Review
Glomerular hyperfiltration of antibiotics
D.W. de Lange

Clinical image
Periodic $SvO_2$ fluctuations in a patient with severe pulmonary emboli
P.E. Spronk

Case reports and abstracts
Intensivistendagen 2014
Referenties:


Raadpleeg de volledige productinformatie alvorens CANCIDAS voor te schrijven

CONTENTS

EDITORIALS

3 Glomerular hyperfiltration, the devil in disguise
H.M. Oudemans-van Straaten

5 Video-laryngoscopy: the eye of the beholder?
T.M. van den Berg, D. Gommers

ORIGINAL ARTICLE

7 Endotracheal intubation by inexperienced registrars in internal medicine: a comparison of video-laryngoscopy versus direct laryngoscopy
H. Biermann, E. van der Heiden, A. Beishuizen, A.R.J. Girbes, M.C. de Waard

REVIEW

10 Glomerular hyperfiltration of antibiotics
D.W. de Lange

CASE REPORTS

15 Cryoglobulinemia complicated by diffuse alveolar haemorrhage

19 Severe anti NMDA encephalitis and EBV infection
S.J. Derksen, B. Goraj, J.P. Molenaar, J.G. van der Hoeven

CLINICAL IMAGE

22 Periodic SvO₂ fluctuations in a patient with severe pulmonary emboli
P.E. Spronk

24 CASE REPORTS INTENSIVISTENLAGEN 2014

42 ABSTRACTS INTENSIVISTENLAGEN 2014

66 Editorial Board

66 International Advisory Board

67 Information for authors

Netherlands Journal of Critical Care is indexed in:

EMBASE
EMCare
Scopus
Wereldwijd meer dan 1 miljoen patiënten met Mycamine behandeld!¹

Hoog gebruiksgemak
• Geen significante drug-drug interacties²
• Geen oplaaddosis en dosisaanpassing²
• Geen specifieke bewaarcondities²

Voor alle leeftijden (0-99)²
Glomerular hyperfiltration is an underdiagnosed condition leading to augmented renal clearance. This condition passes unnoticed, and can lead to serious underdosing of renally excreted antibiotics. In the present issue, Dylan de Lange pays attention to this condition. His contribution is worth reading for its clinical relevance. 1

A typical case of glomerular hyperfiltration is as follows. A 24-year-old previously healthy man was admitted to hospital after a severe motor accident. At the trauma site he was found to be comatose and was intubated. Apart from an instable thoracic-3 vertebral fracture, which was fixated at day three, and some other less important injuries, his cerebral trauma was the most severe of his injuries. He underwent early hemicraniectomy to evacuate an acute subdural hematoma with mass effect. After repositioning of the cranial bone flap three weeks later, a subduro-peritoneal drain was inserted, because his neurological condition deteriorated. He subsequently developed fever. Several blood cultures showed growth of *S. epidermidis* and the pre-emptive vancomycin treatment was continued.

The patient’s renal function appeared to be normal, on admission his serum creatinine was 73 µmol/L and after five weeks of intensive care treatment with persistently decreased consciousness (maximal EMV score of 8), the serum creatinine decreased to 40 µmol/L. Vancomycin blood levels were measured. Initial intravenous dose was twice 1000 mg but this dose had to be increased to 4-times 1300 mg to attain trough levels above 15 mg/L. Of note, this patient additionally exhibited intermittent sympathetic hyperactivity (fever, tachycardia, hypertension, tachypnoea, hyperhidrosis and dystonic posturing) which was successfully treated with hydration, enteral propanolol and intravenous clonidine. 2

This young patient with severe traumatic brain injury had augmented renal clearance with subtherapeutic vancomycin concentrations. In such cases, augmented renal clearance is a devil in disguise. The first reason for this is that the condition passes unnoticed with routine clinical monitoring. Therefore, awareness on the part of the physician is crucial. Patients at risk include younger patients with apparently ‘normal’ renal function who exhibit sympathetic hyperactivity after major trauma, especially head injury, burns or during early sepsis. The precise mechanism is not well known, but the condition is associated with high catecholamine concentrations, fluid loading and low plasma albumin concentration and is reported in up to forty percent of septic and eighty five percent of the young trauma patients with normal renal function. 3,7. The second pitfall is the augmented renal clearance of water soluble antibiotics and other solutes. For example, subtherapeutic concentrations of vancomycin8-9, β-lactam antibiotics, 10 meropenem, 11 piperacilline/tazobactam 11 and levetiracetam 9 are reported in the literature.

How do we incorporate this knowledge into daily practice? Several measures seem necessary. First, in younger patients with trauma, early sepsis and burns, a higher initial dose of antibiotics should be considered to saturate an increased distribution volume. Subsequently, the non-toxic renally excreted antibiotics such as β-lactams, carbapenems and fluoroquinolones should be dosed more frequently or continuously (β-lactams), to prevent concentrations falling below the minimum inhibitory concentration due to augmented renal clearance. With non-toxic drugs, the risk of underdosing is higher than that of overdosing. Second and ideally, therapeutic drug monitoring should be performed. If this option is not available, creatinine clearance from a 2-4-hours urine collection period should be done at regular intervals to monitor augmented renal clearance and guide antibiotic dosing. Glomerular filtration may be markedly increased, creatinine clearances of 310 and of 375 mL/min/1.73 m² have been reported. 11,12 Third and finally, toxic antibiotics such as aminoglycosides, which demonstrate concentration-dependent killing, should be given more frequently in cases of augmented renal clearance, and therapeutic drug monitoring should be performed, not only in patients with diminished renal function but also in those with apparently...
normal renal function. The same strategy is recommended for vancomycin for which continuous infusion may be considered as well.4

The message here is, be aware of glomerular hyperfiltration in younger patients with trauma, sepsis and burns with apparently normal renal function; measure 2–4 hours creatinine clearance regularly, administer antibiotics more frequently and perform therapeutic drug monitoring, not only in patients with diminished but also in those with apparently normal renal function. This strategy is likely to increase treatment success.

References
In this issue of the *Netherlands Journal of Critical Care*, Biermann et al. report on a trial in which they compared the use of direct laryngoscopy using the classical Macintosh laryngoscope (DL) with video-laryngoscopy using the GlideScope (GS) in the hands of inexperienced registrars. The registrars all had to intubate a manikin with both tools, after which the intubation success and time needed for successful intubation were compared. Results showed that intubation using the GS technique had a higher success rate (92% vs 69%, *P*<0.05). However, it took the registrars more time to successfully intubate the manikin with the GS (75 seconds versus 39 seconds).

The GS has been commercially available since 2001. The first major clinical study using the new video-laryngoscope was performed in 2005. In 133 patients in whom both direct laryngoscopy and video-laryngoscopy using the GS were performed, the use of GS resulted in superior or comparable view of the vocal cords. In 35 patients classified as Cormack-Lehane (C/L) 3/4 by DL, the use of GS reclassified them as C/L 1 in 24 and C/L 2 in three patients. Intubation with the GS was successful in 96.3% of patients. Later that year the first randomized clinical trial comparing DL and GS in 200 elective surgical patients was performed. The results showed that GS improved the C/L grade in the majority of patients by G/L > 1. The time needed for intubation was longer in the GS group than in the DL group, but not for patients with G/L 3.

The intubations in these first studies were performed by experienced anesthetists. Because of the better laryngeal view obtained by using GS, the technique has since been investigated in numerous situations with expected difficult intubation: in patients with reduced mouth opening, in patients with immobilized spine, out-of-hospital intubations, and in simulated difficult airway-intubation in a manikin. In all these situations the GS technique proved to be better than DL in terms of intubation success. In obese patients, better glottis views were achieved with the GS but the intubation time was longer. No difference was found in intubation success rate or complications.

The fact that it takes longer to intubate a patient with GS, especially when the C/L grade is low, has been reported frequently. This seems to be due to the more difficult advancement of the tube through the mouth. However, the most difficult skill to learn when intubating patients is obtaining a good view of the glottis. Since the GS has proven to give these better views, it is reasonable to examine the functionality of its use in the hands of relatively inexperienced doctors. Nouruzi-Sedeh et al. performed a study in which inexperienced volunteers, who had only had a tracheal intubation training on a manikin, intubated elective surgical patients either with GS or DL. The success rate of GS was 93% versus 51% for DL. The intubation time for GS was shorter than for DL (63 seconds versus 89 seconds). The same result was found by Ayoub et al.: inexperienced medical students were briefly trained using GS or DL, and subsequently intubated patients with normal airways. The students being trained with, and using the GS achieved higher success rates in less time.

A recently published study by Kory et al. is closer to everyday hospital reality. A cohort of critical care fellows using a GS in urgent endotracheal intubations in critical ill patients was compared with a historical cohort of critical care fellows using direct laryngoscopy. The rate of first-attempt success was higher in the group using GS (91% vs 68%). Also, the rate of unintended oesophageal intubation and the average number of attempts required for successful intubation were lower in the GS group.

Randomized studies on the use of the GlideScope in emergency situations are scarce. The studies that have been performed on urgent intubation in the Emergency Department or in critically ill patients are mostly observational, and they do not show uniform results. Some find intubation with the GS leading to fewer attempts before successful intubation and less time needed for intubation, or fewer oesophageal intubations.
Others find similar success rates for both methods of intubation, and suggest the use of GS for difficult airways.¹³ The study by Platts-Mills et al. shows no difference between success rate and longer time needed for intubation in the GS group.¹⁴ That the prolonged time needed for intubation is not always harmless in an emergency situation is suggested by the only randomized controlled study by Yeatts et al. performed in trauma patients: they retrospectively found longer intubation times and higher mortality among patients with severe neurotrauma who were intubated with GS.¹⁵

The most important limitation of the study by Biermann et al. is, as the authors mention themselves, that it has not been performed in a real life situation. Given the fact that outside office hours the vast number of intubations are required in emergency situations, there are many difficulties including hemodynamic and respiratory deterioration, aspiration and other complications that may be encountered by an inexperienced doctor trying to intubate a patient. Most of these problems will not be less when GS is used. Therefore, all doctors responsible for emergency stabilization of patients need to be thoroughly trained in the management of the acute patient. Emphasis should be placed on the ability to use the balloon, and other noninvasive methods of maintaining airway and breathing in an emergency situation. Once these prerequisites have been met and if the patient is still in urgent need of intubation, or the (thus probably not so inexperienced) doctor feels comfortable with the technique, the GS can be used as an initial means of intubation. This is particularly reasonable if the patient is expected to have a difficult airway. It is too early to say that the GS is superior in these situations; more randomized studies to prove this in a real life emergency situation are needed.

References

Endotracheal intubation by inexperienced registrars in internal medicine: a comparison of video-laryngoscopy versus direct laryngoscopy

H. Biermann*, E. van der Heiden*, A. Beishuizen, A.R.J. Girbes, M.C. de Waard
Department of Intensive Care, Institute for Cardiovascular Research, VU University Medical Centre, Amsterdam, the Netherlands,
*equal contribution

Correspondence
M.C. de Waard – e-mail: mc.dewaard@vumc.nl

Keywords – Video-laryngoscope, GlideScope®, Macintosh, inexperienced personnel, successful tracheal intubation

Abstract
One of the most important tasks involved in the management of critically ill patients is to secure the airway. The preferred method for securing the airway is tracheal intubation followed by mechanical ventilation, but intubation is a difficult skill to acquire. When tracheal intubation using direct laryngoscopy is carried out by inexperienced personnel, there is a high risk of failure. Indirect laryngoscopy which uses a video-laryngoscope requires fewer skills to successfully secure the airway. We hypothesized that the use of the classical Macintosh laryngoscope is less effective in inexperienced hands compared with the video-laryngoscope GlideScope®, both in terms of successful intubation of the trachea and the time needed to achieve it. We asked thirty-nine registrars in internal medicine with negligible intubation experience to intubate a manikin airway model using a Macintosh laryngoscope and a video-laryngoscope GlideScope®. Inexperienced registrars with a mean duration of clinical experience as medical doctor of 1.7±1.0 years had a higher intubation success rate using the GlideScope® technique compared to the Macintosh technique (92% versus 69% respectively, ρ<0.05). However, the mean time needed for successful intubation was longer using the video-laryngoscope GlideScope® compared to the classical Macintosh laryngoscope (75±40 versus 39 ± 12 seconds respectively, ρ<0.05). In this study inexperienced registrars in internal medicine were able to intubate a manikin with a very high success rate using indirect video-laryngoscopy; however, the technique took more time to complete when compared with direct laryngoscopy.

Introduction
To obtain a secure airway is of vital importance in the management of a critically ill patient. The preferred method of securing the airway is endotracheal intubation followed by mechanical ventilation. Direct laryngoscopy with intubation remains difficult for medical personnel who do not have sufficient clinical experience with the technique. Indirect video-laryngoscopy may require a lower level of technical expertise and experience to successfully intubate and these laryngoscopes are now commercially available. The image obtained by the video-laryngoscope GlideScope® is displayed on a monitor and provides better laryngeal views than conventional laryngoscopes. In a meta-analysis of Griesdale et al. the GlideScope® video technique was associated with improved glottis visualisation compared to direct laryngoscopy. Several studies have assessed the use of video and conventional laryngoscopes in terms of success rate. A manikin study for emergent intubation during cardiopulmonary resuscitation by inexperienced medical practitioners demonstrated that when the GlideScope® video-laryngoscope was used, the time to successful intubation was shorter and the success rate higher than when the Macintosh laryngoscope was used. Controversially, data from studies in the emergency department suggest that the success rate of intubation by emergency medicine residents on the first attempt did not differ between GlideScope® and Macintosh and that intubation using GlideScope® required more time. Also, studies with inexperienced medical students and experienced anaesthesiologists showed that intubation with the GlideScope® took more time when a manikin was used and with easy intubation conditions. After extensive training of medical personnel and under close supervision of an anaesthesiologist, the intubation success rate in a manikin was over 90% when the GlideScope® technique was used.10 In this study we compared the use of the classical Macintosh laryngoscope and the GlideScope® video-laryngoscope by inexperienced untrained registrars in internal medicine in terms of successful endotracheal intubation, using an airway model.
Materials and methods

Protocol

Registrars in internal medicine, with no or negligible prior experience of laryngoscopy, performed tracheal intubation on an airway model (SimMan®, Laerdal Benelux B.V., Netherlands) using a conventional laryngoscope (Macintosh, Welch Allyn Inc., USA) and a video-laryngoscope (GlideScope®, Verathon Inc., USA). Whole-class explanation and demonstration of both intubation scenarios was given by an experienced specialist. Before the first intubation attempt, the registrars were randomly assigned to either the Macintosh or GlideScope® group by lot. When the GlideScope® was used in the first attempt, the Macintosh was used in the second attempt, and vice versa. The time from the first insertion of the laryngoscope in the mouth until successful intubation was recorded. A maximum time of three minutes was allowed for each intubation attempt. The registrars were allowed to perform only one intubation attempt for each laryngoscope type. For each registrar, age, gender, number of years of clinical experience as medical doctor, previous anaesthesiology training and estimated total number of performed intubations and those performed during the last year were recorded. Time (seconds) needed to intubate and success of the intubation (yes/no) were scored. Intubations were scored as successful when the endotracheal tube was inserted in the trachea and the intubation attempt was finished within a three-minute timeframe. Failed attempts like unsuccessful intubation or oesophageal intubation and whether the registrar recognized this failed attempt were recorded.

Statistical analysis

Continuous variables are presented as mean ± standard deviation (sd). Categorical variables are reported as counts and percentages. To test for significant differences between the two groups we used the Student’s t-test for continuous variables and the Fisher exact test for categorical variables. A wo-sided P≤0.05 was considered to indicate statistical significance.

Results

The group of participants consisted of 25 female and 14 male registrars in internal medicine of 29±3 years old, with no or negligible intubation experience. The mean duration of clinical experience as medical doctor was 1.7±1.0 years. All 39 participants performed two intubation attempts in an airway model using both the Macintosh laryngoscope and the GlideScope® video-laryngoscope. Eighteen of the 39 participants started with the Macintosh laryngoscope followed by the GlideScope® and 21 the other way round. The order in which the laryngoscopes were used did not affect intubation time or the intubation success rate. Furthermore, no effect of years of clinical experience as a medical doctor or estimated number of performed intubations in the past on intubation time was observed.

Intubation time using the Macintosh laryngoscope was 39±12 seconds (n=39) compared to 75±40 seconds (n=39) for the GlideScope® (P<0.05; figure 1A). However, more intubations failed within the three-minute time frame in the Macintosh group (12 out of 39 = 31%) compared to the GlideScope® group (3 out of 39 = 8%; P<0.05; figure 1B). All twelve unsuccessful intubations within the Macintosh group were identified as oesophageal intubations, of which only two were recognized as intubation failures by the participants. The three failed intubations in the GlideScope® group were due to exceeding the three minutes intubation attempt timeframe. Time needed for successful intubation was 35±10 seconds (n=27) in the Macintosh group and 66±24 seconds (n=36) using the GlideScope® (P<0.05).

Discussion

Endotracheal intubation is the preferred technique for securing an airway in compromised patients. Accordingly, the skill required to perform tracheal intubation is taught to both medical and paramedical healthcare professionals. Mulcaster et al. have shown that it takes approximately 50 intubations to acquire a 90% or higher success rate using direct laryngoscopy. Taking into account that many of the trained health care professionals perform intubations infrequently, it would be beneficial to rely on a technique that is easy to learn, perform, and has a high success rate.

Our manikin study shows that the GlideScope® technique led to a higher intubation success rate in registrars in internal medicine inexperienced in performing laryngoscopy, compared to direct laryngoscopy. However, the time needed to successfully intubate was longer using the GlideScope® technique. This was consistent with another study that compared success rate and speed of intubation by novices.
Endotracheal intubation by inexperienced registrars in internal medicine: a comparison of video-laryngoscopy versus direct laryngoscopy


Glomerular hyperfiltration of antibiotics

D.W. de Lange
Department of Intensive Care Medicine and the National Poison Information Center (NPIC), University Medical Center, University Utrecht, the Netherlands

Correspondence
D.W. de Lange – e-mail: D.W.deLange@umcutrecht.nl

Keywords – Antibiotic, renal clearance, ICU, pharmacokinetics, pharmacodynamics

Abstract
Normal glomerular filtration rate (GFR) declines with age and in disease. Diminished GFRs are seen in many patients on the ICU. The clearance of toxins and pharmaceuticals might be (temporarily) diminished especially in patients with septic or circulatory shock. Most physicians are aware of this and adjust the dosage of antibiotics accordingly: the dosage is reduced or the administration interval is prolonged. However, some patients have an increased clearance of antimicrobials, so-called glomerular hyperfiltration. Glomerular hyperfiltration is present whenever the GFR exceeds 160 ml/min/1.73 m² in men and 150 ml/min/1.73 m² in women. This is especially seen in young, male patients after neurotrauma, polytrauma or burn patients. The consequences of glomerular hyperfiltration might be that antibiotics are cleared more rapidly and concentrations fall below optimal levels. This compromises effective antimicrobial therapy when it is most important: directly from the beginning of treatment. Therapeutic Drug Monitoring (TDM) of all classes of antibiotics is needed in ICUs that treat critically ill patients at risk of glomerular hyperfiltration.

Acute kidney injury on the ICU
Acute kidney injury is a common complication of acute illness, affecting approximately 2-7% of hospitalised patients and more than 35% of critically ill patients. Acute kidney injury (AKI) consists of a rapid and sustained decline in the glomerular filtration rate (GFR) that results in the inability of the kidneys to eliminate waste products, toxins, antibiotics and other medications, or to maintain proper fluid and electrolyte balances. Most ICUs measure creatinine levels on a daily basis. Whenever creatinine levels increase (and estimated GFRs diminish) we interpret these changes as renal dysfunction, particularly in combination with oliguria (urine output <0.5 mL/kg/h). Whenever this occurs, most clinicians are quite eager to modify their dosage schemes of renally excreted antibiotics: either the dosage is reduced or the administration interval is prolonged. However, it remains questionable whether this is a sound decision in all circumstances.

Hyperdynamic circulation and glomerular hyperfiltration
The hemodynamic manifestations Systemic Inflammatory Response Syndrome (SIRS) are low systemic vascular resistance and a high cardiac output. The impact of this hyperdynamic circulation upon renal function is still being studied. In animal models of early sepsis, renal blood flow has been documented to increase parallel to cardiac output. In a later phase of sepsis the renal blood flow is diminished, resulting in decreased creatinine clearance. One of the first measures to improve cardiovascular function in patients with SIRS is fluid resuscitation followed by the application of vasopressors. Again, animal research has shown that crystalloids and vasoactive drugs can result in an increase of creatinine clearance. Data from these studies suggest that in critically ill patients without significant renal dysfunction and in whom adequate resuscitation has been achieved, renal clearance might actually be increased in the acute phase: this is known as glomerular hyperfiltration.

How do we measure GFR when renal function is unstable?
The gold standard estimations of GFR include urinary clearance of iohexal and clearance of various radionuclide markers, among which 99mTc-labeled diethylenetriaminepentaacetic acid (DTPA), 51Cr-labeled EDTA, and 125I-labeled iothalamate. However, these test methods are cumbersome and are almost never used in daily practice. Numerous equations have been used to estimate the GFR from serum creatinine levels in patients with chronic kidney diseases. The Modification of Diet in Renal Disease (MDRD), the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) and
Cockcroft-Gault formula are the most widely used estimations for GFR in patients with chronic but stable kidney disease. Unfortunately, all have a poor application in the critically ill, especially when renal function is not stable.\(^3\)\(^\text{-}^5\) Although these calculations are somewhat more useful than a single creatinine concentration, the use of such equations to estimate the GFR should be discouraged in critically ill patients.\(^3\)\(^\text{-}^6\) A possible better way to estimate GFR in critically ill patients is a urinary creatinine collection taken over 4 to 12 hours.\(^5\)\(^\text{-}^9\) However, the optimal time period in which creatinine clearance should be measured in unstable critically ill patients is still debatable. The GFR is influenced by circadian rhythm and intra-individual variability is likely to be substantial. Because rapid changes in renal function might occur in the critically ill, more frequent sampling of urine creatinine collection has been advocated.

**What is glomerular hyperfiltration?**

One of the most important functions of the kidney is to excrete circulating metabolites, toxins, waste products and pharmaceutical products such as antibiotics. This can be achieved by a combination of glomerular filtration, tubular secretion and reabsorption. Glomerular hyperfiltration means that the renal clearance of waste products and antibiotics is above normal limits. Accurately defining this is difficult because we cannot agree upon “normal renal function” in any population, let alone in critically ill patients! However, the most accepted definition of “normal renal function” is the GFR of approximately 130 mL/min/1.73 m\(^2\) in young, healthy, adult males and 120 mL/min/1.73 m\(^2\) in young, healthy, adult females.\(^14\) Importantly, these values decline over age (figure 1). One of the most sensible definitions of “glomerular hyperfiltration” is a GFR >10% higher than the normal limits. This means a GFR of >160 mL/min/1.73 m\(^2\) in young men and a GFR >150 mL/min/1.73 m\(^2\) in young women.\(^8\) These conservative thresholds are likely to identify patients that truly have “glomerular hyperfiltration”. In a single-centre observational cohort\(^\text{(n=89)}\) 17.9% of the patients had such “glomerular hyperfiltration” on admission and 75% had hypoalbuminaemia.\(^15\) During the first week of admission, the percentage of patients with glomerular hyperfiltration rose to 30%. The patients with an elevated GFR were primarily younger, polytrauma victims or postoperative patients, were less severely ill (lower APACHE II scores) and had higher urine outputs. In a subgroup of patients with traumatic brain injury, who received norepinephrine treatment, increased creatinine clearance had been noticed. These increased GFRs (>150 mL/min/1.73 m\(^2\)) were already present before the initiation of norepinephrine treatment and remained elevated for the duration of this study (24 hours).\(^16\) Quite similar results had been found in a much older study. Here the effects of a combination of dopamine and norepinephrine were studied in 20 young, stable patients with brain trauma. The mean GFR at the beginning of the study was 152 mL/min/1.73 m\(^2\).\(^17\) Recently these results have been confirmed in another study involving patients with brain trauma.\(^7\) Based upon the definitions of glomerular hyperfiltration as stated above, they found that in 17 out of 20 (85%) patients, renal clearance was clearly increased (mean GFR of 179 with interquartile range of 159-198 mL/min/1.73 m\(^2\)). The mean age of this population was 26 years and they were receiving 3% NaCl infusions and vasopressor therapy to maintain a cerebral perfusion pressure >60 mmHg. From these small and uncontrolled case series, which all used proper creatinine clearance in urine samples, it follows that younger patients, admitted after trauma and/or brain trauma are at particular risk of developing glomerular hyperfiltration. However, higher than normal antimicrobial clearances have been documented in patients with sepsis\(^18\)\(^\text{-}^19\), haematological malignancies\(^20\)\(^\text{-}^21\) and patients with burns\(^22\)\(^\text{-}^23\) as well.

**What are the consequences of glomerular hyperfiltration?**

Why should we be bothered with glomerular hyperfiltration? A faster excretion of waste products and toxins is a good thing and the effects of other pharmaceuticals can be dosed according to their pharmacodynamic effect. If midazolam metabolites are excreted in a more rapid fashion, we will just increase the infusion rates until the patient is sufficiently sedated. Unfortunately, not all effects of pharmaceuticals are directly evident. If antibiotics are administered inadequately.

![Figure 1. Declining creatinine clearances over age.](image-url)
this might result in slower eradication of the infection or even introduce resistance. Fortunately, resolution of infection takes time and recognizing whether the antibiotics are working properly will take days. Therefore, glomerular hyperfiltration might be the cause of ineffective antimicrobial therapy just at the time when it counts most: at the start of treatment!

**Pharmacodynamics and glomerular hyperfiltration**

Different classes of antibiotics possess different pharmacodynamic properties. Some antibiotics have concentration dependent killing, while others typically demonstrate time depending killing (see figure 2).

Aminoglycosides, like gentamicin and tobramycin, are classical examples of antibiotics that exhibit concentration dependent killing properties. The higher the peak concentration (also called maximum concentration, $C_{\text{max}}$) in relation to the minimum inhibitory concentration (MIC) of a bacterium the better the killing. The killing of bacteria is optimal whenever the $C_{\text{max}}$/MIC > 10. This means that the peak concentration of an aminoglycoside, in the organ you are trying to treat, should be 10x higher than the MIC of the bacterium. The peak concentration depends on the loading dose of the aminoglycoside and its immediate dilution in the extracellular fluid compartment (the so-called volume of distribution, $V_d$). Aminoglycosides are hydrophilic, rather large molecules. Therefore, their apparent $V_d$ is rather small (no penetration into cells, no penetration into lipophilic compartments) and almost the entire aminoglycoside loading dose is present in a free and unbound fashion. Modern dosage schemes are $>$7 mg/kg once daily. Glomerular hyperfiltration will not influence the $V_d$ and therefore have no influence on the loading dose. However, the clearance of aminoglycosides might be faster than in patients with a normal GFR. Therefore, the frequency of the maintenance dose might be increased to once every 18 hours instead of once daily. Indeed, the $V_d$ of aminoglycosides is unpredictable in critically ill patients and the penetration into organs (like the lung and the abdominal cavity) is limited. As a consequence, the pharmacodynamic goal ($C_{\text{max}}$/MIC$>$10) is often not attained in critically ill patients.

Beta-lactam antibiotics (penicillins, cephalosporins, monobactams and carbapenems) demonstrate time dependent killing (see figure 2). This means that the killing of bacteria by beta-lactam antibiotics is maximal whenever the free unbound concentration of beta-lactams is higher than the minimum inhibitory concentration ($fuT$>MIC) during 70-100% of the time. Again, the direct concentration depends on the loading dose and its immediate dilution into the $V_d$. Unfortunately, the $V_d$ can be highly variable in critically ill patients. Just consider a patient in septic shock who is being aggressively resuscitated with fluids. In such patients, the $V_d$ for hydrophilic antimicrobials (like aminoglycosides, beta-lactams, and vancomycin) might even be doubled. For this reason, a one-size-fits-all loading dose cannot be established in critically ill patients.

However, the trough levels (also called minimum levels, $C_{\text{min}}$) are dependent on binding to proteins and excretion by the liver and kidneys. Whenever there is glomerular hyperfiltration, the beta-lactams will be excreted more efficiently and minimal levels will be reached earlier. Given the pharmacodynamic goal of keeping the trough level above the MIC for as long as possible, the dosage frequency may have to be increased. Just giving higher dosages might lead to higher free fractions and more clearance of antibiotics. An alternative is to administer beta-lactams by continuous infusion. Theoretically the trough levels will be above MIC for all of the time ($fuT$>MIC = 100%). Again, in critically ill patients the volume of distribution and renal clearance are not stable over time.

