based on a cut-off value for pH > 5.5 the nasogastric tube had been removed and replaced unnecessarily in 26 percent of our patients. Implementation of guidelines, made for a general hospital population, can not always be implemented in specific patients groups.

Literature

NV&V richtlijn; Controle positie neusmaagsonde door middel van pH meting.

40.

Factors that influence the application of Crew Resource Management at a large ICU

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Introduction: Since January 2011 the ICU of the Radboud University Nijmegen Medical Centre has implemented Crew Resource Management (CRM) in order to increase patient safety by means of more effective communication, increased quality of teamwork and diminishing human errors. The ICU applies CRM by using four instruments: checklists, a structured submission / transfer form, guidelines related to (professional) communication and briefing – debriefing. In general, when employees learn new behavior this must be generalized to the job and maintained over a period of time1. This process is called transfer of learning. The aim of this study is to gain insight into the factors that influence the transfer of learning concerning the application of Crew Resource Management.
Methods: The validated Learning Transfer Inventory System Model (LTSI-model) was used to gain insight into the transfer of learning2. This model contains sixteen different factors such as *feedback, openness to change, motivation to transfer* and *supervisor support*. A questionnaire based on the validated questionnaire of the LTSI-model was send to all employees of the ICU department. Several factors from the model were excluded and three additional CRM related topics were added. Data were analyzed using SPSS and non-parametric statistics were used (the Mann-Whitney U test).
Results: All 303 relevant healthcare professionals of the ICU, 38 physicians and 265 nurses, received the questionnaire. The total response rate was 49% (148 employees). The response rate of the ICU physicians was 47% and the ICU nurses was 49%.
When comparing nurses to physicians it showed that there were significant differences (Table 1). Subsequently we identified if factors were stimulating or constraining the transfer of learning and the application of CRM at the ICU. Eleven factors are identified as supporting factors, of which the physicians indicated seven factors as a strong stimuli and the nurses one factor. In addition, both groups indicated the same four factors as neutral factors. Finally, no barriers were identified (Table 2).
Conclusion: In conclusion, physicians score higher on many factors compared to nurses and *feedback*, indicated as a neutral factor by both nurses and physicians, may play a key role in the application of CRM.

References

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FACTOR	MEDIAN PHYSICIANS	MEDIAN NURSES	P
Motivation to transfer!	4.33	4.00	.017
Peer Support	4.00	3.75	.008
Supervisor Support	3.80	3.60	.048
Personal capacity to transfer	4.14	3.86	.000
Opportunity to use	4.00	4.00	.048
Teams!	4.00	3.80	.032
CRM tools	3.94	3.81	.034
CRM Believe	4.08	3.67	.008

Table 1. Significant differences between physicians and nurses (Mann-Whitney U test)
Significant at p < .050
Reliability value < .60 for nurses and / or physicians

41.

Abnormally Low Or Abnormally High Resting Sto2 Values Are Associated With High Risk Of Mortality In Critically Ill Patients

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Background: Near-infrared spectroscopy (NIRS) provides a direct measurement of tissue O2 saturation (StO2) in the microcirculation of a volume of tissue. It assists clinicians to monitor peripheral circulation to early detect peripheral tissue hipoperfusion. The device shows a trended real-time display of StO2 and a value lower than 75% is usually indicative of inadequate perfusion. However, inadequate tissue perfusion may be also related to high StO2 values, since it can reflect impaired cellular utilization of oxygen. Considering the normal variation in healthy population (75-85%), StO2 values out of this range may be considered abnormal. Therefore, StO2 may be classified as normal (75-85%), abnormally low (<75%) or abnormally high (>85%). The objective of this study was to propose the discretization of StO2 values in these three groups and to investigate if it can more adequately predict ICU mortality.
Methods: StO2 was continuously monitored over the thenar eminence using InSpectra Model 325 probe (Hutchinson Technology Inc.) at ICU admission and every 24 h thereafter until day 3. After we stratified StO2 values as normal (75-85%), abnormally low (<75%) or abnormally high (StO2>85%), we performed a generalized mixed-model analysis to estimate odds ratio for mortality at each combination of days with abnormally high and low StO2 values.
Results: We prospectively studied 222 consecutive critically ill patients (age: 57±16 yrs; 147 male/75 female) during 3 consecutive days. Fifty eight patients had circulatory shock (septic:20; nonseptic:38). No difference in resting StO2 values was seen between survivor and nonsurvivors: mean (SE), 82% (0.6) vs. 81% (1.1). Table 1 shows odds ratio for mortality at each day stratified by groups. We found that the presence of an abnormally low or abnormally high StO2 significantly predict mortality. Figure 1 shows the proportion of normal and abnormal StO2 values in survivors and nonsurvivors.
Conclusions: Patients with abnormally low as well as patients with abnormally high StO2 values had significantly higher odds of mortality than did patients with normal StO2 values.

Table 1. Odds Ratio for mortality when StO2 is abnormal

	ODDS RATIO (OR)	OR 95% CI	P VALUE
Admission	2.8	1.4-5.4	0.003
Day 1	3.9	1.8-8.5	0.001
Day 2	1.7	0.8-3.9	0.19
Day 3	3.2	1.1-9.8	0.03

42.

Non-invasive early diagnosis of ventilator associated pneumonia: Can electronic nose technology reliably discriminate infected critically ill patients?

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2 Department of Medical Microbiology
Maastricht University Medical Centre+, The Netherlands

Background: Ventilator associated pneumonia (VAP) is a nosocomial infection occurring in the intensive care unit (ICU). This infection prolongs length of stay in ICU and on mechanical ventilation, increases morbidity, mortality, antibiotic use and health care related costs. The currently best diagnostic approach is broncho-alveolar lavage (BAL) from the site of the presumed infection and subsequently cytological and microbiological analysis of the lavage fluids. However, this technique is invasive and carries risks. It has limitations in patients with severe pulmonary disease and high respiratory support settings. BAL is laborious, time consuming and it takes up to 48 hours before final results are available and the diagnosis of VAP can be confirmed or rejected. Therefore, we are looking for a new diagnostic tool that is non-invasive and fast but also equally valid and accurate as BAL. Electronic nose technology (e-nose) is an established method and has already been applied for industrial purposes. E-nose comprises different panels of hybrid metal oxide semiconductor sensors. They analyze an applied gas by creating a specific temperature-time-conductivity spectrum. We propose that microorganisms causing pneumonia release a specific spectrum of volatile organic compounds (VOC) into the exhaled air. We hypothesized different combinations of VOC's would cause changes in conductance detectable by e-nose to discriminate patients with VAP from colonized, non-infected patients as reliable as BAL.
Methods: Air samples from critically ill, ventilated patients with a suspicion of VAP were analysed using an e-nose with different sets of metal oxide sensors (Diagnose, C-it, Zutphen, The Netherlands). Sensors were periodically heated between 200°C and 320°C in cycles of 20 seconds divided over 32 steps. VOC´s present in the breath samples developed an electrical response in the sensor and this was measured as changes in conductance as a function of temperature and time. For statistical analysis IBM SPSS statistic 20 was used comprising principal component analysis and logistic regression to calculate a model for discrimination between VAP and control. The outcome of the logistic regression was used to construct a ROC-curve.
Results: During the study period we identified 35 patients with VAP based on the diagnostic criteria of more than 2% intracellular microorganisms in BAL fluid and/or a bacterial growth of more than 10^4 CFU/ml. We compared the e-nose data of these patients with 68 critically ill patients without VAP. The presumed changes of VOC´s in the exhaled air of mechanically ventilated patients with VAP did not lead to changes in the temperature-conductivity-time spectrum that was detectable by the applied e-nose sensors. In case of a preferably high sensitivity for VAP of >96% we found a low specificity of 18%. With such a high amount of false positive results there is no value in clinical practice.
Conclusion: E-nose technology was unable to discriminate patients with VAP in the present study and is currently not applicable to clinical practice.

43.

Peripheral perfusion alterations after major abdominal surgery are associated with postoperative complications

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Background: Impairment of perfusion of the peripheral circulation is strongly associated with inflammation, organ failure and outcome in critically ill patients. Similarly, tissue hypoperfusion and inflammation are the main causes for the occurrence of complications after surgery. However, it is unknown whether derangement of the peripheral circulation is more likely to occur in patients developing postoperative complications. We therefore wanted to determine whether repeated assessment of the peripheral perfusion in the days following surgery could help to identify patients that develop postoperative complications.
Methods: We prospectively followed 158 consecutive patients who underwent elective major abdominal surgery and were admitted to the Intensive Care Unit, Post Anesthesia Care Unit, or surgical ward. Hemodynamic measurements and peripheral perfusion parameters were collected one day prior to surgery (BL), directly after surgery (D0), and on the first (D1), second (D2), and third (D3) postoperative days. Peripheral perfusion was evaluated using a combination of the capillary refill time (CRT), peripheral perfusion index (PPI), and forearm-to-fingertip skin temperature gradient (Tskin-diff). Abnormal peripheral perfusion was considered as a CRT > 5 seconds, PPI < 1.4 %, or Tskin-diff > 4 °C. Postoperative complications were predefined and classified into 'no', 'mild', and 'moderate' complications (Grade 0-II) and 'severe' complications and death (Grade III-IV) according to the contracted Accordion Severity Grading System (1).
Results: Overall 111 patients were included and the rate of major complications was 18.0%. Systemic hemodynamic variables were comparable between groups. Table 1 shows the time course for the different peripheral perfusion variables. Before surgery (BL) there was no difference in peripheral perfusion between patients who developed minor or major complications. Directly after surgery (D0) however, CRT was significantly impaired in the patients who subsequently developed major complications compared to those who did not. This difference persisted until D3. Correspondingly, Tskindiff was significantly altered at D1, and PPI at D2 and persisted over time in patients who eventually developed major complications. In the presence of persistent abnormal peripheral perfusion at D2 and D3, the odds to develop major postoperative complications are higher, respectively (9.4; 95% CI, 3.1 - 28.8) and (7.2; 95% CI, 2.4 - 21.7), compared to patients with normal peripheral perfusion.
Conclusion: Following major abdominal surgery, abnormal peripheral perfusion is more present in patients who developed complications and may predict outcome, apparently independent of systemic hemodynamics.

Reference

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	BL		D1		D2		D3		D4	
	Minor	Major	Minor	Major	Minor	Major	Minor	Major	Minor	Major
CRT	2.5 (0.1)	2.5 (0.2)	3.7 (0.2)	5.1 (0.5) *	2.9 (0.2)	5.8 (0.7)**	2.7 (0.1)	5.9 (0.6)**	2.7 (0.2)	6.1 (0.7)**
PPI	3.8 (0.3)	3.2 (0.3)	3.5 (0.4)	2.6 (0.7)	4.9 (0.0)	2.6 (0.7)	3.9 (0.3)	1.7 (0.4)**	4.4 (0.3)	2.2 (0.5)**
Tskin-diff	2.0 (0.2)	2.7 (0.5)	2.7 (0.2)	3.2 (0.4)	2.2 (0.2)	3.6 (0.5)**	2.1 (0.2)	4.2 (0.6)**	2.1 (0.2)	4.1 (0.7)**

Table 1. Peripheral perfusion parameters

Data is presented as mean ± SE.
* p<0.05, ** p<0.01 between groups on specific time-point, by linear mixed model analysis

44.

Changes in circulating oxytocin and its association with brain function during systemic inflammation

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Background: Inflammation increases oxytocin in animal experiments and is also known to be involved in complex regulation of behavioural responses. The role of oxytocin during systemic inflammation in healthy and critically ill humans is not clear and also its role in the inflammation-associated changes in cerebral function and cognition has not been examined in humans.
Methods: Fifteen healthy male volunteers received 2 ng/kg *Escheria coli* lipopolysaccharide (LPS) intravenously. Oxytocin, IL-6, brain specific proteins (BSP), electroencephalography (EEG) and cognitive function tests (CFTs) were determined. In addition, in 44 ICU-patients with infection/SIRS diagnosed with or without delirium, as expression of cognitive functioning, biomarkers, including oxytocin levels were determined within 24 hours following the onset of delirium. Delirium was diagnosed using the confusion assessment method-ICU (CAM-ICU).
Results: During experimental endotoxemia all plasma cytokines and body temperature significantly increased, reaching peak values 1.5-4 hrs following LPS administration. Oxytocin concentrations also significantly increased, reaching its peak value after 2 hrs. We found no correlation between IL-6 as measure of inflammation and the rise in oxytocin (r= -0.18; p=0.95). Also no correlations between the increase in oxytocin and changes in BSP's, EEG or cognitive function tests could be detected (data not shown).

In the group of ICU-patients with an infection/SIRS, a total of 26 were diagnosed with delirium and 18 without delirium. Delirious ICU-patients had a significantly higher level of oxytocin (figure 1) compared with non-delirious ICU-patients (median 4.6 [IQR 3.1-8.0] versus median 1.9 [IQR 1.2-5.1] pmol/L, respectively; *p=0.006*). Again, we found no correlation between IL-6 and oxytocin levels in infectious ICU-patients (r=0.15; *p=0.35*).
Conclusion: Short-term induced systemic inflammation results in increased levels of oxytocin, but did not provoke cognitive dysfunction. In infectious ICU-patients higher oxytocin levels were found in patients that suffered from delirium, compared to those who did not. No clear association between IL-6 and oxytocin was found. This is the first study that shows that oxytocin is increased during inflammation and associated with the presence of delirium in ICU-patients with an infection. In view of the role of oxytocin in human behaviour, this observation suggests that inflammation-induced increase in oxytocin may be involved in the development of delirium.

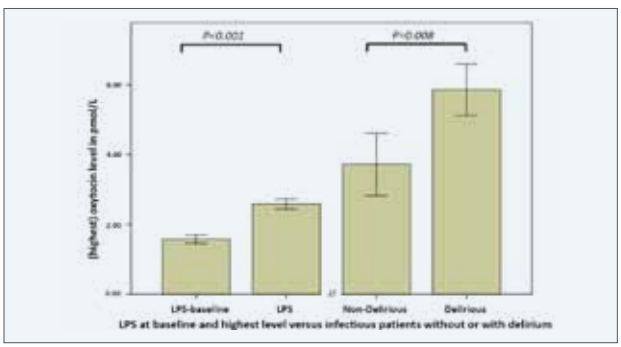

Figure 1. Results of both studies, where a higher oxcytocine level can be seen in both the healthy male volunteers who received (LPS) as well as in the group of ICU patients with a longstanding inflammation, in which the delirious patients showed the highest levels.

45.

Nitroglycerin dose-dependent increases peripheral perufsion and improves tissue oxygenation in patients with circulatory shock: Results of a prospective, cross-over study

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Background: Several clinical studies have assessed the effect of vasodilators as potential adjunctive therapy to recruit microvascular perfusion in circulatory shock. Some clinical investigators have proposed the administration of nitroglycerine (NTG) as a therapeutic approach to recruit the microcirculatory units and improve peripheral tissue oxygenation in septic shock and cardiogenic shock with benefic results. This scenario has led to growing interest in non invasive methods designed to monitor perfusion in peripheral tissues during vasodilator therapy. We question, therefore, whether NTG dose-dependent improves peripheral perfusion, as assessed by clinical assessment, body temperature gradient, and near-infrared spectrodcopy (NIRS) in patients admitted to intensive care unit (ICU) for circulatory shock resuscitation.
Methods: The institutional review board approved the study. All patients admitted for circulatory shock resuscitation were included. Peripheral circulation parameters included capillary refill time (CRT), forearm-to-fingertip skin-temperature gradient (Tskin-diff) and peripheral tissue oxygenation (StO_2). Global hemodynamic variables included heart rate (HR), central venous pressure (CVP), and mean arterial pressure (MAP). NTG was given as a bolus followed by a continuous intravenous infusion of 2mg/h and doubled stepwise (4 mg/h; 8 mg/h; 16 mg/h) at each 15 minutes interval until an improvement in peripheral perfusion was observed. A second set of baseline measurements were recorded after 30 minutes of NTG infusion cessation.
Results: Of 15 patients included in the study (age 63±14 yrs; 9 males), 12 had septic shock. In all patients, NTG infusion significantly decreased MAP at the maximum dose time point (T_{MX}) and the lowest value recorded was 51 mmHg. Table 1 shows the time course of peripheral perfusion parameters during NTG infusion at T_{BL1}, T_{MX} and T_{BL2}. The magnitude of changes in StO2 was more accentuated for lower StO2 values (StO2<75%): 11% vs. 4%, P<0.05.
Conclusion: NTG dose-dependent improves peripheral perfusion and can be used to titrate vasodilator therapy to recruit microvascular perfusion.

Table 1. Global hemodynamic variables recorded in the three different time points during execution of the study protocol (n = 15). Time points are defined as before nitroglycerin infusion (T_{BL1}), at the maximum dose of nitroglycerin (T_{MX}) and 30 min after cessation of nitroglycerin (T_{BL2}). Cardiac index and stroke volume were measured in 6 patients. Data are mean (SE)

	T_{BL1}	T_{MX}	T_{BL2}
HR (bpm)	95 (4.3)	97 (4.4)	98 (4.4)
SBP (mmHg)	113 (4.6)	94 (4.0)*	111 (3.8)*
DBP (mmHg)	52 (4.9)	49 (4.8)*	57 (4.9)*
MAP (mmHg)	75 (3.0)	61 (2.9)*	71 (2.3)*
CI, n=6 (L/min/m2)	4.1 (0.4)	3,8 (0.5)	3,9 (0.4)
SV, n=6 (ml)	78 (15)	66 (14)	77 (12)

HR=heart rate; SBP=systolic blood pressure; DBP=diastolic blood pressure; MAP=mean arterial blood pressure; CI=cardiac index; SV=stroke volumev
* P<0.05 vs. previous time point (linear model for repeated measurements)

46.

Voriconazole pharmacokinetics in a patient on ECMO

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Background: Venovenous Extra Corporal Membrane Oxygenation (VV ECMO) is known to affect pharmacokinetics of different drugs. Therapeutic Drug Monitoring (TDM) by means of determining trough levels is therefore recommended if possible.