The range of protein binding of beta-lactams is enormous. Some beta-lactams are predominantly bound to albumin, like ceftiraxone (85-95% is protein bound), while others are hardly bound to albumin, like amoxicillin (17-20% is protein bound). Unfortunately, critically ill patients often have hypoalbuminaemia. In the Saline versus Albumin Fluid Evaluation (SAFE)-study, hypoalbuminaemia (<25 g/L) was seen in 40.5% of the patients on admission to the ICU.
Glomerular hyperfiltration of antibiotics

Table 1. Suggested reading

<table>
<thead>
<tr>
<th>Suggested reading</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marta Ulldehomins and co-authors emphasise how often hypoalbuminaemia is seen in the ICU. They highlight the consequences of hypoalbuminaemia on different classes of antibiotics. A list of antibiotics with their estimated protein binding is included. Clin Pharmacokinet. 2011;50:99-110.</td>
</tr>
<tr>
<td>Frederico Pea and Pierluigi Viale describe which chemical properties are important for an antimicrobial in order to reach its target organ. They also explain the concentration needed for optimal killing and conclude that certain antimicrobials (especially the aminoglycosides) do not attain sufficient concentrations in target organs. This seriously limits their use. A list with proposed antimicrobial dosage schemes is included. Crit Care. 2009;13:214.</td>
</tr>
<tr>
<td>Andrew Udy and co-authors describe the consequences of augmented renal clearance (=glomerular hyperfiltration) of various antibiotic classes. They describe the difficulties of assessing glomerular filtration rate in critically ill patients and suggest that creatine clearance in urine is probably the best estimation. Clin Pharmacokinet. 2010;49:1-16.</td>
</tr>
</tbody>
</table>

Table 1. Suggested reading

<table>
<thead>
<tr>
<th>Suggested reading</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marta Ulldehomins and co-authors emphasise how often hypoalbuminaemia is seen in the ICU. They highlight the consequences of hypoalbuminaemia on different classes of antibiotics. A list of antibiotics with their estimated protein binding is included. Clin Pharmacokinet. 2011;50:99-110.</td>
</tr>
<tr>
<td>Frederico Pea and Pierluigi Viale describe which chemical properties are important for an antimicrobial in order to reach its target organ. They also explain the concentration needed for optimal killing and conclude that certain antimicrobials (especially the aminoglycosides) do not attain sufficient concentrations in target organs. This seriously limits their use. A list with proposed antimicrobial dosage schemes is included. Crit Care. 2009;13:214.</td>
</tr>
<tr>
<td>Andrew Udy and co-authors describe the consequences of augmented renal clearance (=glomerular hyperfiltration) of various antibiotic classes. They describe the difficulties of assessing glomerular filtration rate in critically ill patients and suggest that creatine clearance in urine is probably the best estimation. Clin Pharmacokinet. 2010;49:1-16.</td>
</tr>
</tbody>
</table>

results in a higher free and unbound antibiotic fraction. Although this means that the “active fraction” has increased it also means that the fraction available for renal clearance is higher. This is particularly true for beta-lactam antibiotics with a high protein binding, like ceftriaxone. In patients with hypoalbuminaemia (and normal GFR) ceftriaxone clearance might be doubled, leading to trough levels below the MIC too.31 The pharmacodynamic goal (fu>T>MIC 70-100%) might therefore, not be reached.

Clearly, we cannot predict the initial Vd, the GFR and the hypoalbuminaemia in critically ill patients and changes over time are commonplace on the ICU. A prerequisite for the administration of beta-lactams in critically ill patients is therapeutic drug monitoring (TDM). We have to assure whether the free and unbound trough levels remain above the MIC whenever something changes in our patients. Additionally, TDM can minimise the risk of toxicity in excessive dosing. At present only very few hospitals in the Netherlands are able to provide this necessary TDM.

Conclusions

Glomerular hyperfiltration (>150 ml/min/1.73 m² in women and >160 ml/min/1.73 m² in men) is seen in a substantial subpopulation on the ICU. Especially younger patients with neurotrauma, polytrauma, burns or sepsis, appear to be at risk of higher than normal clearance of antibiotics. In addition, hypoalbuminaemia causes higher free and unbound fractions of antibiotics, and thereby further increases renal clearance of protein bound antibiotics. Both lead to suboptimal concentrations of antibiotics and possibly less effective antimicrobial therapy. Creatinine concentrations and estimations of the glomerular filtration rate (GFR) are inadequate for measuring such elevated clearance in clinical practice. Because rapid changes in renal function might occur in the critically ill, measuring creatinine clearance with short period urine collections seems the best available option. All kinds of pharmacokinetic conditions, like hypoalbuminaemia, clearance and volume of distribution, are constantly changing in critically ill patients. Therefore, Therapeutic Drug Monitoring (TDM) of all antimicrobials (including beta-lactam antibiotics) should be available in hospitals treating critically ill patients.

References


Cryoglobulinemia complicated by diffuse alveolar haemorrhage

J.E.M. Schilders¹, A.J.B.W. Brouwers², H.C.T. van Zaanen¹
Departments of Internal Medicine, Division of ¹Haematology and ²Intensive Care, Sint Franciscus Gasthuis Rotterdam

Correspondence
H.C.T. van Zaanen – e-mail: h.vanzaanen@sfg.nl

Keywords – Alveolar haemorrhage, cryoglobulinemia, vasculitis

Abstract
Objective: This case report describes a 58-year old man with respiratory insufficiency caused by a systemic immune complex vasculitis. A brief review of the literature is given.
Patient/Subject: A 58-year old man presented with respiratory insufficiency caused by a systemic immune complex vasculitis. His symptoms were haemoptysis due to alveolar haemorrhage, a leukocytoclastic vasculitis of the skin and glomerulonephritis. He was diagnosed with cryoglobulinemia and was successfully treated with prednisone and rituximab.
Conclusion: Cryoglobulinemia should be considered in small vessel vasculitis. Diffuse alveolar haemorrhage is a rare complication of type 2 cryoglobulinemia.

Introduction
Immunoglobulin M (IgM) associated disorders, such as cold agglutinin disease, cryoglobulinemia and peripheral neuropathy, are caused by autoreactivity of IgM paraproteins. Waldenström macroglobulinemia or signs of lymphoma are usually absent and the M-protein is low.
Cold agglutinin disease is characterized by antibodies directed against the I/i antigens on erythrocytes. This can be induced by viral infections (i.e. EBV, CMV) or *Mycoplasma pneumoniae*, for example. Clinical features consist of acrocyanosis and haemolytic anemia.
Cryoglobulinemia is defined as presence of one or more immunoglobulins in the serum that precipitate at temperatures below 37°C and dissolve again on rewarming. Cryoglobulinemia is usually classified into three types according to Brouet’s classification. Type 1 is characterized by the presence of a monoclonal immunoglobulin which can be seen in lymphoproliferative disorders such as chronic lymphatic leukaemia, multiple myeloma or non-Hodgkin lymphoma. Type 2 has a monoclonal component (mostly IgM) and polyclonal immunoglobulin which can lead to immune-complex vasculitis. Type 3 has polyclonal immunoglobulins of different isotypes. Types 2 and 3 are also called mixed type cryoglobulinemia.¹ There is a wide range of symptoms. Patients can be asymptomatic, but they can also have a hyperviscosity syndrome and on rare occasions present with multi organ failure. Criteria for the classification of cryoglobulinemia patients are based on serologic, pathologic and clinical findings. 70% of cases classify as a mixed type cryoglobulinemia (type 2), which has a strong association with the hepatitis C virus (HCV) infection. We present a patient with hepatitis C negative mixed type cryoglobulinemia with alveolar haemorrhage caused by vasculitis.

Case report
A 58-year old male was admitted with erythematous lesions on his lower extremities and decreased renal function. Skin biopsy showed a leukocytoclastic vasculitis, immunofluorescence was not performed. On the ward the patient’s renal function declined with creatinine levels increasing from 92 to 170 µmol/L (normal 70-106 µmol/L). Over 40% dysmorphic erythrocytes, proteinuria and hyaline casts were present in the urine, suggesting glomerulonephritis. Unfortunately, renal biopsy was inconclusive since it did not contain enough glomeruli.
C-reactive protein was 14 mg/L, haemoglobin 5.5 mmol/L, thrombocytes 174 x10⁹/L and leukocytes 15.1x10⁹/L with a normal differentiation. Liver enzymes were normal. Before admission to the ward he was treated with clarithromycin for a presumed pulmonary infection that showed on his chest X ray (figure 1). All cultures remained negative.
A few days after admission the patient developed progressive hypoxemia and haemoptysis and was admitted to the Intensive Care for intubation and mechanical ventilation. CT scan of the lungs showed bilateral thickening of interlobular septa with cysts and ground-glass opacification (figure 2). Bronchoalveolar lavage showed red blood cells, 67% T-lymphocytes, 6% granulocytes and 14% alveolar macrophages. Because of the haemorrhage a biopsy was not performed. All tests for auto-immune diseases (ANA, ENA, ANCA, anti-GBM and anti-CCP) were negative except for a positive IgM rheumatoid factor. Decreased levels of C3 (0.59 gr/L), C4 (<0.1 gr/L) and...
an elevated Clq-binding test of 93% (normal <8%) suggested an immune complex disease. The viral serology including hepatitis B, C, EBV, CMV and HIV were also negative. Because of a suspected seronegative granulomatosis with polyangiitis he was started on prednisone 1dd 60mg, cyclophosphamide 1dd 100mg for a total of ten days (1.5mg/kg adjusted for acute kidney injury) and plasmapheresis, with poor result. Decreased levels IgG (0.6 g/L) and IgA (0.6 g/L) were found with a slightly increased IgM (2.33 g/L), however, this test was performed after initial treatment. Morphology of the bone marrow biopsy showed no abnormalities. Immunological examination showed 1% plasma cells and 15% monoclonal B-lymphocytes with an increased kappa/lambda ratio of 47 (normal <4.9).

The level of free light chains kappa in the serum was elevated (109 mg/L), the ratio of kappa/lambda free light chains was also increased (ratio 23, normal 0.26-1.65) and cryoglobulins were present. Hepatitis C RNA could not be detected.

We concluded that clinical and laboratory findings suggested a hepatitis C virus negative mixed cryoglobulinemia (type 2) with multi organ involvement including diffuse alveolar haemorrhage, which led to respiratory failure, leukocytoclastic vasculitis of the skin and glomerulonephritis caused by an immune complex vasculitis.

The patient was treated with prednisone 1mg/kg daily and rituximab 375 mg/m², a monoclonal antibody against CD20 on B-lymphocytes, initially weekly for four weeks and later every three months for a total of two years according to the Non Hodgkin Lymphoma protocol. After several weeks of treatment his clinical condition improved. Chest X-rays improved significantly and normalized over time. Currently, 17 months later, he is no longer on steroids and is doing well. Kappa/lambda ratios, IgM, complement levels etc. normalized and cryoglobulins can not be detected anymore.

**Discussion**

Our patient was diagnosed with cryoglobulinemia after initial treatment with prednisone, cyclophosphamide and plasmapheresis for presumed granulomatosis with polyangiitis. We found decreased levels of IgG and IgA plus a slightly increased IgM with cryo-activity. It is possible that IgM levels were even higher prior to this treatment. Free light chains kappa in the serum were elevated and a low concentration of monoclonal B-lymphocytes in the bone marrow was found. CT scan did not show lymphadenopathy or organomegaly and an underlying malignancy could not be detected despite a population of monoclonal B-cell lymphocytes in the bone marrow. Our patient had several minor and major criteria to support the diagnosis of cryoglobulinemia, including a positive IgM rheumatoid factor, an activated immune system, detection of cryoglobulins and a monoclonal B-lymphocyte population.

There are three subtypes of cryoglobulinemia. Type 1 is characterized by the presence of a monoclonal immunoglobulin which can be seen with lymphoproliferative disorders such as multiple myeloma, NHL or chronic lymphatic leukemia. Patients with type 1 cryoglobulinemia are typically asymptomatic but can have a hyperviscosity syndrome. Type 2 has a monoclonal component, mostly IgM, and polyclonal immunoglobulins, type 3 has polyclonal immunoglobulins of different isotypes. Type 2 and 3 (mixed types) are associated with different infectious, immunological or malignant disorders. Mixed type cryoglobulinemia is rare and the prevalence is unknown. The M:F sex ratio of type 2 is 1:3.7 with an onset normally between the fourth and sixth decade. In 70-100% of cases hepatitis C virus antibodies are
In mixed cryoglobulinemias immune complex mediated
of HCV infection. This patient had a type 2 cryoglobulinemia without evidence
ulinemia. Together with the other results we concluded that
in this patient, is typically more frequent in type 1 cryoglob -
hyperviscosity. Immune complex mediated vasculitis, as seen
macroglobulinemia or NHL and he did not have symptoms of
fulfil the criteria for multiple myeloma, CLL, Waldenströms
in the bone marrow without a HCV infection, he did not
made. Although this patient had monoclonal B-lymphocytes
our patient, the diagnosis of mixed cryoglobulinemia was
skin ulcers. Based on previous major and minor criteria in
hepatitis, glomerulonephritis, peripheral neuropathy and
occurs in 10-15% of patients; B-cell NHL is most common but
malignancies. There are no standardized diagnostic or classification
criteria for cryoglobulinemic vasculitis with diffuse alveolar
haemorrhage. To start with the more common disorders like
infections, malignancies and chronic heart failure should be
ruled out. In patients with pulmonary abnormalities, clues that
can lead to the diagnosis of cryoglobulinemia, are typically
skin purpura, glomerulonephritis, unexplained low C4 levels,
monoclonal gammopathy and neuropathy.

Pathophysiology
Chronic stimulation of the immune system by lymphoprolifera
tive disorders, infections or autoimmune diseases cause
clonal expansion of B cells which can create cryoglobulins. This
can lead to vascular occlusion and hyperviscosity syndrome
which is frequently observed in type 1 cryoglobulinemia. In
mixed cryoglobulinemias immune complex mediated
vasculitis is more often observed, mainly affecting arterioles,
capillaries and venules. Very rarely this involves alveoli. Mixed type cryoglobulinemia is related to the hepatitis C virus.
The HCV E1/E2 glycoprotein is able to bind to CD81 on the
B-lymphocyte which leads to proliferation of B-lymphocytes. The pathophysiology in hepatitis C virus negative patients
remains unclear.

Clinical manifestations and diagnosis
In over 50% of cases clinical features are mild and slowly
progressive, but in over 30% of cases patients have severe
vasculitis with involvement of multiple organs. In a series of
over 200 patients, the most common symptoms were found to
be purpura, arthralgias and neuropathies. 70% of patients have
hepatitis while glomerulonephritis is present in about 30%.
Alveolar vasculitis has been described in about 3% of cases, so
it is very rare. 4,6,7 To assess for cryoglobulins, blood should be drawn into tubes
that are placed directly into warm water (37 ºC), after this the
serum is separated by centrifugation at the same temperature.
To see if precipitation occurs, the serum is kept at 4 ºC for
a maximum of three days. Criteria for the classification and
diagnosis of cryoglobulinemia are based on serologic, pathologic and clinical findings. The presence of cryoglobulins in
the serum together with major criteria like activation of the
immune system, purpura and leukocytoclastic vasculitis
confirm the diagnosis. Minor criteria include a positive
IgM rheumatoid factor, positive screening for HCV/HBV,
a clonal B-cell population in the bone marrow, chronic
hepatitis, glomerulonephritis, peripheral neuropathy and
skin ulcers. Based on previous major and minor criteria in
our patient, the diagnosis of mixed cryoglobulinemia was
made. Although this patient had monoclonal B-lymphocytes
in the bone marrow without a HCV infection, he did not
fulfil the criteria for multiple myeloma, CLL, Waldenströms
macroglobulinemia or NHL and he did not have symptoms of
hyperviscosity. Immune complex mediated vasculitis, as seen
in this patient, is typically more frequent in type 2 cryoglob-
ulinemia. Together with the other results we concluded that
this patient had a type 2 cryoglobulinemia without evidence of
HCV infection.

There are no standardized diagnostic or classification
criteria for cryoglobulinemic vasculitis with diffuse alveolar
haemorrhage. To start with the more common disorders like
infections, malignancies and chronic heart failure should be
ruled out. In patients with pulmonary abnormalities, clues that
can lead to the diagnosis of cryoglobulinemia, are typically
skin purpura, glomerulonephritis, unexplained low C4 levels,
monoclonal gammopathy and neuropathy.

Prognosis and treatment
Treatment depends on the clinical features; patients who are
asymptomatic do not need any treatment. Early manifestations
may respond to low doses of corticosteroids. In patients with
an active Hepatitis C infection, antiviral therapy is indicated
with PEG interferon-alpha and ribavirin. 5 HCV serology alone
is not sufficient, HCV RNA is necessary to confirm an HCV
infection and to start treatment. More severe symptoms like
vasculitis need to be treated with high doses of corticosteroids,
immunosuppressive drugs or even plasmapheresis when
patients suffer from the hyperviscosity syndrome. Rituximab
plays an important role in treating B-cell NHL and has also
proved to be effective in treating mixed cryoglobulinemia. 10,11
Malignancy is a late complication of cryoglobulinemia and
occurs in 10-15% of patients; B-cell NHL is most common but
also hepatocellular carcinoma and papillary thyroid carcinoma
can occur. 2,3 Due to complications like liver cirrhosis, renal
failure and malignancies, the survival rates of patients with
this condition are significantly low. 5 The role of rituximab for treatment in the long term is
uncertain, but given the analogy with low grade NHL, in this
patient, we will continue rituximab every three months for two
years, according to low grade NHL protocol.
In summary, the diagnosis of cryoglobulinemia should
be considered in small vessel vasculitis. Diffuse alveolar
haemorrhage due to vasculitis caused by cryoglobulinemia
is very rare. Rituximab is effective in the treatment of
(mixed) type 2 cryoglobulinemia. Follow up of patients with
cryoglobulinemia is required because of an increased risk of
malignancies.

Acknowledgment
The authors have no competing interests.

References
1. Brouet JC, Clauvel JP, Danon F et al. Biological and clinical significance of cryo-
clinical, and serological features and survival in 231 patients. Semin Arthritis
4. Abel G, Zhang QX, Agnello V. Hepatitis C virus infection in type II mixed cryo-
Severe anti NMDA encephalitis and EBV infection

S.J. Derksen1, B. Goraj2, J.P. Molenaar3, J.G. van der Hoeven1
Departments of 1Intensive Care, 2Radiology, 3Neurology, Radboud University Medical Centre, Nijmegen, the Netherlands

Correspondence
S.J. Derksen – e-mail: sjieuwke@me.com

Keywords – Anti NMDA encephalitis, EBV and limbic encephalitis

Abstract
N-methyl-D-aspartate (NMDA) receptor antibody encephalitis is an immunotherapy-responsive panencephalitis. Patients usually present with characteristic clinical features in a specific order. We describe a patient who developed anti NMDA receptor encephalitis with a positive liquor EBV titer, suggesting formation of antibodies including anti NMDA. After a prolonged ICU stay the patient had a slow but full recovery. Despite severe neurological symptoms, in general, the prognosis of anti NMDA receptor encephalitis is good and warrants prolonged intensive care treatment when indicated.

Introduction
N-methyl-D-aspartate (NMDA) receptor antibody encephalitis is an immunotherapy-responsive panencephalitis.1-3 Patients usually present with characteristic clinical features in a specific order.1,2,4 After a prodomal flu-like illness, patients develop psychiatric symptoms with short term memory loss followed by orofacial dyskinesias, limb choreoathetosis, catatonia and autonomic instability. Another characteristic feature is a persistent amnesia of the entire process.5 This report describes a patient with chronic use of immunosuppressants and with a positive spinal fluid Epstein Barr virus (EBV) titer who developed anti NMDA encephalitis.

Case report
For eight weeks a 26-year-old male had experienced several episodes with blackouts and strong feelings of romantic love and joy, lasting several minutes. These episodes increased in frequency and the patient showed signs of confusion. Two weeks before admission in the referring hospital the patient developed anxiety attacks, became confused and exhibited echolalia. There was also indecisiveness, sleepiness and difficulties with speech. Eight weeks after the first symptoms arose, the patient was admitted to the referring hospital. An EEG was consistent with encephalopathy. Neural imaging including an MRI showed no abnormalities but spinal fluid analysis showed a mild lymphocytic pleocytosis. Cultures of both spinal fluid and blood were negative. The patient became bedridden and because of further deterioration that included inability to walk or speak and increasing confusion, he was transferred to our hospital for evaluation.

The patient had had a renal transplant in 2003 for reflux nephropathy. His medication consisted of prednisone 10 mg once daily and mycofenolate mofetil 500 mg twice daily. After transplantation the patient had multiple urinary tract infections due to kidney stones.

On arrival in our hospital, 12 days after admission in the referring hospital, neurologic examination showed non-fluent speech with difficulty finding words and following more complex commands. The patient had a cautious and broad-based gait and there was a slight tremor of both hands without myoclonus. Deep tendon reflexes were symmetrical and lively, with bilateral clonus of the ankle reflex and Babinski’s sign. Testing of cranial nerves, strength, sensibility and coordination showed no abnormalities.

The patient was admitted to the neurology ward. After admission his symptoms progressed. He developed catatonia with dyskinesias in the face and mouth, manifesting as orofacial movements with clenching of the teeth or forcefully opening his mouth for several minutes. Because of catatonia and dyskinesias he was transferred to our medium care unit five days after admission, where he was given midazolam intravenously. Thyroid and adrenal function were normal. Kidney and liver function tests as well as a full blood count were normal. CSF showed lymphocytic pleocytosis and an increased protein concentration (95% lymphocytes, protein 864 mg/l). Cultures of blood and CSF were negative. Viral studies of blood and CSF for neurotropic viruses, HSV, CMV, enterovirus, parechovirus and varicella zoster were negative. However, a PCR for EBV from CSF became positive with 30,000 copies per ml and EBV ebna IgG 152 U/ml and EBV vca IgG >200 U/ml in blood became positive a few days later. A diagnosis of EBV encephalitis was made and ganciclovir 200 mg twice daily
was started and mycophenolate sodium was discontinued. An initial MRI showed no abnormalities, but a second T2-FLAIR MRI showed a subtle diffuse increase of signal intensity of the white matter bilaterally (Figure 1). An EEG showed slow delta-theta activity.

After an initial improvement and despite aggressive treatment of the EBV encephalitis with ganciclovir and immunoglobulins, given at a dose of 0.4 gr/kg/day for five days, epileptic seizures continued and the patient became catatonic for longer periods. During the following four weeks the patient deteriorated further and needed continuous sedation to treat the seizures and catatonia.

Three weeks after admission, the patient was transferred to the ICU for mechanical ventilation. Since there had been no improvement after the start of antiviral treatment and because of the sequence of symptoms and by now nearly permanent catatonia – only interrupted by seizures – limbic encephalitis was suspected. CSF auto-antibody testing was performed and was positive for anti N-methyl-D-aspartate (NMDA) receptor antibodies. Subsequently a diagnosis of anti NMDA (receptor) encephalitis was made. The patient was treated with immunoglobulins, in the same dose as mentioned, and methylprednisolone, with little improvement. For two weeks the patient exhibited signs of autonomic instability, with fluctuations of blood pressure, cardiac rhythm and fever and he was eventually treated with rituximab (700 mg; 375 mg/m²) weekly for four weeks. Thereafter the patient improved slowly and was extubated after four weeks and discharged eight days later. The patient continued to improve but on discharge he still showed apathy, marked rigidity and short term memory loss. A few months after discharge the patient had made a full recovery. An extensive work up (abdominal/scrotal ultrasound; CT scan thorax/abdomen; PET-CT) showed no evidence of an underlying tumor.

**Discussion**

N-methyl-D-aspartate receptor antibody encephalitis is an immunotherapy-responsive limbic panencephalitis.\(^1\)\(^-\)\(^3\) This disorder is associated with a misdirected autoimmune response with formation of antibodies against the NR1 subunit of the NMDA receptor.\(^4\)\(^-\)\(^6\) NMDA receptors are ligand-gated cation channels on neural cell membranes with crucial roles in synaptic transmission and plasticity and are predominantly concentrated in the hippocampus and forebrain.\(^4\)\(^-\)\(^5\) About 60% cases occur as a paraneoplastic process, most commonly an ovarian teratoma.\(^1\) Anti NMDA limbic encephalitis affects young people, predominantly young women.\(^1\) In male patients the detection of a tumor is rare, but testicular germ cell tumors, teratoma of the mediastinum, small cell lung carcinoma, Hodgkin's lymphoma and neuroblastoma have been found.\(^5\)\(^-\)\(^6\) Patients present with characteristic clinical features in a specific order and many patients have initially been seen by psychiatrists but subsequently developed seizures and complex symptoms requiring multidisciplinary care.\(^4\)\(^-\)\(^7\) The

![Figure 1. T2-FLAIR MRI with subtle diffuse increase of signal intensity of white matter bilaterally.](image-url)
development of autonomic instability and stupor may require mechanical ventilation for weeks or even months and seizures should be treated aggressively.\textsuperscript{1,2} Symptoms usually start with a prodromal flu-like illness with fever, malaise, headache or fatigue, after which psychiatric symptoms develop, the most common being anxiety, agitation, delusions and hallucinations with short term memory loss followed by orofacial dyskinesias, limb choreoathetosis, catatonia and autonomic instability with fluctuations of blood pressure, temperature and cardiac rhythm. Another characteristic feature is a persistent amnesia of the entire process.\textsuperscript{1,2,5}

CSF reveals inflammatory changes in >90% of cases with an elevated white cell count, mainly lymphocytes and mildly elevated protein content with oligoclonal bands.\textsuperscript{2-4,5} EEG studies are abnormal in >90% of cases and usually show diffuse delta-theta activity.\textsuperscript{5,7,9} Brain MRI is often normal initially, but 55% of cases will show non-focal cortical hyper intensity in FLAIR setting, predominantly in the medial temporal lobes.\textsuperscript{2-4,8} These findings can be asymmetric. MRI abnormalities are not prerequisite for the diagnosis. The finding of N-methyl-D-aspartate receptor antibodies in CSF, however, together with the characteristic clinical picture confirms the diagnosis.

The concentration of NMDA receptor antibodies correlates well with the clinical state in individual patients.\textsuperscript{5,8} Therefore, the major aim of therapy is to reduce NMDA receptor antibodies.\textsuperscript{4,5,8} For patients with an underlying tumor, removal of the malignancy is of paramount importance.\textsuperscript{1,2,6} In addition, immunotherapies appear to hasten recovery. In nonparaneoplastic cases immunotherapies are administered, again with the aim of reducing NMDA receptor antibody levels. Commonly used immunotherapies in this case series include corticosteroids, intravenous immunoglobulins and plasma exchange. Patients who do not improve with these first line therapies may improve with rituximab and/or cyclophosphamide.\textsuperscript{4-6}

Our patient who was known to have a chronic use of immunosuppressants and a positive spinal fluid EBV titer, developed anti NMDA receptor encephalitis. Patients with long term immunosuppressant therapies are typically at risk for infection or reactivation of EBV. A typical aspect of EBV infection is proliferation of B cells with accompanying antibody formation. These antibodies may be directed against the NMDA receptor. Although extensive studies of CSF, brain biopsies and autopsies in other cases of anti NMDA receptor encephalitis were negative for viruses,\textsuperscript{5,6} a viral pathogenesis in general is suggested by the prodromal flu-like illness and in this case particularly by a concurrent high spinal EBV load (104). This does not mean that EBV encephalitis per se is the cause of anti NMDA receptor encephalitis, but strongly suggests pathogenicity of the anti NMDA receptor antibody itself.

**Conclusion**
We describe a specific neurological syndrome (limbic encephalitis) associated with auto antibodies against the NMDA receptor temporarily related to EBV encephalitis. Despite severe neurological symptoms, anti NMDA receptor encephalitis generally has a good prognosis and warrants prolonged intensive care treatment if indicated.

**References**

After a long flight from Asia, a 44-year-old woman was admitted to our hospital following collapse and with dyspnoea. CT-scanning confirmed the diagnosis of pulmonary emboli. A “saddle embolus” bridging across both pulmonary arteries provided the explanation for her symptoms. Thrombolysis was started immediately and she was admitted to the ICU. After being admitted for 12 hours, she developed severe shock with an extended right cardiac ventricle. An ultrasound guided continuous SvO$_2$ central venous catheter was inserted into the right internal jugular vein. After a few hours, the image in figure 1 was obtained.

We were puzzled by the periodic fluctuations in SvO$_2$ with decreasing amplitude and zoomed in to analyze the duration of the periodicity. This proved to be 10 minutes (figure 2), exactly the default time used by the anti-decubitus mattress to inflate/deflate. After shutting down the mattress the periodicity disappeared (data not shown). The patient fully recovered and was successfully discharged from the ICU three days later.

An explanation of the observed phenomenon may be the periodic sequential inflation of the mattress in a caudal-cranial direction with concomitant increase in venous return, thus influencing the SvO$_2$. However, the mattress does not inflate in this way, i.e. areas distributed amongst all body areas are intermittently inflated and deflated. One could also hypothesize that the periodic inflation of the mattress intermittently decreased the patient’s thoracic wall compliance. This may in turn have resulted in an increase in intrathoracic pressure with subsequent decrease in venous return and a drop in the SvO$_2$. The patient was given IV fluids during the same period to maintain an adequate preload with a concomitant decrease in the amplitude of the periodic SvO$_2$ fluctuations.

We think this case description may be of importance for intensive care nurses and physicians when they make bedside observations in patients with continuous SvO$_2$ monitoring.
Op 6 en 7 februari 2014 worden de jaarlijkse Intensivistendagen gehouden in ‘s-Hertogenbosch. Niet alleen een nieuwe locatie, maar ook een nieuw tweedaags programma!

Bekende onderdelen
- een selectie van nationale wetenschap in de vorm van abstracts en proefschriften
- de postersessies
- de thematische ‘year in review’ presentaties

Nieuwe onderdelen
- de internationale keynote lecture door professor Mervyn Singer
- de NVIC erelezing door een gerenommeerde collega

Verder
- interactieve workshops over het omgaan met ethisch-culturele dilemma’s en het beoordelen van wetenschappelijke artikelen

Ontmoeting
Tussen de bedrijven door is er natuurlijk tijd om u door de vertegenwoordigers van de industrie te laten bijpraten. De Intensivistendagen zijn de gelegenheid bij uitstek om kennis te nemen van de nieuwste ontwikkelingen in de Intensive Care geneeskunde, maar ook om elkaar te ontmoeten en bij te praten tijdens de borrel of het feest.

Tot ziens in Den Bosch!
Disastrous consequences: Influenza A and pneumococcal co-infection
A. Ruiter, M.L.J. Scheer
Department of Intensive Care Medicine, Martini Hospital Groningen, The Netherlands

Introduction: Pneumococcal infection after influenza A infection lead more frequently to an invasive pneumonia. We describe a patient with influenza A and a pneumococcal co-infection who developed a severe septic shock with cavitary pneumonia and multi organ failure. Early recognition and treatment of a co-infection is important in the prevention of a more serious course of the disease.