In our centre a 56-year old patient on VV ECMO was being treated with voriconazole for an invasive *Aspergillus* infection. We measured trough levels for almost three weeks and adjusted dosage according to guidelines [trough level 2-5 mg/l]. Since we did not reach the recommended values after increasing the dosage several times we hypothesized that pharmacokinetics of voriconazole in patients on ECMO are different in that voriconazole is cleared quicker and that TDM alone might not be enough to guarantee adequate trough levels in the early, critical phase of treating an often fatal infection.
Methods: Measuring voriconazole plasma concentration from t=0 every hour up until t=6 hours after administration of voriconazole (600 mg = 7 mg/kg, 3 times daily) in a patient with pulmonary *Aspergillus* infection on ECMO (Novalung ILa activve ®) and on CVVH. A plasma concentration curve was made and Tmax, Cmax, T1/2 and AUC were estimated with Winnonlin. Our data were compared with those from patients not on ECMO (1,2). Furthermore our patient was tested for CYP2C19 genotype. To make sure there was no bias because of a potential CYP219 fast metabolism, we inhibited the metabolism of voriconazole by administering omeprazole to our patient.
Results: The plasma concentration curve of voriconazole in time after administration of 7 mg/kg in our patient was used to subtract pharmacokinetic data. Tmax was reached after one hour (1-2h in patients not on ECMO). T1/2 in patients not on ECMO is 6h. The 5h in our patient therefore seems rather quick. Cmax was higher (11.8 vs 3-4.7 mg/L) and the AUC in our patient was comparable to data of patients on a standard dose voriconazole (3-4 mg/kg, two times daily). CYP219 testing showed a normal genotype.
Conclusion: A high dose of voriconazole (7 mg/kg, 3 times daily) was needed to create an AUC in our patient on ECMO that was comparable to exposure in normal patients. Taken together with the relatively short T1/2 and the high Cmax it seems that (part of the) voriconazole leaves the system quicker than when not on ECMO. In conclusion, our data confirm that pharmacokinetics of voriconazole are different during ECMO. Clearance of voriconazole seems to go faster and higher dosages are necessary to achieve adequate trough levels. Starting with a higher dosage and/or estimating the AUC early in treatment could possibly prevent inadequate treatment.

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47.

Long-term outcome of delirium in critically ill patients

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Background: In Intensive Care Unit (ICU) patients, little research has been performed on the relationship between delirium and long-term outcome, including health-related quality of life (HRQoL), cognitive functioning and mortality. In addition, results seem to be inconsistent. Furthermore, in studies that reported increased mortality in delirious patients, no proper adjustments were made for severity of illness during ICU admission.
Objectives: To investigate the association between ICU delirium and long-term HRQoL, cognitive functioning and mortality. The hypothesis was that delirious patients have worse long-term outcome in comparison with non-delirious patients.
Methods: A prospective observational cohort study was conducted. A median of 12 months after ICU discharge, questionnaires were sent to all survivors. HRQoL and cognitive functioning were measured with the EuroQol-6D. Age, gender and severity of illness were considered relevant covariates. Severity of illness was estimated using the APACHE-IV score and the maximal SOFA score during admission. HRQoL was investigated with linear regression analysis, cognitive functioning using logistic regression and mortality with Cox regression analysis.
Results: The patient population consisted of 690 patients admitted to the ICU, subdivided into delirious (n = 257) and non-delirious patients (n = 433). During follow-up, 181 (26%) patients died. The response rate of the questionnaire was 70.6%. After adjusting for the predefined covariates, delirium was significantly associated with a lower HRQoL (adjusted β: -0.137; 95% Confidence Interval (CI) -0.140 to -0.005) and more mild and severe cognitive impairment (adjusted odds ratio: respectively: 2.3; 95% CI 1.3 to 4.2 and 5.8; 95% CI 1.3 to 15.2). No significant association between delirium and long-term mortality was found (adjusted hazard ratio: 1.0; 95% CI 0.7 to1.4).
Conclusion: Delirium during ICU admission was associated with lower HRQoL and worse cognitive functioning, one year after discharge. Furthermore, delirium on the ICU was not associated with long-term mortality after adjusting for relevant covariates, including severity of illness during ICU admission.

48.

The reliability of dynamic indices for goal directed fluid therapy during open abdominal surgery

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Background: Optimizing the cardiac stroke volume during high risk surgery may decreases the incidence of postoperative complications and the length of stay in the ICU. Because dynamic indices are strongly correlated with stroke volume, it is suggested that these variables should be used for goal directed fluid therapy during high-risk surgery. The reliability of these variables depends on many physiological factors, such as abdominal and thoracic compliance, that are influenced by surgery. It has been shown that a decrease in thoracic compliance increases the arterial waveform derived variables. Because the abdomen acts as a resistance to the diaphragm, it was hypothesized that by opening the abdomen the thoracic compliance increases, resulting in a decrease in heart-lung interaction and dynamic indices. The aim of this study was to assess the effect of laparotomy on arterial waveform derived variables.
Methods: Twenty patients on controlled mechanical ventilation undergoing elective laparotomy were included in this study. The non-invasive continuous blood pressure and bladder pressure, as surrogate for abdominal pressure, were recorded shortly before and after opening of the abdomen. The non-invasive continuous blood pressure was recorded using an inflatable finger cuff in combination with a Nexfin™ Monitor (BMEYE, Amsterdam, The Netherlands). Based on waveform analysis of the non invasive continuous blood pressure the Cardiac Index (CI), Pulse Pressure Variation (PPV) and Stroke Volume Variation (SVV) were determined.
Results: Ten patients were excluded for analysis because their cardiovascular status was changed by fluid therapy or epidural medication between the two measurements. In three of the remaining patients only PPV and SVV could be determined from the arterial waveform due to technical difficulties. PPV and SVV both decreased as a result of the opening of the abdomen, with 45% [p=0.003] and 59% [p=0.017], respectively while CI remained unchanged.
Conclusion: Laparotomy causes a decrease in the magnitude of dynamic indices of fluid responsiveness like PPV and SVV. Therefore current threshold values are not valid under these conditions. In order to decrease postoperative complications, the altered physiology during surgery should be taken into account when using perioperative goal directed fluid therapy. This may also apply to ICU patients with open abdomen management of intra-abdominal sepsis.

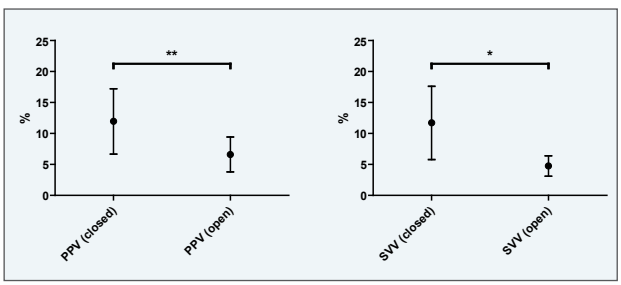

Figure 1. Comparison of waveform derived variables (PPV, SVV) at closed abdomen and at opened abdomen. *P < 0.05; **P < 0.01.

49.

Epidemiology of delirium in the Intensive Care Unit

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Background: Delirium is a common syndrome in the Intensive Care Unit (ICU) which impairs outcome. Large prospective studies focusing on the epidemiology of delirium on the ICU are scarce. We conducted a study to investigate the occurrence rate of delirium, length of delirium episodes, and delirium subtype frequencies.
Methods: This prospective observational study was performed in the ICU of the University Medical Center Utrecht (UMCU). All patients admitted for more than 24 hours between January 2011 and March 2012, aged 18 years or older, were included. We excluded patients with another neurological disease than delirium. Patients were daily screened for delirium using the Confusion Assessment Manual for the ICU (CAM-ICU) by research nurses and junior medical doctors. In the analyses, patients were divided into three study groups: delirium during ICU admission, never delirium during ICU stay, or unable to asses throughout ICU admission. Delirium subtypes were defined using the Richmond Agitation and Sedation Scale.
Results: A total of 1,832 patients were assessed. After exclusion, a study population of 637 patients remained. Of these patients, 293 (46%) were delirious at any time during their ICU admission, 289 (45%) never developed delirium and 55 (9%) of the patients could never be assessed. Of the delirious patients, 208 (71%) had one delirium episode during ICU admission. Of the total number of episodes (n = 457), 186 episodes (41%) had a duration of one day and 89 episodes (19%) lasted for more than 5 days. Furthermore, 276 (61%) of the episodes had a mixed subtype, followed by 156 (34%) hypo-active and 24 (5%) the hyperactive subtype.
Conclusion: This study is one of the largest investigations on the epidemiology of delirium in the ICU and the first study describing the occurrence rate and duration of different delirium episodes in ICU patients. Most delirious patients experienced one delirious episode with the maximum duration of one day, and most delirium episodes belonged to the mixed subtype.

50.

Pulmonary embolism in Mycoplasma pneumoniae community-acquired pneumonia: a case series and epidemiologic analysis

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Background: *Mycoplasma pneumoniae* (MP) is a common causative bacterial pathogen of community-acquired pneumonia (CAP). It may present with both pulmonary and extrapulmonary manifestations. Symptoms are usually transient and hospitalization is infrequently needed. Recently, we encountered three cases with MP severe CAP and pulmonary embolism (PE). In the literature, only five cases have been described. We assessed whether MP CAP may be a risk factor for the occurrence of PE in adults.
Methods: We describe 3 cases of *Mycoplasma pneumoniae* CAP with coexistent pulmonary embolism. We searched our hospital database for 8 years to find similar cases with MP CAP, PE and coexistent diagnoses. An epidemiologic analysis was made based on our hospital and national RIVM data.
Results: Between December 2011 and June 2012, one male (age 27) and two females (age 33, 47) were admitted to our hospital with respiratory symptoms caused by MP CAP and PE. MP CAP was confirmed by a positive PCR and presence of multilobular infiltrates on chest X-ray. PE was diagnosed by CT-angiography. Risk factors for PE were present in two patients (pregnancy, hyperhomocysteinemia) and risk factors for complicated MP infection in one (Down's Syndrome). Two patients had to be treated with invasive mechanical ventilation, with an ICU LOS of 9 and 10 days. One patient developed shock and was treated with thrombolytic therapy. All patients received anticoagulant therapy and antibiotics. Average hospital LOS was 17,3 days.
From the 1st of January 2004 until the 31st of December 2011, 26 patients have been discharged with the diagnosis MP CAP (average 3.3 per annum, 7 cases in 2011) and 1280 patients have been discharged with a diagnosis of PE (average 160 per annum). During the observation period, the first two cases of concurrent MP CAP and PE presented in December 2011 and the third in June 2012. Before, no coexisting diagnoses of MPP and PE were found. Based on national epidemiological data, the expected rate of MP CAP annually is 600/100.000. Analysis of the 2011 data suggests that the diagnosis MP CAP may be a risk factor for the occurrence of PE, with a risk ratio of 1.77 (NS). We feel that our findings may be of clinical relevance, although due to low numbers the risk ratio does not reach statistical significance.
Conclusion: *Mycoplasma pneumoniae* pneumonia has recently been complicated by pulmonary embolism in three patients. MP CAP may be a risk factor for PE. Among causes of these observations we suggest improved diagnostics of MP by PCR and changes in first line antibiotic guidelines for treatment of pneumonia. Pathophysiologically, acquired pro-thrombotic factors, direct vascular damage by cytokines and a change in virulence of the pathogen may play a role. Clinical awareness of PE in MP CAP is warranted to facilitate early diagnosis and adequate treatment. As new national antibiotic guidelines for general practitioners advise amoxicillin as a first line therapy in CAP, cases of MP CAP with PE may be seen more frequently in The Netherlands.

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CASE REPORTS

1.

Piperacillin/tazobactam induced collaps

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Introduction: Drug induced haemolytic anaemia is not common. Although, the most common drugs to cause haemolytic anaemia are antibiotics, only few cases have been reported of piperacillin/tazobactam. We describe a patient presenting with collaps and hemodynamic instability who developed an immune haemolytic anaemia due to piperacillin/tazobactam.
Case report: A 29 year old woman was admitted to the department of pulmonology of our university hospital because of an exacerbation of cystic fibrosis. Her dyspnea was increased without having fever. Laboratory tests showed leukocytes of 16.3 10^E9/L (3.5-11.0 10^E9/L) and a CRP of 12 mg/L (<10 mg/L). The chest radiograph showed a central consolidation in the left lung. Due to a multi-resistant *Stenotrophomonas maltophilia* in her endotracheal aspirate she was treated with piperacillin/tazobactam, which she had been treated with before. Eight days after starting piperacillin/tazobactam the patient collapsed and became hemodynamically instable. Initially, it was thought to be due to a gastrointestinal bleeding because one of the nurses mentioned dark stools suspect for melaena. However, gastroscopy and partial colonoscopy showed no evidence of gastrointestinal blood loss. The patient was treated with intravenous crystalloid and blood transfusion. Additional laboratory studies showed a hemoglobin of 2.4 mmol/L (7.3-9.7 mmol/L), decreased haptoglobine (0.04 g/L) (0.25-1.90 g/L), increased free hemoglobin (135.4 umol/L) (<5.3 umol/L), increased lactate dehydrogenase (1098 U/L) (120-250 U/L) and an increased total bilirubin (163.1 umol/L) (<20 umol/L), all indicating haemolysis. Since the Coombs test (direct antiglobulin test) was positive, the working diagnosis was an autoimmune haemolytic anaemia, most probably caused by piperacillin/tazobactam which was discontinued. The patient was treated with prednisolone 1mg/kg and plasmapheresis which was performed twice. The patient recoverd quickly and hemoglobin level returned to 7.5 mmol/L (7.3-9.7 mmol/L). Additional blood-plasma analysis revealed antibodies to piperacillin.
Discussion: A new anaemia developing in patients without overt bloodloss, treated with multiple medicines should arouse the suspicion of an iatrogenic etiology. Drug induced immune haemolytic anaemia may be a life threatening process due to systemic hypoperfusion and hypoxia following the rapid drop in hemoglobin level. The antibodies causing drug induced immune haemolytic anaemia can be drug-independent or drug-dependent. Piperacillin has first been described a few years ago to be the cause of immune haemolytic anaemia by drug-dependent antibodies. Haemolysis wil subside as soon as administration of the responsible drug is discontinued. Patients benefit from expeditious initiation of supportive care, including restoring intravascular volume and blood transfusion. There are few data suggesting steroids to be helpfull when haemolytic anaemia is caused bij drug-dependent antibodies. We gave our patient 1 mg/kg prednisolone. Plasma exchange might be necessary in severe cases when the patient is hemodynamically instable and there are signs of hypoperfusion. This case report illustrates the importance of early identification of drug induced immune haemolytic anaemia which can be a rare, but lethal complication of a commonly used antibiotic.

2.

Idiopathic Giant Cell Myocarditis; a rare cause of Death due to very rapid progressive Heart Failure

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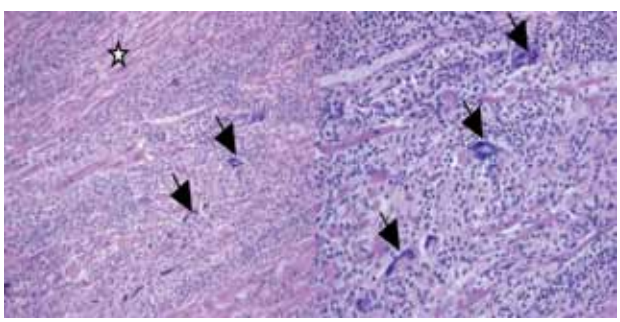
Introduction: Idiopathic Giant Cell Myocarditis (IGCM) is a rare but often devastating disease. It is characterized by rapid cardiac detoriation with ventricular arrhythmias, congestive heart failure and associated high mortality.
Case report: A 61-year-old male with a medical history of diabetes mellitus type II and hypertension presented at our emergency department complaining of progressive cough, fever and dyspnea for 4 days. Physical examination was unremarkable. Blood tests revealed elevated infection parameters (Leucocytes 20x10^6/l, CRP 148 mg/l) and renal insufficiency (Creatinin 199 umol/l). Chest X-ray and ultrasonography of the kidneys were normal. The patient was admitted to the internal medicine ward with the initial diagnosis of airway infection and renal insufficiency. Antibiotic treatment was started. After admission he became progressively unstable with respiratory insufficiency and atrial fibrillation. Nine days after onset of the initial symptoms the patient detoriated fast. He showed both clinical and radiological signs of acute left sided heart failure and cardiomegaly. ECG showed atrial fibrillation but no specific ischemic changes. Cardiac enzymes were elevated (CK 429 u/l, CK-MB 42,9 ug/l, Troponine 24 ug/l). Intubation was performed. Transthoracic echocardiography after conversion to sinus rhythm revealed severe left ventricular hypertrophy, hyperdynamic chambers without wall motion disorders and pericardial effusion without signs of cardiac tamponade. Despite hemodynamic optimalisation he developed asystole and resuscitation was initiated. After 30 minutes without output resuscitation was ceased. Autopsy revealed 400 ml pericardial effusion, macroscopically myocardial hypertrophy with abnormal pale discoloration of 75% of the circumference of the left ventricle and wide open coronary arteries. Microscopically there was a massive infiltration of lymphocytes, eosinophils and especially histiocytes, many of which multinucleated (giant cells) in close relationship with individual necrotic myocardial cells. This histologic picture is consistent with the diagnosis of Idiopathic Giant Cell Myocarditis (pictures). Serologic tests for cardiotropic viruses were negative and levels of ANA and ANCA were normal.



The left picture shows some remaining myocardial tissue (asterisk) and a massive infiltration with giant cells(arrows)
Discussion: The first sign of a cardiac problem was the progressive elevation of cardiac enzymes suggesting progressive myocardial damage. However, ECG revealed no specific ischemic changes and echocardiography showed twice nonconclusive changes. The patient died of heart-failure due to IGCM. Diagnosis of IGCM is difficult; symptoms, ECG and echocardiographic findings in IGCM can be nonspecific.(1) Only endomyocardial biopsy can be diagnostic with a sensitivity up to 84% and should be considered in patients with acute heart failure or ventricular arrhytmia who fail to improve despite standard medical care.(2) Treatment is heart transplantation. Ventricular assist devices have been used to bridge the time. Aggressive treatment with immunosuppressiva can prolonge transplant free survival. Prognosis of IGCM is poor; the overall rate of death or cardiac transplantation is 89%.