Case history: A 64-year-old female was admitted to the ICU with respiratory failure en septic shock with multiple organ failure. Her medical history compromised atrial fibrillation and hyperthyroidism. She suffered from fever, coughing and dyspnoea which started one week before admission. The chest radiograph showed bilateral infiltrates (figure 1).

Diagnostic tests showed positive PCR for pneumococcus and influenza A. Complementary blood cultures showed *Streptococcus pneumoniae*. Immediately after taking blood cultures and viral PCR, we started antibiopic and antiviral therapy.

Intubation, inotropic support and continuous venous hemofiltration were required.

The patient underwent prolonged postural drainage, prone position and several bronchoscopies treating sputum retention. A computed tomography of the chest revealed cavitating pneumonia (figure 2).

After a few weeks the patient recovered from the multiple organ failure and started weaning from the ventilator. She was discharged from the ICU after two months of admission (figure 3).

After two months of rehabilitation the patient restarted her work as a nurse.

Discussion: Approximately 250.000-500.000 people die of influenza worldwide, of which a significant fraction of influenza deaths can be attributed to bacterial infections, either during, or closely following influenza infection. An important influenza co-infection is pneumonia, caused primarily by *Streptococcus pneumoniae*.1

Although the mechanisms underlying the association between the severity of influenza and pneumococcal infections are still poorly understood, there are a number of mechanisms involved. Viral infections facilitate bacterial colonization, adhesion and translocation through the epithelial barrier. In fact, clearing the way for bacterial disease. Pneumococcal infection after influenza infection lead more frequently to invasive pneumonia. In conclusion, it is clinically relevant to start with the combination of antiviral and antibacterial treatment in case of suspicion of a co-infection. This is of particular importance during the influenza season.1 The co-treatment is only beneficial when the antiviral therapy is started within the first few days of onset of pneumonia. This can prevent the occurrence of a serious invasive pneumonia.1

Conclusion: This case showed a severe cavitary pneumonia following Influenza A and pneumococcal co-infection. We successfully treated this patient with prompt administration of antibiotics combined with antiviral therapy. Nevertheless a cavitary pneumonia developed with a prolonged treatment on the ICU. In conclusion, doctors should be aware of the fulminant course of the disease due to influenza and pneumococcal co-infection.
Figure 3. Chest radiograph at discharge: improved with only a few abnormalities left

References


2. Hypokalemic paralysis and profound metabolic acidosis in a woman with Sjögren’s disease

Y.J. Beijer1, T. Tobé2, M. Otten1, C.M. Pleizier2, J.H. van der Werf4, J.W. Fijen1, L.E.M. Haas1

1Department of Intensive Care, Diakonessenhuis, Utrecht, The Netherlands, 2Department of Internal Medicine, Nephrology, Diakonessenhuis, Utrecht, The Netherlands, 3Department of Neurology, Diakonessenhuis, Utrecht, 4Department of Rheumatology, Diakonessenhuis, Utrecht, The Netherlands

Case: A 52-year-old woman presented with a rapid progressive proximal muscle weakness in both upper (Medical Research Council (MRC) grade 3-4) and lower (MRC 2) extremities and neck flexors (MRC 3) as well, since last week. She also documented anorexia, weight loss and constipation, for which she had used laxatives last week but abuse was not suspected. She was diagnosed with Sjögren’s Syndrome (SS) four months before. The diagnosis was based on xerostomia, keratoconjunctivitis sicca, a positive Schirmer test and positive antinuclear antibodies with both positive anti-Ro/SSA and anti-La/SSB.

The laboratory results and the ECG on admission are shown in table 1 and figure 1. Remarkable was the severe hypokalemia (1.5 mmol/l), the profound non-aniongap acidosis (bicarbonate 4.6 mmol/l, anion gap 13.6 mmol/L, albumin 41 g/l) and elevated creatine kinase (CK). Despite the profound metabolic acidosis, urine pH was 6.5. The anion gap in urine was 31 mmol/L with a urine osmolgap of 14 mOsm/kg.

Both the urinary anion gap and the urine osmolgap suggested the inability to produce ammonium. In combination with low bicarbonate and hypokalaemia, renal tubular acidosis (RTA) type I was diagnosed. The woman received high doses intravenous potassium via a central venous catheter and when serum level was raised above 3.0 mmol/L, supplementation of bicarbonate was added. Her myopathy recovered soon after normalization of serum potassium and subsequently she was successfully treated with potassium citrate tablets (tid 1500 mg).

Discussion: Distal (type 1) RTA is an uncommon disorder, particularly in adults. The primary defect is impaired distal acidification with reduced urinary ammonium excretion. The hallmark features of RTA are hyperchloremic metabolic acidosis with a normal anion gap and a urine pH above 5.5, with or without associated defects in potassium homeostasis. The major causes of distal RTA in adults are autoimmune diseases, e.g. SS (table 2). In up to 25 per cent of patients with SS, interstitial nephritis with a defect in distal acidification occurs. The underlying mechanism is incompletely understood.

Differential diagnosis included multiple myeloma, but in our patient a recent protein electrophoresis was normal. This is important, because particularly haematological malignancies are more frequent in patients with SS and can also cause RTA type I. Differential diagnosis of normal anion gap (hyperchloremic) metabolic acidosis also included diarrhea, but there was no history of diarrhea or intoxication in this patient who did not use diuretics. Normal anion gap metabolic acidosis due to laxative abuse exists in the presence of normal distal acidification, and hence it was unlikely to be the case of acidosis in this case.

The aim of therapy is to achieve a relatively normal serum bicarbonate concentration. Adults with distal RTA can be treated with 1 to 2 mEq/kg/day sodium bicarbonate or sodium citrate. Potassium citrate is indicated when hypokalaemia persists despite correction of the serum bicarbonate, like in this case.

Conclusion: Although RTA is a rare disorder, it is quite common in SS patients and these patients can present with profound hypokalaemia and metabolic acidosis.

Figure 1. ECG, showing characteristic changes; depression of the ST segment and a prolonged QT interval

The Netherlands Journal of Critical Care
Case Reports Intensivistendagen 2014
Table 1. Laboratory results

<table>
<thead>
<tr>
<th>LABORATORY TEST</th>
<th>VALUE</th>
<th>REFERENCE VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-reactive protein (CRP)</td>
<td>17 mg/L</td>
<td>&lt; 10 mg/L</td>
</tr>
<tr>
<td>ESR</td>
<td>50 mm/hr</td>
<td>2-12 mm/hr</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>6.6 mmol/L</td>
<td>7.0-9.2 mmol/L</td>
</tr>
<tr>
<td>MCV</td>
<td>87 fl</td>
<td>82-98 fl</td>
</tr>
<tr>
<td>Leucocytes count</td>
<td>13.4 x10^9/L</td>
<td>4.0-10.0 x10^9/L</td>
</tr>
<tr>
<td>Sodium</td>
<td>134 mmol/L</td>
<td>135-145 mmol/L</td>
</tr>
<tr>
<td>Potassium</td>
<td>1.5 mmol/L</td>
<td>3.5-5.0 mmol/L</td>
</tr>
<tr>
<td>Urea</td>
<td>11 mmol/L</td>
<td>2.5-6.4 mmol/L</td>
</tr>
<tr>
<td>Creatinin</td>
<td>173 µmol/L</td>
<td>44-80 µmol/L</td>
</tr>
<tr>
<td>Chloride</td>
<td>116 mmol/L</td>
<td>98-108 mmol/L</td>
</tr>
<tr>
<td>Calcium</td>
<td>2.25 mmol/L</td>
<td>2.10-2.55 mmol/L</td>
</tr>
<tr>
<td>Magnesium</td>
<td>1.12 mmol/L</td>
<td>0.65-1.05 mmol/L</td>
</tr>
<tr>
<td>Gamma-glutamyltransferase (GGT)</td>
<td>20 U/L</td>
<td>&lt; 38 U/L</td>
</tr>
<tr>
<td>Alkaline phosphatase (ALP)</td>
<td>50 U/L</td>
<td>&lt; 98 U/L</td>
</tr>
<tr>
<td>Alanine aminotransferase (ALT)</td>
<td>40 U/L</td>
<td>&lt; 34 U/L</td>
</tr>
<tr>
<td>Aspartate aminotransferase (AST)</td>
<td>80 U/L</td>
<td>&lt; 31 U/L</td>
</tr>
<tr>
<td>Lactate dehydrogenase (LDH)</td>
<td>167 U/L</td>
<td>&lt; 220 U/L</td>
</tr>
<tr>
<td>Creatine kinase</td>
<td>1264 U/L</td>
<td>&lt; 145 U/L</td>
</tr>
<tr>
<td>Albumin</td>
<td>41 g/L</td>
<td>35-55 g/L</td>
</tr>
<tr>
<td>Glucose</td>
<td>5.9 mmol/L</td>
<td>3.0-7.0 mmol/L</td>
</tr>
<tr>
<td>TSH</td>
<td>3.37 mU/L</td>
<td>0.35-4.50 mU/L</td>
</tr>
<tr>
<td>pH</td>
<td>7.22</td>
<td>7.35-7.45</td>
</tr>
<tr>
<td>pCO2</td>
<td>1.5 kPa</td>
<td>4.7-6.4 kPa</td>
</tr>
<tr>
<td>pO2</td>
<td>16.0 kPa</td>
<td>10.0-13.3 kPa</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>4.6 mmol/L</td>
<td>22.29 mmol/L</td>
</tr>
<tr>
<td>Base excess</td>
<td>-20.6 mmol/L</td>
<td>-3.0-3.0 mmol/L</td>
</tr>
<tr>
<td>Urinary pH</td>
<td>6.5</td>
<td>4.0-8.0</td>
</tr>
<tr>
<td>Urinary sodium</td>
<td>14 mmol/L</td>
<td>25-135 mmol/L</td>
</tr>
<tr>
<td>Urinary potassium</td>
<td>12 mmol/L</td>
<td>16-67 mmol/L</td>
</tr>
<tr>
<td>Urinary chloride</td>
<td>13 mmol/L</td>
<td>110-250 mmol/L</td>
</tr>
<tr>
<td>glucose in urine</td>
<td>negative</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Major causes of distal renal tubular acidosis (type 1)

<table>
<thead>
<tr>
<th>Category</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary</strong></td>
<td></td>
</tr>
<tr>
<td>Idiopathic (sporadic)</td>
<td>Mainly due to mutations causing defects in the kidney anion exchanger – kAE1 in distal tubule intercalated cells.</td>
</tr>
<tr>
<td>Familial</td>
<td></td>
</tr>
<tr>
<td>Autosomal dominant</td>
<td></td>
</tr>
<tr>
<td>Autosomal recessive</td>
<td>Mainly due to mutations causing defects in V-ATPase in distal tubule intercalated cells.</td>
</tr>
<tr>
<td><strong>Secondary</strong></td>
<td></td>
</tr>
<tr>
<td>Autoimmune disorders</td>
<td></td>
</tr>
<tr>
<td>• Sjögren’s syndrome</td>
<td></td>
</tr>
<tr>
<td>• Autoimmune hepatitis/primary biliary cirrhosis</td>
<td></td>
</tr>
<tr>
<td>• Systemic lupus erythematous</td>
<td></td>
</tr>
<tr>
<td>• Rheumatoid arthritis</td>
<td></td>
</tr>
<tr>
<td>Drugs</td>
<td></td>
</tr>
<tr>
<td>• Lithium</td>
<td></td>
</tr>
<tr>
<td>• Amphotericin B</td>
<td></td>
</tr>
<tr>
<td>• Toluene inhalation</td>
<td></td>
</tr>
<tr>
<td>• Ifosfamide</td>
<td></td>
</tr>
<tr>
<td>Hypercalciuric conditions</td>
<td></td>
</tr>
<tr>
<td>• Sarcoidiosis</td>
<td></td>
</tr>
<tr>
<td>• Hyperparathyroidism</td>
<td></td>
</tr>
<tr>
<td>• Vitamin D intoxication</td>
<td></td>
</tr>
<tr>
<td>• Idiopathic hypercalciuria</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>• Sickle cell disease</td>
<td></td>
</tr>
<tr>
<td>• Obstructive uropathy</td>
<td></td>
</tr>
<tr>
<td>• Renal transplant rejection</td>
<td></td>
</tr>
<tr>
<td>• Wilson’s disease</td>
<td></td>
</tr>
<tr>
<td>• Medullary sponge kidney</td>
<td></td>
</tr>
</tbody>
</table>

**References**


3. The powerful double-edged sword of thrombolysis

Y.J. Beijer1, M. Otten1, L.H. Conemans2, H. Doğan3, J.W. Fijen, L.E.M. Haas1

1Intensive Care Unit, Diakonessenhuis, Utrecht, The Netherlands, 2Department of Pulmonology, University Medical Center, Utrecht, The Netherlands, 3Department of Radiology, Diakonessenhuis, Utrecht, The Netherlands

**Background:** We present a case in which the direct therapeutic effects of thrombolysis in massive pulmonary embolism are made visible, clinically as well as by diagnostic imaging and invasive haemodynamic measurements. Thereby, we show the feared side effect, severe bleeding, which unfortunately occurred.

**Case:** An 82-year-old diabetic male was admitted to the ICU with a hyperosmolar hyperglycemic syndrome, luted by prednisone use for a recent myasthenic crisis. He was treated with intravenous fluids, insulin and low molecular weight heparin (LMWH) in a prophylactic dose. Glucose and electrolytes normalized and no myasthenic crisis occurred. Patient was hypoxic at admission, but further clinical examination and chest X-ray (CXR) were non-diagnostic. The next day he became severely hypoxic and haemodynamically unstable and therefore invasive mechanical ventilation was started. An electrocardiogram (ECG) showed a sinus tachycardia with S1Q3T3 pattern en incomplete rbbb (Figure 1) and beds ide echocardiography revealed a dilated right ventricle. Pulmonary embolism (PE) was suspected and subsequently computed tomography (CT) pulmonary angiography confirmed extended saddle embolisms (Figure 2a), with signs of severe right ventricular dilatation and left sided shift of the interventricular septum (RV/LV diameter ratio 2.8). The patient was treated with alteplase (rtPA), in the absence of any contraindications to thrombolysis, and subsequent LMWH in therapeutic dose. Significantly increased dead space ventilation with a Vd/Vt ratio of 70%, normalized after thrombolysis (about 24%).

The patient recovered well, but suffered an arterial bleeding after radial artery puncture. He was resuscitated with crystalloids, erythrocytes, platelets and Fresh Frozen Plasma. The LMWH was discontinued for the next week, patient developed a ventilator-associated pneumonia (VAP) with refractory septic shock and eventually he died.
Discussion: Since it is generally known that the adverse effects of thrombolytic therapy can be devastating, the indication and potential benefits must be carefully weighed against the risks in each patient. Contraindications to thrombolytic therapy are recent (intracranial) surgery or head trauma, an active intracranial neoplasm, a history of stroke, severe hypertension, an active or recent internal bleeding, bleeding diathesis and thrombocytopenia. Although thrombolytic therapy can be lifesaving and leads to early haemodynamic improvement, it has not been proven to improve mortality in unselected patients. However, in patients with major pulmonary embolism who are haemodynamically compromised, a consistent trend toward improved mortality has been repeatedly found. But as said, with a significant increased risk for major bleeding, compared to anticoagulation alone.

Figure 1. ECG

Typical ECG with S1Q3T3 pattern en incomplete RBBB

Figure 2. Chest computed tomography

Computed tomography scan of the chest, before (a. and c.) and after (b. and d.) thrombolysis.

Figure a & c: show the saddle embolus with concomitant right ventricular (RV) dilatation en shift of the septum to the left. The calculated RV/LV diameter ratio is significantly elevated; 2.8.

Figure b & d: show that the saddle embolus is almost completely dissolved after thrombolysis and the calculated RV/LV ratio decreased (although it was still elevated; 1.16). Thereby, it shows a large hematoma of 14 x 8 cm underneath the right M. Pectoralis.

Figure 3. Invasive haemodynamic measurements

Graphic with mean pulmonary artery pressures (PAP) measured by Swan-Ganz catheter one week after thrombolysis.

Conclusion: This case demonstrates the effectiveness of thrombolytic therapy in predominantly dissolving massive pulmonary embolism with normalization of PAP pressures, but at cost of the feared side effect. Because of this massive bleeding risk and the absence of strong evidence of mortality improvement, thrombolytic therapy should be used only in carefully selected cases.

References

4.

Giant-cell myocarditis – a giant challenge

B.M.A. Pieters, D.W. Donker

University Medical Center Utrecht, Utrecht, The Netherlands

Introduction: Giant-cell myocarditis (GCM) is a rare disease carrying an unfavourable prognosis. A majority develops progressive heart failure and life-threatening arrhythmias. Thus, a timely diagnosis is essential and can only be obtained by myocardial biopsy. If medical therapy fails, only cardiac mechanical support and transplantation can be considered, although their therapeutic benefit in GCM remains to be debated. Here, we describe the clinical challenges one faces when managing a patient with GCM.

Case: A 22-year-old male without any medical history was referred in cardiogenic shock after complaining of general malaise for days. After stabilization upon medical treatment and routine diagnostics, right-ventricular endomyocardial biopsies revealed GCM. Yet, despite immunosuppressive therapy (steroids, cyclosporine and azathioprine) and intensified heart failure therapy, cardiac contractility deteriorated, necessitating the implantation of a bi-ventricular assist device (Thoratec®CentriMag®). Weaning from mechanical support was impossible, and 6 weeks after presentation cardiac transplantation was performed, allowing clinical discharge (day 65).
biopsies revealed GCM recurrence 2 months after transplantation in the absence of heart failure and was successfully treated with methylprednisolone (3 days) and intensified prednisolone therapy.

**Discussion:** This exceptional case of recent-onset, unexplained heart failure emphasizes the incremental diagnostic value of an early endomyocardial biopsy (EMB). The diagnosis of GCM cannot be established by any other diagnostic means. Therefore, it is of utmost importance to consider EMB early in the diagnostic work-up. Although GCM is a rare, idiopathic disease, the diagnosis has important therapeutic implications, i.e., the initiation of immunosuppressants. In our case, combined immunosuppression and adjuvant medical unloading did not reverse clinical deterioration due to terminal bi-ventricular failure. Generally, cardiac transplantation is the treatment of choice in refractory GCM, but this therapeutic option is limited by the paucity of donor organs. Alternatively, short-term mechanical support as a ‘bridge-to-transplantation’ can be considered, as we did. Yet, bi-ventricular support is cumbersome and bears significant risks of bleeding, thromboembolism and infection. Moreover, modern bi-ventricular short-term support devices, e.g., veno-arterial extracorporeal membrane oxygenation (ECMO), are designed for limited use (a few weeks). Thus, the time interval to transplantation may exceed the durability of the short-term device. In contrast, long-term pulsatile bi-ventricular support devices disqualify for a ‘high-urgency’ waiting list and carry unacceptably high complication rates including irreversible pulmonary hypertension after months of support which precludes cardiac transplantation. Moreover, GCM is well-known to potentially recur in the transplanted heart, but has been reported to allow successful treatment by adapting immunosuppressants, as in this case.

**Conclusion:** Severe, idiopathic heart failure of recent onset should prompt EMB in order to establish a diagnosis. Rarely, GCM may be encountered which carries a poor prognosis but may be treated by employing a challenging therapeutic strategy combining medical and mechanical cardiac support towards transplantation.

**References**


We present a case where a patient is referred to the ICU with obstructive shock following colonoscopy.

**Case:** A 69-year-old man was admitted to the ICU with tachypnea, hypotension and abdominal discomfort following gastro- and colonoscopy. He had a history of urolithiasis, DVT and non-insulin-dependent type 2 diabetes mellitus. He was referred to the hospital for analysis of microcytic anaemia. With gastroscopy no explanation was found, biopsies from duodenum were taken. During colonoscopy a narrowing colon tumor is observed, biopsies are taken and the tumor is marked proximal and distal of the tumor. Within a few hours the patients deteriorates with abdominal pain and shock and is admitted to the ICU. At physical examination we find extreme abdominal distension with redness of the lower limbs and an erection of the penis. Perforation or bleeding with obstructive shock is suspected. A radiograph of the chest shows a massive amount of intra-abdominal air (figure 1). With prompt needle decompression of the abdomen the patients circulation dramatically improved. Subsequent laparotomy show s a pneumoperitoneum with a perforation of the tumor. After sigmoid resection and antibiotics the patient recovered.

**Figure 1.** Plain radiograph of the chest: a massive amount of intrabdominal free air is striking

**Shock after colonoscopy**

*J. Boddé, M. Scheer*

Department of Critical Care, Martini Hospital Groningen, The Netherlands

**Introduction:** An increase in intra-abdominal-pressure (IAP) can lead to an abdominal compartment syndrome (ACS) with obstructive shock and multiple organ failure. One of the causes is a pneumoperitoneum.

**Discussion:** ACS is defined as an increase in IAP which is associated with new organ failure or dysfunction.1 Especially in ICU patients ACS is a known complication in trauma-patients, burn-victims, intra-abdominal surgery, polytransfusion, intra-abdominal bleeding and ascites and edema due infection, inflammation or malignancies.2 We present a rare cause of ACS caused by perforation of a colontumor after biopsy during colonoscopy. Perforation during colonoscopy is a rare complication itself with an estimated incidence of 0.03% to 2%.2 During colonoscopy insufflation of air is used to visualize the intestinal wall. If perforation occurs but not recognized, it can lead to a tension-pneumoperitoneum.2 Probably the omentum acts as a one-way-valve preventing air to flow back into the intestine. The use of needle-decompression is usefull as a salvage procedure.
during resuscitation, although it has been described as sole therapy in one case. This is well reflected by our case in which circulation dramatically improved after decompression by needle, before further surgical intervention was planned. In general colonic perforation is associated with high morbidity, up to 50%. Therefore surgical management is widely recommended.

Conclusion: ACS as a result of perforation following colonoscopy is a rare but most serious complication. It should be considered in the patient in shock after colonoscopy. Endoscopists but intensivists as well, should be aware of this complication and its clinical signs. Although not a definitive therapy needle-decompression is quick, readily available and particular helpful in resuscitation of acute ACS due to pneumoperitoneum. Afterwards swift surgical intervention is still warranted.

References

6. Unexplained hypoxia and Budd Chiari syndrome in a patient with antiphospholipid syndrome

J.J.H. Bunge1, U.S. Wiersema2, A. Moelker3, E.T.T.L. Tjwa4, J. van Bommel1
1Department of Intensive Care, Erasmus MC, Rotterdam, The Netherlands, 2Department of Hepatology, Erasmus MC, Rotterdam, The Netherlands, 3Department of Radiology, Erasmus MC, Rotterdam, The Netherlands

Case report: A 23-year-old woman was admitted for analysis and treatment of a suspected Budd-Chiari syndrome. Her medical history reported antiphospholipid syndrome, complicated by pulmonary emboli and thrombosis of the superior vena cava (SVC) and brachiocephalic vein in the previous year. The Budd-Chiari syndrome was caused by a suprahepatic inferior vena cava (IVC) thrombus. On admission she already complained of dyspnoea d’effort. A day after admission, there was progressive respiratory failure. She was transferred to the Intensive Care, where she soon needed to be intubated and ventilated. On suspicion of pneumonia, antibiotics were started. However, her condition did not improve and marked hypoxia persisted despite high FiO2 and ventilation pressures. A CT scan, with iodine contrast injected through the femoral vein, ruled out new pulmonary embolism, and showed only marginal pleural effusion and atelectasis, and no signs of interstitial lung disease. The differential diagnosis, in the setting of Budd-Chiari syndrome, included portopulmonary hypertension, or shunting due to hepatopulmonary syndrome. However, pulmonary artery catheterization revealed normal pressures. Contrast echocardiography was unremarkable and showed no signs of a right-left shunt. In addition, (99 m)Technetium-macro aggregated albumin (MAA) perfusion scanning showed 22% MAA-capture in cerebrum/kidney, possibly indicating pulmonary shunting. Upon further respiratory deterioration over time, a CT scan was repeatedly to rule out new pulmonary embolism. This time the iodine contrast was administered through the right arm, revealing a totally occluded SVC and a severe stenosis of the distal azygos vein due to thrombosis. There were extensive chest wall collaterals, as well as collaterals that appeared to have a close relation with the right pulmonary veins. There was hardly any contrast in the right atrium and pulmonary arteries, but dense contrast enhancement in the right pulmonary veins, left atrium and left ventricle, suggesting direct shunting between systemic veins and pulmonary veins based on a SVC syndrome, rather than hepatopulmonary syndrome. Based on these findings a stent was placed to dilate the azygos-SVC junction. In the same procedure, a stent was placed over the calcified stenosis in the IVC. Oxygenation markedly improved directly after stent placement and the patient was weaned from the ventilator within 24 hours. She was discharged to from the ICU 4 days after the procedure. The ascites resolved completely within two weeks. This case illustrates the different diagnostic steps in a patient with refractory hypoxia. The diagnosis was only made after (co-incidently) altering the route of contrast administration. In the end, there was a relatively simple solution for the clinical problem.

7. Massive airembolus after LVAD placement in a patient with dilating end-stage heart failure

J.V. Dikkeboer, P.R. Wijnandts
University Medical Center Utrecht, Utrecht, The Netherlands

Background: In the treatment of end-stage heart failure left ventricular assist devices (LVAD) are well-known therapeutic options as a bridge to transplantation or even a bridge to destination in patients deteriorating under maximal inotropic therapy. Early complications include perioperative hemorrhage, air embolism, and right ventricular failure. Beyond the perioperative period, late complications consist primarily of infection, thromboembolism, and primary device failure. In this case report we would like to share our experience in one of the severe complications that might appear after implantation of an LVAD.

Methods/Case: A 65-year-old female was admitted at our hospital suffering from dilating cardiomyopathy. In the previous decade she had been treated repeatedly for heart failure. Despite resynchronization therapy with pacemaker the estimated left ventricular function decreased from 25 to 10 %. Because of atrial fibrillation there was a progressive deterioration of right and left ventricular function, with pronounced clinical deterioration despite inotropic support. Patient underwent an aortic valve repair, a tricuspid valve repair because of severe aortic- and tricuspid
regurgitation and implantation of a Centrimag LVAD. After weaning from cardiopulmonary bypass, haemodynamic support was provided by low dose dobutamine, milrinone, amiodarone and high dose norepinephrine. At admittance to the Intensive Care Unit (ICU) patient showed signs of low cardiac output, which was corrected by fluid resuscitation. Trans esophageal ultrasound (TEE) showed no evidence of cardiac tamponade. Approximately an hour after arrival at the ICU there was a sudden drop of cardiac output (CO). Measured blood flow dropped below 1 L/min, with preservation of LVAD rpm. Pulmonary artery catheter showed a drop of CO, with only a slight increase in CVD or PAP. Resuscitation started immediately by fluid therapy and increasing inotropic support. Patient was hypoxic with poor circulation of the extremities. Physical examination showed normal bilateral lung sounds. Inspection of the LVAD showed massive amounts of air in the cannula, with an airlock at the pump. Patient was immediately put in Trendelenburg position to try to avoid air-embolus to the brain. TEE showed marginal right- and left ventricular movement, with no evident opening of the aortic valve. There was a pronounced air-embolus in the ascending and descending aorta (figure 1). Re-thoracotomy performed on the ICU did not show a luxation of the apex-cannula. After advancing of the cannula into the left ventricle circulation swiftly restored. TEE showed increased right and left ventricular movement, with no evidence of outflow obstruction (figure 2). Negative pressure in the trabecular system of the left ventricle could have caused the aspiration of air in the apex-cannula. Patient recovered haemodynamically in the next days. She did not regain consciousness and developed epileptic seizures. CT-cerebrum showed widely spread ischemia. Patient died shortly after discontinuation of treatment.

Results/Conclusion: Air was aspirated into the LVAD. Causing airlock in the pump, outflow obstruction and fatal air-emboli to the brain. There was no evidence of displacement of the cannula during re-thoracotomy. Advancement of the apex-cannula caused swift haemodynamic stabilization. Special care should be taken positioning of the cannula and testing for air-emboli, because of possibly fatal consequences.

Reference

Blinded by septic shock

K. Kooning¹, M. Otten¹, R. v.d. Ploeg ², L. Lelyveld¹

¹Department of Intensive Care Medicine, Diakonessenhuis, Utrecht, The Netherlands, ²Department of Ophthalmology, Diakonessenhuis, Utrecht, The Netherlands

Introduction: The majority of patients discharged from critical care experience problems with physical, non-physical and social functioning. We report on bilateral blindness as a rare and disabling complication in a young survivor of septic shock.

Case report: A 42-year-old male with a history of psoriatic arthritis, for which he used methotrexate, presented to our Emergency Department with abdominal discomfort two days after an inguinal hernia repair. Ultrasound showed abdominal wall hematoma and he was admitted to the surgical ward. Within 12 hours of admission he developed septic shock. The patient was admitted to the Intensive Care Unit (ICU), was resuscitated with fluids and vasopressors and treated with antibiotics (ceftriaxone and metronidazole). Emergency surgical exploration showed necrotizing fasciitis and aggressive surgical debridement was performed. Cultures revealed hemolytic Group A streptococcus and antibiotic treatment was switched to penicillin and clindamycin. Intravenous immunoglobulin was added for treatment of toxic shock syndrome.

The patient suffered from severe septic shock with multiple organ failure, including diffuse intravascular coagulation (DIC) and acute respiratory distress syndrome. High dose vasopressor therapy was needed (noradrenaline 2.7 mcg/kg/min and adrenaline 0.08 mcg/kg/min). After extubation he reported blindness with both eyes. His pupils were dilated and unresponsive to light. Ophthalmological evaluation revealed peripapillary retinal hemorrhages without signs of papillary edema. Magnetic resonance imaging showed fluid surrounding the optic nerves. Visually evoked potentials were negative. The patient was diagnosed with bilateral posterior ischemic optic neuropathy (PION). A course of steroids was considered to treat optic nerve edema but was found unsafe at that moment since he still had an active infection. Two weeks after diagnosing PION a course of dexamethasone was started.

Figure 1. Air in the ascending aorta

Figure 2. After repositioning of apex-cannula
without improvement of vision. Follow-up ophthalmological examination showed regression of retinal hemorrhages but four months after diagnosis he still had no light perception or pupillary reaction to light and fundoscopy revealed bilateral optic nerve pallor.

Discussion: PION is a watershed infarction of the optic nerve and it is a rare but serious complication of critical illness. Blood supply to the posterior optic nerve is almost entirely dependent on the pial vasculature, which is very susceptible to ischemia. Factors associated with PION are hypotension, anemia, venous congestion, prone position, large blood loss, use of vasopressors and preexisting vaso-occlusive disease. Other causes of PION are listed in Table 1. A course of steroids can decrease optic nerve edema and thereby improve outcome. Spontaneous recovery or improvement of PION is unlikely.

The exact cause of PION in this case remains unclear. The patient suffered from severe septic shock with multiple organ failure and received high dose vasopressor therapy. However, he did not exhibit other signs of systemic hypoperfusion such as renal failure or gastrointestinal problems. He was never ventilated in prone position, did not suffer from excessive blood loss or anemia and was not known to have vaso-occlusive disease. The presence of retinal bleeds in the initial ophthalmologic examination leads us to think DIC played a contributing role in causing PION in our patient.

Conclusion: We report on a rare complication of septic shock: bilateral irreversible complete vision loss due to PION.

Reference

Table 1.

<table>
<thead>
<tr>
<th>Etiology of PION</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) a combination of systemic hypotension and anemia (due to blood loss)</td>
</tr>
<tr>
<td>2) giant cell arteritis, vasculitis (herpes zoster, polyarteritis nodosa, lupus erythematosus)</td>
</tr>
<tr>
<td>3) infiltrative causes</td>
</tr>
<tr>
<td>4) compression</td>
</tr>
<tr>
<td>5) idiopathic</td>
</tr>
</tbody>
</table>

Ictal asystole: a rare complication of epilepsy

M.J. Boer, M.J. van Dam
Department of Intensive Care Medicine, University Medical Center Utrecht, Utrecht, The Netherlands

Background: Epilepsy can be associated with a variety of cardiac arrhythmias. Ictal asystole (IA) is a rare, and potentially fatal complication.

Methods: A 32-year-old, 17 weeks pregnant patient was brought to the emergency room after return of spontaneous circulation after cardiac arrest. She had a history of partial complex epilepsy. She used carbamazepine which was stopped at the beginning of her pregnancy. After a seizure she remained unconscious and cardiopulmonary resuscitation (CPR) was started. The ambulance arrived after 10 minutes and continued CPR with a monitored asystole. She had return of spontaneous circulation and on arrival at the ER her blood pressure (BP) was 170/100 mmHg, pulse of 131/min. Her Glasgow Coma Scale (GCS) was 3 with normal brain stem reflexes. CT cerebrum showed diffuse swelling with compressed ventricles and a hypodensity of the right parietal lobe, considered to be preexistent. There were no signs of intracranial hemorrhage nor signs of brain stem compression (picture 1). Her blood work showed a bloodgas with a pH of 6.75 a pCO2 of 71 mmHg and a lactate of 16.6mmol/l. A transthoracic echocardiography (TTE) showed a hyperdynamic left ventricle without regional wall motion abnormalities and no valve abnormalities. There were no signs of pulmonary embolism on a CT angiogram. She was admitted to the ICU for therapeutic hypothermia according to protocol. After rewarming a somatosensory evoked potential (SSEP) was performed which was not conclusive due to technical difficulties so an electroencephalogram (EEG) was performed which showed burst suppression without reactivity. One day later the EEG showed an isoelectric trace, without any cortical activity and no signs of non-convulsive state. Treatment was discontinued and she died.

Results: Epileptic seizures are accompanied by cardiac arrhythmias 2% of which are IA or bradycardia. Schuele et al found an 0.27% incidence after evaluating 6825 cases of epilepsy.1 Schuele used EEG and R-R interval monitoring and found asystole in 10 out of 6825 patients; eight in patients with temporal epilepsy and two of other origin. Risk factors for IA are refractory epilepsy, most often temporal epilepsy, cardiac abnormalities and some anti-epileptic drugs (AED). There is some debate whether epilepsy triggers a respiratory arrest and concurrent hypoxia causing cerebral hypoperfusion and myocardial hypoxia and asystole or whether epilepsy alone is responsible through a autonomous response and discharge of the vagal centers in the medulla which leads to asystole resulting in cerebral hypoperfusion and atonia. This latter cardio-inhibitory pathway may be associated with temporal epilepsy.1

Treatment of IA or bradycardia requires better antiepileptic treatment and sometimes pacemaker implantation. Strzelczyk et al proposed the following algorithm.2

Conclusion: Ictal asystole is a rare complication of epilepsy with difficult etiology but is potentially fatal. In our patient the asystole was preceded by a seizure which probably led to cerebral hypoperfusion and ischemia of both the heart and brain. Surviving patients should receive aggressive treatment with AED, epilepsy surgery, pacemaker implantation or a combination of treatments.

References
A case of fatal asthma after use of a dietary supplement containing creatine

M.P.M. Roukens¹, E.S. Brugman¹, H.W. Niessen², A.R.J. Girbes¹

¹Department of Intensive care, VUMC, Amsterdam, The Netherlands, ²Department of Pathology, VUMC, Amsterdam, The Netherlands

A 49-year-old man, with a history of mild allergic asthma necessitating occasional salbutamol inhalation therapy, developed a severe asthma attack some 30 minutes after intensive workout and a first-time ingestion of a protein shake containing creatine. Following self-administered incremental doses of salbutamol he was found unresponsive. On arrival of the paramedics asystole and respiratory arrest were diagnosed. Extensive successful resuscitation was initiated and the patient was transported to our hospital. The ventilation during transport was reported to be extremely difficult. On presentation at the emergency room we saw a patient with a striking rash covering all body parts. Capnography could not be obtained; the ET tube appeared to be placed in the oesophagus. After endotracheal reintubation the patient developed again pulseless electric activity combined with unmeasurable high EtCO₂, high ventilation pressures and expiratory wheezing, suggesting a severe bronchusobstruction with dynamic hyperinflation. Initial bloodgas analysis revealed a severe combined respiratory and metabolic acidosis: pH of 6.78 pO₂ 282 kPa pCO₂ 161 kPa HCO₃⁻ 23.8 mmol/l BE -11.3 SaO₂ 0.99. Leucocyte count showed marked eosinophilia. Cardiac massage was combined with adrenaline iv and nebulisation, ketamine infusion, magnesium sulphate iv, as well as salbutamol, ipratropium and steroids. The patient was mechanically ventilated with low frequency and prolonged expiratory time allowing normalisation of intrathoracic pressures. After restoration of circulation, mild therapeutic hypothermia was induced. Unfortunately, on rewarming patient was found to have absent brain stem reflexes and brain death was declared according to national protocol. Autopsy showed severe pulmonary oedema with eosinophilic and neutrophilic infiltrates in the alveoli and parabronchial tissue, consistent with fatal allergic asthma (figure 1).

Although findings at autopsy could not be specifically linked to a distinctive allergenic cause, several clinical features in this case report are indicative for an allergic reaction after a first time ingestion of a creatine supplement. Creatine has been widely used as the most effective nutritional supplement with a proven ergogenic value in high-intensity exercise as well as longer duration exercise tasks, increasing muscle strength and lean body mass). Also creatine supplementation is used in conditions where muscle wasting is a key feature like myopathies, neurodegenerative and brain disorders, heart failure and COPD. Side effects seem to be limited to water retention; however when the maximal daily dose is exceeded, reports on kidney failure and hepatitis exist. In bodybuilder communities on the internet however, worsening of allergic asthmatic symptoms are frequently mentioned after use of creatine containing supplement; no case-report is yet available in the current literature on this matter. Vieira and co-workers were on different occasions able to demonstrate in a model of sensitized mice that creatine supplementa-
tion exacerbates allergic inflammation, airway responsiveness, excessive mucus production and airway remodelling through activation of Th2 and IGF-1 pathways, all of which also have been proven to play a role in the development of human fatal asthma attacks. Therefore to our knowledge this is the first case in literature where the use of creatine supplementation can clinically be linked to a fatal allergic asthma.

References

Figure 1. Cross-section of lung tissue, clearly visible are congested vessels, inflammatory infiltrate and invasion of neutrophils and eosinophils

Mirizzi syndrome mimicking malignancy: the right sequence in diagnostic interventions

A. Tel, P. Ott, R. Sayilar, M. Scheer
Department of Intensive Care Medicine, Martini Hospital Groningen, The Netherlands

Introduction: The Mirizzi syndrome is a rare cause of obstructive jaundice and should be considered in the differential diagnosis of all patients with these signs. We describe a case of obstructive jaundice with severe complications due to diagnostic interventions. The sequence of these diagnostic and therapeutic interventions is important as complications could be prevented.

Case: A 55-year-old male patient with a history of Helicobacter Pylori gastritis presented with jaundice and itch since two weeks. On physical examination he was icteric without pain, the remainder was unremarkable. Blood test showed serum total bilirubine level of 147 umol/L, direct bilirubine 88 umol/L, alkaline phosphatase 241 U/L and γ-GT 97 U/L. Abdominal ultrasound revealed dilated intra- and extra-hepatic biliary ducts, probably based on intraluminal obstruction of the common bile duct (CBD). The patient underwent an Endoscopic Retrograde Cholangiopancreatography (ERCP) which showed a proximal dilatation of the CBD (figure 1). Because of a stenosis in the medial part of the CBD an endoprosthesis was placed. A few hours after ERCP, the patient developed a hemorrhagic shock. He was admitted to the ICU where he received blood transfusion and fresh frozen plasma. Immediate CT angiography revealed a massive bleeding in the area of the papilla duodenii from one of the branches of the arteria hepatica propria (figure 2). Hemostasis was achieved by embolization. The next day our patient developed fever and further elevated bilirubine levels. Reassessment of the CT scan revealed a large, layered gallstone (size 3-4.5 cm) in the gallbladder neck as the cause of the obstruction (figure 3). The patient underwent laparoscopic cholecystectomy which was converted to an open procedure. A large gallstone was seen in the gallbladder neck that caused erosion of the lateral wall of the common bile duct (figure 4). Two days after surgery the patient was discharged from the ICU.

Discussion: Mirizzi’s syndrome is characterized by a compression of the CBD or common hepatic duct caused by a gallstone which is impacted in the cystic duct or neck of the gallbladder. It causes obstruction and jaundice by an extrinsic compression of the CBD (type I) or may be accompanied by a cholecystobiliary fistula compromising the CBD wall (type II-IV). The primary radiologic tests to diagnose the Mirizzi syndrome are computed tomography combined with ERCP or MRCP.

Conclusion: In this case the patient went for ERCP after dilated biliary ducts were seen on abdominal sonography. If our patient went for computed tomography before ERCP a hemorrhagic shock could have been prevented. In conclusion, the right sequence of diagnostic and therapeutic interventions in obstructive jaundice should be accurately chosen since it may lead to severe complications.

References

Figure 1. ERCP with a proximal dilatation of the CBD and intrahepatic gallways with external compression in region of cystic duct
Introduction: Cerebral fat embolism is an uncommon but serious complication of long-bone fracture. The classic fat embolism syndrome is characterized by the clinical triad of respiratory insufficiency, altered mental status and petechiae. Here we present two cases of cerebral fat embolism syndrome (CFES) and isolated high lactate levels without haemodynamic instability.

Patient A: A 26-year-old man was admitted to our hospital after being hit by a car. On arrival he had a maximal Glasgow Coma Score. Conventional radiology revealed fractures of both femura and a fracture of the left tibia. Treatment was entirely conservative. The patient was admitted to our intensive care unit (ICU) and within a few hour his consciousness decreased to an Eye Motor Verbal score of 3. Subsequently, his respiratory condition deteriorated quickly and the clinical picture and MRI (figure 1) were most suspect for CFES. Although there were no signs of sepsis, cardiac failure or ischemia, our patient had an persistent isolated lactate level between 4.9-8.2 mmol/l (figure 2). The patient died within 48 hours after admission to our hospital.

Patient B: A 19-year-old man presented with multiple trauma after a car accident. He had multiple fractures of the sacrum and femurs on both sides, a fracture of the right lower leg, and a tibia plateau fracture on the right. The patient underwent surgery and a total of three external fixtures were placed on both legs. The patient had a maximal Eye and Motor score while still on the ventilator. Several hours later he rapidly lost consciousness and within 20 minutes his Eye Motor Verbal score was E1M1Vtube. Almost at the same time the pulmonary condition of our patient deteriorated quickly. Given the neurological signs, in combination with the pulmonary deterioration, a diagnosis of fat embolism syndrome was suspected. Although there were no signs of sepsis, cardiac failure, or ischemia, our patient had an isolated lactate level of 3.1-5.5 mmol/L (figure 1). The patient died within 48 hours after admission to our hospital.

Discussion: Although the diagnosis CFES is difficult, several scoring systems have been developed to diagnose CFES. Here we suggest that lactate in the absence of haemodynamic instability could additionally be used in diagnosing CFES, adding it to its present criteria.

Although glucose is assumed to be the main energy source for all living tissue, there are indications that lactate, and not glucose, is preferentially metabolized by neurons in the brain. For example, lactate is an important metabolic precursor for cerebral gluconeogenesis and ATP under physiologic, but also pathological conditions. At rest, the human brain releases a small amount of lactate. However, during cerebral activation, as seen during exercise, the plasma lactate increases and the brain takes up lactate in proportion to the arterial concentration.
is hypothesized that diffuse damage to the brain causes that neurons cannot use lactate whereas astrocytes and oligodendrocytes keep producing lactate with a net increase in lactate levels. Possibly, adding lactate to the existing criteria for CFES, might increase the sensitivity of diagnosing CFES.

References

Figure 1. MRI

Figure 2. Lactate levels

13.

Diffuse alveolar hemorrhage, a rare but possible fatal complication after combined anticoagulant therapy for acute myocardial infarction


Maastricht University Medical Center, Maastricht, The Netherlands

Case report: Diffuse alveolar hemorrhage (DAH) is a possible life-threatening medical condition. Bland pulmonary hemorrhage due to elevated left ventricular end diastolic pressure is an underdiagnosed cause. Because of its low prevalence, DAH is a real diagnostic challenge. A 69-year-old man with a past medical history of myocardial infarction, presented to our emergency department (ED) after a witnessed out-of-hospital cardiac arrest while cycling. Basic life support was started immediately. Upon arrival of the ambulance, the presenting rhythm was ventricular fibrillation with subsequent return of spontaneous circulation after defibrillation. He remained comatose and arrived intubated in our ED. Electrocardiogram showed an atrial flutter without ST-elevation. Transthoracic echocardiography demonstrated an overall poor left ventricular function with an estimated ejection fraction of 30%. Prasugrel 60 mg, acetylsalicylic acid 300 mg and 5000 units of heparin were given because of the likelihood of a new ischemic event. A coronary angiogram revealed a culprit lesion in the right coronary artery. A bare metal stent was placed with good angiographic result. Because the patient vomited after administration of prasugrel in the ED, a loading dose of 600 mg clopidogrel was administered. After the PCI the patient was admitted to our intensive care unit. Therapeutic hypothermia was initiated. The respiratory situation deteriorated rapidly with a chest X-ray showing bilateral consolidations. Copious amounts of bloody secretions were aspirated from the endotracheal tube. Therapeutic hypothermia was stopped because of bradycardia and bleeding. Bronchoscopy showed diffuse bleeding in the distal regions of the bronchial tree suggesting DAH. Chest X-ray was repeated showing an increase in bilateral consolidations. The patient succumbed to refractory respiratory failure due to massive DAH.

In cardiac asthma there is a disruption of the layers of the alveolar-capillary unit due to elevated capillary hydrostatic pressures, a phenomenon also known as pulmonary capillary stress failure. A rise in capillary hydrostatic pressure favours the formation of edema in the interstitial compartment removed from the critical gas-exchanging regions. Once fluid forms in the interstitium, it is transported to the interlobular septae, the peribronchovascular space and finally to the hila and pleural space. Lymphatic vessels within these regions are highly recruitable and are able to increase the clearance of lung water by more than 10-fold. When this compensatory mechanism fails and all layers are disrupted, red blood cells may be seen traversing the alveolar-capillary membrane, resulting in the well-known pink frothy expectorations. Taking this pathophysiological finding into account, we believe that administration of anticoagulant therapy in patients with acute ischemic heart failure will increase the risk of diffuse alveolar hemorrhage, in this case a fatal complication.
This case suggests that administration of anticoagulant therapy after myocardial infarction can cause a fatal diffuse alveolar hemorrhage, especially if the patient is in acute ischemic heart failure. Diffuse alveolar hemorrhage can be mistaken for acute heart failure with similar radiological and clinical findings. Therapy should not only consist of treating acute heart failure, but cessation of implicated drugs and reversal of excess anticoagulation should be considered.

14.

Oxaliplatin induced multi organ failure: a condition intensivists should be aware of

S. Janssen, D.C.J.J. Bergmans, W.N.K.A. van Mook
Maastricht University Medical Center, Maastricht, The Netherlands

Background: Oxaliplatin is increasingly used in both adjuvant and palliative chemotherapy regimens for intestinal carcinoma. Consequently, more patients will be admitted to the intensive care unit (ICU) whilst on such a regimen. Common adverse effects include pancytopenia, mucositis, neuropathy and anaphylaxis. Less known are the potentially lethal hepatic effects, which will be illustrated in the following case.

Case: A 70-year-old female was transferred to our ICU from another hospital. Her medical history revealed non-metastasized rectum carcinoma, treated with neo-adjuvant chemotherapy and radical resection. Adjuvant treatment consisted of standard dose oxaliplatin and capecitabine. She was admitted with hypotension and metabolic acidosis due to mucositis. This was complicated by a pulseless electrical activity, resulting in an non-ST-elevation myocardial infarction. In the following days, sepsis of unknown origin with respiratory, renal and liver insufficiency with ascites developed. Laboratory results showed bilirubin 200 µmol/L, ASAT 160 U/L, ALAT 76 U/L, AF 779 IU/L and γ-GT 440 U/L. Moreover, thrombocytopenia with secondary intestinal bleeding occurred. She was intubated and platelet transfusion and antibiotics were administered. Gastroduodenoscopy showed multiple erosive ulcerations likely due to mucositis.

She was then transferred to our hospital because of lack of continuous venous haemodialysis capability in the referring center. Thrombocytopenia persisted at 23 10^9/l, in spite of transfusion. diffuse intravascular coagulation was deemed unlikely with fibrinogen at 2.1g/l, PT 16,1s and aPTT 40s. Analysis of liver failure included extensive cultures, virus assays, computed tomography and ultrasound imaging to rule out metastasis or macrovascular obstruction and echocardiography to exclude both forward and backward failure. Besides the oxaliplatin, no other cause was found for this multiple organ failure. In spite of maximal supportive therapy, the patient died 6 days after admission. Unfortunately, postmortem confirmation of the diagnosis was declined by the family.

Discussion: Whereas the metabolic derangement due to diarrhea was probably caused by capecitabine related mucositis, the ensuing symptomatology is more likely due to oxaliplatin toxicity. Literature reports that oxaliplatin can cause sinusoidal injury syndrome (SOS), with subsequent, potentially fatal liver damage. Drug-induced thrombocytopenic purpura has been also described with oxaliplatin use. However, no fragmentocytes were found. The thrombocytopenia might also have been a drug-induced immune thrombocytopenia. This has however mainly been described whilst on oxaliplatin treatment, and recovers after discontinuation. Disseminated intravascular coagulation has also been shown after oxaliplatin use, but was excluded in this case. SOS therefore was the most likely diagnosis.

SOS has been described after oxaliplatin use. Most cases develop mild to moderate symptoms, and have a good prognosis. Severe SOS however, which accounts for 25-30% of cases, has a high mortality rate, especially if renal failure occurs. Treatment consists mainly of supportive care. If multi organ failure has not yet developed, anticoagulation may benefit outcome. Defibrotide, a polydeoxyribonucleotide, may benefit even those in severe SOS, but is not yet commonly available.

Conclusion: In case of prolonged thrombocytopenia and liver insufficiency after administration of oxaliplatin, intensivists should be aware of the possibility of oxaliplatin toxicity as the causal entity.

References

15.

First Pieris Japonica intoxication described in a human

S. van Roosmalen, J.A.H. van Oers
Department of Intensive Care Medicine, St Elisabeth Hospital, Tilburg, The Netherlands

Introduction: The Pieris Japonica (Japanese Pieris) plant is a member of the Ericaceae family, which also includes rhododendrons and azaleas. It is a shrub or small tree with oval to lanceolate leaves with finely serrated margins. They are more and more used as decoration in European gardening. They are also known to be toxic to animals, especially ruminants. These animals are often exposed to these plants in their grazing environment. A few reports have been published about intoxications of goats. As far as we are aware, this is the first report ever written about an intoxication in a human being.

Case: A 62-year-old woman was presented to the emergency room (ER) of the St Elisabeth Hospital with salivation, nausea, vomiting, bradycardia, hypotension and ‘different behaviour’. Four ours before presentation, during her daily walk, she ate two branches of the Pieris Japonica plant. The woman is living in an environment for mentally disabled people. Her mentally performance is estimated at 0.5 years old. In the ambulance her heart rate began slowing down to 40 beats per minute and her blood pressure dropped to 60/20. After one gift of atropine (0.3 mg) her blood pressure and heart rate stabilized. No further resuscitation was necessary.
Colchicine poisoning; hesitate before extubate?

L. C. M. Schenning, M. C. M. de Groot, J. J. Weenink

Department of Intensive Care, Spaarne Hospital, Hoofddorp, The Netherlands

Case report: A 50-year-old woman with a history of gout and an unspecified psychiatric disorder was admitted comatose at an ED elsewhere 12-24h after an estimated ingestion of 15mg colchicine, 1600 mg clopimamine, 600 mg fenobarbital and three different benzodiazepines. She was intubated before transfer to our ICU. At admittance a EIM1V1 coma score persisted, without haemodynamically disturbances and unaffected oxygenation. Laboratory tests were unremarkable beside a creatine kinase (CK) of 3668 U/l. ECG showed normal sinus rhythm with prolonged QRS and QTc. Treatment was started with activated charcoal, magnesium sulphate and hyperhydration with saline and bicarbonate. The next day patient fully awakened and appeared haemodynamically and respiratory normal with minimal support. CK level decreased and the conduction abnormalities normalized. Therefore it was decided to extubate.

Eight hours after extubation, 36-48h after ingestion, her condition suddenly deteriorated with shock, bilateral inspiratory crackels and severe hypoxic respiratory failure not improving after applying non-invasive positive pressure ventilation. Chest X-ray showed bilateral alveolar consolidations compatible with (non-)cardiogenic lung edema. The patient was re-intubated and subsequently treated with lung protective ventilation in prone position. The following week she gradually improved although the ICU treatment was complicated by pneumonia, delirium and hypophosphatemia. On day 7 she was extubated and on day 9 she could be discharged from the hospital apparently without any residual symptoms.

Conclusion: Colchicine poisoning is a potential life-threatening condition. As our case report underlines, the initially mild clinical course may be misleading and acute deterioration may reveal. It is important to be aware of the subsequent clinical stages and patients should be closely monitored for several days after colchicine poisoning.

References

Table 1. Clinical stages of colchicine poisoning.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Time of onset</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal phase</td>
<td>0-24 hours post-ingestion</td>
<td>• Nausea, vomiting, diarrhea, abdominal discomfort • Hypovolemia • Leukocytosis</td>
</tr>
<tr>
<td>Multi-organ failure phase</td>
<td>1-7 days post-ingestion</td>
<td>• (Adult) Respiratory distress syndrome (ARDS) • Cardiac arrhythmias, failure, arrest • Encephalopathy, brain edema, convulsions • Renal failure • Liver failure • Disseminated intravascular coagulation • Bone marrow suppression, pancytopenia • Metabolic acidosis, hypokalemia, hyponatremia, hypocalcemia, hypo(hyper)glycemia, hypophosphatemia • Myopathy, neuropathy • Secondary sepsis</td>
</tr>
<tr>
<td>Recovery phase</td>
<td>7-21 days post-ingestion</td>
<td>• Resolution of organ system derangements • Rebound leukocytosis • Alopecia</td>
</tr>
</tbody>
</table>

Discussion: The poisonous principle of the plant is the acetylandromedol toxin. It binds to and modifies the sodium channels of cell membranes, leading to prolonged depolarization and excitation. It favors calcium movement into the cells and thereby results in a positive inotropic effect, similar to that of digitoxis (although structurally unrelated). Bradycardia, hypotension and atrioventricular block are serious cardiovascular effects that may be lethal. As little as 0.2% of the body weight of leaves of the Pieris Japonica plant may be toxic and even lethal. We should be aware of the risks of this plant, particularly because of the low toxic dosage and the apparent increase in popularity in Europe.
Microscopic polyangiitis with primary central nervous system manifestations

W.B. Prins1, H.L. Leavis2, M.J. van Dam1

1Department of Intensive Care Medicine, University Medical Center Utrecht, Utrecht, The Netherlands, 2Department of Rheumatology and Clinical Immunology, University Medical Center Utrecht, Utrecht, The Netherlands

Background: Vasculitis presenting with central nervous system manifestations is a rare diagnosis in the ICU.

Methods (Case): A 41-year-old woman with a medical history of mild asthma developed sensory loss of her lower extremities after she was admitted to hospital with acute onset of pain in the interscapular area. Eight months earlier she experienced paraesthesias and sensory loss of her lower body, with no abnormalities detected by lumbar puncture or magnetic resonance imaging (MRI). Now, MRI of the spinal cord demonstrated a subdural hematoma at the thoracic level (Th4-7) (figure 1) and dexamethasone was started to treat the myelopathy. Two weeks later she developed paralysis of her right leg and progressive general weakness leading to respiratory insufficiency requiring mechanical ventilation. Consecutive MRI showed an additional hematoma at the cervical (C3-5) level as well as ischemic areas (corpus callosum, medulla oblongata) in the brain. One day later her state of consciousness decreased to a Glasgow Coma Scale of E4M4V1, with a fixed gaze to the right. A third MRI revealed multifocal microinfarcts with magnetic resonance angiography (MRA) demonstrating stenoses in multiple cerebral arteries (figure 2). Differential diagnosis included infective endocarditis, coagulation disorder, vasculitis and lymphoma. Diagnostic tests were performed accordingly. Broad-spectrum antibiotics were started after cultures had been taken. The next day she developed an exanthematous rash. Although uncertain, high dose methylprednisolone was started to treat the suspected vasculitis. In order to ascertain the diagnosis, biopsy of the affected brain tissue was done. In the following days her condition did not improve and renal function deteriorated. Haemodynamic instability occurred as a result of gastrointestinal bleeding. Unfortunately, none of the test results could confirm the presence of vasculitis until one week after ICU admission. P-ANCA was present and directed against myeloperoxidase (ANCA-MPO > 100Iu/ml), indicative of microscopic polyangiitis (MPA). Treatment was optimised by pulse cyclophosphamide. Plasmapheresis and rituximab were added because of acute severe disease.

Results (discussion): MPA is a systemic vasculitis affecting small- and medium-sized blood vessels and is associated with myeloperoxidase-antineutrophil cytoplasm antibodies (MPO-ANCA). Almost any organ system can be affected and therefore symptoms can vary. Although neurological involvement is not uncommon, this mainly concerns the peripheral nervous system.1 The unusual presentation of MPA in our case led to delay in diagnosis and irresoluteness about the most correct therapy. Early recognition and prompt therapy of vasculitis is crucial to prevent serious morbidity and mortality. We would like to stress that CNS manifestations can be the first presentation of MPA. Because the majority of patients with MPA present with glomerulonephritis or lung haemorrhage,7 clinical studies have focussed on this patient population and even here the role of plasma exchange or other adjunctive therapies remains unclear. Recently, rituximab was proven at least as effective as cyclophosphamide for the induction of remission in patients with severe disease.8 Unfortunately, our patient only partially recovered from her cerebral ischaemic insults and remains severely disabled.

Conclusion: MPA is a systemic disorder that can present with primary central nervous system manifestations. Early recognition and therapy are critical.
Inadvertent placement of a Central Venous Catheter (CVC) in the subclavian artery. How to manage this problem?

T.E. van der Krieken1, P.C. Hartman2, G.N.M. Stultiën3, L.M. Keeris1

1Department of Intensive Care, Elkerliek Hospital, Helmond, The Netherlands, 2Department of Radiology, Elkerliek Hospital, Helmond, The Netherlands, 3Department of Vascular Surgery, Elkerliek Hospital, Helmond, The Netherlands

Background: Inadvertent puncture and catheterization of the subclavian artery is a known complication of infraclavicular catheterization for central venous access. Removal of the CVC without precautions can lead to severe complications.

Objectives: Management of inadvertent placement of a CVC in the subclavian artery.

Case report: A 74-year-old woman with an unremarkable medical history was recently diagnosed with an adenocarcinoma of the stomach. She received neo-adjuvantive chemotherapy and developed severe diarrhea. Patient was admitted to our ICU with deep hypovolemic shock due to dehydration. She was hemodynamically unstable and, besides aggressive rehydration, required inotropy. Insertion of a 7 French left subclavian CVC procedure was uncomplicated. No excessive backflow was noticed. While the X-ray showed a ‘correct’ position of the CVC, an arterial pressure curve was registered. The consulted vascular surgeon advised not to remove the CVC and placement of an endovascular stent in a clinically more stable situation. It was not ruled out that the CVC had penetrated the vein prior entering the artery. Therefore, the use of a percutaneous closure device would not be sufficient. A 59 x 7 mm stent-graft was placed via the right femoral artery without compromising the vertebral and mammary artery. An indentation was dilated with a 7 mm balloon. The CVC was removed without complications.