Conclusion: Idiopathic Giant Cell Myocarditis is a rare and devastating disease. The disease course can progress rapidly into acute heart failure and life threatening arrhythmias. Myocardial biopsy should be initiated in severely ill patients with suspected myocarditis. The requirement of heart transplantation and immunosuppressive therapies should be considered early.

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3

Recombinant factor VIIa: life-saving therapy in a patient with massive bleeding and hepatic failure

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Introduction: The conventional management of coagulopathy in patients with massive bleeding due to acute or chronic hepatic disease is supportive, and includes fresh-frozen plasma, desmopressin, vitamin K and platelets. Recombinant factor VIIa is not commonly used as a treatment of coagulopathy secondary to hepatic cirrhosis and may be a therapeutic option in patients who fail to respond to the conventional therapy.

Case Report: A 48 year old male was admitted to the internal ward with a painful haematoma in the right leg. Patient's medical history consisted of a recently diagnosed hepatic cirrhosis, Child Pugh class B, due to alcohol abuse. Further laboratory evaluation revealed an anemia (haemoglobin 5.5 mmol/L), thrombocytopenia (70x10^9/L), mildly elevated International Normalized Ratio (INR, 1.51) and normal Activated Partial Thromboplastin time (APTT, 30 seconds).

Abdominal ultrasound and computed tomography revealed a right sided psoas bleeding, signs of hepatic cirrhosis, gastric varices and splenomegaly. The initial diagnosis was a spontaneous psoas bleeding in a patient with alcoholic hepatic cirrhosis and a coagulopathy.

Twelve days after admittance, the patient developed a hypovolemic shock caused by an intra-abdominal haemorrhage originating from the psoas bleeding. The patient was admitted to the ICU. Treatment consisted of vitamin K, tranexamic acid, fibrinogen, prothrombincomplex, packed cells, fresh frozen plasma and platelets. Under adequate therapy there was an ongoing bleeding. Previously conducted supplementary coagulation studies revealed a factor VII deficiency (factor VII activity 25%, normal range 60-140%). There was no history of a pre-existing coagulopathy, the most probable cause for the acquired factor VII deficiency was hepatic failure. A single dose of recombinant factor VIIa (90 µg/kg) was given, after which the bleeding stopped. No further therapy was necessary. See graphic.

Discussion: In vascular injury tissue factor is released which binds to factor VII (FVII) and further activates the coagulation cascade. FVII is a vitamin K dependant glycoprotein, synthesized in the liver. A FVII deficiency can be acquired or hereditary. An acquired FVII deficiency is most often secondary to hepatic disease or vitamin K antagonists. In hepatic disease a deficiency of all vitamin K dependant clotting factors is expected, although the levels of FVII are disproportionately low. The spectrum of bleeding problems in a FVII deficiency is variable and muscle bleedings are seen in 20% of the cases.[1] The management of acquired FVII deficiency is supportive. However, in case of failure of conventional therapy, recombinant factor VIIa can be life-saving.[1,2]

Conclusion: In patients with a life-threatening bleeding and hepatic failure an acquired factor VII deficiency must be considered. In case of an ongoing bleeding, despite conventional supportive therapy, recombinant factor VIIa should be considered as life-saving therapy.

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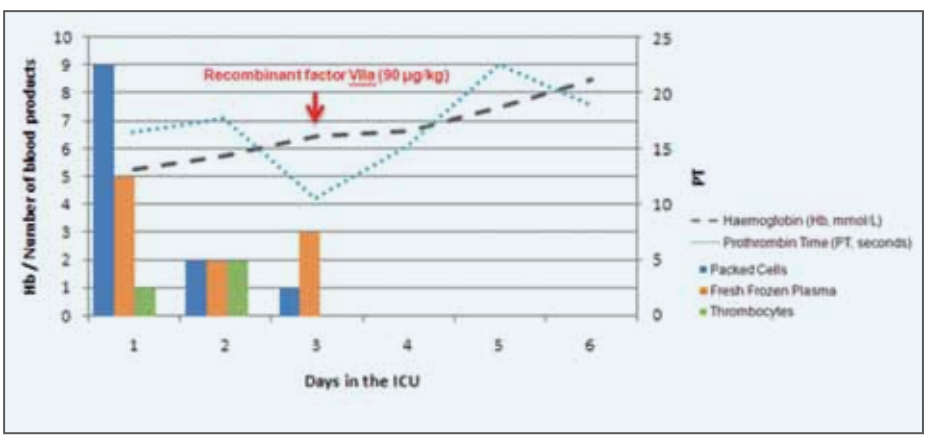

Graphic. Course of haemoglobin, prothrombin time and number of blood products.

4.

Pneumopericardium in an immunocompromised patient

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Introduction: Invasive pulmonary aspergillosis (IPA) is frequently seen in immunocompromised patients and is an important cause of mortality in patients with haematologic malignancies.We describe a rare case of pneumopericardium as a complication of IPA that developed in the course of a relapse of acute myelogenous leukemia.

Case report: A 59-year old woman was admitted to our intensive care unit because of respiratory failure followed by cardiac arrest for which she was intubated and resuscitated. She was known with an acute myelogenous leukemia two years earlier that had relapsed recently, for which she underwent a second allogenic stem cell transplantation with prolonged neutropenia, high dose corticosteroid and cyclosporine therapy. One week after ICU admission she deteriorated with a fever and an increase in infection parameters. Chest radiography revealed no evident abnormalities besides some bilateral atelectasis. Bronchoscopy with bronchoalveolar lavage was performed showing a positive galactomannan antigen (8.82) for which voriconazol therapy was started. In the following days she further deteriorated with galactomannan antigen detected in serum (1.06) and amphotericine B was added to the treatment. Sputum cultures showed *Aspergillus spp.* once one week earlier.

On the 20th day of admission chest radiography showed the typical appearance of a pneumopericardium which was confirmed by HRCT (fig.1), that now also revealed aspergillomas in the lower left and right middle pulmonary lobe, with the suspicion of a fistula to the pericardium. Despite double anti-fungal therapy during 5 days there was progression of the IPA with further deterioration of the patient's clinical condition. After consultation of the cardiothoracic surgeon it was concluded that there were no therapeutical options for this patient. She died after treatment was discontinued. Autopsy confirmed pneumopericardium with purulent effusion and a fistula of the aspergilloma in the right middle pulmonary lobe to the pericardium(fig.2). Postmortem cultures from pericardial effusion revealed *Aspergillus fumigatus*.

Discussion and conclusion: Our patient developed IPA after a second allogenic stem cell transplantation for a relapsed acute myelogenous leukemia. She developed the rare complication of pneumopericardium and pericarditis and died after treatment was discontinued. To our knowledge only 8 cases have been reported describing pneumopericardium as a complication of IPA. In contrast to these cases, diagnosis of IPA in our patient was based on galactomannan immuno-assay, initially without radiologic abnormalities suspect for aspergillomas.

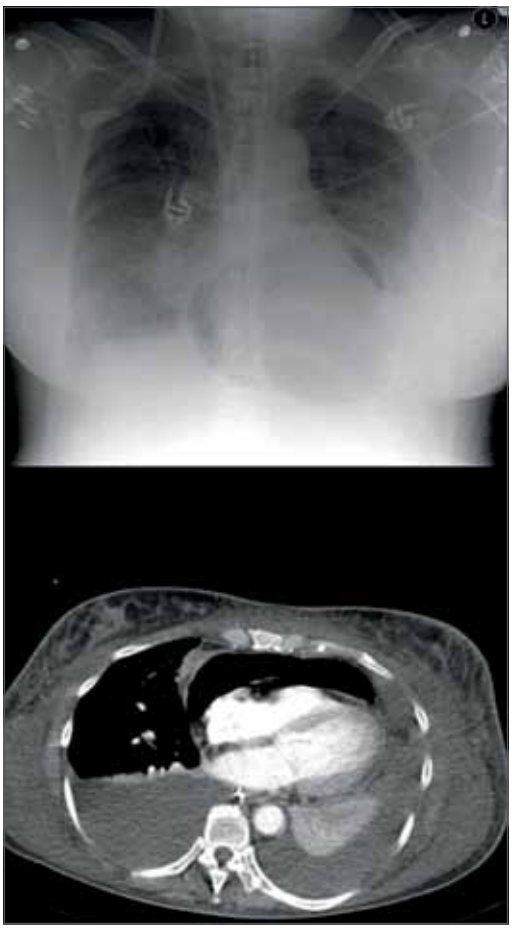

Figure.1. Chest radiography showing the typical appearance of pneumopericardium that was confirmed by high resolution CT.

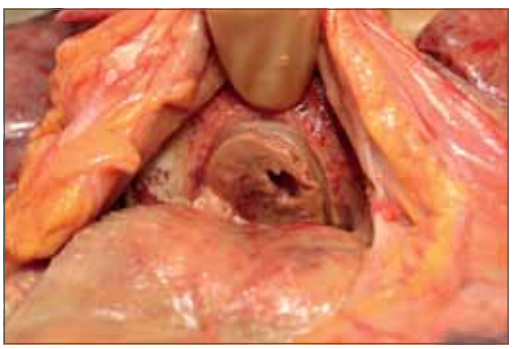

Figure.2. A fistula of the aspergilloma in the right middle pulmonary lobe to the pericardium was seen at autopsy.

5.

Extensive panniculitis mimicking necrotizing fasciitis

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Introduction: Panniculitis refers to a broad spectrum of diseases that involve inflammation of the subcutaneous fat with variable clinical presentation. This ambiguity makes it difficult to determine its frequency. We report a patient presenting with a severe and extensive form of panniculitis. Initially the clinical presentation was interpreted as related to an infectious problem.

Case: A 53 year old female with known diabetes type 2 who, in the past 4 months, was repeatedly hospitalized with a clinical presentation of recurrent infections in all extremities. She was treated with antibiotics empirically as well as based on one Staphylococcus Aureus positive blood culture one month before admission. The patient underwent surgical exploration of abscesses in her left upper leg and right wrist and was admitted postoperatively on our intensive care unit with a tentative diagnosis of necrotizing fasciitis. During admittance the clinical symptoms associated with fulminant fasciitis did not develop. Because of suspected osteomyelitis (a possible source of infection) of her right foot radiographically, amputation of the right 4th and 5th metatarsal was performed in conjunction with exploration of the progressive abscess formation in her right leg (See figure 1). At surgery softened subcutaneous tissue was seen with intact fascia. Hence, necrotizing fasciitis was regarded as unlikely. Multiple investigations did not reveal a specific source of a spreading infection. Moreover, blood and pus cultures as well as a PCR on microbial content remained negative. In an ultimate attempt find a possible source of infection a PET-CT was performed showing extensive FDG uptake between the subcutaneous and muscular layers of thorax, shoulders, upper legs and right buttock, associated with inflammation (See figure 2). Pathological examination of a deep surgical skin biopsy revealed a predominantly lobular panniculitis. (figure 3). The patient was treated with high dose methylprednisolone on which she clinically improved and could soon be discharged from the intensive care for further recovery and wound management.

Discussion: Our patient, first suspected of having recurrent infections, was finally diagnosed as a systemic predominantly lobular panniculitis. The specific cause of the panniculitis remained unknown. The differential diagnosis of a lobular panniculitis is broad and the different entities are difficult to separate morphologically. Because of the extensive plasma cell invasion of the tissue a lupus panniculitis was considered. However, autoimmune serology was negative. Other potential causes are an alpha-1-antitrypsin deficiency as well as a subcutaneous t-cell lymphoma of which the latter could not be found. Finally, a collective name for lobular panniculitis with a yet undefined cause exists[1]: Weber-Christian panniculitis.

Conclusion: An autoimmune process should be considered in patients who do not respond normally to treatment of a suspected infectious process. Early recognition of an autoimmune process could reduce morbidity and mortality.

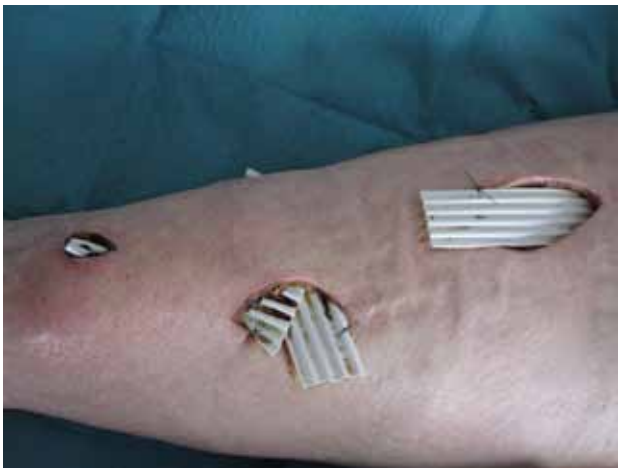

Figure 1. Right upper leg. Exploration revealed subcutaneous pus over the complete lateral and cranial side of the fascia lata. Fascia itself was intact. Drains keep the wound open as to ensure drainage.

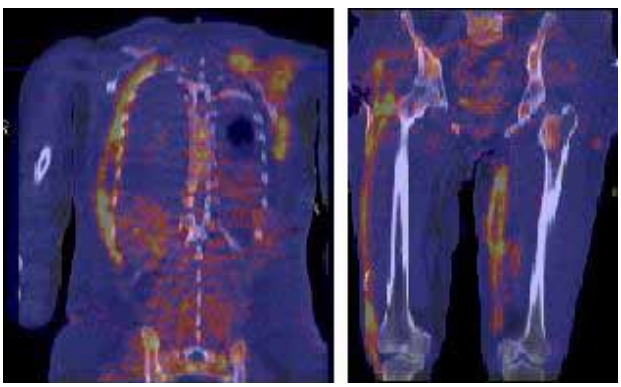

Figure 2. Image from PET-CT scan showing extensive FDG uptake between the subcutaneous and muscular layers of thorax, shoulders, upper legs and right buttock.

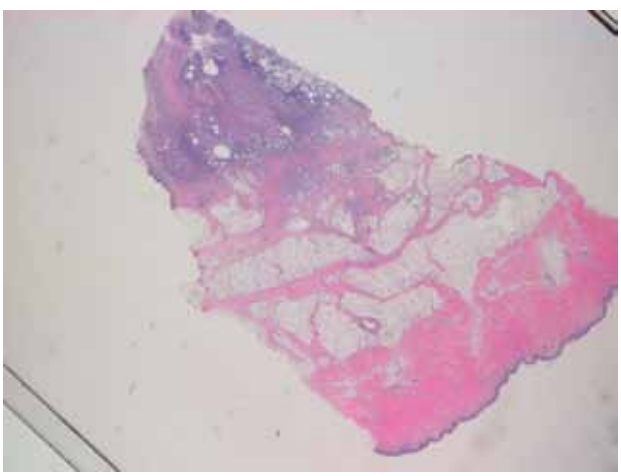

Figure 3. Low power view of the deep skin biopsy revealing predominantly lobular panniculitis (upper left area).

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6.

Auto-resuscitation in a patient with severe brain injury

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In the procedure of non-heart beating organ donation (NHB), the patient is brought to the operating theatre for organ retrieval shortly after dying. Auto-resuscitation, a situation defined as an unassisted return of spontaneous circulation after cardiac arrest, has been described. This occurs mainly after cardiac arrest due to cardiac causes. We describe a case of auto-resuscitation after severe brain trauma.

A male patient, 23 years old, who committed a Tentamen Suicidii by jumping of a 3 floor high building was intubated on the street and presented at the Emergency Room.

His GCS was E1M5V2. Pupillary reflexes were intact, corneal reflexes were absent. Other injuries were lung contusions with haemato-pneumothorax. Chest tubes were placed. For haemodynamic instability vasopressive drugs were used. CT-scan of the head showed many fractures and a traumatic subdural haematoma with a 14 mm midline shift. Prognosis was considered very poor, but patient was transferred to the ICU. As all organs were severely damaged, organ donation could not be executed and treatment was withdrawn after visits from family and friends. The oral-pharyngeal tube was removed and all supportive care was stopped. After electrical and mechanical asystole for several minutes, death was confirmed and communicated to the family. Then, surprisingly, after approximately 1 minute circulatory and respiratory functions came back, although breathing remained insufficiently with low oxygen saturations. Patient died 45 minutes later.

This phenomenon of 'auto-resuscitation' (AR) or 'Lazarus phenomenon' might be a problem in NHB organ donation procedures. Internationally, the "stand-off time" period, after which rapid cannulation, perfusion and cooling takes place to reduce warm ischemic time, varies between 75 seconds and 10 minutes.

ICU doctors who are involved in NHB procedures should be aware of the phenomenon of auto-resuscitation and take enough time to confirm death with certainty. Experts in this field should be consulted on how it affects the organ donation procedure itself.

7.

Renal artery stenosis; a classic presentation, a rare cause…

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The classic symptoms of a bilateral severe renal artery stenosis are usually refractory hypertension, chronic kidney failure and sometimes "flash" pulmonary oedema. The stenosis of the renal arteries causes reduction in renal perfusion, resulting in volume expansion due to reduced diuresis. There is also an increased renin release from the under perfused kidney. Whether treatment of RAS is beneficial for improvement of renal function remains controversial. In the general population, RAS is mostly caused by atherosclerosis or fibromuscular dysplasia.

In this case report, a patient is described with an unusual cause of renal artery stenosis. The patient presented at the intensive care unit with acute anuric renal failure and hypertensive urgency, following a nephrectomy, which was complicated by massive blood loss. Because the acute renal failure was first presumed to be due to acute tubular necrosis, the diagnosis of a nearly complete iatrogenic RAS was not made until six weeks after surgery. The stenosis was caused by five misplaced surgical clips on the artery of the remaining kidney. The hypertension was initially treated with angiotensin-converting-enzyme inhibition. Eight weeks after the initial surgery, a successful revascularization procedure was performed, leading to recovery of kidney function.

8.

A case of fast deteriorating paraneoplastic limbic encephalitis in the Intensive Care

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Introduction: Limbic encephalitis is a rare paraneoplastic disorder characterized by subacute cognitive dysfunction with severe memory impairment, seizures and psychiatric features including depression, anxiety and hallucinations. The diagnosis is difficult, clinical markers are often lacking and symptoms usually precede the diagnosis of cancer.

We report a unique case of limbic encephalitis characterized by a very fast clinical deterioration.

Case Report: A 68-year old woman was admitted to our hospital because of altered consciousness, collapse, anxiety and memory loss. She had a smoking history of 50 pack-years. Culture and PCR of cerebrospinal fluid showed no bacterial or viral infection. EEG revealed an asymmetrical focal abnormality of the temporal cortex right more than left, in accordance with encephalitis. Because of clinical deterioration a brain MRI was performed. The MRI revealed high intensity signaling in both temporal lobes, particularly on fluid attenuated inversion recovery.

On day 12 she was admitted to the ICU because of respiratory insufficiency and coma, with a Glasgow Come Score of 3. Laboratory evaluation showed Anti-Hu 1:3200, (reference < 400). On suspicion of a malignancy a CT-thorax/abdomen was performed, which revealed mediastinal lymphadenopathy without a primary tumor.

Her neurological state deteriorated, causing need for mandatory ventilation. Because of the fast deterioration with a Rankin scale score of 5, age > 60 years, and the absence of a detectable tumor, a good functional outcome was not expected. Treatment was stopped and patient died within minutes.

Autopsy revealed mediastinal metastasis of a small-cell lung carcinoma without detectable lung tumour. The brain autopsy showed inflammatory changes in the mediotemporale cortex including hippocampus on both sights, typical of limbic encephalitis.

Discussion and conclusion: Limbic encephalitis is a neurological disorder that is not caused by tumor or its metastases. It is often associated with anti-Hu antibodies and small-cell lung carcinoma. Anti-Hu antibodies not only react with neuronal nuclei, but also with Hu-antigens expressed in the associated tumor, suggesting that these disorders are caused by an immune response directed against ectopically expressed neuronal antigens in the tumor that subsequently cross reacts with similar antigens in the nervous system. Often the tumor is diagnosed after the onset of neurological symptoms with a median interval of 3.5 months[1].

Anti-tumor treatment appears to halt the process and may leave patients in a less disabled condition, whereas immunotherapy is largely ineffective. Four factors that are independently associated with mortality: age > 60 years, Rankin scale score at diagnose > 3, more than one area of the nervous system involved and absence of treatment[2]. The functional outcome overall is poor[1,2]. Early diagnose and treatment is mandatory to improve outcome in these patients.

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9.

An unusual cause of intestinal ischemia

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Introduction: Intestinal ischemia is often seen in the ICU, mostly caused by hypoperfusion in combination with atherosclerosis, thrombosis or embolism. We describe a patient who presented with intestinal ischemia due to a more unusual cause: polyarteritis nodosa (PAN).

Case Report: A 59-year old lady, with an extensive medical history including hysterectomy, adhesiolysis, M.Sjogren and non-Hodgkin Lymphoma and recently unexplained abdominal complaints, was admitted to our ICU because of respiratory distress caused by bilateral pleural fluid. She was intubated and ventilated and pleural fluid was removed and analysed. Results showed a transudate and neither signs of infection nor malignancy. A laparotomy was performed because of ongoing abdominal pain, hemodynamic instability and suspected ileus. It showed intestinal ischemia requiring right hemicolectomy and resection of 1,5 meter small intestine. Cultures were taken and antibiotics were prescribed. Three days after surgery the digits of her right hand and left foot became ischemic. Antiphospholipid-syndrome and an embolic event from a cardiac source were both excluded. Cultures stayed negative. Viral serology for hepatitis B, C and HIV came back negative.

Re-evaluation of the bowel-segments by the pathologist revealed necrotizing vasculitis. In combination with her medical history, the signs and symptoms, this was conclusive for PAN. Several days after surgery she developed renal insufficiency and renal replacement therapy was initiated. Ultrasonography showed no urinary tract obstruction. The CT-scan showed multiple small lesions in the cortex of both kidneys, presumably infarctions. Pulse high dose methylprednisolone (1000mg/day) was started and tapered and cyclophosphamide was given. Further intestinal ischemia did not occur after therapy was initiated, renal function recovered after a period of renal replacement therapy and the digital necrosis did not expand and was treated conservatively until auto-amputation occurred. The pleural transudate was likely caused by PAN, cultures and pathology were negative.

Discussion: PAN is a systemic necrotizing vasculitis that affects medium-sized muscular arteries. Patients typically present with systemic symptoms: fatigue, weight loss and fever. The kidneys (renal failure and hypertension), skin, joints, muscles, nerves and gastrointestinal tract are commonly involved. Lungs are often spared. Treatment consists of steroids combined with a cytotoxic agent. PAN is a clinical diagnosis, which should be confirmed by tissue biopsy. The classification criteria of the American College of Rheumatology were not intended to be diagnostic tools, but have nevertheless been widely adopted as such. An international study is now conducted to develop a revised classification system and a validated set of diagnostic criteria [1].

In conclusion: intestinal ischemia caused by vasculitis is rare, but should be thought of, especially when other symptoms could point to a systemic vasculitis.

Classification criteria Polyarteritis Nodosa[1] (American College of Rheumatology)
Weight loss > 4 kg
Livedo reticularis
Testicular pain
Myalgia or weakness
Mono- or polyneuropathy
New onset hypertension
Renal dysfunction (BUN >14 mmol/l, Creatinin>132umol/l)
Hepatitis B infection
Characteristic arteriographic abnormalities
Biopsy of small or medium-sized artery containing polymorphonuclear cells

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10.

Peripheral Veno-Arterial Extracorporeal Life Support Despite Impending Left Ventricular Thrombosis
A Bridge To Resolution

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Left ventricular (LV) thrombosis is a feared complication of veno-arterial extracorporeal life support (VA-ELS). During VA-ELS, progressive intracavitary thrombus formation may be inevitable despite anticoagulation in the virtual absence of contractility and blood flow. Therefore, large LV thrombi are considered a relative contraindication for VA-ELS.

A 50-year old male without any medical history, presented with acute cardiogenic shock necessitating mechanical ventilation, and being refractory to intra-aortic balloon pump (IABP) and catecholamines. Electrocardiography was non-diagnostic, coronary artery disease was excluded by angiography and myocardial biopsy showed no active myocarditis. Echocardiography demonstrated multiple large LV thrombi and severe hypokinesia (Figure). Upon further deterioration, peripheral VA-ELS was initiated. Cardiac contractility improved gradually (Figure) and successful weaning from catecholamines, IABP, VA-ELS and ventilation was achieved within 12 days. LV thrombus resolution occurred under therapeutic anticoagulation and inodilators within 15 days (Figure); hospital discharge on day 37.

In advanced heart failure, LV thrombi are reported as highly prevalent (11-44%). Adhering to current contraindications, VA-ELS might thus be withheld in a considerable number of patients.

Yet, the favourable outcome reported here, challenges current VA-ELS contraindications. It is well recognized, that VA-ELS reduces preload and increases afterload, compromising LV contractility and blood flow. Thus, it is of utmost importance to ensure aortic valve opening in order to avoid progressive LV thrombosis. However, despite anticoagulation and inotropes, the LV might remain akinetic for days ultimately resulting in refractory LV thrombosis.

In our patient, we sought to avoid impending LV thrombosis despite virtual LV akinesia and aortic valve standstill upon initiation of VA-ELS. Therefore, we combined VA-ELS with IABP resulting in aortic valve opening. In addition, native LV output was optimized by reducing VA-ELS to acceptable levels in conjunction with inodilators monitored by serial echocardiography (Figure). Minimum requirements of LV contractility and flow for prevention and resolution of LV thrombi during VA-ELS have yet to be determined.

This case illustrates that the presence of large LV thrombi may not be a contraindication for VA-ELS. We show, that combined VA-ELS/ IABP support allows resolution of LV thrombus even in a virtually akinetic LV. Thus, in the emergency setting, it seems appropriate to consider combined support despite a seemingly impending LV thrombosis.

Conclusion: In severe refractory cardiogenic shock, VA-ELS should be considered even in the presence of multiple intracavitary thrombi and impending LV thrombosis. We illustrate, that adjunctive IABP support establishes LV ejection during VA-ELS, promoting LV thrombus resolution.

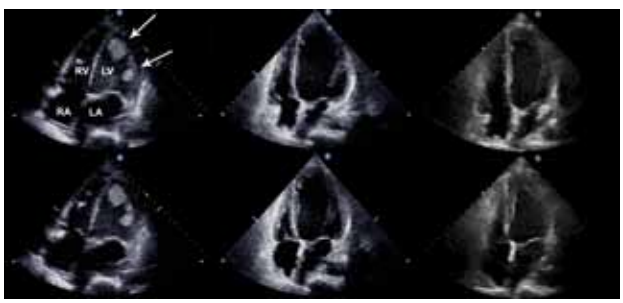

Figure. Serial transthoracic echocardiograms (right atrium, RA; left atrium, LA; right ventricle, RV, left ventricle LV), during diastole (top) and systole (bottom) on presentation (left, LV ejection fraction (EF) 5%), after 29 days (mid, LV EF 27%) and 4 months (right, LV EF 45%). Please note large LV thrombi (arrows).

11.

CMV Colitis in a critically ill immunocompetent patient in the ICU

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Context: Cytomegalovirus (CMV) can present with severe manifestations that are associated with significant morbidity and mortatily, especially in immunocompromised patients. CMV infections in immunocompetent patients are usually transient and do no show many symptoms. The seroprevalence varies in different geographical areas and it ranges from 30-100%.

We present a CMV colitis in a immunocompetent male patient who was critically ill due to severe biliary pancreatitis. The aim of this abstract is to gain more attention and focus on CMV infection in immunocompetent patients, to recognize risk factors for CMV infection in high suspicion patients.

Case outline: A 72 year old man was admitted to the ICU of Albert Schweitzer Hospital because of acute biliary pancreatitis. His medical history included rheuma/atritis psoriatica, coronary arterial bypass graft (CABG), diabetes mellitus and a gastric ulcer.

Due to respiratoir failure he got intubated and put on ventilation troughout his stay at the ICU. Immediately he developed multi-organ failure (pulmones, renal, cardiovascular, intestines) which restored over a few weeks. He developed sepsis without focus which was treated empirical. Multiple times he received blood transfusion. Later on several large amounts of ascites compromised his ventilation, which was released with abdominal drains without growth of micro-organism. An intercurrent clostridium diarrhea was treated. Because of persistent intestinal problems and diarrea a colonoscopy was performed suggestive of ischemia. Biopsy and PCR confirmed a CMV colitis after 7 days. Ganciclovir was given without clear improvement. HIV-test was negative. He developed a SIRS which was followed by another septic shock with multi-organ failure. Treatment was stopped after 56 days.

Assessment of problem: Diagnosis of CMV infection in critically ill immunocompetent patient has no uniform guidelines. The major therapeutic strategies used by clinicians are prophylactic or preemptive therapy. The first step is to start the therapy universally (prophylactic therapy) and the next is to give antivarals to specific high-risk patients (preemptive therapy). The basic principle of preemptive therapy is to initiate antivirals for patients displaying viremia early in the clinical course to halt the progression to end organ disease. The problem of antivirals is that it comes with adverse effects such as bone marrow suppression.

Discussion: In this case and in general the diagnosis of CMV infection causes delay which can be catastrophal. Endoscopic findings or of CMV infections can resemble other common conditions (ischemia). Therefore, a high index of suspicion is important, and adequate biopsies and serological studies are vital for early diagnosis.

Targeting antivirals in all critically ill patients in the ICU might be impractical as these antiviral frequently have bone marrow suppression. The clinicians should thus be aware of the possibility of CMV reaction

in otherwise immunocompetent patients admitted in the ICU who have risk factors such as positive CMV serology, (long) mechanical ventilation, severe sepsis, or blood transfusion, (patient had 3). Preemptive treatment was the right one in this case.
Main lesson: Recognition of risk factors: positive CMV serology, (long) mechanical ventilation, severe sepsis, or blood transfusion which need to be treated with preemptive therapy, especially in symptomatic immunocompetent patients.

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12.

Thromboelastometry (ROTEM) guidance for titration of recombinant factor VIIa in acquired hemophilia A.

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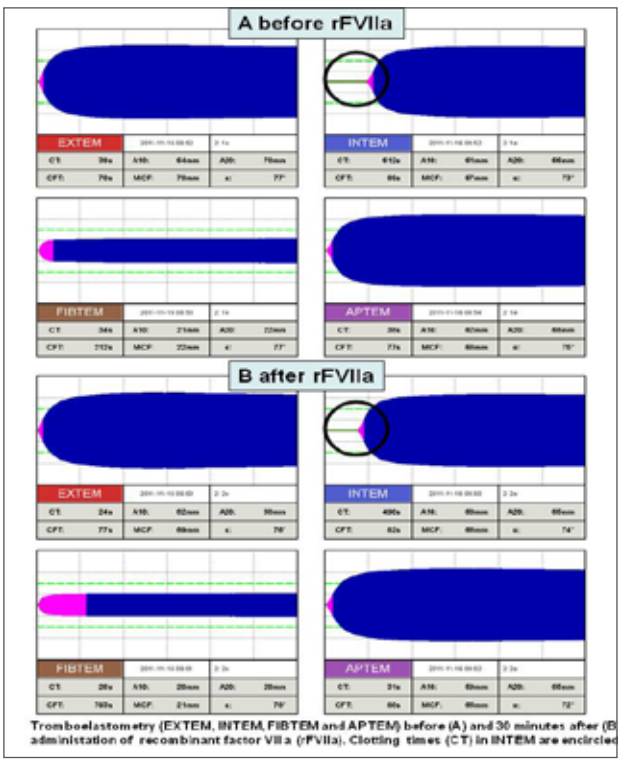
A 62-year-old man was admitted to the ICU with excessive bleeding after fasciotomy of the right forearm due to a compartment syndrome after coronary angiography via the radial artery. Bleeding persisted in the absence of surgical bleeding and despite treatment with a high amount of bloodproducts, local hemostatics and tranexaminic acid, the patient remained bleeding. Laboratory analysis revealed an isolated prolonged aPTT and a high FVIII inhibitor titer (>300 Bethesda units (BU)) according to a severe idiopathic acquired hemophilia A. Treatment was initiated with recombinant factor VIIa (rFVIIa) 90 mcg/kg i.v. twice daily. Later immunosuppression with prednisolon/rituximab was added. In the standard laboratory measurements the isolated prolonged aPTT dropped to 65 seconds hereupon. To avoid complications due to over- or under dosage of rFVIIa we performed thromboelastometry analyses before and 30 minutes after administration. As expected EXTEM, APTEM and FIBTEM were normal. The INTEM-assays revealed a clear reduction in clotting times from 574 - 612 to 440 - 490 seconds, still remaining above normal values (100-240 sec) without clinical signs of bleeding. With immunosuppressive therapy FVIII inhibitor titer dropped to 18 BU and FVIII increased to 29%. After two months the patient was discharged from the hospital in a good clinical condition.

Conclusion: In acquired hemophilia A thromboelastometry seems a useful monitoring-tool for titration of rFVIIa-therapy in excessive bleeding.



Tromboelastometry (EXTEM, INTEM, FIBTEM and APTEM) before (A) and 30 minutes after (B) administation of recombinant factor VIIa (rFVIIa). Clotting times (CT) in INTEM are encircled

13.

An atypical PR3-ANCA-positive vasculitis

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Introduction: Systemic necrotizing vasculitides can cause life-threatening conditions that require patients to be admitted to intensive care (IC). Early and accurate diagnosis of these conditions is vital so that appropriate treatment can be started promptly. Vasculitides are traditionally classified according to the size of the vessels affected (Fig. 1). The presence of anti-neutrophil cytoplasmic antibodies (ANCA) is associated with small vessel vasculitides. Proteinase 3 (PR3 or cytoplasmic (c))-ANCA is a biomarker for Wegener's granulomatosis. Clinical presentation and identification of the organs affected are also used to diagnose specific vasculitides. We present a patient with a PR3-ANCA-positive vasculitis that could not be diagnosed using the current classification system.
Case: A 70-year-old male was hospitalized after suffering from fever and chills for more than a week. His medical history revealed an aneurysm of the middle cerebral artery that was clipped 25 years ago. The patient complained of muscle pain and cramps. A physical examination detected no abnormalities. Laboratory tests showed an increased level of C-reactive protein (249 mg/L; normal < 5 mg/L), slightly elevated levels of liver enzymes, and normal kidney function. The results of a chest X-ray and urine analysis were normal. Several days later, the patient developed a peripheral neuropathy of the nervus medianus of both hands. Arthritis of the left wrist was diagnosed and puncture of the joint showed no abnormalities. Broad-spectrum antibiotics were administered intravenously; however, fever persisted. Eight days after hospitalization, the patient developed a right hemiparesis with loss of consciousness. A CT scan revealed multiple cerebral infarctions in the brain. Transesophageal echocardiography did not detect endocarditis. Cerebralspinal fluid analysis was normal. The patient had variable Glasgow Coma Scores and so was transferred to IC. The patient's neurological condition deteriorated and he was intubated and ventilated. Total body PET-CT revealed multiple cerebral infarctions and pronounced inflammation of the ascending and arcus aortae (Fig. 2). Urine analysis was repeated and detected dysmorphic erythrocytes (25%) and an elevated level of microalbuminuria (3.3 mg/mL; normal < 2.5 mg/mL). Plasma creatinine levels were normal. The PR3-ANCA titer was elevated (234 U/mL; normal < 6 U/mL). A conventional abdominal angiography showed arterial aneurysms in the liver and the left kidney. The common hepatic artery was stenotic. All bacterial cultures were negative. An atypical PR3-ANCA-positive vasculitis affecting large, medium and small-sized vessels was diagnosed, and treatment with high dosages of

methylprednisolone and cyclophosphamide was started. The patient's neurological condition gradually improved and he was weaned off the ventilator.