Discussion: Arterial catheterization of a subclavian CVC occurs in 1% of all infraclavicular procedures. Catheterization in hypovolemic patients is difficult due to venous collapse. Risk factor for inadvertent arterial catheterization is, such as in our case, an emergency procedure. Inadvertent arterial catheterization should be suspected when pulsatile backflow or local hematoma occurs. Control X-ray was performed and the position of the CVC was reported “correct” by the radiologist. If arterial catheterization is recognized, the catheter should be left in place. A systematic approach is necessary for planning the best treatment; endovascular, surgical or percutaneous.

References

Figure 1. False correct position of the CVC

Figure 2. Stentgraft in correct position
An outbreak of *Scabies norvegica* in the intensive care; a challenging diagnosis with severe consequences

M.R. Kruijt-Spanier, J. Koeze

University Medical Center Groningen, Groningen, The Netherlands

**Background:** In contrast to scabies vulgaris caused by *Sarcoptes scabiei mites*, variety hominis, 1, crusted scabies or *Scabies norvegica* is a complicated and far more contagious form with a higher mite load, consequently making this type of scabies much easier to transmit. 1,2 Especially immunocompromised patients are vulnerable to this form of scabies. 2 If an intensive care unit is faced by this problem, adequate management is essential to control institutional spread.

**Objectives:** To raise awareness for the possibility of *Scabies norvegica*-infection in immunocompromised patients, which is – of course – often the case at an intensive care unit.

**Methods:** Descriptive case and overview of the measures taken to control and prevent this highly contagious infection.

**Results:** A 21-year-old Somalian female with a known medical history of cystic fibrosis (CF) was admitted to our ICU with severe respiratory insufficiency, leading to a bilateral lung transplant one week later. Besides anticipated postoperative complications, a marked eosinophilia was present, for which an extensive differential diagnosis was investigated. Under the diagnosis of allograft rejection or an allergic reaction to medication (possibly morphine), she was treated with high-dose steroids. Despite this treatment, hypereosinophilia persisted. Also, she suffered from a pre-existing itch over her entire body, which persisted during further reconvalescence. Four months after admission she had developed multiple hyperkeratotic skin lesions. Dermatology diagnosed *Scabies norvegica*, confirmed by skin scrapings revealing several mites and eggs. Therapy with topical permethrin 5% and oral ivermectin was started, under which regimen her skin lesions resolved and the eosinophilia decreased. As a consequence, all patients close to and all of the healthcare workers involved in this patient’s care were informed. A total of 185 healthcare workers were screened, while to and all of the healthcare workers involved in this patient's care

were informed. A total of 185 healthcare workers were screened, while

**Conclusions:** In the majority of scabies-outbreaks, the index patient is an immunocompromised individual with unrecognized *Scabies norvegica*, who is more prone to develop crusted scabies because of masking of symptoms. Although rare, we therefore suggest that scabies be considered early in patients with itching skin-lesions of unknown origin, especially because of the burden and costs of the consequences of such an outbreak in terms of institutional precaution measures.

**References**


Fungal infection causing ischemia of the spinal cord

N. Ayub, M. Jak, M.D. Hazenberg, A.C. de Pont

AMC, Amsterdam, The Netherlands

**Case report:** A 62-year-old woman diagnosed with acute myeloid leukemia was admitted to the intensive care unit with acute respiratory failure after being treated with the second induction cycle according to the HOVON 102B protocol. The chest-X-ray showed pleural effusion in the left lower quadrant while the laboratory results showed a leukocyte count of 0.1 x 10^9/L. The patient was intubated and mechanically ventilated. She was treated with filgrastim, vancomycin and meropenem for a suspected pulmonary infection. During the course of the treatment, she developed paraplegia of both legs with loss of sensation. An MRI of the spinal cord showed a paravertebral mass compressing the artery of Adamkiewicz, thereby causing spinal cord ischemia. A biopsy taken from this mass showed signs of a massive invasive fungal infection. The treatment was changed to liposomal amphotericin-B, to which the patient responded well. She was weaned from the ventilator and discharged from the intensive care unit, albeit with persistent paraplegia.

**Discussion:** Acute occlusion of the single artery of Adamkiewicz results in an anterior spinal artery syndrome that involves paraplegia with loss of reflexes, loss of pain and temperature sensation and loss of sphincter control with sparing of vibration and position sensation. The neurologic symptoms typically progress over a period of a few minutes to a few hours and recovery is poor. Occlusion of the artery of Adamkiewicz has been described in a variety of conditions: preexisting abnormalities of the aorta, surgery of aorta, abdomen, spinal cord and lower limbs and spontaneous or traumatic thromboembolism. It has also been described in less common conditions such as epidural analgesia, cartilage embolus after a Valsalva maneuver, sclerotherapy for esophageal varices, and acute Schistosomamansoni infection. The main etiology of the anterior spinal artery syndrome during sepsis is compression of the anterior spinal artery by an epidural abscess, the most common causative organism being *S. aureus*.

Fungal infections causing paraplegia have been described only twice before. A patient with Crohn’s disease treated with tumor necrosis factor antagonist therapy developed caseating granulomas in the spinal cord, revealing fungal hyphae consistent with Aspergillus and a patient with a prosthetic aortic valve experienced acute aortic occlusion by thrombotic material containing *Aspergillus niger*. Despite extensive antifungal therapy, both patients died. To our knowledge, this is the first report of an invasive fungal infection presenting as a mass
causing paraplegia by compressing the artery of Adamkiewicz, initially successfully treated with an antifungal agent. Voriconazole and liposomal amphotericin B are the antifungal agents recommended for the treatment of invasive fungal infections. In addition, surgical resection may be curative, especially in case of persistent invasive aspergillosis and in patients needing additional immunosuppressive therapy.

In conclusion, the case above illustrates that an invasive fungal infection may present as a mass compressing other structures, in this case leading to paraplegia due to spinal cord ischemia.

References

Figure 1. MRI (T2-axial): the lumbar spinal cord showing a paravertebral mass compressing the artery of Adamkiewicz.

---

**Stone Heart Syndrome**

H.G. Jongsma-van Netten1, L.C. Otterspoor1,2

1University Medical Centre Utrecht, Utrecht, The Netherlands, Catharina Hospital, Eindhoven, The Netherlands
2Eindhoven, The Netherlands

**Introduction:** Forty years ago, severe ischemic contracture of the heart was a known, but uncommon complication of open-heart surgery using cardiopulmonary bypass. Since the introduction of myocardial hypothermia during surgery, this Stone Heart Syndrome is rarely seen anymore. However, to illustrate that this complication is not just a problem from the past, we describe a patient who recently underwent a standard mitral valve repair and developed a Stone Heart.

**Case description:** A 50-year-old man with severe mitral valve regurgitation, was admitted for a mitral valve repair. After starting cardiopulmonary bypass and before cross-clamping the aorta, a refractory ventricular tachycardia developed. The following mitral valve repair was uncomplicated. Immediately after discontinuing the perfusion, the left ventricle became thickened and hard as stone, the right ventricle contracted only slightly. There were no signs of local infarction or surgical complications. The electrocardiogram showed an asystole. A peripheral extracorporeal membrane oxygenation (ECMO) support system was implanted and the patient was transferred to a hospital with heart transplantation facilities. The next day the ECMO was centralised and blood and thrombi were removed from the pericardium. A large thrombus in the left atrium was left untouched because of the risk of air embolism. In the following days the heart did not recover and despite ECMO support he developed severe respiratory failure, acute kidney failure, liver failure and a persistent coma after discontinuing the sedation. Because of this multiple organ failure without therapeutic options, treatment was stopped nine days after the first operation. Autopsy revealed a heavy and solid heart, with thrombi in the left atrium, both ventricles and pulmonary veins and circular necrosis of the myocardium of both ventricles. Microscopy showed generalised coagulation necrosis and typical contraction bands in the myocardium. The coronary arteries were all open.

**Discussion:** The Stone Heart Syndrome was first described in 1972 and is typically occurring in patients undergoing open-heart surgery using cardiopulmonary bypass. During or after the extracorporeal perfusion, a sudden irreversible ischemic contracture of the heart develops. The hypothesis is that a combination of ATP depletion and intracellular calcium overload due to ischemia and reperfusion are responsible for the extreme contraction and the lack of relaxation. Because of the contraction, intramyocardial coronary arteries are compressed, which causes secondary ischemia. Risk factors include left ventricular hypertrophy, aortic valve disease and pulmonary hypertension. There are no therapeutic options, except for heart transplantation. Because of the contraction of the myocardium, no intraventricular assist device can be implanted. Therefore, the only way to bridge to decision is implanting an ECMO system. If the patient has no contraindications, the ECMO can bridge the patient to a heart transplantation. Induced hypothermia during surgery may prevent the Stone heart.

This case illustrates that even today, patients without any risk factors undergoing a standard open-heart surgery procedure, may develop a Stone Heart Syndrome. If confronted with this phenomenon, an ECMO system may be implanted as a bridge to heart transplantation.

References
**Abstracts Intensivistendagen 2014**

**1. Delirium detection based on monitoring of blinks and eye movements**


Department of Intensive Care Medicine, Brain Center Rudolf Magnus, University Medical Center Utrecht, The Netherlands; Department of Neurology and Neurosurgery, Brain Center Rudolf Magnus, University Medical Center Utrecht, The Netherlands; Department of Psychiatry, Brain Center Rudolf Magnus, University Medical Center Utrecht, The Netherlands; Department of Geriatrics, University Medical Center Utrecht, The Netherlands; Department of Cardio-Thoracic Surgery, University Medical Center Utrecht, The Netherlands

**Background:** Delirium is a common disorder in intensive care unit (ICU) patients and associated with impaired long-term outcome. Despite its frequency and impact, delirium is poorly recognized in ICU patients with current delirium screening tools as the confusion assessment method for the ICU. Numerous studies have shown by using actigraphy that delirium is associated with a change in motor activity level. However, actigraphy requires the patient to move the limbs spontaneously, which may be difficult in ICU patients because of pain, ICU acquired weakness, and use of physical restraint. Blinks and eye movements are less affected by these issues, and a decrease in eye movement velocity has been associated with a decrease of the level of consciousness. As the level of consciousness and motor activity can be affected in delirium, we hypothesized that monitoring of blinks and eye movements could provide a new approach for delirium detection. The objective of this study was to investigate whether blinks and eye movements are different in delirious patients compared to non-delirious patients.

**Methods:** Electro-encephalography and electro-oculography recordings were made in 28 delirious- and 28 age- and gender-matched non-delirious postoperative cardiac surgery patients. Patients were evaluated for delirium by a geriatrician, psychiatrist or neurologist using the Diagnostic and Statistical Manual of mental disorders IV criteria. Blinks were automatically extracted from electro-oculograms and eye movements from electro-encephalography recordings using independent component analysis. The number and duration of eye movements and blinks were compared between patients with and without delirium, based on the classification of the delirium experts described above. Eye movements were assessed during eyes open and eyes closed condition.

**Results:** There were no significant differences between patients with and without delirium in age (mean ± SD 75 ± 5.7 versus 74 ± 8.6; p=0.21), gender (n=14 (54%) males versus n=16 (57%) males; p=0.81), bypass time (median(interquartile range) 129 (95-158) versus 108 (77-168); p=0.07) and Euroscore (median(interquartile range) 7 (6-9) versus 7 (5-8); p=0.17).

During eyes open registrations, delirious patients showed, compared to non-delirious patients, a significant decrease in the number of blinks per minute and number of vertical eye movements per minute, as well as an increase in the average duration of blinks (Table 1). During eyes closed, the average duration of horizontal eye movements was significantly increased in delirious patients compared to patients without delirium (Table 1).

**Conclusion:** This is the first study with automatic eye movement detection in delirious patients. We found that spontaneous eye movements, in particular blinks, were affected in delirious patients, which holds promise for the development of an objective tool to detect delirium.

**References:**


**Table 1. Eye movements in patients with and without delirium**

<table>
<thead>
<tr>
<th>Eyes</th>
<th>Variable</th>
<th>Delirium Median (IQR)</th>
<th>Non-delirium Median (IQR)</th>
<th>p-value</th>
<th>AUC (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Open</td>
<td>Number of eye movements</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Horizontal</td>
<td>6 (0-51) n=23</td>
<td>26 (0-55) n=28</td>
<td>0.54</td>
<td>0.55</td>
<td>(0.39-0.71)</td>
</tr>
<tr>
<td>Vertical</td>
<td>1 (0-13) n=23</td>
<td>15 (2-54) n=28</td>
<td>0.01</td>
<td>0.70</td>
<td>(0.55-0.85)</td>
</tr>
<tr>
<td>Blinks</td>
<td>12 (5-18) n=23</td>
<td>18 (8-25) n=27</td>
<td>0.02</td>
<td>0.65</td>
<td>(0.50-0.80)</td>
</tr>
<tr>
<td>Closed</td>
<td>Number of eye movements</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Horizontal</td>
<td>0 (0-42) n=27</td>
<td>0 (0-51) n=27</td>
<td>0.37</td>
<td>0.57</td>
<td>(0.41-0.72)</td>
</tr>
<tr>
<td>Vertical</td>
<td>5 (0-47) n=27</td>
<td>10 (0-52) n=27</td>
<td>0.40</td>
<td>0.56</td>
<td>(0.41-0.72)</td>
</tr>
</tbody>
</table>
**The number of patients differs per variable, due to the impossibility of determining the duration of eye movements when patients had no eye movements and exclusion of patients for specific conditions. Five delirious patients were unable to keep their eyes open during the registration and excluded for eyes open analysis. One delirious patient would not close his eyes and excluded for eyes closed analysis. The 18 electrode was defect during eyes closed registration in one non-delirious patient and therefore excluded from eyes closed analysis. The electro-oculography channel of one non-delirious patient was defect and therefore, excluded for the analysis of blinks.**

**Abbreviations:** AUC= Area Under the Curve; CI= Confidence Interval; IQR= Interquartile Range; n= Number of patients for which variable could be determined.
2. Delirium detection using EEG: what and how to measure?

A.W. van der Kooi1, I.J. Zaal1, F.A.M. Klijn1, H.L. Koek1, T. Numan1, R.C.A. Meijer4, F.S.S. Leijten1, A.J.C. Slooter1

1Department of Intensive Care Medicine, Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht, The Netherlands, 2Department of Psychiatry, Brain Center Rudolf Magnus, University Medical Centre Utrecht, Utrecht, The Netherlands, 3Department of Geriatrics, University Medical Centre Utrecht, Utrecht, The Netherlands, 4Department of Cardiothoracic Surgery, University Medical Centre Utrecht, Utrecht, The Netherlands, 5Department of Neurology and Neurosurgery, Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht, The Netherlands

**Background:** Despite its frequency and impact, delirium is poorly recognized with current screening methods in critically ill patients.1 Electro-encephalography (EEG) is a sensitive tool for delirium diagnosis, but inconvenient in routine patient care.2 To perform EEG-based monitoring of delirium with a limited number of electrodes, we studied the optimal electrode derivation and EEG characteristic to discriminate delirium from non-delirium.

**Methods:** Standard EEGs were recorded in 28 delirious and 28 age- and gender-matched non-delirious postoperative cardiac surgery patients. A geriatrician, psychiatrist or neurologist evaluated the patient for delirium using the Diagnostic and Statistical Manual of mental disorders IV criteria. The first minute of artefact-free data with eyes closed and with eyes open was selected. For eyes-closed recordings, all possible bipolar derivations were studied, while for eyes-open only occipital and parietal electrodes were used. For each derivation, 6 EEG parameters were evaluated: relative power in the delta, theta, alpha and beta frequency band, peak frequency and slow-fast ratio. Using a Mann-Whitney U-test, all combinations of derivations and parameters were compared between delirious and non-delirious patients and p-values were ranked and corrected for multiple testing (eyes closed $\alpha_{\text{adjusted}}=4.0 \times 10^{-5}$; eyes open $\alpha_{\text{adjusted}}=5.6 \times 10^{-4}$).

**Results:** There were no significant differences between patients with and without delirium in age (mean ± SD 76 ± 5.7 versus 74 ± 6.6; $p=0.2$), sex (81% versus 85%; $p=0.1$), duration of mechanical ventilation (mean ± SD 12 ± 6.7 versus 11 ± 7.2 days; $p=0.2$), and duration of ICU stay (mean ± SD 4 ± 1.6 versus 3 ± 1.6 days; $p=0.1$). Delirium diagnosis occurred in 10.3% of patients. The mean duration of delirium was 1.9 ± 0.7 days. ICU patients were more likely to experience delirium than the non-ICU patients (15.5% versus 4.4%; $p=0.01$). Delirium diagnosis occurred in 10.3% of patients. The mean duration of delirium was 1.9 ± 0.7 days. ICU patients were more likely to experience delirium than the non-ICU patients (15.5% versus 4.4%; $p=0.01$).

### Table 1. Listing the 10 combinations of EEG derivation and EEG characteristic that showed the lowest p-value in discriminating delirium from non-delirium for registration with eyes closed

<table>
<thead>
<tr>
<th>Rank</th>
<th>p-value*</th>
<th>Derivation</th>
<th>Characteristic</th>
<th>Delirium, median (IQR)</th>
<th>Non-delirium, median (IQR)</th>
<th>AUC</th>
<th>Sens (%)</th>
<th>Spec (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.8e-12</td>
<td>F8-Pz</td>
<td>Relative delta</td>
<td>0.59 (0.47-0.71)</td>
<td>0.20 (0.17-0.26)</td>
<td>0.99</td>
<td>100</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td>3.7e-12</td>
<td>F8-P3</td>
<td>Relative delta</td>
<td>0.59 (0.46-0.69)</td>
<td>0.19 (0.15-0.26)</td>
<td>0.99</td>
<td>96</td>
<td>96</td>
</tr>
<tr>
<td>3</td>
<td>1.1e-11</td>
<td>F8-O2</td>
<td>Relative delta</td>
<td>0.60 (0.49-0.73)</td>
<td>0.23 (0.18-0.30)</td>
<td>0.99</td>
<td>96</td>
<td>96</td>
</tr>
<tr>
<td>4</td>
<td>1.5e-11</td>
<td>Fp2-O1</td>
<td>Relative delta</td>
<td>0.66 (0.60-0.75)</td>
<td>0.27 (0.23-0.36)</td>
<td>0.99</td>
<td>96</td>
<td>95</td>
</tr>
<tr>
<td>5</td>
<td>1.7e-11</td>
<td>F8-F4</td>
<td>Relative delta</td>
<td>0.60 (0.43-0.70)</td>
<td>0.20 (0.17-0.26)</td>
<td>0.98</td>
<td>96</td>
<td>92</td>
</tr>
<tr>
<td>6</td>
<td>2.2e-11</td>
<td>F8-O1</td>
<td>Relative delta</td>
<td>0.62 (0.48-0.72)</td>
<td>0.22 (0.17-0.26)</td>
<td>0.99</td>
<td>96</td>
<td>95</td>
</tr>
<tr>
<td>7</td>
<td>2.4e-11</td>
<td>F8-Cz</td>
<td>Relative delta</td>
<td>0.57 (0.46-0.67)</td>
<td>0.26 (0.20-0.33)</td>
<td>0.98</td>
<td>91</td>
<td>96</td>
</tr>
<tr>
<td>8</td>
<td>2.4e-11</td>
<td>F8-C3</td>
<td>Relative delta</td>
<td>0.57 (0.49-0.67)</td>
<td>0.21 (0.17-0.30)</td>
<td>0.98</td>
<td>91</td>
<td>92</td>
</tr>
<tr>
<td>9</td>
<td>2.9e-11</td>
<td>Fp2-Pz</td>
<td>Relative delta</td>
<td>0.64 (0.53-0.72)</td>
<td>0.28 (0.22-0.36)</td>
<td>0.99</td>
<td>100</td>
<td>95</td>
</tr>
<tr>
<td>10</td>
<td>3.0e-11</td>
<td>Cz-O1</td>
<td>Relative delta</td>
<td>0.50 (0.37-0.57)</td>
<td>0.17 (0.10-0.25)</td>
<td>0.96</td>
<td>92</td>
<td>88</td>
</tr>
</tbody>
</table>

*All p-values were smaller than $4.0 \times 10^{-5}$. Therefore, all combinations in this table showed a statistically significantly difference between delirium and non-delirium.

**Abbreviations:** AUC = Area Under the Curve of the receiver operating curve; IQR = Inter Quartile Range; Relative delta = Relative power in the delta frequency band; Sens = Sensitivity; Spec = Specificity.

### Table 2. Listing the 10 combinations of EEG derivation and EEG characteristic that showed the lowest p-value in discriminating delirium from non-delirium for registration with eyes open

<table>
<thead>
<tr>
<th>Rank</th>
<th>p-value*</th>
<th>Derivation</th>
<th>Characteristic</th>
<th>Delirium, median (IQR)</th>
<th>Non-delirium, median (IQR)</th>
<th>AUC</th>
<th>Sens (%)</th>
<th>Spec (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.0e-07</td>
<td>P7-P4</td>
<td>Relative alpha</td>
<td>0.12 (0.09-0.15)</td>
<td>0.33 (0.19-0.39)</td>
<td>0.90</td>
<td>85</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>4.2e-07</td>
<td>P3-P4</td>
<td>Relative alpha</td>
<td>0.14 (0.11-0.17)</td>
<td>0.34 (0.23-0.43)</td>
<td>0.89</td>
<td>81</td>
<td>91</td>
</tr>
<tr>
<td>3</td>
<td>1.6e-06</td>
<td>P7-O1</td>
<td>Relative delta</td>
<td>0.44 (0.36-0.54)</td>
<td>0.24 (0.17-0.33)</td>
<td>0.88</td>
<td>86</td>
<td>85</td>
</tr>
<tr>
<td>4</td>
<td>3.2e-06</td>
<td>P7-O1</td>
<td>Relative alpha</td>
<td>0.10 (0.08-0.14)</td>
<td>0.26 (0.19-0.33)</td>
<td>0.87</td>
<td>81</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>3.5e-06</td>
<td>P3-P4</td>
<td>Slow Fast ratio</td>
<td>4.0 (2.5-5.2)</td>
<td>1.0 (0.6-1.7)</td>
<td>0.87</td>
<td>77</td>
<td>89</td>
</tr>
<tr>
<td>6</td>
<td>4.0e-06</td>
<td>P4-O1</td>
<td>Relative alpha</td>
<td>0.13 (0.09-0.17)</td>
<td>0.29 (0.19-0.39)</td>
<td>0.87</td>
<td>78</td>
<td>90</td>
</tr>
<tr>
<td>7</td>
<td>6.1e-06</td>
<td>P7-P8</td>
<td>Relative alpha</td>
<td>0.11 (0.09-0.16)</td>
<td>0.31 (0.19-0.39)</td>
<td>0.86</td>
<td>81</td>
<td>95</td>
</tr>
<tr>
<td>8</td>
<td>7.9e-06</td>
<td>P7-P4</td>
<td>Slow Fast ratio</td>
<td>4.0 (2.9-5.6)</td>
<td>1.1 (0.7-2.2)</td>
<td>0.86</td>
<td>77</td>
<td>88</td>
</tr>
<tr>
<td>9</td>
<td>9.4e-06</td>
<td>P3-P8</td>
<td>Relative alpha</td>
<td>0.13 (0.09-0.16)</td>
<td>0.32 (0.19-0.43)</td>
<td>0.86</td>
<td>78</td>
<td>90</td>
</tr>
<tr>
<td>10</td>
<td>1.1e-05</td>
<td>P7-O2</td>
<td>Relative alpha</td>
<td>0.11 (0.09-0.15)</td>
<td>0.29 (0.19-0.37)</td>
<td>0.86</td>
<td>76</td>
<td>95</td>
</tr>
</tbody>
</table>

*All p-values were smaller than $5.6 \times 10^{-4}$. Therefore, all combinations in this table showed a statistically significantly difference between delirium and non-delirium.

**Abbreviations:** AUC = Area Under the Curve; IQR = Inter Quartile Range; Relative alpha = Relative power in the alpha frequency band; Relative delta = Relative power in the delta frequency band; Sens = Sensitivity; Spec = Specificity.
Background: In recent years there has been growing interest in the quality of life of critically ill patients after discharge of the intensive care unit (ICU). Long term ICU-therapy can result in medical, physical and psychological problems afterwards. Aim of this observational transversal study was to assess the health related quality of life (HRQL) of critically ill patients six months and five years after ICU discharge and to identify patients at risk for decreased HRQL.

Methods: All patients treated in the ICU more than 72 hours last 5 years were eligible for inclusion in this study. Patients who were discharged six months and five years before start of this study were included. After inclusion, patients were tracked by using the hospital information system. If a patient was recorded to be alive, they were asked to participate and to fill out the RAND-36 questionnaire. As a reference group, a gender-and-age matched population (n=1742) was used. The HRQL scores between the two groups and the reference group were analyzed by means of the one-sample t-test. Results of the independent variables influencing the HRQL of patients were statistically analyzed with use of multiple linear regression. A p value of <0.05 was regarded as statistically significant.

Results: The ‘six-months’ cohort contained 114 patients. Of these 114 patients 69 (61%) were still alive, 59 were able to participate the study of which 36 (61%) completed the questionnaire. The ‘five-year’ cohort consisted of 370 patients; 157 (42%) of them were still alive, 119 were able to participate of whom 75 (63%) completed the questionnaire. Results of the HRQL measured by the RAND-36 for the ‘six-month cohort’ are given in table 1, together with the results of the control population. As shown, the HRQL-subcategories physical functioning, social functioning, emotional role limitations, physical role limitation and vitality were all statistically significant lower than the Reference group. The results of the HRQL analysis of the ‘five-year’ cohort are also shown in table 1. The subcategories physical functioning, social functioning, physical role limitation and vitality were all significantly lower than the Reference group. According to multiple regression analysis, age, gender, BMI, length of ICU-stay and co-morbidity significantly correlated with a lower HRQL of the subcategory physical functioning in critically ill patients after ICU discharge.

Conclusion: Critically ill patients being treated in ICU for more than 72 hours consider their HRQL significantly lower than the reference group. This counts for both patients six months after ICU discharge as patients 5 years after ICU discharge, though on some of the subcategories HRQL is improving. The long-term experienced the HRQL-subcategory physical functioning is influenced by patient characteristics – age, gender, BMI and co-morbidity – and length of stay in the ICU.

References
4.

Influenza A and B virus infection 2012-2013: incidence, characteristics and outcome in critically ill patients in two Dutch intensive care units

D. Jansen1,2, R. van den Berg2, G. Bosman2, P. Vos1, J.A.H. van Oers1

1Intensive Care Unit, St Elisabeth Hospital, Tilburg, The Netherlands; 2Intensive Care Unit, Tweesteden Hospital, Tilburg, The Netherlands

Background: With 18 weeks (17th of December 2012 – 21st of April 2013), this season’s flu epidemic was by far the longest in the past 20 years. Its peak incidence was 160 new influenza-like diseases per 100,000 inhabitants weekly. In the whole country, intensive care units (ICUs) were highly occupied with patients with flu symptoms. The aim of this study is to describe the incidence of influenza-related ICU admission, demographic characteristics, clinical features and outcome of laboratory-confirmed influenza A or B infection in critically ill patients admitted to our ICUs during the winter of 2012-2013.

Methods: A retrospective, observational multicenter cohort study was conducted in two Dutch ICUs: a 30-bed mixed medical/neuro)surgical ICU of St. Elisabeth hospital and a 12-bed mixed medical/surgical ICU of Tweestened hospital. All critically ill patients (≥ 16 years) with confirmed influenza A or B virus infection that were admitted between December 2012 and April 2013 were studied. Data of demographics, clinical features and treatment were collected. Primary outcome was mortality; secondary outcomes included length of stay in the ICU and hospital and disease severity. The non-parametric Mann-Whitney U test was performed to compare the characteristics between survivors and non-survivors in both ICUs. A p-value <0.05 was considered statistically significant.

Results: In 148 ICU patients polymerase chain-reaction (PCR) analyses for Influenza A and B were performed; 19 of them were positive for Influenza A and 16 for Influenza B. Demographic characteristics, clinical features and outcome are presented in Table 1. A positive culture occurred in 22.9% of the respiratory cultures and in 17.1% of the blood cultures with Staphylococcus aureus respectively Streptococcus pyogenes as most common pathogens. Differences between survivors and non-survivors are shown in Table 2. Conclusion: The Influenza epidemic during the winter of 2012-2013 lasted longer than those during previous years and more patients were affected. ICU admission was associated with an age above 65, the presence of COPD and/or a bacterial superinfection. Mean ICU mortality was 28.6%, as predicted by APACHE II and PSI score. There were no significant differences between survivors and non-survivors with respect to disease severity, comorbidities and duration of ventilation.

References
1. www.nivel.nl/griep.