Discussion. We report a case of a PR3-ANCA-positive vasculitis with aortitis; aneurysms of medium-sized arteries in the liver, brain and kidney; and an active urinary sediment. This vasculitis could not be diagnosed using the current classification system, as vessels of various sizes were affected. It is unclear whether this case represents a new disease, an overlap syndrome, or an ANCA-associated vasculitis with an atypical presentation. ANCA-positive vasculitis in which large- and medium-sized vessels are affected may simply reflect the full spectrum of ANCA-associated vasculitides[1].

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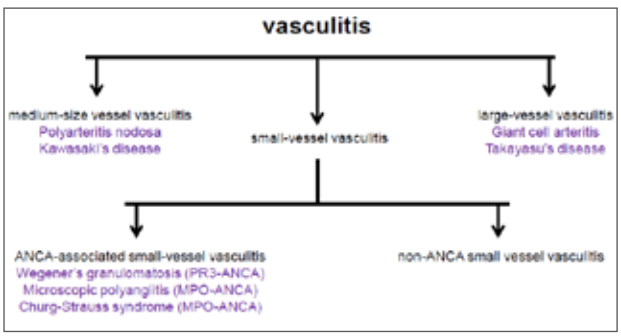

Figure 1. Current classification according to vessel size. ANCA = antineutrophil cytoplasmic antibodies; PR3 = proteinase 3; MPO = myeloperoxidase.

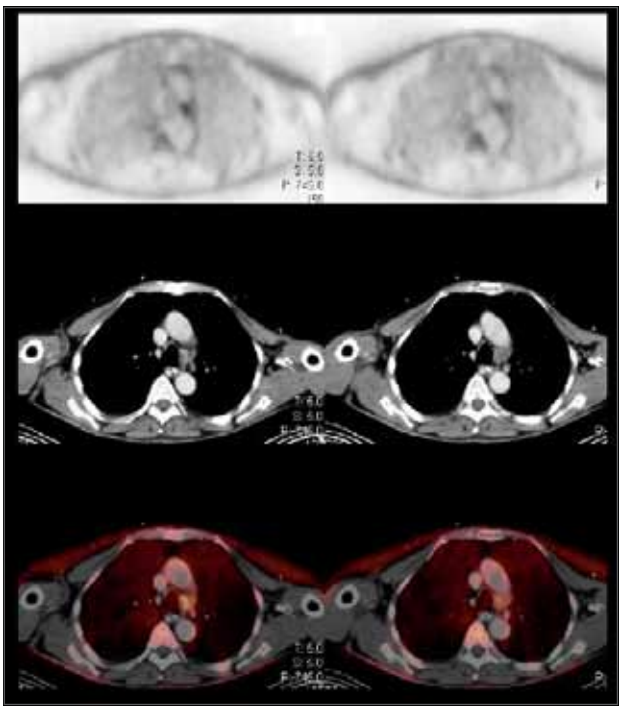

Figure 2. PET-CT: increased uptake of 18-fluoredeoxyglucose of the ascending and arcus aortae.

14.

A male adolescent with sudden cyanosis

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Introduction: Acquired methemoglobinemia (metHb) above 30% can cause a life threatening situation because the reduced oxygen delivery to tissues induces multiple organ dysfunction (MODS) and even death[1]. We present a case of an asymptomatic patient with an acquired metHb of 70%.

Case: A 19 year-old male was admitted to our emergency department with sudden and progressive cyanosis. His medical history revealed recurrent urinary tract infections caused by vesicourethral reflux, depression and a suicide attempt 4 years ago.

At presentation patient had no complaints. The cyanosis had appeared suddenly and existed for a couple of hours. The patient could not remember doing something different than usual. Physical examination revealed no abnormalities apart from severe cyanosis. Arterial haemoglobin saturation (SaO_2), measured with a pulse oximeter, was 99% while given 100% oxygen through a non-rebreather mask. A blood sample had a chocolate brown colour. Laboratory tests showed a PaO_2 of 240 mmHg, a SaO_2 of 95%, a metHb of 70% and a lactate level of 7.1 mmol/L (Table 1). The results of a chest X-ray and electrocardiogram were normal. An intoxication was suspected and after confronting the patient he admitted to have taken nitrite granules in an attempt to commit suicide. He did not have a clear recollection of either the time of ingestion nor the amount ingested. However he stated that about 3-4 hours prior to admission he ingested the nitrites.

Patient was admitted to the Intensive Care and treatment with 100% oxygen was continued. Gradually the metHb levels and cyanosis decreased. Patient remained in a good clinical condition and developed no signs of MODS. About 17-18 hours after nitrite ingestion metHb and lactate levels normalized (Table 1).

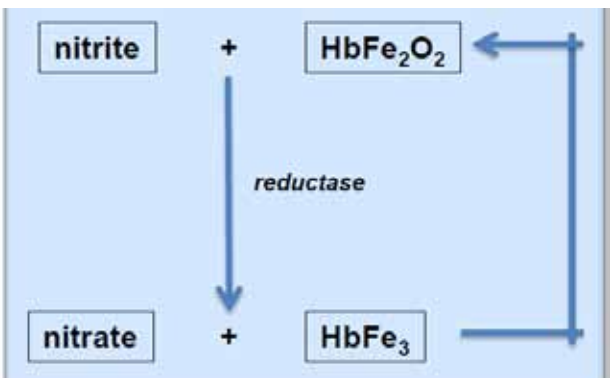

Figure 1. Ingested nitrite reacts with oxygenated hemoglobin (HbFe2O2) to form nitrate and methemoglobin (HbFe3).

Discussion: We report a patient with a severe metHb of 70%, caused by ingestion of nitrite granules, who remained asymptomatic and developed no signs of MODS.

Acquired metHb must be suspected in patients with a clinical apparent cyanosis and normal SaO_2 with pulse oximetry. Ingested nitrite reacts with oxygenated haemoglobin to produce nitrate and metHb in a reversible process (Fig 1). The excessive produced metHb is unable to bind oxygen and causes ischaemic organ dysfunction. A metHb above 30% is known to be a severe and life threatening condition due to ischaemic organ failure.

Treatment of metHb depends upon the clinical setting. It is advised to start treatment with 100% oxygen together with infusion of methylene blue (MB) if metHb is above 30% and the patient is symptomatic. In our patient we decided not to start treatment with MB, despite the severe cyanosis and a metHb of 70%, because the patient was still asymptomatic 3-4 hours after ingestion and the Tmax of nitrite had already passed. It is remarkable that our patient developed no signs of ischaemic organ dysfunction, even laboratory tests remained perfectly normal (Table 1). Therefore, in asymptomatic patients with severe acquired metHb, a treatment policy of wait and see, apart from 100% oxygen, seems safe if the pharmacokinetics of the ingested toxin is known.

References:

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	admission	after 14 hours	reference
pH	7.33	7.40	7.35 – 7.45
pCO_2	39	47	35 – 40 mmHg
pO_2	240	271	75 – 100 mmHg
bicarbonate	21	29	23 – 30 mmol/L
saturation	95	99	90 – 100 %
MetHb	70	2.7	0.0 – 5.0 %
lactate	7.1	0.9	< 2.0 mmol/L
hemoglobin	8.9		8.5 – 11 mmol/L
leucocytes	22.7		4 – 10 10^9/L
platelets	232		150 – 400 10^9/L
creatinin	121	87	60 – 110 umol/L
ASAT	18	17	0 – 35 U/L
ALAT	20	16	0 – 45 U/L
LDH		162	0 – 248 U/L
AF	78	66	0 – 120 U/L
γGT	26	24	0 – 55 U/L
amylase		46	0 – 100 U/L
CK	151	152	0 – 171 U/L
glucose	9.5	6.4	3.5 – 5.6 mmol/L
PTT	11		11 – 13 sec
APTT	33		24 – 35 sec

Table 1. Laboratory tests at admission (3-4 hours after ingestion of nitrite) and 14 hours after admission.

15.

Autopsy of a patient suffering from alcoholism and severe self-neglect

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Introduction: Alcohol abuse causes a wide spectrum of medical, psychiatric and social problems. Over time, patients often deteriorate and can develop liver cirrhosis, pancreatitis, polyneuropathy, cardiomyopathy, and nutritional deficiencies. Patients may also suffer from cognitive impairment, depression, social isolation, self-neglect, and cachexia.

Case: A 62 year-old male was hospitalized suffering from hemodynamic instability. His medical history revealed excessive smoking and chronic alcohol abuse for over 20 years, depression, recurrent pancreatitis and severe self-neglect. A year before his hospitalization, the patient was found at home lying in his own urine and stools and in a generally poor condition. He was admitted to intensive care (IC) suffering from mycoplasma pneumonia. After several months he was readmitted to hospital with acute kidney injury caused by dehydration, malnutrition and chronic diarrhoea. It was not deemed necessary to perform a chest X-ray. The patient was rehydrated and the kidney injury resolved. Psychiatric attendants felt the patient's home situation had become unsustainable because of the level of self-neglect. However, since the patient refused to be admitted to a nursing home, he was sent home with extra homecare and access to psychiatric help.

The patient was readmitted to our IC four months later, and complained of progressive weight loss, general weakness, shortness of breath and fatigue. He had not drunk alcohol for a year. The patient was suffering from severe self-neglect and cachexia. Severe shock and respiratory distress were diagnosed. Laboratory tests showed moderate signs of infection, lactic acidosis, kidney injury and increased levels of liver enzymes. A chest X-ray showed consolidations of the right lung with pleural effusion (Fig 1). The patient was suspected to be suffering from septic shock caused by pneumonia, and treatment with antibiotics, steroids and vitamins was begun. The patient was intubated and ventilated, and resuscitation with fluids, dobutamine and noradrenaline was started. However, anuria persisted and the patient's lactate level increased to 12.3 mmol/L. Drainage of the right pleural effusion had no clinical effect. A CT scan showed extensive pericardial effusion, consolidation of the right lower lobe (RLL) with pleural effusion, and an arterial embolus in the RLL. The haemorrhagic pericardial effusion (1200 mL) was drained, and the patient's lactate level began to decrease. However, a few hours later the patient developed atrial fibrillation with conversion to sinus bradycardia without output. The patient died within 26 hours of hospitalization. An autopsy showed pronounced end-stage metastatic disease characterised by; primary adenocarcinoma in the right upper lobe; metastases in both lungs, pleural cavity, lymph nodes, pericardium, myocardium, liver, adrenal glands; and generalized tumour emboli.

Discussion: When a patient suffering from alcoholism and severe self-neglect exhibits signs of cachexia, it can be presumed that the cause is alcohol-related. However, the widespread metastatic disease in our patient must have been present for a long time. Autopsies can provide valuable information to aid physicians when diagnosing and treating patients with similar symptoms in the future. Even when the cause of a disease appears obvious, other possibilities should still be considered.

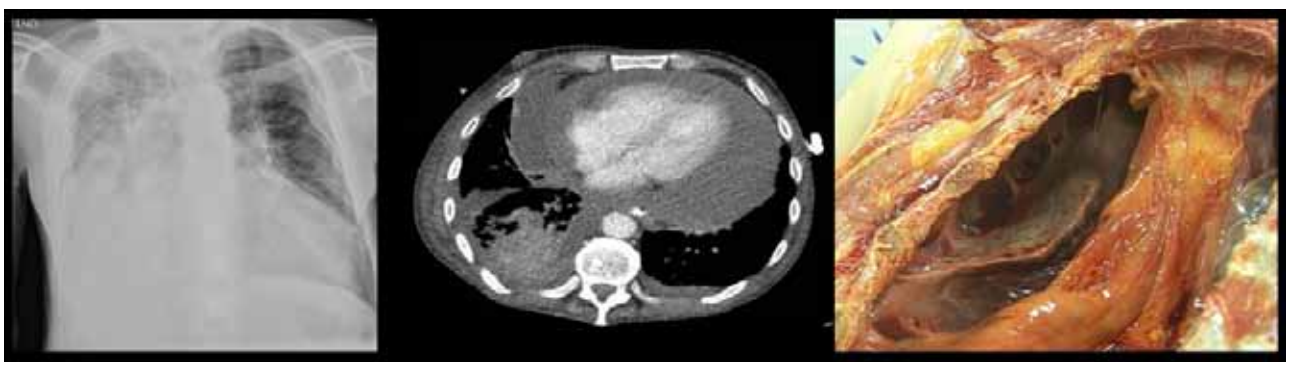

Figure 1. Chest X-ray (left), CT-scan (middle) and autopsy of the thorax (right). Chest X-ray thorax: cardiomegalia; consolidation of the right lung and pleural effusion. CT-scan: consolidation and pleural effusion of the RLL and pericardial effusion. Autopsy of the thorax with extensive pleural adhesions in the right hemithorax and consolidation of the right lung.

16.

Short and long-term dynamics of lactic acidosis in a patient treated with linezolid

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A 35-year old woman was admitted to our ICU after bilateral lung transplantation for end-stage idiopathic pulmonary hypertension. Because of right ventricular failure the patient was initially supported by veno-arterial extra corporeal life support. During the first week after ICU admission the patient underwent multiple thoracotomies to treat bleeding in the right hemithorax. One week after ICU-admission the patient developed positive blood and pleural cultures with Enterococcus faecium, This infection was treated with intravenous teicoplanin. Five weeks later the patient was still in the ICU and showed progressive lethargy. A spinal tap revealed Enterococcus faecium meningitis, and an antibiotic regimen of intravenous linezolid and intrathecal vancomycin was added to the teicoplanin. Four weeks later the patient developed a progressive, life-threatening lactic acidosis. After ruling out other causes, such as bowel ischemia, linezolid was considered the most likely cause. Discontinuation of linezolid therapy was associated with an immediate and sharp decline in lactic acid levels. Moreover, we retrospectively observed that after each of the twice daily doses of linezolid a temporary rise in lactic acid levels occurred.

Linezolid, member of the oxazolidinone antibiotics, and mainly used to threat infection with Gram-positive bacteria, blocks initiation of bacterial protein synthesis by binding to ribosomes. The most commonly reported adverse effects are gastrointestinal disturbances, thrombocytopenia and anemia. The development of lactic acidosis is almost exclusively reported in patients treated for longer periods (> 6 weeks), indicating that the cumulative dose is important. Lactic acidosis associated with prolonged linezolid treatment is caused by inhibition of mitochondrial protein synthesis. 1 2

This case report demonstrates a direct relationship between linezolid and lactic acid levels. Lactic acid levels in these patients may reach dangerous levels, probably because of progressive mitochondrial dysfunction. We hypothesize that susceptibility for developing lactic acidosis may vary between patients treated for prolonged periods with linezolid. We pledge for careful monitoring of lactic acid levels in all patients being treated with linezolid for prolonged periods.

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17.

Post-partum interstitial lung disease

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Case report: A 39 year old woman was admitted to the ICU because of respiratory distress and hypoxaemia, 5 days after delivery of a healthy daughter. The pregnancy was initiated with intra-uterine insemination (IUI), leading to a dichorionic and diamniotic twin pregnancy with a vanishing fetus after 10 weeks. She had been under close surveillance by the gynaecologist, all routine visits were unremarkable, except for a slight shortness of breath in the last weeks of the pregnancy, without fever.

Physical examination at admission revealed a dyspnoeic patient, haemodynamically stable, heart rate of 110/min, oxygen saturation of 79%, a respiratory rate of 36/min and bilateral basal crackles on auscultation. She showed no cyanosis, edema or jugular venous distension. Examination of the abdomen was normal and there was little vaginal bleeding.

Chest X-ray demonstrated a diffuse interstitial lung disease. Computed tomography scanning of the thorax showed bilateral nodules with unsharp demarcations and patchy ground-glass opacities. Pulmonary embolisms were ruled out.

Laboratory results showed a haemoglobin level of 4.8 mmol/l, thrombocytes of 127 x 10^9/l and LDH of 922 U/l, but otherwise no signs of haemolysis or extended clotting time. Renal function was normal and she did not have proteinuria.

The patient was treated with amoxicilline and ciprofloxacine for the possibility of pneumonia and non-invasive positive pressure ventilation (NPPV) for hypoxaemia. After one day high dose steroids were given considering the diagnosis of auto-immune interstitial lung disease.

Two days after admission the patient was intubated for progressive hypoxaemia and exhaustion. She had to be ventilated in prone position. Bloody secretion was removed through the tube. A bronchoscopy showed diffuse bleeding, without edema or stenoses. A bronchoalveolar lavage was performed.

At admission we had a long list of differential diagnoses, which we ruled out as quickly as possible. Post-partum cardiomyopathy was ruled out by normal NTproBNP value and normal echocardiography. There was no renal involvement, so no eclampsia. Auto-immune disease was made unlikely by negative serology.

Microbiological investigations were all negative, including bacterial culture, Ziehl-Neelsen stain and multiplex ligation-dependent probe amplification (MLPA).

The clinical condition of the patient detoriated, the indices of the mechanical ventilation worsened, and the pulmonary haemorrhage was hard to control. She was transfusion dependent, the LDH level raised quickly to 2000U/l. A diagnosis of persistent gestational trophoblastic disease was considered. The beta HCG level was 300.000 U/l, thereafter we made a diagnosis of pulmonary metastases of choriocarcinoma.

The patient was transferred to a tertiary centre, and was treated with high dose chemotherapy.

In conclusion, this case describes a 39 year old post-partum women with respiratory insufficiency based on pulmonary haemorrhage, caused by pulmonary metastases of a choriocarcinoma.

The presentation is remarkable, because of the sudden onset and severity of symptoms shortly after a full-term pregnancy. A persistent trophoblastic tumour usually develops from a mola-pregnancy, but can develop after a full-term pregnancy or miscarriage.

Choriocarcinoma usually metastasizes to the lungs, but also to brain, liver and vagina. Metastases have a high bleeding tendency, which explained the bloody secretions in the respiratory tract.

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18.

Prolonged ventilation in MERRF syndrome

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A 27 years old female was found at home unconscious with a oxygen saturation of 34% while breathing ambient air. While receiving bag mask ventilation she was transported to our hospital. At the emergency department a chest radiograph showed complete atelectasis of the left lung. The laboratory test results showed elevated C-reactive protein, liver transaminases, LDH and cardiac markers. Arterial blood gas analyses showed a combined respiratory and metabolic acidosis. The trachea of the patient was intubated, she received empirically treatment with amoxicilline/clavulanic acid and gentamicine and was transported to the ICU for mechanical ventilation. Ten years before her current admission the diagnosis of Myoclonus Epilepsy with Ragged Red Fibers (MERRF) was made.

The MERRF syndrome is caused by a mutation of mitochondrial DNA (mtDNA) causing pathological dysfunction of the respiratory chain leading to a reduced capacity for production of ATP by way of aerobic metabolism. The organs most reliant on aerobic metabolism, like the nervous system and muscles are preferentially affected, hence the name mitochondrial myoencephalopathy. The most frequent symptoms of the MERRF syndrome are myoclonia, generalized epilepsy, ataxia and muscle weakness. Because of their way of inheritance and replication the distribution of mtDNA mutations differs between cells and tissues, a phenomenon called heteroplasmy. Heteroplasmy and other factors make MERRF a condition with variable (severity of) symptoms and rate of progression, the percentage of heteroplasmy changing over time.[1]

The sputum culture showed C.Albicans and S.Aureus and the patient received treatment with amoxicilline/clavulanic acid and anidulafungine. After pulmonary and hemodynamic stabilization elevated lactic acid persisted as a consequence of mitochondrial dysfunction. Three days after admission the patient was extubated. Within hours after extubation difficulty coughing and alveolar hypoventilation occurred and the same day the trachea was re-intubated with rapid reversal of the gas exchange abnormalities. Five days after the first extubation a second attempt was made. A similar clinical picture developed and the trachea was re-intubated. The next day a tracheotomy was made. The acute respiratory failure and difficulty weaning were accounted to the progression of MERRF syndrome. A plan was made for prolonged weaning from mechanical ventilation. The patient was finally extubated four weeks after initial presentation still requiring non-invasive ventilation at night.

Presumably the acute development of respiratory failure in this young patient was provoked by a respiratory tract infection. The acute response of the patients body as well as the weaning trajectory being complicated by muscle weakness and a diminished aerobic metabolism because of mitochondrial dysfunction. Case descriptions of patients with mitochondrial dysfunction indicate the occurrence of centrally mediated hypoventilation as a third causative factor. Paroxysmal depressed ventilatory drive is described with acute respiratory failure and prolonged mechanical ventilation.[2]

This case describes the possible vulnerability for developing respiratory failure with mitochondrial myoencephalopathies. The natural progression of MERRF syndrome being unpredictable this case demonstrates the occurrence of a prolonged weaning trajectory. During ICU admission for respiratory failure the possible presence of centrally mediated hypoventilation should be taken into account in patients with MERRF syndrome.

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19.

Subarachnoid hemorrhage after Heimlich maneuver

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Introduction: The Heimlich maneuver can be performed as an emergency procedure for initial management of foreign body airway obstruction. When performed correctly it is a safe and effective procedure with minimal complications. Most common complications are rib fractures, abdominal bruises and nausea. A small variety of rare complications have been reported in literature such as traumatic abdominal or diaphragm injuries (stomach, jejunum, pancreas, spleen and acute thrombosis of an abdominal aortic aneurysm), thoracic injuries (pneumomediastinum, aortic valve cusp rupture, diaphragmatic herniation), internal carotid artery dissection and retinal detachment. We describe a patient with an acute subarachnoid hemorrhage after performing the Heimlich maneuver.

Case description: A 62-year old man choked on a piece of chicken at home. He became cyanotic and lost consciousness. The Heimlich maneuver was performed successfully by his family after which he regained consciousness. Some minutes later he reported that he was not feeling well, became unconscious again and showed abnormal extensor spasms. He recovered spontaneous, became fully conscious, but complained of nausea and bifrontal headache. He was admitted at the emergency department of a peripheral hospital. The neurologist could not find any focal neurologic deficits and the symptoms were initially considered as post-anoxic. An hour later the patient needed to be resuscitated because of ventricular tachycardia after which he regained spontaneous circulation. He did not show any neurologic reaction and pupil reactions were negative. Brain CT scanning revealed a massive subarachnoid hemorrhage with blood around the brainstem and in the 3th and 4th ventricle. No neurosurgical treatment options were identified after referral to our university medical center. Haemodynamic and respiratory instability caused by cardiac depression and/or neurogenic pulmonary edema necessitated high doses of inotropes and vasopressors, as well as high ventilator settings. The repeated CT scan showed multiple infarctions the next day. After cessation of sedation the patient still had an E1M2Vt score with negative pupil reactions. An extremely poor prognosis necessitated cessation of treatment and the patient died. Post-mortem investigation was denied.

Discussion: This patient presented with a subarachnoid hemorrhage immediately after the Heimlich maneuver was performed. To our knowledge, this has never been described in literature. Choking without any other neurologic symptoms as a presenting symptom of SAB is unlikely. Furthermore, the initial full recovery of the patient makes a SAB secondary to the Heimlich maneuver more likely.

The underlying pathophysiological mechanisms predisposing patients to a SAB after performing the Heimlich maneuver could relate to increases in high abdominal and thoracic pressure. This could have caused a sudden rise in blood pressure and consequently a rupture of a cerebral aneurysm. Previously described case reports of internal carotid artery dissection, prosthetic and native aortic valve cusp rupture (two cases) after the Heimlich maneuver refer to the same pathophysiological mechanism.

It is known that triggers that induce a sudden and short increase in blood pressure, such as vigorous physical exercise, sexual activity, smoking and Valsalva maneuver can cause an aneurysmal rupture.

20.

Helium Balloons – not always party time

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Introduction: 1.647 people died due to suicide in The Netherlands in 2011. Almost 45% died due to hanging or strangulation, almost 20% following an intoxication, 12% after jumping in front of a train and about 8% after jumping from a building1. Other methods are rare. We describe a patient, admitted to the ICU after a suicide attempt by inhalation of helium.

Case description: A 21 year-old-woman, known with a Borderline personality disorder, was found unresponsively by her parents, after she had sent them a "farewell sms". A plastic bag had been tied around her neck; the bag was connected to a helium tank. In the apartment her parents found a book containing a chapter in which suicide by inhalation of helium was described in detail.

Her parents started basic life support. When the ambulance arrived 10 minutes later the patient was circulatory stable and breathing spontaneously. The first SpO2 measured was 85%. On the emergency ward the Glascow Coma Scale was 5, which improved to 7 after flumazenil, suggesting an intoxication of benzodiazepines as well. Other intoxications were excluded.

The patient was transported to the ICU, where she was sedated, intubated and mechanical ventilation was initiated. Mild therapeutic hypothermia for neuroprotection was induced for 24 hours. After cooling and sedation were stopped, the Glasgow Coma Scale was 4. Eyes were divergent, with errant movements and there was a myoclonus of the legs. Over the next days she seemed to improve slowly, until she started having epileptic seizures on day 6. Benzodiazepines and fenytoin were started, and on day 7 propofol was started to induce burst suppression on EEG. Nevertheless epilepsia returned immediately after ceasing propofol and EEG showed activity suggestive for epilepsia and decortication. It was decided that further treatment was futile. Treatment aiming for recovery was switched to end of life care and the patient deceased soon after.

Discussion: This case report presents a patient after a suicide attempt by inhalation of helium. Helium is an odorless, colorless, tasteless, nonirritating and inert gas. Helium itself is not toxic. When used in a confined space, like a tied bag, helium replaces oxygen in the blood. The remaining blood's oxygen will be consumed rapidly after which death will occur in several minutes. Nausea, vomiting, tremors, convulsions, arrhythmias and gasping may take place. Clearly, the basic mechanism of death is asphyxia.

Suicide by inhalation of helium has recently received some attention in the media. Right to die advocates suggest it is an a human way to die, especially for the terminally ill and elderly when euthanasia is denied. Different books exist, containing detailed information about committing suicide by inhalation of helium, moreover clear instruction movies (e.g. http://www.youtube.com/watch?v=UWfWl-xJnnY), are easily accessible on the internet. This case illustrates that we should be aware that (otherwise) healthy psychiatric patients have access to these resources as well and might commit suicide in this unusual manner.

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21.

An abundance of air: Pneumatosis Intestinalis, pneumothorax, pneumomediastinum, retropneumoperitoneum and pneumoperitoneum

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Introduction: This case report outlines a patient who suddenly developed a collection of free air throughout her body.
A pneumotosis intestinalis in conjunction with a pneumoperitoneum generally needs an acute surgical laparotomy, but not in this case.

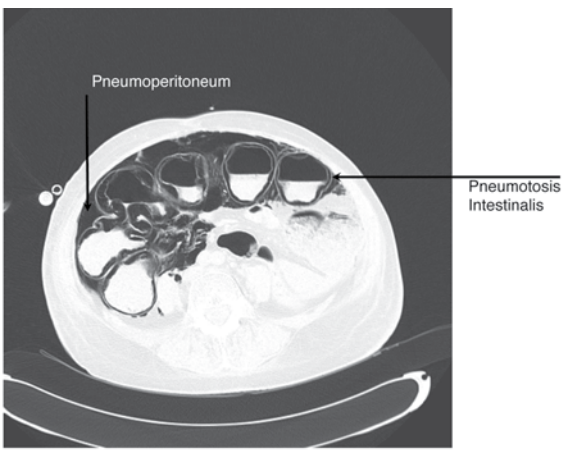
Case Report: In December 2009, a 66 year-old female patient was admitted to our hospital because of dyspnea. Her medical history included a precursor B lymphoblastic leukemia in December 2007. In July 2008, she received an allogenic stem cell transplantation after which she developed a graft-versus-host skin disease (grade 2), which resolved after treatment with prednisone.

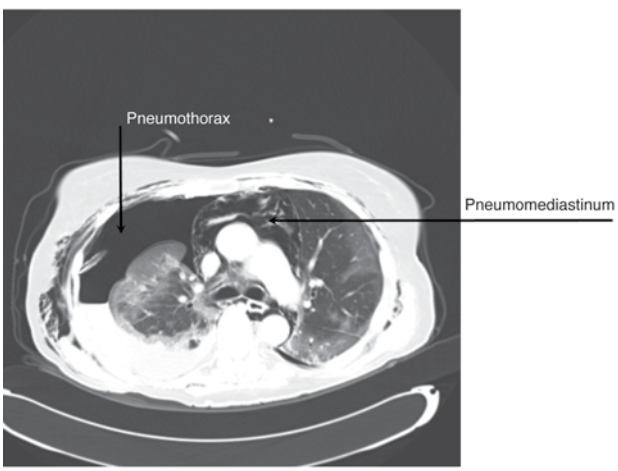
As she became progressively short of breath, a CT-scan was made which showed bilateral pulmonary infiltrates.

In order to confirm the diagnosis GVHD of the lung, an open lung biopsy was performed. Not before eleven days after surgery, the lung had finally re-expanded and the thoracic drain was clamped, after which she experienced acute dyspnea.

A chest x-ray showed a complete recollapsed lung with pneumoperitoneum. A CT scan of thorax and abdomen showed extensive subcutaneous emphysema and right sided pneumothorax, pneumomediastinum, pneumoperitoneum, retropneumoperitoneum and Pneumatosis Intestinalis of her colon (Afb. 1)

Pneumatosis Intestinalis (PI) refers to the presence of gas within the wall of the intestine.
In literature there are at least 58 causes mentioned of Pneumatosis Intestinalis, ranging from well known life threatening to lesser known non-emergency accompaniments of a number of underlying diseases[1],





caused via different although not fully understood pathophysiological mechanisms.

The patient had numerous reasons to develop PI: she underwent a stem cell transplant, with extensive graft-versus-host disease on prednisone, cyclosporine and lactoluse and she developed a pneumothorax at the end. Finally as she was on high dose prednisone the unremarkable physical abdominal exam could still be hiding a perforated bowel.

The sequelae of events however plus the appearance of retropneumoperitoneum (so called decompression pathways) suggests in this case it was her complete collapse of her right lung which led to the collection of free air throughout her body.

With this assumption we adopted a policy of watchful waiting as we couldn't fully rule out an perforated bowel.

After placing a thoracic drain her situation slowly improved.

Unfortunately despite aggressive treatment the GVHD didnt and she passed away two weeks later.

Conclusion: In this article we described a patient with an extensive pneumatosis intestinalis and pneumoperitoneum which can often lead to an exploratory laparotomy.

After reviewing all the options we concluded that the cause of this patient radiologic condition was a pneumothorax, although a pulmonary source is relatively rare.

We have shown that despite of the dramatic radiologic pictures the cause can be relatively benign.

PI is still a rare condition, but on the rise. Clinicians should be aware of the causes and pathophysiological mechanisms because a negative exploratory laparotomy could have its impact on individual morbidity and mortality, especially in the new increasing group of PI-patients: the immunocompromised.

Without deteriorating vital signs or clear peritonitis a policy of watchful waiting is strongly advised

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22.

Hyperlactatemia in Aneurysmal Subarchnoidal Hemmorhage, friend or foe?

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A previously healthy 28-year-old woman presented at our emergency department following an acute onset of severe headache and loss of consciousness. A medical team had already intubated her trachea in her home because of loss of consciousness and marked hypoxemia. At the emergency department we observed an intubated patient with pink saliva coming out the tracheal tube. Bilateral inspiratory crackles were present and chest radiograph showed bilateral infiltrates. These findings were consistent with a diagnosis of Neurogenic Pulmonary Edema (NPE). A cerebral CT-angiogram showed an Aneurysmal Subarachnoid Hemorrhage (ASH), originating from an aneurysm of the right internal carotid artery. A transthoracic cardiac echocardiogram showed severe global wall motion abnormalities of the left and right ventricle, consistent with neurogenic stress cardiomyopathy (NSC). Because of hemodynamic instability, cardiac output guided resuscitation was started at the Intensive Care Unit (ICU) by infusion of intravenous fluids, enoximone and noradrenaline. The low cardiac index, blood pressure and ScvO2, as well as the sinustachycardia responded well to therapy (Table 1). Despite the improvement in hemodynamic parameters the plasma lactate was still rising and plateaued after 9 hours at 9,4 mmol/l. The hyperlactatemia persisted for more than 24 hours. On day one of her admittance the aneurysm was successfully coiled. A CT-scan showed mild frontal ischemia. Her further stay at the ICU and the neurology ward was uncomplicated and after three months het clinical condition was fair.

Lactate can be produced in aerobic and anaerobic conditions. For instance in sepsis, before volumetric expansion, the hyperlactatemia is cause by tissue hypoxia, i.e. anaerobic metabolism. Research shows that after this volumetric expansion the lactate is produced under aerobic conditions and frequently causes a persistent hyperlactatemia. There is increasing evidence that similar mechanisms occur during brain injury. Under normal conditions the brain uses glucose as predominant energy substrate and is a small producer of lactate. However, under conditions of hypoglycemia and hyperlactatemia the brain uses increasing amounts of lactate as energy substrate. Experimental research suggests a probable protective effect of lactate on cerebral metabolism during brain injury.

We present a case of a young female with a persistent hyperlactatemia after an ASH complicated by NPE and NSC, despite normalization of hemodynamic parameters. Although the exact mechanism is unclear, this case clearly demonstrates that hyperlactatemia is not caused by circulatory shock or tissue hypoperfusion alone. In these patients, lactate still reflects disease severity but is not resolved by further optimization of systemic oxygen transport.

TIME (HOURS)*	LACTATE (MMOL/L)	SCVO2 (%)	CARDIAC INDEX (L/MIN/M2)
0	2,1		
2	4,3	55	1,8
5	4,1	60	
7	5,8	74	
9	9,4	69	3,5
11	7,6	71	3,5
19	4,4	69	3,5
29	3,3	70	4,0
39	2,0	70	4,0

Table 1. Lactate, ScvO2 and cardiac index over time

*Time in hours from admittance at the emergency department

23.

Severe hypertriglyceridemia in diabetic keto-acidosis: a case-report

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Introduction: Diabetic ketoacidosis is a serious acute complication of diabetes mellitus requiring immediate care. The diagnosis is based on the trias hyperglycaemia, ketonuria and metabolic acidosis (1).
Case: A 21-year old man was diagnosed with a severe diabetic ketoacidosis. Bloodsamples showed lipemic blood due to severe hypertriglyceridemia: 107.9 mmol/L (reference values: 0.00 - 2.00 mmol/L). Treatment consisted of insuline, glucose and fluid repletion with added potassium. The hypertriglyceridemia almost normalized within 6 days: 2.40 (0.00 – 2.00) mmol/L.
Discussion: Diabetic ketoacidosis originates from a shortage of insuline; this results in hyperglycemia while the intracellular glucose is exhausted (2). Hereupon, a different source of energy for the cells is mobilized from fat tissue: fatty acids. The liver metabolizes fatty acids into triglycerides and ketoacids (2).

Hypertriglyceridemia this severe is exceptional. The cause is sought in genetic factors, diet and obisity (3,4).

Treatment normalizing the level of glucose will result in cessation of mobilisation of fatty acids. Heparine has been considered a treatment for this hypertriglyceridemia. However further research did not show clear positive effects (5,6).
Conclusion: Exeptional hypertriglyceridemia can occur in diabetic ketoacidosis. Treatment is aimed on normalizing the intracellular glucose level. Different causes of severe hypertriglyceridemia are being considered.