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>EZ (n=23)</th>
<th>TSZ (n=12)</th>
<th>ALL (n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, male/female</td>
<td>17/6</td>
<td>3/9</td>
</tr>
<tr>
<td>Age, median [IQR]</td>
<td>76 [64.5-82]</td>
<td>59 [53.5-69.8]</td>
</tr>
<tr>
<td>Current tobacco use, no. (%)</td>
<td>2 (8.7)</td>
<td>3 (25.0)</td>
</tr>
<tr>
<td>COPD, no. (%)</td>
<td>14 (60.9)</td>
<td>6 (50.0)</td>
</tr>
<tr>
<td>Reason of ICU admission, no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia (viral/bacterial)</td>
<td>7 (30.5)</td>
<td>4 (33.3)</td>
</tr>
<tr>
<td>Emphysema/bronchitis</td>
<td>6 (26.1)</td>
<td>5 (41.7)</td>
</tr>
<tr>
<td>Sepsis/shock</td>
<td>4 (17.4)</td>
<td>3 (25.0)</td>
</tr>
<tr>
<td>Others</td>
<td>6 (26.0)</td>
<td>(0.0)</td>
</tr>
<tr>
<td>Use of antibiotics at home, no. (%)</td>
<td>3 (13.0)</td>
<td>(0.0)</td>
</tr>
<tr>
<td>Clinical Symptoms, no (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>11 (47.8)</td>
<td>8 (66.7)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>22 (95.7)</td>
<td>12 (100.0)</td>
</tr>
<tr>
<td>Clinical findings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temperature (°C), mean ± SD</td>
<td>37.1 ± 1.0</td>
<td>37.1 ± 1.3</td>
</tr>
<tr>
<td>Respiratory rate (min), mean ± SD</td>
<td>24 ± 7</td>
<td>30 ± 9</td>
</tr>
<tr>
<td>Laboratory findings, median [IQR]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukocytes</td>
<td>10.9 [7.7-16.9]</td>
<td>11.4 [6.2-19.7]</td>
</tr>
<tr>
<td>Bacterial superinfection, no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory culture positive</td>
<td>4 (17.4)</td>
<td>4 (33.3)</td>
</tr>
<tr>
<td>Blood culture positive</td>
<td>4 (17.4)</td>
<td>2 (16.7)</td>
</tr>
<tr>
<td>Mechanical ventilation, no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-invasive</td>
<td>16 (69.6)</td>
<td>9 (75.0)</td>
</tr>
<tr>
<td>Invasive</td>
<td>14 (60.9)</td>
<td>8 (66.7)</td>
</tr>
<tr>
<td>Disease severity, median [IQR]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>APACHE II score</td>
<td>17 [15.5-23.5]</td>
<td>23 [18.5-25.5]</td>
</tr>
<tr>
<td>PSI score*</td>
<td>133.0 [108-143.5]</td>
<td>132.0 [122.75-141.5]</td>
</tr>
<tr>
<td>CURB-65 score*</td>
<td>2.0 [1.5-2.0]</td>
<td>1.0 [1.0-1.75]</td>
</tr>
<tr>
<td>Mortality in ICU, no. (%)</td>
<td>8 (34.8)</td>
<td>2 (16.7)</td>
</tr>
</tbody>
</table>

* In ‘Community acquired pneumonia’ (CAP) patients

Table 2. Survivors versus non-survivors

<table>
<thead>
<tr>
<th></th>
<th>Survivors (n=25)</th>
<th>Non-survivors (n=10)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, male/female</td>
<td>14/11</td>
<td>6/4</td>
<td>0.84</td>
</tr>
<tr>
<td>Age, median [IQR]</td>
<td>68.0 [54-79]</td>
<td>71.5 [62-78.8]</td>
<td>0.76</td>
</tr>
<tr>
<td>COPD, no. (%)</td>
<td>15 (60.0)</td>
<td>5 (50.0)</td>
<td>0.61</td>
</tr>
<tr>
<td>Bacterial superinfection, no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory culture positive</td>
<td>6 (24.0)</td>
<td>2 (20.0)</td>
<td>0.80</td>
</tr>
<tr>
<td>Blood culture positive</td>
<td>4 (16.0)</td>
<td>2 (20.0)</td>
<td>0.80</td>
</tr>
<tr>
<td>Mechanical ventilation, no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-invasive</td>
<td>18 (72.0)</td>
<td>7 (70.0)</td>
<td>0.91</td>
</tr>
<tr>
<td>Invasive</td>
<td>15 (60.0)</td>
<td>7 (70.0)</td>
<td>0.59</td>
</tr>
<tr>
<td>PaO2/FiO2 at admission, median [IQR]</td>
<td>192 [76-254]</td>
<td>244 [150-300]</td>
<td>0.18</td>
</tr>
<tr>
<td>Duration of ventilation (hours), median [IQR]</td>
<td>62 [42-208]</td>
<td>45 [20-53]</td>
<td>0.18</td>
</tr>
<tr>
<td>Disease severity, median [IQR]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>APACHE II score</td>
<td>18 [16-23]</td>
<td>24.5 [18-34.8]</td>
<td>0.08</td>
</tr>
<tr>
<td>PSI score*</td>
<td>132 [108-147.75]</td>
<td>#</td>
<td>#</td>
</tr>
<tr>
<td>CURB-65 score*</td>
<td>1.5 [1.0-2.0]</td>
<td>#</td>
<td>#</td>
</tr>
</tbody>
</table>

* In ‘Community acquired pneumonia’ (CAP) patients. \( n=35 \)
Hyperoxemia is not associated with increased in-hospital mortality in critically ill patients

L.W. de Boo, A.E. van den Berg, R. Baak, P. Melief, I.A. Meynaar
Department of Intensive Care Medicine, Haga Hospital, The Hague, The Netherlands

Background: Several studies have demonstrated an association between increased in-hospital mortality and hyperoxemia in critically ill patients. The aim of this study was to test the hypothesis that hyperoxemia is independently associated with increased in-hospital mortality.

Methods: For this retrospective observational study, we included all consecutive patients admitted to the Hospital ICU (a combined medical and surgical tertiary Intensive Care Unit, 16 beds) between January 2010 and December 2012. Patient characteristics and outcome are routinely collected. We also collected the highest PaO₂ values in the first 24 hours after ICU admission. For the purpose of analysis we divided these PaO₂ values in hyperoxemia (defined as PaO₂ >13.31 kPa), hypoxemia (PaO₂ <9.29 kPa) and normoxemia (PaO₂ 9.3-13.3 kPa). The primary outcome was in-hospital mortality.

Results: During the study period we admitted 4158 individual patients to the ICU. Patients characteristics are shown in Table 1. Univariate analysis shows that hyperoxemia during the first 24 hours of ICU treatment was associated with increased in-hospital mortality (Table 2). However, on multivariate analysis, after correction for illness severity (APACHE IV score), hyperoxemia was not an independent predictor of in-hospital mortality. On the contrary and as to be expected hypoxemia was an independent risk factor for in-hospital mortality even after correction for illness severity (Table 3). Similar results were seen were groups were divided differently.

Conclusion: In conclusion hyperoxemia was not an independent predictor of in-hospital mortality after correction for illness severity (APACHE IV score). This contradict the results found in previously studies. On the contrary, and as to be expected, hypoxia was an independent risk factor for mortality even after correction for illness severity.

Table 1. Characteristics of patients admitted to the ICU (n=4158)

<table>
<thead>
<tr>
<th></th>
<th>All patients (n=4158)</th>
<th>Hospital survivors (n=3651)</th>
<th>Hospital nonsurvivors (n=507)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>65.1 (13.9)</td>
<td>64.5 (13.9)</td>
<td>69.3 (13.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>APACHE IV score</td>
<td>64.4 (30.7)</td>
<td>57.84 (22.8)</td>
<td>114.7 (36.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>APACHE IV expected mortality</td>
<td>0.03 (0.01-0.18)</td>
<td>0.03 (0.01-0.10)</td>
<td>0.75 (0.36-0.91)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lowest PaO₂ first 24 hrs, kPa</td>
<td>11.0 (3.3)</td>
<td>11.1 (3.1)</td>
<td>10.3 (4.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Highest PaO₂ first 24 hrs, kPa</td>
<td>19.8 (9.3)</td>
<td>19.1 (8.0)</td>
<td>24.9 (14.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Admission type</td>
<td>Medical</td>
<td>1106</td>
<td>770 (69.6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Planned surgery</td>
<td>2625</td>
<td>2599 (97.5%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Emergency surgery</td>
<td>427</td>
<td>322 (75.4%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diagnostic category</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cardiac surgery</td>
<td>2650</td>
<td>2584 (97.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Sepsis</td>
<td>215</td>
<td>135 (62.8%)</td>
<td>80 (37.2%)</td>
</tr>
<tr>
<td></td>
<td>Overdose</td>
<td>106</td>
<td>104 (98.1%)</td>
<td>2 (1.9%)</td>
</tr>
<tr>
<td></td>
<td>CPR</td>
<td>298</td>
<td>145 (48.7%)</td>
<td>153 (51.3%)</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>889</td>
<td>683 (76.8%)</td>
<td>206 (23.2%)</td>
</tr>
<tr>
<td>Length of stay ICU, days</td>
<td>0.9 (0.7-1.9)</td>
<td>0.9 (0.7-1.5)</td>
<td>2.1 (0.8-5.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Length of stay Hospital, days</td>
<td>8.2 (6.2-14.5)</td>
<td>8.3 (6.3-14.7)</td>
<td>5.2 (2.0-13.5)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are presented as mean (SD), median (IQR) or number (%) as appropriate. Abbreviations: APACHE = acute physiology and chronic health evaluation; hrs = hours; PaO₂ = partial pressure of oxygen in arterial blood; CPR = cardiopulmonary resuscitation; ICU = intensive care unit. A total of 4082 patients fulfilled APACHE IV inclusion criteria.

Table 2. Highest PaO₂ values in data from the first 24 hours after ICU admission and in-hospital mortality

<table>
<thead>
<tr>
<th>Highest PaO₂ first 24 hrs</th>
<th>In-hospital mortality</th>
<th>Relative risk (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normoxemia (9.3-13.3 kPa)</td>
<td>67/796 (8.4%)</td>
<td>Reference = 1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypoxemia (&lt;9.29 kPa)</td>
<td>17/30 (56.7%)</td>
<td>6.73 (4.57-9.92)</td>
<td></td>
</tr>
<tr>
<td>Hyperoxemia (&gt;13.3 kPa)</td>
<td>359/2662 (13.5%)</td>
<td>1.60 (1.25-2.05)</td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Multivariate analysis of predictors of in-hospital mortality

<table>
<thead>
<tr>
<th></th>
<th>Wald</th>
<th>p</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highest PaO₂ first 24 hrs</td>
<td></td>
<td>&lt;0.001</td>
<td>1.056 (1.052-1.060)</td>
</tr>
<tr>
<td>Hypoxemia (ref = normoxemia)</td>
<td>27</td>
<td>&lt;0.001</td>
<td>13.6 (4.9-38.0)</td>
</tr>
<tr>
<td>Hyperoxemia (ref = normoxemia)</td>
<td>0</td>
<td>0.988</td>
<td>1.0 (0.7-1.4)</td>
</tr>
</tbody>
</table>

References

Critical care pain observation tool: a single center observational study

E. Berger, M. Anderson, R. Birjmohun, N. Kusadasi
Intensive Care Unit, Vlietland Hospital, Schiedam, The Netherlands

Introduction: Currently the Numeric Rating Scale (NRS) is used by nurses to determine whether and to what extent the patient experiences pain. However, this is only applicable for patients who are approachable. Mirror conversations with former ICU-patients of our hospital showed that almost half of them has had suffered more or less pain during their stay. Sedated and ventilated patients can usually not express their pain verbally. The only way for these patients to express pain is non-verbal, by their behaviour. The intensive care team needs to pick up on these signals. A measuring instrument based on behaviour as a result of pain can be a tool to detect pain and to achieve the best possible patient care. The literature describes different scales to measure pain. The Critical-care Pain Observation Tool (CPOT) seems to be most appropriate for use at the ICU. Various studies show different...
results with a varying correlation from moderate to very strong, regarding the unambiguous use of the CPOT by various reviewers.

**Aim of the study:** To demonstrate whether the CPOT-score simultaneously taken by a pain and an ICU nurse and an intensivist is comparable, whether the instrument is reliable and applicable in daily practice of the ICU, and whether this pain management can easily be implemented.

**Study design:** A single center observational study.

**Methods:** A CPOT score was performed at 30 intubated patients at rest by three reviewers independently of each other. The CPOT has four categories with behavioural characteristics. These indicators are facial expression, body movements, compliance with the ventilator (intubated patients) or vocalization (extubated patients) and muscle tension. Each category has a score of 0-2. A total score of more than one point at rest means that the reviewer gives the patient the nursing diagnosis ‘pain’. SPSS 20 was used for the data analysis. The correlation was calculated by Spearman’s rank correlation (a nonparametric measure of statistical dependence between two variables).

**Results:** 30 patient were enrolled. Only four patients were able to perform the NRS. Three of them were consistent with the CPOT score. The total CPOT scores ranged from zero to two points. This yielded the following data (Table 1). A coefficient of 0.73 means a strong correlation between the pain consultant and the ICU nurse. A coefficient of 0.59 / 0.62 means a moderate correlation between the intensivist and the both nurses.

**Table 1. Spearman’s rank correlation between the reviewers**

<table>
<thead>
<tr>
<th></th>
<th>Pain nurse</th>
<th>ICU-nurse</th>
<th>Intensivist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain nurse</td>
<td>0.73</td>
<td>0.62</td>
<td></td>
</tr>
<tr>
<td>ICU-nurse</td>
<td>0.73</td>
<td>-</td>
<td>0.59</td>
</tr>
<tr>
<td>Intensivist</td>
<td>0.62</td>
<td>0.59</td>
<td>-</td>
</tr>
</tbody>
</table>

Correlation is significant (1-sided) at 0.05.

**Conclusion:** In order to avoid fluctuations in pain management in our hospital we were curious about the differences between reviewers. From this study it can be concluded that there is a strong positive correlation in the use of the CPOT between the pain-consultant and the ICU nurse. A coefficient of 0.59 / 0.62 means a moderate correlation between the intensivist and the both nurses. These results show that the CPOT is acceptable and useful in practice and can easily be implemented.

**7. A systematic review of risk factors for delirium in the intensive care unit**

**I.J. Zaal1, J.W. Devlin1, A.J.C. Slooter1**

1Department of Intensive Care Medicine, University Medical Center Utrecht, Utrecht, The Netherlands, 1School of Pharmacy, Northeastern University, Boston, United States

**Background:** Clear delineation of variables that predispose or precipitate delirium in the intensive care unit (ICU) is important when formulating prevention strategies and in statistical model building in etiologic research. We systematically reviewed studies evaluating ≥ 1 variable as a potential risk factor for ICU delirium.

**Methods:** Five electronic databases were searched from 2000 to February 2013 for studies that at least daily evaluated critically ill adults, not undergoing cardiac surgery, for delirium with a validated assessment method, and used either multivariate analysis or randomization to evaluate variables as potential risk factors for delirium occurrence (PROSPERO #CRD42013004886). In duplicate, data was abstracted and quality was scored using SIGN checklists [i.e. high (HQ), acceptable (AQ), unacceptable]. The presence of substantial inter-study heterogeneity prevented statistical pooling and consequently, reported variables were quantitatively evaluated using 3 criteria: number of studies evaluating the variable, the quality of each of these studies, and whether the direction of association was consistent (i.e., across ≥ 75% of the studies). The strength of evidence was defined as: strong (consistent findings in ≥ 2 HQ studies), moderate (consistent findings in 1 HQ study and ≥ 1 AQ studies), weak (1 HQ study or consistent findings in ≥ 3 AQ studies) or inconclusive (inconsistent findings or consistent findings in ≤ 2 AQ studies).

**Results:** Among the 25 (observational (n=21); randomized (n=4)) studies included, 64% were of high quality and 90 different variables were evaluated. Risk factors for delirium at ICU admission deemed strong were age, hypertension, dementia, pre-ICU emergency surgery or trauma, APACHE II score and sepsis. In the first 24-48 hours of ICU admission metabolic acidosis, iatrogenic coma and the use of mechanical ventilation, morphine or epidural analgesia are risk factors with strong evidence in the literature. Risk factors classified as moderate were nicotine consumption, alcohol consumption, moderate cognitive impairment, admission with infection or respiratory insufficiency and medical (rather than surgical) admission. All other variables, including several laboratory or environmental parameters, were either weak or inconclusive.

**Conclusion:** Among 90 variables hypothesized to increase the risk for delirium occurrence in the ICU, only 18 have either a strong or moderate level of evidence in the literature to support their role as risk factors.

**8. The association between benzodiazepine use and delirium in the ICU: a prospective cohort study**

**I.J. Zaal1, J. Devlin2, A. van der Kooi1, P.K. Klouwenberg1, M. Hazelbag3, D. Ong1, R. Groenewold1, A. Slooter1**

1Department of Intensive Care Medicine, University Medical Center Utrecht, Utrecht, The Netherlands, 2School of Pharmacy, Northeastern University, Boston, United States, 3Julius Centre for Health Sciences & Primary Care, University Medical Centre Utrecht, Utrecht, The Netherlands

**Background:** Prior ICU studies reporting benzodiazepine (BZ) exposure to be a risk factor for delirium have failed to include important confounders and to differentiate BZ intermittent administration (either oral or IV) from BZ continuous IV infusion. This study aims to further clarify this proposed association.
Methods: This ongoing, prospective, cohort study included consecutive adults, admitted to a 32-bed mixed ICU ≥ 24 hour over a 2 year period without a baseline neurological condition, who were evaluated at least twice daily for coma (RASS ≤ -4) and delirium. All delirium assessments were completed using a validated protocol (ISICEM 2011: P335) that included CAM-ICU assessments by both research physicians and the bedside nurse and a review of the patient record. A multinomial logistic regression model was used to quantify the odds of a daily transition to delirium and accounted for 5 different outcomes (coma, delirium, neither of these, death and ICU discharge), both fixed confounders estimated at ICU admission (n=7) and time-varying confounders which were defined per day (n=10), daily BZ use in mg (adjusted to midazolam equivalents), BZ administration method (i.e. none, intermittent administration only or continuous IV infusion including bolus administrations) and the 3 daily mental states (i.e. coma, delirium or neither of these).

Results: Among 866 patients evaluated [age (60 ± 16 yrs), mechanical ventilated (94%), medical admission (50%), APACHE IV (76 ± 29)], 50% had delirium on 24% of their total (n=8338) ICU days. BZs were administered to 78% of patients on 49% of these patients’ ICU days. Among comatose patients the relative risk ratio for being delirious the following day versus being neither comatose nor delirious the following day for every mg increase in BZ administered was 1.15 (1.00-1.31, p=0.02) for intermittent administration and 0.93 (0.87-1.00, p=0.02) for continuous IV infusion. The administration of BZ to patients with neither coma nor delirium was not associated with delirium the following day with relative risk ratio of 1.0 (0.98-1.02, p=0.50) for intermittent administration and 1.0 (0.99-1.01, p=0.44) for continuous IV infusion.

Conclusions: BZ use appears not to be a risk factor for transitioning to delirium in patients who are awake and non-delirious. Among comatose patients, the effect of BZ use on a transition to delirium is less clear, and may depend on whether BZ are administered intermittently or by continuous IV infusion.

Intoxicated ICU patients: death after hospital discharge

R. Brandenburg1, S. Brinkman3,4, N.F. de Keizer2,4, J. Meulenbelt1,4,5, D.W. de Lange1,4,6

1Department of Intensive Care and Emergency Medicine, University Medical Center Utrecht, The Netherlands, 2Department of Medical Informatics, Academic Medical Centre, University of Amsterdam, The Netherlands, 3National Intensive Care Evaluation (NICe) Foundation, Amsterdam, The Netherlands, 4Dutch National Poison Information Center (NPIC), University Medical Center Utrecht, The Netherlands, 5Institute for Risk Assessment Sciences (IRAS), University of Utrecht, The Netherlands

Background: For a physician, a patient with acute intoxication can be difficult to evaluate and allocate. This is mostly because an intoxication could give a broad range of symptoms (from harmless to life-threatening), that may change quickly. If a physician considers ICU admission, the decision to admit a patient is often based on assumptions about the short term survival. However, we feel that long-term outcome should also be taken into account. Indeed, little is achieved when a patient dies soon after hospital discharge.1

The aim of this study is to use APACHE IV intoxication subgroups to assess and compare (case-mix adjusted) in-hospital and long-term mortality of ICU patients admitted with acute intoxication.

Methods: Design: Cohort of ICU admissions from a national ICU-registry (NICe) linked to records from an insurance-claims database. Setting: 81 ICUs (85% of all Dutch ICUs). Patients: 7331 admissions between January 1st 2008 and October 1st 2011.

Measurements: Kaplan-Meier curves were used to compare the unadjusted mortality of the total intoxicated population and for specific intoxication subgroups based on the APACHE IV reasons for admission: (a) alcohol(s), (b) analgesics, (c) antidepressants, (d) street drugs, (e) sedatives, (f) poisoning (carbon monoxide, arsenic or cyanide), (g) other toxins and (h) combinations. The case-mix adjusted mortality was assessed by the Odds Ratio (OR) adjusted for age, gender, severity of illness, intubation status, recurrent intoxication, and several co-morbidities.

Results: The ICU mortality was 1.2%, the in-hospital mortality was 2.1%. The mortality 1, 3, 6, 12 and 24 months after ICU admission was 2.8%, 4.1%, 5.2%, 6.5% and 9.3% respectively. Street drugs had the highest mortality two years after ICU admission (12.3%); a combination of different intoxications had the lowest mortality two years after ICU admission (6.3%).

The adjusted observed mortality showed that intoxications with street drugs and “other toxins” have a significant higher mortality 1 month after ICU admission, OR adj = 1.63 and OR adj =1.78 respectively. Intoxications with alcohol or antidepressants have a significant lower mortality 1 month after ICU admission (OR adj = 0.50 and OR adj =0.46 respectively). These differences weren’t found in the adjusted mortality 3 months upward of ICU admission.

Conclusion: The difference between the in-hospital mortality and the mortality after two years is substantial. The first 3 months after ICU admission there is a difference in mortality between the subgroups; not thereafter.

References

Mortality of patients readmitted to the ICU

A.E. van den Berg, R. Baak, P. Melief, I. Meynaar

ICU, Haga Hospital, The Hague, The Netherlands

Introduction: We studied our ICU database to see whether patients who require readmission to the ICU during the same hospital admission have a worse prognosis as compared to patient who are not readmitted.

Patients and Methods: We included all patients admitted to the ICU of the Haga Hospital between January 1st, 2010, and December 31st, 2012,
in the study. The ICU is a level 3, intensivist-led, 16-bed mixed medical surgical unit. All specialties including cardiothoracic and neurosurgery are available in our hospital. We extracted all relevant patient data including APACHE IV score, expected mortality and hospital mortality from our database. The study endpoint was hospital mortality.

**Results:** During the study period a total of 4,492 patients were admitted to the ICU, 4,280 of whom were admitted only once while 212 patients were admitted more than once during the same hospital admission (table 1).

From table 1 we learn that hospital mortality is twice as high in patients readmitted to the ICU as compared to patients with only one ICU admission (25.5% versus 12.0%). This might be explained by the fact that patients readmitted to the ICU were sicker at the first ICU admission (mean APACHE IV score 75.5 versus 63.4, mean expected hospital mortality 28.3 versus 16.2%). To correct for illness severity on admission we performed logistic regression analysis (table 2).

Table 2 shows that readmission to the ICU is an independent risk factor for hospital mortality.

**Conclusion:** In patients readmitted to the ICU, hospital mortality is about twice as high as compared to patients who were not readmitted, even after correction for illness severity on admission.

**Background:** In patients with acute respiratory distress syndrome (ARDS) the use of assisted instead of controlled ventilation is subject of debate. Although, assisted ventilation improves gas exchange of the lungs and prevents respiratory muscle weakness it is not free of risks, such as the lack of control of tidal volume (Vt). Indeed, early administration of a neuromuscular blocking agent, improves survival in patients with severe ARDS. It was reasoned that muscle paralysis might result in less lung injury through elimination of patient-ventilator asynchrony, thereby allowing better control of volumes and pressures. Neuromechanically adjusted ventilatory assist (NAVA) is a ventilator mode that uses the electrical activity of the diaphragm to cycle the ventilator and to adapt the level of support. NAVA provides better patient-ventilator interaction compared to conventional modes and might therefore be more suitable in ARDS patients. Alternatively, NAVA provides proportional assist, tidal volume and lung distending pressure may be higher than recommended in ARDS patients. The aim of the present study is to compare Vt and transpulmonary pressure (Ptp) during NAVA and conventional modes in patients with ARDS. In addition, we studied patient-ventilator interaction in these patients.

**Methods:** Ten adult patients with moderate ARDS were included in this physiological study. After obtaining informed consent, patients were instrumented with a multi-electrode nasogastric tube with an esophageal balloon. Consequently, patients were ventilated in a randomized order in pressure control (PC), pressure support (PS) and NAVA for 30 minutes each. During this period, airway pressure (Paw), esophageal pressure (Pes), flow and electrical activity of diaphragm (EAdi) were recorded. Ptp was calculated as Paw – Pes. Patient-ventilator interaction was analyzed using a computer algorithm.

**Results:** Although peak Paw tended to be higher with NAVA, mean Paw and Ptp are lower with NAVA in comparison to PC and PS (p<0.05, figure 1). Median tidal volume was not different between groups (figure 2A). However, the coefficient of variation of Vt is higher with NAVA in comparison to the other modes (p<0.05; figure 2B). In addition, the percentage of delivered breaths exceeding a patient’s average Vt with more than 2 mL/kg is higher (p<0.05) with NAVA (4.1 [IQR 1.3-14.5%]) than with PS (0.0 [IQR 0.0-2.2%]) and PC (0.3 [IQR 0.0-2.0%]). Patient-ventilator interaction, given by the NeuroSync index, is best with NAVA (6.5 [IQR 5.5-10.5]) followed by PS (13.1 [IQR 10.5-29.9]) and PC (28.9 [IQR 12.8-54.5]) (p<0.0001).

**Conclusion:** In conclusion, these preliminary results demonstrate that in patients with moderate ARDS, NAVA is feasible and results in lower mean transpulmonary pressures and equal tidal volumes compared to conventional modes. Furthermore, the physiological variability of breathing is better preserved with NAVA, leading to an improved patient-ventilator interaction. However, due to this higher breath-by-breath variability care should be taken in ventilating patients with NAVA who have a high respiratory drive.

**Neurally adjusted ventilation in patients with acute respiratory distress syndrome: ahead with caution!**

**J. Doorduin1, C.A. Sinderby2,4, J. Beck3,4, J.G. van der Hoeven1, L.M.A. Heunks1**

1Department of Critical Care Medicine, Radboudumc, The Netherlands, 2Department of Medicine, Division of Critical Care Medicine, The Netherlands, 3Department of Pediatrics, St. Michael’s Hospital, University of Toronto, Canada, 4Keenan Research Centre in the Li Ka Shing Knowledge Institute of St. Michael’s Hospital, University of Toronto, Canada
Surveillance cultures in intensive care units: a study on current practice providing future perspectives

J.B.J. Scholte1, W.N.K.A. Van Mook1, C.F.M. Linssen, H.A. van Dessel1, D.C.J.J. Bergmans1, P.H.M. Savelkoul1, P.M.H.J. Roekaerts1

1Department of Intensive Care Medicine, Maastricht UMC+, The Netherlands, 2Department of Microbiology, Atrium Medical Center, Heerlen, 3Department of Microbiology, Maastricht UMC, The Netherlands

Background: Evidence for obtaining surveillance cultures (SC) in intensive care units (ICUs) is scarce. This study explored SC implementation, underlying motives for obtaining SC and the clinical decision making process based on SC results.

Methods: A questionnaire was distributed to Heads of Department (HOD) and microbiologists of all Intensive Care Departments in the Netherlands.

Results: Response rates were high, as presented in figure 1. SC were routinely obtained according to 55/75 (73%) and 33/38 (87%) of HOD and microbiologists, respectively. SC were more often obtained in higher level ICUs.1 Most frequently, SC were obtained twice weekly and sampled from trachea (74-87%), pharynx (74-88%), and rectum (68-84%). Major reasons to obtain SC included perceived optimization of treatment of the individual patient (58% and 73%), prevention of multiple drug resistant (MDR) micro-organisms (28% and 35%), and resistance monitoring (27%). On suspicion of infection of a yet unknown source, micro-organisms identified by SC were generally targeted, while in absence of signs of infection, these micro-organisms were not targeted. A third of HOD target micro-organisms identified by SC in absence of signs of infection at the sampled site. Microbiologist were more reluctant to target these micro-organisms.

Conclusion: SC implementation is common practice in Dutch ICUs and SC are presumed to optimize individual patients’ treatment by targeting micro-organisms identified by SC when infection is suspected and origin unknown. Consensus is lacking on how to deal with SC when the focus of infection is not at the sampled site and therefore SC may sometimes create more upheaval than intelligibility.

References


Effect of oxygen status on inflammatory parameters in humans

H.D. Kiers1, 2, G.J. Scheffer3, J.G. van der Hoeven1, P. Pickkers1, M. Kox1, 2

1Department of Intensive Care Medicine, Radboudumc, Nijmegen, The Netherlands, 2Department of Anesthesiology, Radboudumc, Nijmegen, The Netherlands

Background: The optimization of oxygen delivery is a cornerstone of critical care medicine. In vitro and animal studies have shown that oxygen status (i.e. hypoxia or hyperoxia) directly influences the inflammatory response. Hypoxia exerts pro-inflammatory effects, suppos-
edly mediated by the transcription factor hypoxia inducible factor 1α (HIF1α). On the other hand, hyperoxia is related to immune suppression, possibly through increasing oxidative stress. As such, permissive hypoxia or hyperoxia could be a cheap, non-pharmacological, non-invasive treatment modality to modulate the immune response in inflammatory conditions such as sepsis. However, human data on the effects of oxygen status on the inflammatory response are scarce. The aim of this study was to investigate the effects of systemic hypoxia and hyperoxia on inflammatory parameters in healthy subjects.