TIME AFTER PRESENTATION	GLUCOSE (MMOL/L) <7	PH 7.35-7.45	TRIGLYCERIDES (MMOL/L) 0.00-2.00
0 hours*	39.8	6.80	107.9
7 hours	14.6	7.22	113.2
36 hours	10.3	7.37	40.40
3 days	9.8	7.38	33.60
5 days	13.0	-	5.20
6 days	7.5	-	2.40
5 weeks	7.2	-	2.00

Table1. Laboratory tests

Physical quantity, (unit of measurement), reference values
* venous blood blood; other measurements are arterial

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24.

A strongyloides stercoralis Infection, a delicate balance

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A Strongyloides stercolaris infection in humans, occurres when the infective filariform larvae penetrates the skin. An internal autoinfection cycle allows the parasite to reside within the asymptomatic host for years. Clinical illness, manifested as massive overwhelming strongyloidiasis infection, presents primarily with gastrointestinal and respiratory tract symptoms. Risk factors of a intestinal hyperinfection are due to a compromised immune system leading to dysfunction of TH-2 helper cells. Accleration of the autoinfection cycle, the result of immunosuppresssion whether iatrogenic (corticosteroids, chemotherapeutic agents) or disease related, may result in the hyperinfection syndrome which may lead to disseminated Strongyloidiasis with the propensity to invade virtually every organ system. (1) .

Our patient, a 52-year old man from Surinam, presented to the internal medicine department after a spell of abdominal discomfort. Recently he had been diagnosed with HTLV-I associated adult T-cell leukemia/lymphoma (ATLL) and had reached partial remission after 6 cycles of CHOP-chemotherapy. His condition deteriorated within the next 24 hours and he was transferred to our ICU with the development of septic shock. Because of the patients immunocompromised state an opportunistic infection was suspected. A high resolution CT scan showed an interstitial pneumonia in both lungs. A diagnostic bronchoscopy with bronchoalveolar lavage (BAL) revealed a Strongyloides stercoralis hyperinfection with filariform larvae. PCR analysis on the BAL sample also identified an active CMV and PCP infection with low cycle threshold values of 23 and 26 respectively, indicating high loads. The patient was given ivermectin (200 µg/kg once daily) for 7 days as well as ganciclovir (5 mg/kg twice daily adopted to renal function), methylprednisolon (200 mg daily) and trimethoprim/sulfamethoxazole (1920 mg trice daily). Because of questionable absorption due to gastric distention ivermectin enemas were initiated (200 µg/kg once daily) next to the oral route for 7 days (2). In disseminated strongyloidiasis, involvement of other organs such as the central nervous system may be seen. Our patient developed a central diabetes insipidus which responded to desmopressin. Albendazol (400 mg twice daily) was added to the anti-helminthic therapy because of its ability to pass the blood-brain barrier. With an ominous lack of eosinophilia in the peripheral blood count (3) and the development of PCP associated pneumothoraces, the patient's clinical and specifically neurological condition progressively deteriorated. He died despite all efforts.
Post-mortem investigation confirmed the presence of Strongloides in the lungs and brain (figure 1 & 2), CMV in the lungs and heart in addition to an unexpected Aspergillus infection in the lungs (Aspergillus galactomannan antigen Elisa was negative in serum, BAL and sputumcultures during admission). Heart and bone marrow revealed lymphoid infiltrates with the typical ATLL immunophenotype.

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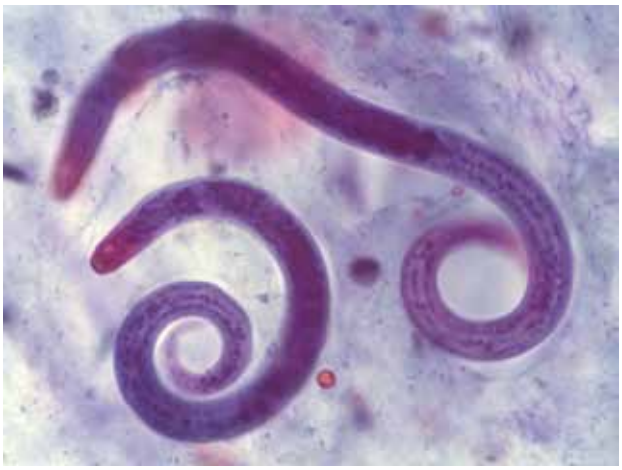

Figure 1. PAP staining of the BAL fluid with filariform larvae, confirming the diagnosis of Strongyloides stercoralis

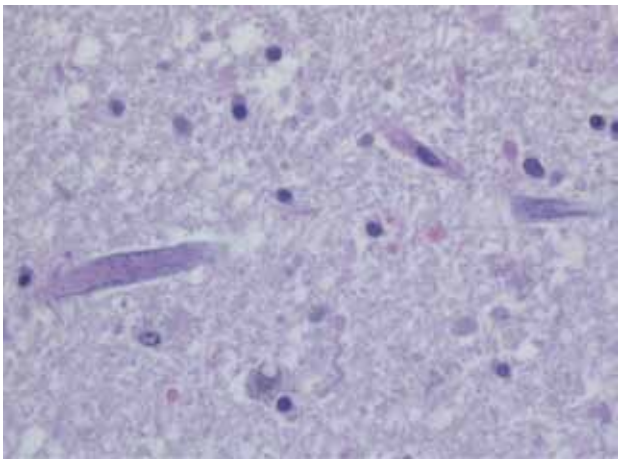

Figure 2. Hematoxylin and Eosin (H&E) staining of post mortem brain tissue with filariform larva , *Strongyloides stercoralis*

25.

Coma blisters: Old killer, same disguise

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A 22-year old man, living with his parents, was found unconscious in his bed and brought to the emergency department of the local hospital. . He had no medical history and had been healthy until this day. At admission he was deeply comatose with a Glasgow Coma Scale of 3. Physical examination was unremarkable, except for the presence of large bullae on his forehead, as well as on the volar side of his forearm, his right hand and his left side. There was no fever. Laboratory examination was unremarkable and standard toxicology screening was negative. Heteroanamnesis reveiled no history of skin problems or allergies. A CT scan of his brain showed no cerebral pathology. Because of respiratory insufficiency, the patient was intubated and then transferred to the ICU of our hospital for further diagnosis and treatment.

Cerebral spinal fluid was examined for signs of meningitis, but turned out negative. The large blisters could not be related to specific conditions, except as pressure injuries from the head on the arm.

Because the lack of positive symptoms a more extensive toxicology screening was performed. This time high levels of pentobarbital were found in the urine. The diagnosis barbiturate intoxication was confirmed by very high plasma levels. Further treatment was supportive. The plasma levels gradually declined and the patient could be extubated when he woke up on the fourth day of admission. The blisters resolved spontaneously. .

Blister formation used to be a very common phenomenon in barbiturate-induced coma, especially in the previous century when these drugs were still frequently used. The association was so strong that the condition was referred to as “coma blisters”1. It is not clear whether the blisters are caused by a direct toxic effect of pentobarbital or by local pressure in the immobilized patient. The same skin lesions have been seen in comas induced by other central nervous system depressants and in non-drug induced comas2. Our patient was found with his forehead lying on his forearm and the location of some blisters corresponded with local pressure points.

The patient admitted to have ingested a large amount of pentobarbital in an attempted suicide. He had obtained a large amount of this drug via a webshop in Japan. It was sold without restriction as a so-called “suicide-kit” and was delivered to his home address by mail order without his parents noticing.

This case demonstrates that the presence of blisters in a comatose patient is highly suggestive for intoxication as cause for the loss of consciousness, especially in case of long immobilization. Furthermore, the unrestricted availability of very strong drugs in internet shops urges for more extensive toxicology screening.

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26.

Mean systemic filling pressure in determining fluid responsiveness post-cardiac surgery: a case report

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Background: The assessment of the cardiovascular state in critically ill patients is subject to difficulties due to insufficient information about the circulating volume and cardiac performance supplied by currently used standardized hemodynamic parameters, for example mean arterial blood pressure (MAP) and cardiac output (CO). There is a clinical necessity for adequate determination of the venous side of the circulation and therefore reliable predictors of fluid responsiveness are highly relevant.

Case presentation: A 56-year old woman is referred to our institution with a type A aortic dissection, with no previous medical history and a good preserved cardiac function without valvular disease. A classical Bentall operation is performed, complicated by diffuse oozing around the aortic root, for which packing with three bandage gauzes (to be removed in later setting), blood transfusion, fluid resuscitation and dobutamine 5µg/kg/min infusion is applied. The patient is transferred to the intensive care unit (ICU). Coagulation is successfully restored and after two hours the mean arterial blood pressure (MAP) is 50 mmHg, central venous pressure (CVP) 5 mmHg and a cardiac output (CO) of 3,5L/min. Despite fluid resuscitation with 2L of Ringer’s Lactate over 4 hours, a low output state persists with a decrease in MAP, low CO (3-4L/min), central venous oxygen saturation (ScVO2) of 56%, oliguria, low peripheral (27.6°C) and central (35.2C°) body temperature, and a pulse pressure variation of 26, without any result of administration of norepinephrine. Determination of fluid responsiveness

is performed using pulse contour cardiac output data connected to a recently developed monitoring guidance device, which retrieves data (MAP, CO, CVP and arterial oxygen saturation) from existing bedside physiological monitors. The system adequately determines mean systemic filling pressure (P_{ms}) using a numerical algorithm and heart performance (eH, the quotient of P_{ms} minus right atrial pressure, divided by P_{ms}, range 0–1). Measurements in our patient shows P_{ms} of 11 mmHg and a eH 0.55. In addition a passive leg raising test (PLR) is performed in order to predict fluid responsiveness by this self volume challenge. An increase in P_{ms} is observed from 11 mmHg to 13 mmHg within 2 minutes. This accompanies an increase in MAP, but particularly CO, which is the outcome variable in this manoeuvre and increases from 5.10L/min to 6.10L/min. According to the literature, an increase of ≥ 10% of baseline after PLR or fluid challenge (FC) is indicative of successful fluid responsiveness. No change in heart performance is observed. Accordingly, after 2 minutes, we performed a FC with 500 mL Ringer's Lactate, infused within 4 minutes with a pressurized cuff. P_{ms} increases from 10 mmHg to 14.40 mmHg, cardiac output from 4.80L/min to 6.30 L/min after FC, indicative of successful fluid resuscitation. No change in heart performance is observed (0.54).

Conclusion: Determination of cardiovascular filling status in critically ill patients is incomplete, due to the lack of ability to measure venous compliance, volume and resistance. New hemodynamic monitoring devices could have great clinical implications in terms of determining and fine-tuning tailored hemodynamic therapy at bedside.

27.

Strongyloides stercoralis hyperinfection syndrome after cardiac surgery

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Case description: A 64 year old male was admitted to our intensive care unit for post-operative care after aortic valve replacement. His previous medical history was relevant for giant cell arteritis for which he was using 60 milligrams of prednisone daily. The patient was weaned from inotropics and detubated on the third postoperative day. Subsequently the patient developed a respiratory insufficiency consistent with a clinical diagnosis of decompensated heart failure. The patient was reintubated and treated with inotropics. Leucocytosis, elevated inflammatory parameters and hypothermia developed along with vasoplegia consistent with a septic shock and since copious amounts of sputum were retrieved from the lungs a ventilator associated pneumonia was suspected. A chest X ray was obtained (figure 1) and was interpreted as decompensated heart failure combined with pneumonia. Sputum was investigated for Gram stain and surprisingly high numbers of mobile *Strongyloides stercoralis* larvae were observed. The same day blood cultures grew *E. coli* and *E. faecium*. and a diagnosis of *Strongyloides stercoralis* hyperinfection syndrome was made. Since dissemination to the central nervous system was suspected a lumbar puncture was performed and showed a prominent leucocyte influx into the cerebrospinal compartment. Broad spectrum antibiotics and, ivermectine (12 gram orally QD) were started. During the first few days of treatment the clinical situation progressively deteriorated and severe multi organ failure developed. Due to gastroparesis insufficient ivermectine uptake was suspected and subcutaneous ivermectin therapy, which is an off label use of the compound, was started. Thereafter the number of live larvae decreased in sputum samples decreased massively in a few days. Currently the patient is still being treated at our intensive care unit and, after two weeks of intensive treatment, is still suffering from severe multi organ failure. An evaluation of risk factors for *Strongyloides stercoralis* revealed that the patient travelled to Indonesia several years before.

Discussion: *Strongyloides stercoralis* is a helminthic parasite which can complete its life cycle entirely within the human host.(1) Infection with the parasite is highly prevalent in developing countries. Together with depressed cell-mediated immunity, autoinfection can give rise to potentially fatal hyperinfection with disseminated disease.(2) Clinical findings in hyperinfection syndrome may be attributable to the direct consequences of organ invasion or to secondary Gram negative bacteraemia, pneumonia or meningitis due to bloodstream seeding.(3) This dissemination of filariform larvae from the gastro intestinal tract to lungs, liver, heart, central nervous system and endocrine glands often results in severe and ongoing septic shock. *Strongyloides stercoralis* hyperinfection syndrome is a rare clinical entity in the Western world for which mortality rates exceeding 80% have been reported.(4) The likelihood of developing the hyperinfection syndrome is increased if cell-mediated immunity is impaired and strongly associated with the use of corticosteroids.(5). We here report a case of *Srongyloides stercoralis* hyperinfection syndrome and disseminated polymicrobial sepsis after cardiac surgery, in a patient who used steroids. This report illustrates that *Strongyloides stercoralis* hyperinfection syndrome with disseminated disease should be suspected in immunosuppressed patients with polymicrobial sepsis who are at risk for *Strongyloides stercoralis* infection.

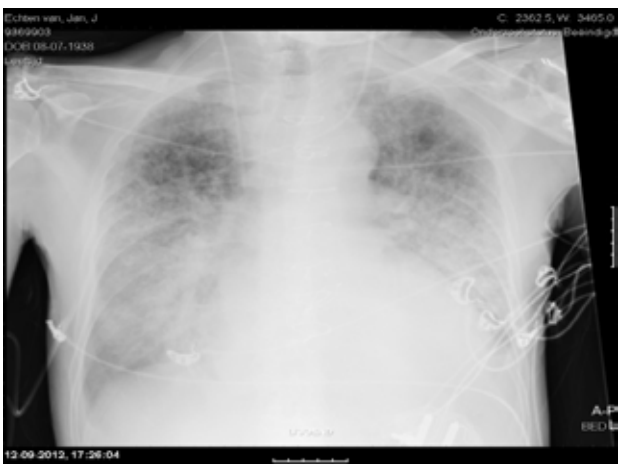

Figure 1: chest X ray

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28.

A mediastinal mass due to a "non-pathogenic" pathogen A deadly commensale

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Introduction: This case describes a patient with a mediastinal mass which turned out to be a hematoma caused by a very rare culprit: Propionibacterium granulosum.

Although a constituent of normal skinflora it should never be easily discarded when cultured in blood.

Case-report: A 34-year old man presents with cardiac ischemia was referred to the ICU. His previous medical history was relatively unremarkable. A couple months earlier that year he was admitted to a nearby community hospital with idiopathic pericarditis.

An echocardiogram at that time showed some pericardial effusion and a congenital bicuspid aortic valve. The effusion did not reveal any pathogen. Cultures were discarded after five days.

In August 2009 he was readmitted with fever. A CT scan of his thorax (Figure 1) showed a mediastinal mass suspected to be lymphoma, which partly compressed the left main coronary artery causing cardiac ischemia.

To confirm the suspicion of lymphoma he was scheduled for biopsy. With opening of the mediastinum a murky seropurulent fluid was seen.

Exploration of the mediastinum showed, besides the hematoma and indurated left atrium, a defect in the aortic wall (abcess) near the left coronary sinus, vegetations on the sclerotic bicuspid aortic valve and a left coronary stem that was fully indurated by ongoing chronic infection. A surgical correction of the extensive damage proved to be unsuccessful and patient didn't survive.

Cultures taken from the murky fluid, blood and cardiac tissue all came back positive for Propionibacterium granulosum. It took 10 days to be able to see any growth.

Propionibacterium granulosum is a Gram-positive coccobacil, which generally is a non-pathogenic constituent of the skin and oropharyngeal microflora.

A better known micro-organism of the same species is Propionibacterium Acnes, a causative organism in the skin condition Acne vulgaris.

Proprionibacterium species are seldom involved in a clinical disease.

The International Collaboration on Endocarditis Merged Database1 over a period of 20 years identified only 15 cases of endocarditis due to Propionibacterium species, but then in general Proprionibacterium acnes.

As it is a slow-growing pathogen the clinical course is indolent. Patient present themselves in an advanced state with non-specific clinical signs.

Due to its slow-growing characteristics, even despite highest vigilance the diagnosis via cultures will in general take some time as well.

Conclusion: This case shows that P. granulosum , although in general non-virulent, can be a fatal pathogen.

As it is a slow growing pathogen the clinical course is in general non-specific. In this case the Duke criteria to diagnose endocarditis were never met.

It would be prudent not to consider P.granulosum as a mere skin contaminant when cultured.

Be aware to let the microbiologist know of the clinical suspicion of endocarditis, otherwise cultures will be discarded before any growth will be detected as might have been the case with this patient when he presented himself months before his death with pericarditis.

In the end it still took 10 days for the cultures to become positive.

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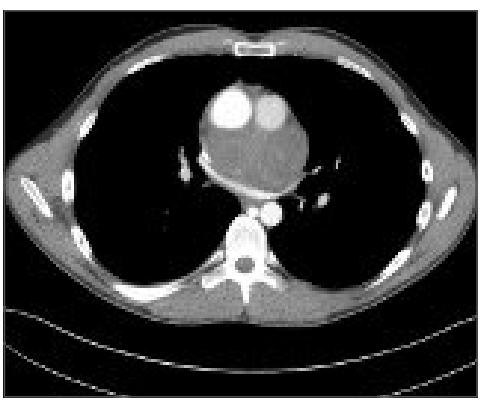

29.

Acyclovir induced acute kidney injury, delirium and seizures

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Introduction: Acyclovir is the drug of choice for treatment of herpes encephalitis. Although the drug is this widely used, complications may nevertheless occasionally arise.

Case description: A 55-year old female patient was analyzed for transient paresis of the right arm. A transient ischemic attack was considered most likely. Carbasalate calcium and dipyridamole were started. One month later the paresis recurred and the patient developed aphasia. MRI scan was normal, cerebrospinal fluid (CSF) analysis revealed lymphocytosis and high protein concentration. Because of suspected viral meningo-encephalitis, treatment with acyclovir, three times daily 10 mg/kg intravenously, was added to the above medications and salmeterol inhalations. Liver and kidney function were normal.

After admission the patient became increasingly delirious, for which haloperidol was started. 2 days later a tonic clonic seizure was successfully treated with diazepam per rectum. 2 hours later the seizure recurred (GCS E1M3V1). Sedation, intubation and transfer to our centre resulted. CT-scanning again revealed no abnormalities.

On admission kidney function was decreased (creatinin 572 µmol/l). Urological ultrasound was normal. After successful detubation (EMV 15), patient had another clonic seizure of the left arm with respiratory insufficiency, necessitating sedation, intubation and initiation of antiepileptic drugs (diphantoin 1250mg iv, followed by levetiracetam 2dd 250mg orally). Acyclovir intoxication was suspected and drug levels in liquor and serum ordered.

PCR of the CSF revealed no viral causes, and acyclovir was stopped. Renal function recovered over a period of 5 days (creatinin level 102 µmol/l). Although CSF Ziehl Neelsen staining initially revealed an acid fast rod, Quantiferron® testing, and repeated CSF staining,and cultures remained negative. Bronchoalveolar lavage (BAL) and subsequent BAL fluid analysis was negative for TBC. Immunological markers for auto-immune encephalitis were negative, including anti-NMDA receptor antigens. Levels of acyclovir and 9-carboxymethoxymethylguanine however proved extremely elevated in serum and were detected in liquor.

After follow up of acyclovir levels, sedation was stopped, and 4 days after admission patient regained consciousness (EMV 15), and remained without seizures. After 5 days ICU discharge followed. Visual hallucinations and delirium disappeared within one week after onset.

Discussion: Although the initial neurological symptoms are so far not fully clarified, the secondary neurological sequelae however resulted from acute kidney injury caused by acyclovir, despite normal baseline kidney function.

Acyclovir itself may cause kidney failure due to accumulation of anisotropic drug crystals in the collecting ducts causing obstructive nephropathy. The acyclovir levels are displayed in figure 1.

It is reported that acyclovir may cause neuropsychiatric symptoms in patients with preexistent altered kidney function, even at non-toxic levels because of accumulation of 9-carboxymethoxymethylguanine, an acyclovir metabolite. Normally 9-carboxymethoxymethylguanine is not detected in CSF (0,8mg/l in our patient). Therefore it is most likely that acyclovir accumulation caused neuropsychiatric symptoms. Even convulsions and coma are reported in literature.

Conclusions: Acyclovir intoxication can arise due to renal toxicity and subsequently cause neuropsychiatric and neurological sequelae. The case described herein illustrates that follow up of renal function, and consequently decreasing acyclovir dosing is warranted, to respectively facilitate early recognition, and subsequent prevention of these complications.

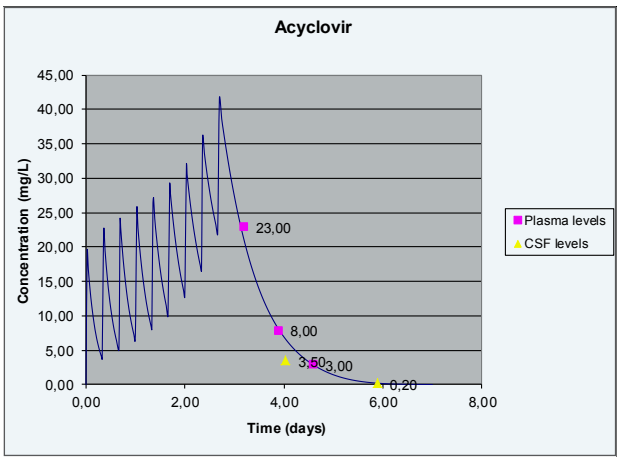

Figure 1.

30.

Superrefractory Status Epilepticus; treatment beyond guidelines

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Background: Status Epilepticus (SE) resistant to first- and second line antiepileptic drugs, is defined as a refractory SE, requiring treatment with anesthetics. Superrefractory status epilepticus (SRSE) is defined as persisting or recurring SE despite anesthetic medication for 24 hours or more, including recurrent SE when reducing or withdrawing anesthetics. Since SRSE is an infrequent condition, guidelines are unavailable and treatment is based on case reports and small series. In this case report, we aim to describe EEG targets and treatment modalities of SRSE.

Case: After a flu-like episode, a 48 years old male was admitted for sepsis of unknown origin and broad spectrum antibiotics were initiated. Two days later the patient developed tonic-clonic seizures. A viral encephalitis was treated empirically. Cerebrospinal fluid, general laboratory tests, and CT-CTa-CTv were unremarkable. Under treatment with phenytoine, levetiracetam, propofol and thiopental SRSE developed, and the patient was transferred to our tertiary university hospital, where a complete diagnostic work-up could not reveal the etiology of the seizures.

Attempts were made to suppress epileptic activity while continuously monitoring the EEG. Initially the aim was to achieve a burst-suppression EEG (Figure 1a). However, uniform repetitive complexes developed (figure 1b) and clinically epileptic activity was present, conform an epileptic breakthrough. It was then decided to aim at a flat EEG (Figure 1c).[1]

Several anesthetic treatment modalities were tried, directed at GABA-A-receptors, NMDA-receptors, K-channels and combinations of these. All remedies did achieve a flat EEG pattern at the cost of serious hemodynamic instability with multiple organ dysfunction syndrome (MODS). Combining these therapies with additional anti-epileptic drugs (topiramate, retigabine) was not beneficial either.

Electric convulsion therapy was applied. And, although seizures were provoked, the autonomic counter-regulation mechanisms necessary to end all epileptic activity did not follow. Furthermore, immunosuppressive therapy was tried fruitlessly. Finally, therapies with an unknown point of action were tried unsuccessfully (such as hypothermia) or were practically unachievable (such as a ketogenic diet) .

After a course of 41 days we ran out of treatment options and the prognosis of the patient was judged infaust. Discontinuing all treatment led to his death.

Discussion: This case illustrates the difficulties of treatment of SRSE

Firstly, epileptic breakthrough during burst-suppression EEG forced us to strive for a flat EEG. To reach this state, high dose anesthetics were necessary, all leading to hemodynamic instability and MODS, forcing us to lower the dose and switch to other medication.

Secondly, only case reports and small series regarding therapy in SRSE are available, since it is an infrequent disorder.[2] In our treatment we tried to make a stepwise approach. Initially, we chose medication based on their known mechanism of action, such as activation of GABA-A-receptors. Secondly, we targeted the potential underlying pathophysiology, by immunomodulating strategies, and evoking autonomic counter-regulation mechanisms by electric convulsion therapy. And lastly, therapies with unknown point of action were tried.

In conclusion, in the absence of guidelines, decisions regarding treatment of SRSE should be based on experience and eminence, but also on a logic pharmacodynamic and pathophysiologic paradigm.

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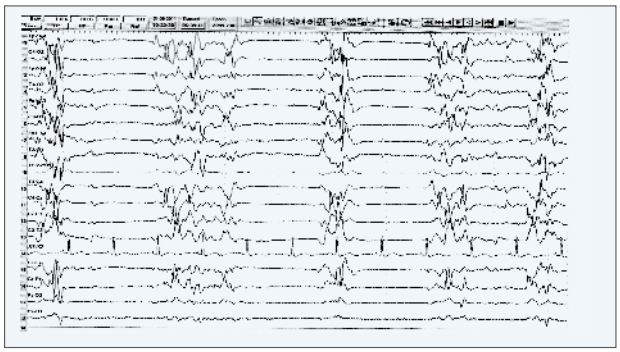
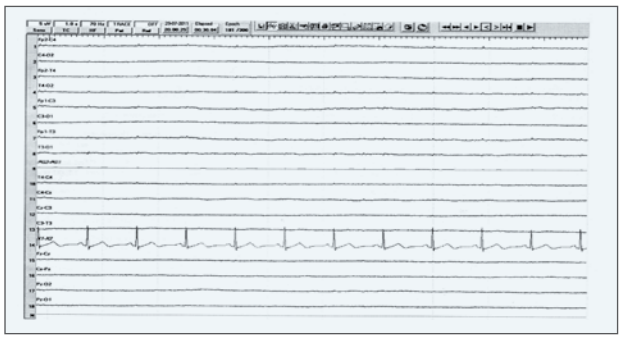
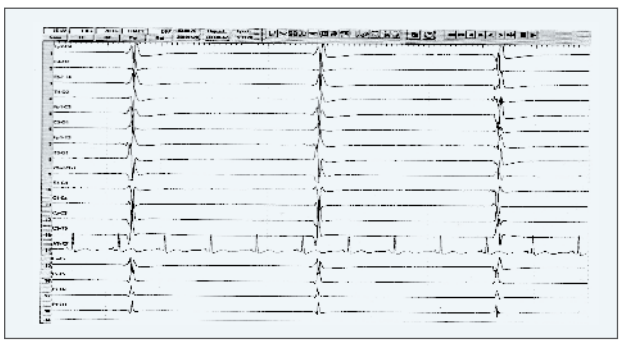
Figure 1. EEG patterns



1a. Burst Suppression



1c. Flat EEG



1b. Uniform repetitive activity

31.

Extracorporeal membrane oxygenation in adult patients with congenital heart disease

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Background: Due to enhanced diagnostic methods, interventional techniques and medical treatment, the prognosis of patients with congenital heart disease has improved dramatically and a substantial part of these patients survives to adulthood, leading to a greater group of these patients who will eventually may develop decompensated heart failure or cardiogenic shock for different reasons. In order to treat these acute decompensations, extracorporeal membrane oxygenation (ECMO), a circulatory and respiratory support system which contains a blood pump and oxygenator, can be applied to provide a bridge to decision. Furthermore, shock induced multi-organ failure can be treated with ECMO after which an intervention can be carried out in a clinically improved state.
Case report 1: A 33- year- old female was admitted with shock and respiratory failure due to acute right sided heart failure caused by stenosis of the pulmonary tract. In the past she had correction of a Tetralogy of Fallot. Veno-arterial ECMO was implanted and allowed us to schedule surgery carefully. Meanwhile, we could optimize our patient clinically after which she underwent pulmonary valve implantation.

Six days after correction, the ECMO could be removed. During five days she was without respiratory or circulatory support, but problems arose again because of an arterial bleeding at the insertion site of the femoral canula complicated by a wound infection. A massive arterial bleeding occurred on the same location just before surgical inspection and she died from hemorrhagic shock.
Case report 2: A 38-year old male with Fontan circulation after correction of his congenital tricuspid atresia had recurrent atrial tachy- arrhythmias. He was admitted to our hospital for a MAZE operation and partial resection of his atria. Postoperatively, the passive pulmonary blood flow was easily compromised due to a rise of the intra-thoracic pressure after which he became hypoxic and hypotensive. Multi-organ failure ensued for which a veno- arterial ECMO was installed eight days after admission to the ICU. Despite ECMO and extensive medical treatment, he deteriorated further and died.
Discussion: We described two patients with congenital heart disease in whom ECMO was used for different reasons. In the first patient, ECMO support was primarily used to optimize the patient for the planned operation. This strategy has been used before mainly on patients awaiting cardiac of lung transplants, but also for children awaiting surgery for congenital heart disease. In the second patient, ECMO support was used to improve the postoperative cardiogenic shock due to a compromised Fontan circulation, to recover from multi-organ failure, but also as a bridge to decision. ECMO stabilized the circulation and prevented further deterioration in the beginning. We suspected another cause for his downhill spiral such as sepsis, for which we needed more time to investigate.

Although our two patients died, ECMO may have advantages for decompensated patients with congenital heart disease, as it can be used as bridge to decision or to surgery, and to treat postcardiotomy shock. ECMO support should be used with caution because of possible serious complications.

32.

Complications of mechanical chest-compression devices. A case report and review of the literature

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Introduction: Mechanical chest-compression devices (MCCDs) are increasingly used during Cardio-Pulmonary Resuscitation (CPR). Properly adjusted, they provide consistent and uninterrupted chest compressions. This improves the quality of CPR and therefore may lead to better survival and neurological outcome. Complications of these devices are still sparsely described.
Aim: This article describes a case of a patient with a stomach blow out, a rare but important complication of MCCDs. Furthermore, it provides a review about the recognized complications of these devices thus far.
Case: A 77-year-old woman was found unconscious next to her bike without detectable pulse. Chest compressions were initiated by bystanders until the ambulance arrived. Pulse less Electrical Activity was observed and a mechanical chest-compression device (LUCAS: Lund University Cardiopulmonary Assist System, Jolife, Sweden) was positioned. Manual mask ventilation and tracheal intubation were difficult to apply. Because of suspected fall of her bike, she was treated according to theAcute Traumatic Life Support protocol. A round and hard abdomen was noted and chest radiography revealed massive subdiaphragmatic free air. A laparotomy was performed directly and a blowoutinjury of the stomach was repaired. The following days she suffered from intestinal and stomach ischemia for which two laparotomies were repeated. Because of continuing clinical deterioration, further treatment was discontinued and she died.
Discussion: We described a case of stomach blow out due mechanical chest-compression. This treatment method is relatively new and currently not much is known about its complications.[1] We conducted a Medline search to provide an overview of its complications known thus far (Table 1). Clinicians should be alert for any complication of CPR, especially when mechanical chest-compression devices are used.

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INJURY	DEVICE	INCIDENCE	REFERENCE	YEAR
Skin lesions	Cardiopump	31%	Luiz	1996
	LUCAS	42%	Smekal	2009
Sternal fracture	Cardiopump	0%	Luiz	1996
	Cardiopump	81%	Rabl	1996
	Cardiopump	93%	Baubin	1999
	LUCAS	Case series	Englund	2006
	LUCAS	29%	Smekal	2009
Rib fractures	Cardiopump	12%	Luiz	1996
	Cardiopump	81%	Rabl	1996
	Cardiopump	86%	Baubin	1999
	LUCAS	Case series	Englund	2006
	LUCAS	47%	Smekal	2009
Mediastinal bleeding	LUCAS	Case series	Englund	2006
	LUCAS	8%	Smekal	2009
Epicardial bleeding	LUCAS	10%	Smekal	2009
Pericardial bleeding	LUCAS	8%	Smekal	2009
Severe cardiac injuries	Cardiopump	6%	Rabl	1996
Thoracic aorta injury	LUCAS	Case series	Englund	2006
	LUCAS	3%	Smekal	2009
Pneumothorax	LUCAS	3%	Smekal	2009
	LUCAS	Case report	Hutchings	2009
Lung injury	LUCAS	3%	Smekal	2009
Liver injury	LUCAS	Case series	Englund	2006
	AutoPulse	Case report	Wind	2009
	LUCAS	Case report	De Rooij	2009
	LUCAS	3%	Smekal	2009
	AutoPulse	Case report	Von Bary	2009
	AutoPulse	Case report	Camden	2011
Spleen injury	AutoPulse	Case report	Wind	2009
Gastric perforation	Cardiopump	Case report	Liu	1996
	LUCAS	Case report	Sajith	2008
	LUCAS	Case report	Platenkamp	2012

33.

Sedating an aggressive or confused patient, what is the limit?

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Case outline: A 21 year old male is brought to the ER showing major aggressive behavior after a seizure. He is known with epilepsy and prescribed valproic acid, but is not compliant. There is a need to fixate him and administer sedatives (haloperidol 5mg and dormicum 20mg), with only short responsiveness. Neurologist and psychiatrist can't find any cause for this behavior. Their diagnosis is posticta encephalopathy. The patient needs to stay at the hospital for observational and safety reasons, but is unmanageable. Deep sedation is proposed. They call the intensive care specialist.
Background: The posticta state is the condition between the end of a seizure and return to baseline condition.(1,2) It is defined by changes in behavior, motor function, and neuropsychological performance.(1,2) The prevalence of aggressive behavior in epilepsy has not been quantified. (3) Anxiety, psychosis, and aggressive behavior are frequent comorbid disorders in patients with epilepsy. Common pathogenic pathways have been hypothesized.(1,2) Duration of the posticta state depends upon several factors: part(s) of the brain affected, length of seizure, medication, age.(4) Few studies have quantified the duration of posticta state. Helmstaedter et al. showed recovery within 1–2 hrs.(5)
Is it justified to sedate this patient? *Pro:* WGBO and BOPZ state: if a patient is potentially harmful, forced intervention is justified to abolish an acute situation.(6,7) Interventions allowed are: seclusion, fixation and forced administering of medicine. Choice and dose of medicaments should be adjusted to expected duration of the situation.(7,8) Because this patient showed only short responsiveness to boluses, continuous administering of sedatives is best to control him. Regarding the diagnosis, a time period has been given. Looking at the risks of sedation and probable intubation we should consider this is a young healthy individual. Advanced age and lung or heart disease are the most important risk factors for complications. (9) Though there are still risks, they could outweigh the risk of him hurting himself. *Con:* Forced treatment of a patient should be considered if there's no alternative option.(7) Sedatives depress respiration, lead to impaired airway reflexes and can cause hypotension.(10,11) Patients should be monitored and intubation is required. This is not without risk.(12) A study on BALs of lung-healthy subjects, before and after intubation, showed modulations of pulmonary defense markers.(13) Also excessively sedated patients can

develop prolonged cognitive impairment and delirium.(11) Another argument is admission to the ICU is expensive. We should take into consideration the diagnosis could still be wrong. This case describes a healthy young man with no sign of danger to any of the vital functions. Why risk it? There should be other options.

Lesson to learn: This might be an exceptional case, but more or less people working on the ICU deal with this question on a daily basis. The prevalence of delirium on the ICU is high. (14) Agitation can be a part of the hyperactive form of delirium.(14) There is a lot of non-medical treatments that could be very effective (14), but we often react by administering sedatives. Even though this is legally not an issue, is that really worth the risks?

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