**Methods:** 20 healthy, non-smoking, male volunteers, aged 18-35 years were randomized to either hypoxia or hyperoxia. All subjects were admitted to the research department of the ICU for 9 hours. After baseline measurements, subjects were exposed to 3.5 hours of hypoxia (FiO₂ titrated to a peripheral saturation of 80 to 85%) or hyperoxia (FiO₂ of 100%) in an air tight respiratory helmet followed by 5.5 hours of exposure to room air without the helmet in place. Blood was obtained at various time points throughout the day as well as the next morning. Parameters obtained were basic hemodynamic and ventilator parameters, symptoms, blood gas analysis, leukocyte differentiation, circulating cytokines, ex vivo stimulation of leukocytes with lipopolysaccharide (LPS), HIF1α expression in neutrophils, monocytes and lymphocytes, and neutrophilic oxidative burst as measured by intracellular reactive oxygen species.

**Results:** Hypoxia (SaO₂ 81.4(± 0.29)%) was induced using an average FiO₂ of 12.1 (+-1.0)%). Hyperoxia (FiO₂ 100%) resulted in an average PaO₂ of 54.9 ± 7.516 kPa. Hypoxic subjects exhibited a significant decrease in PaCO₂ and respiratory rate compared to hyperoxic subjects, and a significant increase in heart rate (figure 1). Hypoxia resulted in headache in 3 out of 10 subjects. Furthermore, hypoxic subjects displayed a significant increase in circulating neutrophils (figure 2), while no changes in other leukocyte subpopulations were observed. Hypoxia or hyperoxia did not induce detectable levels of circulating cytokines, and no effects cytokine production by leukocytes ex vivo stimulated with LPS were observed. There was large interindividual difference in leukocyte HIF1α expression in both hypoxic and hyperoxic subjects with no apparent effects of both treatments. Furthermore, hypoxia and hyperoxia did not influence neutrophilic oxidative burst.

**Conclusion:** Exposure of 3.5 hours to mild hypoxia or hyperoxia does not lead to cytokine production, nor does it change the capacity of leukocytes to produce inflammatory cytokines upon ex vivo stimulation. The extent and duration of hypoxia and hyperoxia used in this study appears not to result in induction of HIF1α or increased reactive oxygen production, respectively.

**Figure 1.** Respiratory and hemodynamic parameters during 3.5 hours of hypoxia and hyperoxia. The oxygen status adjustment period is marked in grey. P-values calculated using two-way ANOVA (interaction term)

**Figure 2.** Neutrophil count during and after 3.5 hours of hypoxia and hyperoxia. The oxygen status adjustment period is marked in grey. P-values calculated using two-way ANOVA (interaction term)
and patient outcome. We investigated the kinetics of suPAR, correlation with the immune response and outcome in multi-trauma patients.

**Methods:** Blood was obtained from adult multi-trauma patients (n=63) on arrival at the emergency room (ER) of the Radboud University Nijmegen Medical Centre and days 1, 3, 5, 7, 10 and 14 following trauma. Plasma concentrations of TNF-α, IL-6, IL-10, IFN-γ, IL-8 and MCP-1 were determined by Luminex, and SuPAR concentrations using ELISA. Clinical data were collected from electronic patient files. Concentrations, areas under the curve (AUC) and regression coefficients were statistically analyzed. Spearman correlation coefficients were calculated and differences between survival/non-survival groups were analyzed using unpaired Student T-tests.

**Results:** SuPAR values at admission to the ER were higher in non-survivors compared to survivors (n=16, mean ± SEM 4.1 ± 0.6 ng/ml versus n=40, 3.0 ± 0.2 ng/ml, p=0.03). SuPAR levels increased in time (figure 1, Kruskal-Wallis, p<0.0001). An increase of SuPAR did not predict or precede death, though. SuPAR AUC from ER to day 5 tended to correlate with injury severity score (r=0.5, p=0.07). Plasma cytokines in the ER did not correlate with SuPAR measured at the same time (e.g. TNF-α r=0.2, p=0.37, IL-10 r=−0.02, p=0.91), while cytokine concentrations at the ER did correlate with SuPAR levels at days 3 (TNF-α r=0.6, p<0.01, IL-10 r=0.5, p=0.02) and 5 (TNF-α r=0.7, p<0.01).

**Conclusion:** Plasma concentrations of SuPAR measured at admission to the ER are associated with overall survival of multi-trauma patients. Furthermore, SuPAR concentrations increased during hospital admission, with most pronounced increases found in patients that suffered more serious injury and related to the innate immune response determined in the ER. These results indicate that SuPAR is a innate immune response-induced late mediator in multi-trauma patients.

**Intestinal Fatty Acid Binding Protein (i-FABP), a possible new marker for intestinal damage in trauma patients**

K. Timmermans1,2, O. Sir3, M. Kox1,2, M. Vaneker1, G.J. Scheffer1, P. Pickkers2

1Department of Anesthesiology, Radboudumc, Nijmegen, The Netherlands, 2Department of Intensive Care Medicine, Radboudumc, Nijmegen, The Netherlands, 3Department of Emergency Medicine, Radboudumc, Nijmegen, The Netherlands

**Background:** Intestinal damage is difficult to determine in multiple trauma patients. Apart from the trauma itself, hemodynamic instability may contribute to intestinal damage. Intestinal Fatty Acid Binding Protein (i-FABP) is exclusively expressed by enterocytes. It is released following enterocyte damage and established to be a good marker for intestinal ischaemia. The aim of this study was to assess intestinal damage using the biomarker i-FABP in trauma patients during the first days of their hospital admission.

**Methods:** We studied adult multitrauma patients (n=92) admitted to the Radboudumc. Blood was obtained at the trauma scene by the helicopter emergency medical services (HEMS), at arrival at the emergency room (ER), and at days 1, 3, 5, 7, 10, and 14 after trauma. Plasma concentrations of i-FABP were determined by ELISA. Clinical data, e.g. Injury Severity Score (ISS), Simplified Acute Physiology Score (SAPS) II score, Mean Arterial blood Pressure (MAP) and hemoglobin (Hb) values were collected from electronic patient files.

**Results:** Plasma i-FABP concentrations were highest immediately following trauma at time points HEMS and ER. From day 3 onwards, i-FABP levels were lower compared with time points HEMS and ER (figure 1). I-FABP values at the ER were correlated with ISS (R=0.32, P<0.01) and patients suffering from abdominal trauma demonstrated higher I-FABP concentrations in comparison with patients with other types of trauma (p<0.01, figure 2). Also the SAPS II score, calculated at day 1, significantly correlated with the i-FABP concentration on the same day (R=0.35, p=0.03).

Finally, patients presenting with a low MAP (<70 mmHg) at the ER, demonstrated higher ER plasma i-FABP concentrations in comparison with patients with a normal (70-99 mmHg) or high (>100 mmHg) MAP (p<0.01, figure 3A). The same pattern was observed for patients with a low Hb (<80% of Reference value) in comparison with patients with a normal Hb (p<0.01, figure 3B).

**Conclusions:** Plasma i-FABP is highest within minutes to hours after trauma and related to the severity and abdominal involvement of the trauma. Hemodynamic instability, determined by low MAP and Hb levels, are also associated with higher levels of marker i-FABP, likely related to secondary ischaemia-induced intestinal damage. I-FABP could serve as an early marker for direct trauma-related and secondary ischemic intestinal damage in trauma patients.
16. Comparison of wrist actigraphy and video-based actigraphy for delirium detection in ICUs

M. van den Boogaard1, E.M. van der Heide2

1Radboudumc, Department of Intensive Care, Nijmegen, The Netherlands, 2Philips Research, Department of Patient Care Solutions, Eindhoven, The Netherlands

Background: Delirium in ICU-patients is mostly assessed by the CAM-ICU and ICDSC at least twice daily. With its fluctuating course delirium is still easily missed. Hence, there is need for an objective, (semi-) automated, continuous measurement method.

Disturbed motor activity pattern (DMAP), a frequent manifested feature in delirious patients, could be interesting for delirium detection. Measurement of DMAP to detect delirium is reported in a few studies, all making use of on-body accelerometer-based techniques. However, these techniques measures movements of one part of the body, missing movements of the rest of body. Video-based actigraphy monitoring has the advantage that altered motions of the whole body can be observed without extra on-body sensors. This could be an interesting method for objective delirium detection. The captured video will be analyzed for DMAP that could be indicative of delirium. Advanced image analysis allows for a more detailed analysis of the context of the movement, going beyond mere activity counts.

Objective: To determine if DMAP measured with video-based actigraphy are indicative for delirium and can be used for continuous delirium detection in ICU-patients.

Method: An observational case-control study including delirious and non-delirious patients. Besides video-monitoring (24-hrs a day, maximum 5 days), a wrist Actiwatch is used measuring activity level of the arm. Patients are screened using CAM-ICU 3/day, and by a delirium expert screening.

Results: In total 31 patients, mean age of 67.8 years, were included of which 21 (67%) were delirious and 10 (33%) were not. Preliminary results showed that activity levels measured with of video-based actigraphy compared with Actiwatch has important advantages to determine whole body activity level. Furthermore, we were able to identify from the video-images DMAP possibly related to delirium.

Conclusion: The actiwatch results were in line with earlier results shown in literature. It confirms that measurement of motoric alterations can be sed for detection of delirium in ICU patients.

Our preliminary results show that for measuring DMAP in delirious patients video-based actigraphy monitoring is superior to wrist-based accelerometer techniques.

Table 1.

<table>
<thead>
<tr>
<th>Characteristics (n=30)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y (mean, SD)</td>
<td>68.2 ± 11</td>
</tr>
<tr>
<td>APACHE II score (mean, SD)</td>
<td>19 ± 4</td>
</tr>
<tr>
<td>PREDELIRIC score (mean, SD)</td>
<td>63 ± 24</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>19 (63)</td>
</tr>
<tr>
<td>Sedation, y (%)</td>
<td>16 (53)</td>
</tr>
<tr>
<td>Medical patients, n (%)</td>
<td>25 (83)</td>
</tr>
<tr>
<td>Sepsis, n (%)</td>
<td>9 (30)</td>
</tr>
<tr>
<td>Died, n (%)</td>
<td>7 (23)</td>
</tr>
<tr>
<td>Delirium, n (%)</td>
<td>21 (70)</td>
</tr>
<tr>
<td>Delirium days (median, IQR)</td>
<td>2.0 [0,2.3]</td>
</tr>
<tr>
<td>Delirium free-days (median, IQR)</td>
<td>2.0 [0,2.3]</td>
</tr>
</tbody>
</table>
Numbers tell the tale in lung protective mechanical ventilation; estimating body weight by eye versus calculating predicted body weight
M.L. Gruijters-van den Bos, M. Vriends, E.R. van Slobbe-Bijlsma
Department of Intensive Care Medicine, Tergooi, The Netherlands

Background: Low tidal volumes are essential in lung protective mechanical ventilation and based on predicted body weight. Predicted body weight (PBW) is calculated using the Devine formula, based on gender and height. In acute situations bodyweight sometimes is estimated by eye. We assessed the hypothesis that estimating by eye results in higher initiating tidal volumes since everyone overestimates predicted body weight.

Methods: All patients admitted to the ICU and in need of mechanical ventilation were included during a six month period in 2010-2011. Medical staff (intensivist, resident and nurse) estimated by eye the body weight of all patients. Mechanical ventilation was started. Hereafter height was measured in centimeters and the predicted body weight was calculated and mechanical ventilation was adjusted if necessary. Initiating tidal volumes were set to 6ml/kg. median

Results: A total of 175 patients was included; 105 patients were excluded because of low height and/or incomplete data collection. Data of 70 patients was analyzed. The entire ICU staff overestimated bodyweight, with a median difference of 4 kg in the nurse group and 5 kg in the resident and intensivist group (0-24 kg) (p<0.001). There were no significant differences between intensivists, residents and nurses. Estimating by eye resulted in higher initiating tidal volumes. Median overestimation was 26 ml (0-220 ml in nurse-group (p<0.001) and 30 ml setting tidal volumes based on estimating bodyweight. Conclusion: Setting tidal volumes based on estimating bodyweight by eye resulted in higher initiating tidal volumes as compared to tidal volumes based on calculated predicted body weight. Nurses, residents and intensivists overestimated body weight. The initial higher tidal volumes were considered as not harmful because of low initial settings (Vt 6 ml/kg), so lung protective ventilation was still warranted.

In conclusion, in patients in need of mechanical ventilation, body weight should be calculated and not estimated by eye to ensure lung protective mechanical ventilation. Numbers do tell the tale.

Reference
19. Effects related to ScvO₂-guided preoperative optimization in open transhiatal esophagectomy patients

B.M. van der Kolk 1,2, M. van den Boogaard 1, J.J. Bonenkamp 2, C.J.H.M. van Laarhoven 1, J.G. van der Hoeven 1, P. Pickkers 1

1Department of Intensive Care Medicine, Radboudumc, Nijmegen, The Netherlands, 2Department of Surgery, Radboudumc, Nijmegen, The Netherlands

Introduction: Open transhiatal esophagectomy is associated with considerable short term postoperative morbidity and mortality. Optimizing the circulation pre-operatively may result in improved wound healing, attenuated risk for anastomotic leakage and prevent infection/sepsis, but may theoretically also lead to more blood loss during surgery. The effects of preoperative optimization in this specific group of high risk surgical patients is unknown.

Methods: A group of consecutive pre-operatively optimized patients was compared with a control group of non-pre-optimized patients which were admitted two years earlier. Preoperative optimization was started one day prior to esophagectomy. Patients were admitted to the intensive care unit (ICU) and received an arterial and jugular line. A ScvO₂ <70% was treated with fluids and inotropics according to the protocol.

Results: 68 patients received pre-operative optimization and 32 patients did not. Optimized patients lost significantly less blood intra-operatively (p=0.01) and needed less blood products (p=0.002) compared with non optimized patients, while the transfusion trigger did not change during these years. Postoperative sepsis occurred in 25% of the non optimized patients and 4% of the optimized patients (p=0.002), anastomotic leakage occurred in 12% of optimized patients and 25% of non-optimized patients (p=0.08). Other postoperative pulmonary and cardiovascular complications did not differ significantly between both groups. Optimized patients had a significantly shorter hospital length of stay median 10 days IQR 8-13 versus median 17 IQR 13-35, (p<0.001) and a shorter duration of mechanical ventilation median 4.7 hrs IQR [3.6-6.8] versus 7.7 hrs IQR [3.5-28.2], (p=0.01) compared with the control group. There was a trend that optimized patients were less readmitted to the ICU 9 versus 25%, (p=0.06) compared to the control group. Within the optimized group delta ScvO₂ increased median 4% [IQR 0-7] and targeted ScvO₂ >70% was achieved in 76.6 of the optimized patients. Patients not reaching the target ScvO₂ were more likely to have a cardiovascular medical history (p<0.02). Not reaching the SvO₂ target or a delta ScvO₂ rise less than 5%, was not associated with an unfavourable course or outcome.

Conclusion: Pre-operative ScvO₂ guided optimization of patients treated with an open transhiatal esophagectomy is associated with a several beneficial effects. However, there is no straightforward explanation for the observed beneficial effects pre-operative optimization that are related to achieved or delta increase in ScvO₂. At this moment, routine use of ScvO₂ guided pre-operative optimization cannot be advised. Nevertheless, we cannot rule out that a more sustained increase in SvO₂, e.g. in the 6 hrs, preceding surgery, could result in a further improvement of the prognosis of these patients. However, this warrants confirmation in a RCT.

20. Alkaline phosphatase attenuates the inflammatory response in human proximal tubule epithelial cells: the potential mechanism of action of the observed beneficial effects in septic patients with acute kidney injury

E. Peters 1,2, S. Heemskerk 1,2, R. Masereeuw 2, P. Pickkers 1

1Department of Intensive Care Medicine, Nijmegen Institute for Infection, Inflammation and Immunity, Radboudumc, Nijmegen, The Netherlands, 2Department of Pharmacology and Toxicology, Nijmegen Centre for Molecular Life Sciences, Radboudumc, Nijmegen, The Netherlands

Background: Sepsis carries a high morbidity and mortality, especially when complicated by acute kidney injury (AKI). Currently, no treatment is available for sepsis-induced AKI. Two phase-II trials showed that kidney function improved in critically ill patients with sepsis-induced AKI after treatment with the enzyme alkaline phosphatase (AP). 1,2 The mechanism of this beneficial effect on the kidney is unknown, but might be related to the dephosphorylation, and thereby detoxification, of endotoxin (lipopolysaccharide, LPS). We investigated the anti-inflammatory properties of AP by using a human proximal tubular cell model.

Methods: Conditionally immortalized human proximal tubular epithelial cells (ciPTEC) were incubated with LPS (10 µg/ml) or TNF-α (10 ng/ml) to induce an inflammatory response. Recombinant human AP (10 U/ml) was added 2 hours prior to the inflammatory insult and the cytokine production of TNF-α, IL-6, and IL-8 was studied after 24 hours by ELISA. Supernatant of peripheral blood mononuclear cells (PBMCs), prestimulated for 24 hours with or without LPS (1 ng/ml), was added to the ciPTEC to mimic endotoxin-induced renal inflammation. AP was added 2 hours prior to this insult and IL-6 and IL-8 were measured after 24 hours. Data are expressed as mean ± SEM (n=5 per group) and the effect of AP was analyzed by one-way ANOVA.

Results: AP pretreatment significantly reduced the LPS induced cytokine response of TNF-α (reduction 40.4 ± 7.9%, p<0.05), IL-6 (reduction 47.5 ± 3.1%, p<0.0001) and IL-8 (reduction 39.6±2.4%, p<0.0001) in ciPTEC (figure 1). Similar effects of AP were observed in ciPTEC stimulated with TNF-α, as the inflammatory response of IL-6 and IL-8 was significantly reduced by AP (IL-6: 21.0 ± 4.2%, p<0.05; IL-8: 21.6 ± 4.6%, p<0.05; figure 2). Inactive AP, lacking enzyme activity so it cannot dephosphorylate molecules, had no effect on both LPS- and TNF-α-induced cytokine response (figure 1 and 2). The supernatant of PBMCs, pre-incubated with LPS, induced the production of IL-6 and IL-8 in the ciPTEC. Stimulating the ciPTEC directly with 1 µg/ml LPS had no effect, demonstrating that the inflammatory response is induced by media-
tors present in the PBMC supernatant. AP treatment could significantly reduce this response (IL-6: 39.2 ± 9.6% reduced, p<0.05; IL-8: 34.9 ± 6.0%, p<0.05; figure 3).

Conclusion: The dephosphorylating property of AP is responsible for the reduction of the cytokine response induced by LPS and TNF-α, as inactive AP had no effect. TNF-α and the inflammatory mediators in the PBMC supernatant itself cannot be dephosphorylated by AP, strongly suggesting that AP targets other molecules as well. A possible target might be ATP which is released by these cells upon stress conditions and can be converted by AP into the cytoprotective adenosine. These findings suggest that the ability of AP to reduce renal inflammation may account for the observed attenuated acute kidney injury in sepsis patients.

References
Background: Delirium often occurs in Intensive Care Unit (ICU) patients and is associated with serious short- and long-term consequences. As a consequence, delirium prevention is imperative, especially in high-risk patients. The recently developed and validated PREDELIRIC model reliably predicts delirium after 24 hours in the ICU.

However, in a relevant number of patients delirium occurs within 24 hours following ICU admission and thus identifying them as high risk is not possible with the PRE-DELIRIC model. Therefore the aim of this study was to develop and validate an Early PREdiction of DELIRium IC (E-PRE-DELIRIC) model based on data available at ICU admission.

Methods: An international multicenter prospective cohort study was carried out in 13 ICUs from 7 countries between October 2011 and June 2012. Every ICU included all eligible patients aged ≥18 years during a period of approximately three months. Data of 16 putative risk factors of delirium were collected immediately after ICU admission. The CAM-ICU was used by well trained ICU nurses to diagnose delirium. CAM-ICU screening compliance and inter-rater reliability (IRR) were measured in order to check the quality of these assessments. Multiple logistic regression analysis was used to develop the E-PRE-DELIRIC model on data of the first two-thirds of every participating hospital. The model was validated on data of the last one-third of every participating hospital. We determined discriminative power using the area under the receiver operating characteristic curve (AUROC) and calculated the linear predictor for each patient for calibration.

Results: In total 5,352 patients were screened, of which 2,433 patients were excluded (Figure 1). The study cohort consisted of 2,919 patients; data of 1,966 patients were included in the development database and data of 953 patients in the validation database. See Table 1 for patient characteristics and delirium incidences. The mean (SD) overall CAM-ICU compliance was 83 ± 16% and the mean IRR was 0.83. The delirium incidence was 24.6% in the development database and 21.8% in the validation database.

Conclusion: In this study we internationally developed and validated an early delirium prediction model (E-PRE-DELIRIC). Using this model patients’ risk for delirium in the ICU can be predicted immediately after admission, allowing the start of delirium preventive interventions immediately after ICU admission.

Factors of influence on the morbidity and mortality after pancreaticoduodenectomy

R.J.C. van den Broek1, E. Olofsen1, B.A. Bonsing2, L.P.H.J. Aarts1, J. Vuyk1

1Department of Anesthesiology, Leiden University Medical Center, Leiden, The Netherlands, 2Department of Surgery, Leiden University Medical Center, Leiden, The Netherlands

Table 1. Complications as classified according to the Clavien-Dindo classification and the International Study Group of Pancreatic Surgery (ISGPS) as occurred in 76 out of 143 patients (53%) after pancreaticoduodenectomy

<table>
<thead>
<tr>
<th>Complication type</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wound infection</td>
<td>15</td>
<td>10.5</td>
</tr>
<tr>
<td>Intrathoracic / intraabdominal infection (abscess)</td>
<td>21</td>
<td>14.7</td>
</tr>
<tr>
<td>Rebleed</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Fistula</td>
<td>25</td>
<td>17.5</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>3</td>
<td>2.1</td>
</tr>
<tr>
<td>Cardiac decompensation</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>12</td>
<td>8.4</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>6</td>
<td>4.2</td>
</tr>
<tr>
<td>Bowel motility disorder</td>
<td>14</td>
<td>9.8</td>
</tr>
<tr>
<td>Other (atrial fibrillation, diarrhea, hepatic infarction, neuropathy etc.)</td>
<td>33</td>
<td>23</td>
</tr>
</tbody>
</table>

References

Table 1. Patients characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Development (n=1966)</th>
<th>Validation (n=953)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years (median [IQR, range])</td>
<td>65 (53-74, 77)</td>
<td>64 (51-73, 76)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>116 (59.4)</td>
<td>551 (57.8)</td>
</tr>
<tr>
<td>Admission category, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Surgery</td>
<td>1021 (51.9)</td>
<td>476 (49.9)</td>
</tr>
<tr>
<td>2. Medical</td>
<td>685 (34.8)</td>
<td>339 (35.6)</td>
</tr>
<tr>
<td>3. Trauma</td>
<td>90 (4.6)</td>
<td>44 (4.6)</td>
</tr>
<tr>
<td>4. Neurology/neurosurgery</td>
<td>170 (8.6)</td>
<td>94 (9.9)</td>
</tr>
<tr>
<td>Urgent admission, n (%)</td>
<td>1166 (59.3)</td>
<td>571 (59.9)</td>
</tr>
<tr>
<td>LOS-ICU, in days</td>
<td>2.0 (1-6, 132)</td>
<td>2.0 (1-5, 125)</td>
</tr>
<tr>
<td>Delirium, n (%)</td>
<td>483 (24.6)</td>
<td>208 (21.8)</td>
</tr>
</tbody>
</table>

Background: The perioperative course of patients undergoing pancreaticoduodenectomy (PD) is associated with surgical and anesthetic challenges reflected in its significant morbidity and 30-day mortality (3-10%). Little is known regarding perioperative factors that affect outcome after PD. We studied the factors of influence on mortality and morbidity after PD.

Methods: With Ethics committee approval, perioperative parameters (amongst others: POSSUM score, presence of epidural blockade, perioperative plasma creatinine concentrations, blood loss, fluid balance, need for postoperative mechanical ventilation or vasopressive agents, complications classified according to the Clavien-Dindo classification and the International Study Group of Pancreatic Surgery (ISGPS), mortality and length of stay) of all patients scheduled for a PD in the LUMC during 2006-2011 were prospectively collected. Univariate and multivariate logistic regression analysis were performed to determine the parameters of influence on morbidity and mortality. A model to improve informedness was developed to allow the prediction of the incidence of complications. Informedness is the probability that an informed decision is made, rather than a guess.

Results: All 143 patients who underwent PD were included in the study. Complications (table 1) occurred in 76 (53%) patients, with a mortality of 5.6% during hospital stay. Mean length of stay was 14 ± 6 days for patients without complications and 27 ± 19 days for patients with complications (p= 0.001). Results of univariate regression analysis are presented in table 2. Mortality and morbidity were, in part, the result of non-influenceable parameters, such as ASA physical status, POSSUM score and the presence of malignancy. Some parameters, however, that are in reach of the clinician, affected outcome. These included epidural analgesia that reduced the risk to develop pneumonia (5.8% versus. 21.7%, p=0.02), and a positive fluid balance that increased the incidence of postoperative intra-abdominal abscesses (p=0.01). Age, gender, BMI, blood loss and length of surgery as individual parameters did not influence the incidence of postoperative complications or mortality in this population. A predictive model with the combined parameters: ASA status, gender, presence of oliguria during surgery, length of surgery, need for postoperative ventilation, fluid balance and plasma creatinine concentration at 24 h after surgery as significant parameters, improved informedness from 0 to 0.24.

Conclusion: Epidural blockade and fluid balance are influenceable perioperative factors that affect outcome after PD. Perioperative care physicians should be aware of this and guide patients for PD accordingly. We developed a model that increases informedness of postoperative complications.
Table 2. P-values of the univariate logistic regression analysis of parameters on mortality and morbidity in patients after pancreaticoduodenectomy. Presented are the p-values of the significant results (p<0.05). All blanks represent non-significant results.

| Parameter                  | Mortality | Complications | Pneumonia | Myocardial infarction | Abscess | Fistula | Pneopressive agents | Postoperative blood loss | Postoperative mechanical ventilation | Peroperative blood loss | Peroperative mechanical ventilation | Total POSSUM score | Physiological POSSUM score | Operative POSSUM score | Epidural analgesia |
|----------------------------|-----------|---------------|-----------|-----------------------|---------|---------|---------------------|--------------------------|----------------------------|----------------------|------------------------|------------------|---------------------|----------------------|-------------------|----------------|
| ASA physical status        | 0.03      | 0.02          | 0.02      | 0.01                  | 0.02    | 0.03    | 0.02                | 0.02                     | 0.02                      | 0.02                | 0.02                  | 0.02             | 0.02                | 0.02                | 0.02              |
| Physiological POSSUM score | 0.05      | 0.02          | 0.02      |                       | 0.01    |         | 0.02                | 0.02                     | 0.02                      | 0.02                | 0.02                  | 0.02             | 0.02                | 0.02                | 0.02              |
| Operative POSSUM score     | 0.01      | 0.01          | 0.01      | 0.01                  | 0.01    |         | 0.01                | 0.01                     | 0.01                      | 0.01                | 0.01                  | 0.01             | 0.01                | 0.01                | 0.01              |
| Total POSSUM score         | 0.01      | 0.01          | 0.01      | 0.01                  | 0.01    |         | 0.01                | 0.01                     | 0.01                      | 0.01                | 0.01                  | 0.01             | 0.01                | 0.01                | 0.01              |
| Epidural analgesia         |           |               | 0.02      |                       |         |         | 0.02                | 0.02                     | 0.02                      | 0.02                | 0.02                  | 0.02             | 0.02                | 0.02                | 0.02              |
| Peroperative blood loss    |           |               | 0.02      |                       |         |         | 0.02                | 0.02                     | 0.02                      | 0.02                | 0.02                  | 0.02             | 0.02                | 0.02                | 0.02              |
| Postoperative mechanical ventilation | 0.02 |               | 0.02      |                       |         |         | 0.02                | 0.02                     | 0.02                      | 0.02                | 0.02                  | 0.02             | 0.02                | 0.02                | 0.02              |
| Pneopressive agents        |           |               | 0.02      |                       |         |         | 0.02                | 0.02                     | 0.02                      | 0.02                | 0.02                  | 0.02             | 0.02                | 0.02                | 0.02              |
| High fluid balance after 24h |           |               | 0.02      |                       | 0.02    | 0.02    | 0.02                | 0.02                     | 0.02                      | 0.02                | 0.02                  | 0.02             | 0.02                | 0.02                | 0.02              |
| Creatinine level after 24h |           |               | 0.03      |                       |         |         | 0.02                | 0.02                     | 0.02                      | 0.02                | 0.02                  | 0.02             | 0.02                | 0.02                | 0.02              |

23.

Using ultrasound of the lung to predict fluid responsiveness and estimate volume status

J.M. Schoonejans, S. Rijkenberg, H. Endeman
Department of Intensive Care, Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands

Background: Excessive fluid resuscitation in critically ill patients is associated with adverse outcome. Determining fluid responsiveness is therefore a pivotal element of intensive care therapy. Many methods of fluid responsiveness have been developed, the majority needing invasive measurements, such as central venous or arterial catheters. The same counts for estimation of the volume status of the patient. Ultrasound of the lung is an non-invasive method to diagnose the interstitial syndrome. The interstitial syndrome is associated with excessive extravascular lung water. In this pilot study we analyzed the relation between parameters of fluid responsiveness, the pulse pressure variation (PPV) and volume status, the central venous pressure (CVP), and the interstitial syndrome.

Methods: Patients were included in case of arterial catheter and central venous catheter (CVC) in place. PPV was measured in ventilated and non-ventilated patients, but only if the patients was in sinus rhythm. Values of CVP were only used for further analysis, if the CVC was in upper diaphragm position. Ultrasound of the lung was performed using the adjusted BLUE protocol. Lungs were classified A, A/B or B in which B represents the interstitial syndrome. A second, hydrostatic, classification was made using the zones of West (empty, partially filled, fully filled lungs) (figure 1).

Results: In 38 patients 82 measurements were done. During 35 ultrasound examination an accurate PPV was measured. PPV is highest in case of an A-profile present (mean 14.0%, SD 8.6%), decreases in an A/B-profile (mean 9.0%, SD 3.6%) and is lowest in the B-profile (mean 7.8%, SD 5.1%), but differences were not statistical significant. This trend was not seen using the hydrostatic classification (figure 1). CVP was measured properly during 37 measurements. The CVP is highest in the B-profile (median 16.5 mmHg, IQR 4.2 mmHg) and lowest in the A-profile (median 9 mmHg, IQR 6.4 mmHg); this difference is statistically significant (p=0.043). The CVP in the A/B profile is lays between those values (median 12.3 mmHg, IQR 8 mmHg). A similar non-significant trend was found using the hydrostatic profiles (figure 2).

Conclusion: This pilot study shows lung ultrasound might be a reliable non-invasive way to measure the limit of fluid responsiveness (measured by PPV) and seems to give a estimation of volume status (measured by CVP). A larger cohort of patients is needed to confirm these findings.

References

Figure 1. Lung profiles using the classification of the BLUE protocol and on basis of the hydrostatic pressure described by West.

Figure 2a-d. CVP in patients with the A, A/B or B-profile (a); difference between A-profile and B-profile is statistically significant (p<0.043). CVP in patients with the hydrostatic profiles empty, partially filled, fully filled (b). PPV in patients with the A, A/B or B-profile (c) and empty, partially and fully filled lungs.
25-OH-vitamin D deficiency is a frequent finding in critically ill patients but is not an independent risk factor for mortality

L.A. Meynnaar1, L. Dawson1, Y. Schriel1, J. Verzijl2, F. van der Dijs2

1ICU, Reinier de Graaf Hospital, Delft, The Netherlands, 2Department of Clinical Chemistry, Reinier de Graaf Hospital, Delft, The Netherlands

Introduction: Some authors found 25-OH-vitamin D to be an independent risk factor for mortality (Venkatram, Crit Care 2011), others did not (Cecchi, Minerva Anesthesiol 2012). Our aim was to study the incidence of vitamin D deficiency and to test the hypothesis that 25-OH-vitamin D deficiency is independently associated with increased mortality in critically ill patients.

Methods: This prospective observational study was done in the 10-bed mixed ICU of the Reinier de Graaf Hospital. For all patients admitted to the ICU between July 1st, 2011 and June 30th, 2013, 25-OH-vitamin D (ARCHITECT 25-OH Vitamin D, Abbott Diagnostics Europe) was measured in leftover blood samples from the first 24 hrs of ICU treatment. Patient characteristics and outcome are collected routinely. Study end point was hospital mortality. The need for informed consent was waived.

Results: 25-OH-vitamin D on ICU admission was available for 955 of 1173 individual patients (81%) admitted during the study period. Patient characteristics are shown in table 1.

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>All patients (n=955)</th>
<th>Survived to hospital discharge (n=824)</th>
<th>Died in hospital (n=131)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>65.0 (16.2)</td>
<td>63.8 (16.5)</td>
<td>72.4 (11.9)</td>
<td>&lt;0.001 (1)</td>
</tr>
<tr>
<td>Apache IV score</td>
<td>58.5 (30.7)</td>
<td>52.7 (25.0)</td>
<td>96.1 (37.5)</td>
<td>&lt;0.001 (1)</td>
</tr>
<tr>
<td>Apache IV exp mort</td>
<td>8.5% (2.8-25.1)</td>
<td>6.6% (2.4-18.4)</td>
<td>49.3% (21.9-81.2)</td>
<td>&lt;0.001 (2)</td>
</tr>
<tr>
<td>Medical</td>
<td>530</td>
<td>430 (81.1%)</td>
<td>100 (18.9%)</td>
<td>&lt;0.001 (3)</td>
</tr>
<tr>
<td>Planned surgery</td>
<td>301</td>
<td>291 (96.7%)</td>
<td>10 (3.3%)</td>
<td></td>
</tr>
<tr>
<td>Emergency surgery</td>
<td>124</td>
<td>103 (83.1%)</td>
<td>21 (16.9%)</td>
<td></td>
</tr>
<tr>
<td>ICU LOS</td>
<td>1.6 (0.8-3.4)</td>
<td>1.5 (0.8-3.1)</td>
<td>2.1 (0.9-5.1)</td>
<td>&lt;0.001 (2)</td>
</tr>
<tr>
<td>HOSP LOS</td>
<td>9.3 (5.1-18.7)</td>
<td>9.9 (5.7-18.3)</td>
<td>6.4 (2.1-19.1)</td>
<td>0.003 (2)</td>
</tr>
<tr>
<td>25-OH-Vit D nmol/L (4)</td>
<td>33.5 (2.0)</td>
<td>34.0 (2.0)</td>
<td>30.5 (2.0)</td>
<td>0.088 (1)</td>
</tr>
</tbody>
</table>

Data presented as mean (SD), median (IQR), number (%) as appropriate. (1) T Test, (2) Mann Whitney U test, (3) Chi-square test, (4) after log conversion. 936 patients fulfilled Apache IV inclusion criteria.

When regarding 25-OH-vitamin D levels below 30 nmol/L as deficient, 55+292=347 patients (36.3%) were deficient. Some use a cut-off level of 50 nmol/L, this would mean that 55+292+344=691 of our patients were deficient (72.4%). Table 2 shows that low 25-OH-vitamin D levels are not associated with increased mortality. We found similar results with univariate logistic regression or when using ROC curves (not shown): no association between 25-OH-vitamin D and hospital mortality. As might be expected, in multivariate analysis including Apache IV score as a measure of illness severity, 25-OH-vitamin D was not an independent risk factor for mortality, with p<0.001 for APACHE IV score and p=0.221 for 25-OH-vitamin D.

Conclusion: In this single centre prospective observational study with 955 patients, depending on the definition of deficiency, one-third to two-thirds of patients admitted to the ICU were 25-OH-vitamin D deficient. 25-OH-vitamin D however was not an independent risk factor for hospital mortality.

Table 2. Univariate analysis for vitamin D levels and hospital mortality

<table>
<thead>
<tr>
<th>Vitamin D level</th>
<th>All patients (n=955)</th>
<th>Survived to hospital discharge (n=824)</th>
<th>Died in hospital (n=131)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vit D &lt;15 nmol/L</td>
<td>55</td>
<td>47 (85.5%)</td>
<td>8 (14.5%)</td>
<td></td>
</tr>
<tr>
<td>Vit D 15-29 nmol/L</td>
<td>292</td>
<td>245 (83.9%)</td>
<td>47 (16.1%)</td>
<td></td>
</tr>
<tr>
<td>Vit D 30-49 nmol/L</td>
<td>344</td>
<td>299 (86.9%)</td>
<td>45 (13.1%)</td>
<td>ns (3)</td>
</tr>
<tr>
<td>Vit D 50-69 nmol/L</td>
<td>163</td>
<td>140 (85.9%)</td>
<td>23 (14.1%)</td>
<td></td>
</tr>
<tr>
<td>Vit D ≥70 nmol/L</td>
<td>101</td>
<td>93 (92.1%)</td>
<td>8 (7.9%)</td>
<td></td>
</tr>
</tbody>
</table>

25-OH-vitamin D deficiency is a frequent finding in critically ill patients but is not an independent risk factor for mortality.

Results of the first 6 months use of dexmedetomidine

C.A.E. Watervoort, N. Embregts, J.A.H. van Oers

Department of Intensive Care Medicine, St Elisabeth Hospital, Tilburg, The Netherlands

Background: Dexmedetomidine is a highly selective α2-agonist with sedative, analgesic and anxiolytic effects. It is known to decrease the duration of mechanical ventilation compared with midazolam 1 and to enhance patient comfort at the ICU compared with midazolam and propofol.1 We started to use dexmedetomidine in December 2012. The aim of the study is to describe our first experiences.

Methods: We performed a retrospective observational study of all patients who had been treated with dexmedetomidine between December 2012 and June 2013 on our 30 bed mixed medical (neuro) surgical ICU. Data of demographics, clinical features, indications to start, maximum dose and duration of dexmedetomidine, duration of mechanical ventilation and ICU stay, delirium assessment by the CAM-ICU and adverse events were collected. Differences in quantitative variables were examined using a Mann Whitney U test and differences in categorical variables were examined using a chi-squared test. A p-value of < 0.05 was considered statistically significant.
**Results:** In 62 patients dexmedetomidine was started 68 times during 6 months. Demographics, clinical features and outcome are presented in Table 1. We identified 3 main groups of indications to start dexmedetomidine: 1. Patients uncomfortable on non-invasive positive pressure ventilation (NIPPV) or difficult to wean from invasive ventilation. 2. Patients in delirium. 3. Patients in which dexmedetomidine was started in an attempt to reduce midazolam and/or propofol and 1 rest group called others. Differences between these groups are presented in Table 2. 58 patients were ventilated (6 NIPPV, 35 invasive ventilation and 17 both). In the delirium group the CAM-ICU was performed 12 times (10 delirium/2 no delirium) before starting dexmedetomidine and 7 times (4 delirium / 3 no delirium) after starting dexmedetomidine. X² 1.56 (NS). There were no differences in unplanned extubations in the different groups.

**Conclusion:** These are our first experiences with a new sedative agent. We were in a learning phase. We prescribed dexmedetomidine most frequently in patients uncomfortable on NIPPV or difficult to wean from invasive ventilation and patients in delirium. There were no significant differences in the maximum dose and duration of dexmedetomidine and outcome parameters. There were no differences in the small amount of CAM-ICU performed in the delirium group after starting dexmedetomidine.

**Reference**

---

**Let’s make things better: volumetric capnography to determine dead space in ARDS patients**

**J.L. Nollet**<sup>1,2</sup>, M.P.A.J. Vugts<sup>2</sup>, L.H. Roesthuis<sup>2</sup>, J. Doorduin<sup>2</sup>, J.G. van der Hoeven<sup>2</sup>, L.M.A. Heunks<sup>2</sup>

<sup>1</sup>Technical Medicine, University of Twente, Enschede, The Netherlands, <sup>2</sup>Department of Critical Care Medicine, Radboudumc, Nijmegen, The Netherlands

**Background:** Bohr’s dead space is the portion of tidal volume not participating in gas exchange with pulmonary blood flow. Determining dead space in clinical practice is becoming increasingly important in critically ill patients with acute respiratory distress syndrome (ARDS). It enables follow-up of treatments, prognostication and it can be used to optimize ventilator settings. However, dead space calculation is cumbersome in ventilated patients using current techniques, like the Douglas bag (DB) and metabolic monitor (MM). Recently, a new non-invasive technique based on volumetric capnography (VCap) was validated in pigs. The aim of this study is to compare VCap with current techniques to determine dead space ventilation in ARDS patients.

**Methods:** In a prospective observational study, 15 patients with moderate ARDS were recruited. Dead space (Vd) was calculated with VCap as fraction of the tidal volume (VT) using the Bohr equation: Vd/VT = (Paco₂−PeCO₂)/PAco₂ where Paco₂ and PeCO₂ are alveolar and mixed expired CO₂ tension, respectively. Both variables were calculated in Matlab from a mathematical fit of the volumetric capnogram (Figure 1). In addition, PeCO₂ was determined by collecting expired air using a DB and via indirect calorimetry with a MM. Consequently, dead space was calculated using the Bohr-Enghoff modification (arterial CO₂ tension (PaCO₂) instead of PACO₂). PaCO₂ was obtained from an arterial blood gas sampled at the same time of collecting expired air.

**Results:** In Table 1, dead space, PeCO₂, PaCO₂ and VCap measured with the DB, MM and VCap are shown. There was anow agreement in dead space between DB and VCap (mean bias (± SD): 33 ± 12%) and a high agreement between DB and MM (mean bias: 2.3 ± 8.9%). Dead space determined with VCap (mean: 53 ± 7.9%) was lower compared to dead space determined with the DB (mean: 73 ± 7.1%, p<0.0001) and MM (mean: 72 ± 8.2%, p<0.0001). There was a higher agreement in PeCO₂ between DB and VCap (mean bias: -2.0 ± 15%), compared to DB and MM (mean bias: -4.9 ± 23%). PaCO₂ was higher compared to PACO₂ (mean: 6.94 ± 1.68kPa versus 3.90 ± 0.80kPa, p<0.0001).

---

**Table 1. Patient characteristics**

<table>
<thead>
<tr>
<th>Total number of patients</th>
<th>Number of times of dexmedetomidine prescription</th>
<th>62</th>
<th>68</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (%)</td>
<td></td>
<td>44 (62%)</td>
<td></td>
</tr>
<tr>
<td>Age (mean +/- sd)</td>
<td></td>
<td>56 +/- 17</td>
<td></td>
</tr>
<tr>
<td>Main reason of admission</td>
<td></td>
<td>30 medical patients (COPD/CHF) 16 surgical patients 15 neuro(surgical) patients (TBI/SAH)</td>
<td></td>
</tr>
<tr>
<td>APACHE II score (median- interquartile range)</td>
<td>20 (14-24)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality number (%)</td>
<td></td>
<td>8 (13%)</td>
<td></td>
</tr>
<tr>
<td>Number of unplanned extubations (%)</td>
<td>5 (8%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 2. Differences between groups**

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>p-value *</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>19</td>
<td>33</td>
<td>8</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>No. dexmed prescriptions</td>
<td>22</td>
<td>34</td>
<td>9</td>
<td>2</td>
<td>67%</td>
</tr>
<tr>
<td>Monotherapy no. (%)</td>
<td>16 (73%)</td>
<td>21 (62%)</td>
<td>0</td>
<td>2</td>
<td>67%</td>
</tr>
<tr>
<td>Maximum dose dexmed mcg/kg/h median (range)</td>
<td>0.4 (0.3-0.5)</td>
<td>0.46 (0.3-0.5)</td>
<td>0.31 (0.2-0.4)</td>
<td>0.4</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of dexmed (hours) median (range)</td>
<td>46 (14-86)</td>
<td>45 (21-78)</td>
<td>47 (23-115)</td>
<td>26</td>
<td>NS</td>
</tr>
<tr>
<td>Ventilator time (hours) median (range)</td>
<td>90 (34-212)</td>
<td>134 (62-254)</td>
<td>99 (45-313)</td>
<td>414</td>
<td>NS</td>
</tr>
<tr>
<td>LOS in days median (range)</td>
<td>9 (3-15)</td>
<td>7 (4-14)</td>
<td>7 (6-16)</td>
<td>23</td>
<td>NS</td>
</tr>
<tr>
<td>Adverse events (hypotension/bradycardia)</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>NS</td>
</tr>
</tbody>
</table>

* p-value differences calculated between group 1,2 and 3 by Mann Whitney U test.
**Conclusion:** The Douglas bag and metabolic monitor both overestimate dead space ventilation. Both methods use PaCO₂ to estimate PACO₂, which however, is inappropriate as PaCO₂ is also affected by pulmonary shunting in patients on controlled mechanical ventilation. The agreement in PeCO₂ between the Douglas bag and volumetric capnography is higher compared to the agreement between the Douglas bag and the metabolic monitor. In conclusion, volumetric capnography measures true Bohr’s dead space, is less prone to measurement errors, noninvasive and therefore the recommended method to determine dead space in ARDS patients.

**Figure 1.** Volumetric capnogram. A volumetric capnogram consists of three phases: phase I, the portion of the tidal volume (Vₜ) free of CO₂; phase II, the portion of the tidal volume which represents CO₂ coming from lung units with different rates of ventilation and perfusion; phase III, the portion of the tidal volume representing pure alveolar gas. PACO₂ and PeCO₂ are the alveolar and arterial and alveolar CO₂ tension (Paco₂ and PAco₂, respectively) determined with the Douglas bag, metabolic monitor and volumetric capnography (mean ± SD).

![Volumetric capnogram](image)

**Table 1.** Results for dead space ventilation (Vd/Vt), mixed expired CO₂ tension (PeCO₂) and arterial and alveolar CO₂ tension (PaCO₂ and PACO₂, respectively) determined with the Douglas bag, metabolic monitor and volumetric capnography (mean ± SD).

<table>
<thead>
<tr>
<th></th>
<th>Douglas bag</th>
<th>Metabolic monitor</th>
<th>Volumetric capnography</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vd/Vt (%)</td>
<td>73 ± 7.1</td>
<td>72 ± 8.2</td>
<td>53 ± 7.9</td>
</tr>
<tr>
<td>PeCO₂ (kPa)</td>
<td>1.77 ± 0.31</td>
<td>1.92 ± 0.60</td>
<td>1.83 ± 0.44</td>
</tr>
<tr>
<td>PaCO₂ (kPa)</td>
<td>6.94 ± 1.68</td>
<td>6.94 ± 1.68</td>
<td>-</td>
</tr>
<tr>
<td>PACO₂ (kPa)</td>
<td>-</td>
<td>-</td>
<td>3.90 ± 0.80</td>
</tr>
</tbody>
</table>

**Respiratory muscle recruitment during mechanical ventilation: effects of ventilator settings**

L.H. Roesthuis¹, J. Doorduin¹, L.M.A. Heunks¹

Department of Critical Care Medicine, Radboudumc, Nijmegen, The Netherlands

**Background:** Mechanical ventilation offers essential ventilatory support to patients with acute respiratory failure. One of the goals of mechanical ventilation is to unload the respiratory muscles, while the respiratory system can recover. Nevertheless, selected patients recruit their accessory respiratory muscles during mechanical ventilation, which could be sign of inadequate unloading. Probably, this is unfavorable because accessory respiratory muscles are not suited for prolonged ventilation. An observational study showed that it is feasible to monitor accessory respiratory muscle recruitment on an intensive care unit by using surface electromyography. Monitoring the accessory respiratory muscles might be useful for optimizing ventilator support and patient comfort. The aim of the current study is to evaluate the effects of ventilator settings on accessory respiratory muscle recruitment in mechanically ventilated patients.

**Methods:** Ten mechanically ventilated patients were recruited from the intensive care unit. Muscle activity from the alaenasi, genioglossus, scalene, sternocleidomastoid and parasternal intercostals was measured using surface electromyography. Diaphragm electromyography was measured using esophageal electrodes. First, pressure support level was reduced every 5 minutes with 3 cm H₂O, starting from 15 cm H₂O till a pressure support level of 0 cm H₂O. Second, pressure trigger sensitivities of -2.5% and -15% of the maximal inspiratory pressure were applied. Electromyography was expressed as the root mean square value. During inspiration, several parameters were calculated for the last two minutes of each study step. In addition, recruitment order and onset times of activity of the accessory respiratory muscles with respect to the diaphragm were determined.

**Results:** Diaphragm activity increased with 45 (28-67)% (n=10), while reducing pressure support levels to 0 cm H₂O. In addition, parasternal intercostal activity increased with 35 (16-70)% (n=8), scalene activity with 40 (22-57)% (n=10), sternocleidomastoid activity with 44 (23-70)% (n=10), genioglossus activity with 61 (7-74)% (n=6) and alaenasi activity with 49 (23-72)% (n=8). For the diaphragm significant differences in muscle activity were obtained between most of the pressure support levels that were compared. For the accessory respiratory muscles significance was reached between the highest two and the lowest pressure support levels (scalene and alaenasi), 15 cm H₂O and 3 cm H₂O (sternocleidomastoid) and 12 cm H₂O and 3 cm H₂O (sternocleidomastoid and genioglossus). Low pressure trigger sensitivity did not increase respiratory muscle recruitment significantly. Recruitment order and onset times of the accessory respiratory muscles did not change with different ventilator settings. Note that upper airway muscles were recruited first and that lower airway muscles had later onset times (figure 1).

**Conclusion:** Accessory respiratory muscle activity tends to increase in response to reduced pressure support levels. These findings suggest that monitoring accessory respiratory muscle recruitment by surface electromyography could be used as a complementary tool to assess inspiratory drive in mechanically ventilated patients. It has the potential to be an easy, non-invasive method to optimize ventilator support.
28.

Hemodynamic management: an international survey among pediatric intensive care physicians

L. Frijns, J. Lemson
Radboudumc, Nijmegen, The Netherlands

Background: Hemodynamic monitoring (HM) is an indispensable part of managing critically ill children and needs to be part of a strategy to provide an improvement in outcome. We conducted a survey to assess the use of various HM modalities by pediatric intensive care physicians, as well as the use of a protocol for hemodynamic management.

Methods: A web-based survey was sent to 400 clinicians in PICUs (pediatric intensive care units) in 29 countries.

Results: 83 clinicians in as many PICUs in 15 countries responded. Heart rate, blood pressure and lactate were considered the most important parameters of 21 clinical, biochemical or HM derived variables (figure 1). Central venous oximetry (ScvO2) and lactate were considered important by respectively 71% and 79% of respondents (percentage attributing a value >7 on a 0-10 scale). 57% of respondents indicate their PICU does not have or does not commonly use a protocol for hemodynamic management. 55% of respondents indicate sometime or frequently use any form of cardiac output (CO) monitoring (figure 2).

Conclusions: 1. ScvO2 and lactate are valued parameters, but despite international campaigns promoting an end goal directed approach to hemodynamic management using these parameters, the use of such protocols is poor. 2. CO monitoring is not widely used by the respondents.

Figure 1. Average of values attributed to parameters when assessing the hemodynamic status of a child in PICU

Figure 2. Use of CO monitoring as indicated by respondents (n=83)

29.

Attributable mortality of delirium in critically ill patients

P. Klein Klouwenberg1, A. Slooter2, C. Spintorn3, D. Ong1, M. Bonten1, I. Zaal1, O. Cremer1
1University Medical Center Utrecht, Utrecht, The Netherlands, 2Utrecht University, Utrecht, The Netherlands

Background: Previous studies have reported that delirium increases the risk of death in critically ill patients, but these studies did not adjust for discharge as a competing risk. The true mortality caused by delirium in intensive care unit (ICU) patients therefore remains unknown.
Hypothesis: New-onset delirium is associated with significant attributable mortality in critically ill patients.

Methods: Over an 18-month period, we prospectively evaluated all adults who were admitted to a 32-bed mixed ICU for at least 24 hours. Patients with an acute neurological condition at baseline were excluded. Patients were screened for delirium twice daily. Delirium assessments were performed using a validated protocol that included a Confusion Assessment Method for the ICU (CAM-ICU) assessment by both a trained observer and the bedside nurse, as well as a review of the patient record (ISICEM 2011: P335). Time-dependent, multivariable Cox regression analysis was used to estimate the direct effect of delirium on outcome by calculating the cause-specific hazard ratios (CSHR) for both ICU discharge and death. To evaluate the overall effect of delirium on death, while taking into account the competing event of ICU discharge, a subdistribution hazard ratio (SHR) was calculated. This SHR provides a summary measure of all separate cause-specific hazards. All analyses were adjusted for age, gender, history of alcohol abuse, APACHE IV score, and admission type.

Results: Among 748 patients evaluated, 366 (49%) subjects developed at least one episode of delirium in the ICU with a median duration of 3 (IQR 2-6) days. Overall, delirium was present on 29% of ICU days (n=6720 days of observation). Median age was 63 (IQR 51-73) years, 66% were male, 45% were medical admissions, 3% had a history of alcohol abuse, and median APACHE IV score was 78 (IQR 59-95). Crude mortality in patients with delirium was 15% (56/366) compared to 5% (18/382) in patients without delirium (p<0.001). In the cause-specific analysis, however, delirium had no direct effect on the risk of death (CSHR 0.70 (95% CI 0.36-1.35)). In contrast, delirium did result in a lower daily probability of being discharged from the ICU (CSHR 0.60 (0.50-0.73)). Patients with delirium were therefore exposed much longer to a daily risk of death, resulting in overall increased ICU mortality (SHR 2.61 (1.48-4.61)).

Conclusions: To our knowledge, this is the first study to estimate delirium-associated ICU mortality using a competing risk analysis. Our findings suggest that the increased risk of death in the ICU due to delirium is merely the result of prolonged ICU stay rather than a direct effect of delirium on mortality.

30.

Significant change in the practice of chest radiography in Dutch intensive care units

M. Tolsma1, T.A. Rijpstra1, M.J. Schulz2, N.J.M. van der Meer2

1Amphia Hospital, Department of Intensive Care, Breda, The Netherlands, 2Department of Intensive Care, University Medical Center, Utrecht, The Netherlands

Background: Chest radiographs (CXR) are frequently obtained in intensive care unit (ICU) patients. The diagnostic and therapeutic efficacy of routine CXRs are now known to be low, but the discussion regarding specific indications for CXRs in critically ill patients and the safety of abandoning routine CXRs is still going on. We performed a new survey under Dutch intensivists on the current practice of chest radiography in their departments.

Methods: A web-based questionnaire was sent to the medical director of all adult ICUs in the Netherlands, containing questions regarding ICU characteristics, ICU patients, daily CXR strategies, indications for routine CXRs and the practice of radiologic evaluation.

Results: Of the 83 ICUs that were contacted, 69 (83%) responded to the survey. Only 7% of ICUs still perform daily routine CXRs for all patients while 65% of ICUs say never to perform CXRs on a routine basis. A daily meeting with a radiologist is established in the majority of ICUs and is judged to be important or even essential. The therapeutic efficacy of routine CXRs was assumed by intensivists to be lower than 10% or to be between 10% and 20%. The efficacy of on-demand CXRs was assumed to be between 10% and 60%. There is consensus between intensivists to perform a routine CXR after endotrachial intubation, chest tube placement or central venous catheterization.

Conclusion: The strategy of daily routine CXRs for critically ill patients has developed from a common practice in 2006 to a rare practice nowadays. Intensivists still assume the value of routine CXRs to be higher than the efficacy that is reported in the literature. This might be due to the clinical value of negative findings which has not been studied before.

References

31.

Stating clear indications for chest radiographs after cardiac surgery increases their efficacy and safely reduces costs

M. Tolsma1, W. Hasselaar1, T.A. Rijpstra1, P.M.J. Rosseel1, T. Scohy1, M. Bentala1, H.A.J. Dijkstra4, N.J.M. van der Meer1

1Department of Intensive Care, Amphia Hospital, Breda, The Netherlands, 2Department of Intensive Care, University Medical Center, Utrecht, The Netherlands, 3Department of CardioThoracic Surgery, Amphia Hospital, Breda, The Netherlands, 4Department of Radiology, Amphia Hospital, Breda, The Netherlands

Introduction: Chest radiographs (CXR) in the intensive care unit (ICU) are frequently obtained routinely for postoperative cardiosurgical patients despite the fact that the diagnostic and therapeutic efficacy of these CXRs is now known to be low. Routine CXRs may only be beneficial for certain indications and the discussion regarding these indications and the safety of abandoning routine CXRs is still continuing. We investigated the efficacy and safety of CXRs performed on specified indications only, directly after cardiac surgery.

Methods: We prospectively included all patients who underwent major cardiac surgery in the year 2012. A direct postoperative CXR
was performed only routinely for certain specified indications. An on-demand CXR could be obtained during the postoperative period according to other specified indications. For all patients who did not have a CXR taken before the morning of the first postoperative day, a control CXR was performed then. All CXR findings were noted including whether or not they led to an intervention. Diagnostic and therapeutic efficacy values were calculated.

**Results:** A total of 1351 patients were included who mainly underwent coronary artery bypass grafting (CABG), valve surgery or a combination of both. 18% of patients underwent minimally invasive cardiac surgery. The diagnostic efficacy for major abnormalities was clearly higher for the postoperative and on-demand CXRs performed on indication, when compared to the next morning routine CXR (6.7% and 6.9% versus 2.9%) (p=0.002). The therapeutic efficacy was also clearly higher for the postoperative and on-demand CXRs (2.9% and 4.1%), while the need for intervention after the morning control CXR was now reduced to be minimally (0.6%) (p=0.002).

**Conclusion:** Stating clear indications for CXRs following cardiac surgery increases the efficacy of these CXRs and safely reduces the total number of CXRs.

**References**

---

**Prospective single centre cohort study into quality of life in Dutch intensive care unit subgroups, one year after admission, using EuroQol-6D**


Department of Intensive Care Medicine, University Medical Centre Utrecht, Utrecht, The Netherlands

**Background:** The ultimate goal of Intensive Care Unit (ICU) admission is to provide long-term survival with the highest possible quality of life (QoL). We investigated mortality and QoL in a large single centre cohort, one year after ICU admission. We aimed to identify subgroups of patients who may be at risk for poor long term outcomes.

**Methods:** From July 2009 to May 2012 we included 5934 consecutive adult patients admitted to a mixed population ICU. There were no exclusion criteria. One-year survival status was determined using the Dutch municipal population register. Subsequently, all survivors received the EuroQoL EQ-5D-3L™ questionnaire. The primary outcome was overall QoL index in surviving patients at one year follow-up, and was compared to overall QoL index of an age and gender-matched control population. Secondary outcome was the incidence of poor ICU outcome defined as either death or low QoL (EuroQoL index <0.4) at one-year follow-up.

**Results:** A total of 5139/5934 patients (86.6%) survived until hospital discharge, while 4535/5934 (76.4%) patients survived to one-year follow-up. The EuroQoL questionnaire was sent to 4377/4535 (96.5%) survivors and returned by 3003/4377 (68.6%). The mean QoL in surviving patients was 0.79 (Standard Deviation [SD] 0.23), versus 0.86 (SD 0.04) in the control population (p<0.001).

Of patients with metastasized malignancy, 73/162 (45.1%) survived, with a mean QoL index of 0.77 (SD 0.21). Of patients with chronic renal failure 156/287 (54.4%) survived, with a mean QoL index of 0.65 (SD 0.28). Of patients admitted with sepsis 317/558 (57.0%) survived, with a mean QoL index of 0.70 (SD 0.27).

Poor ICU outcome was found in 1646/5934 (27.7%) patients. Again, the subgroups worst off were those with metastasized malignancy (91/162; 56.2% poor ICU outcome), chronic renal failure patients (149/287; 51.9%) and those admitted for sepsis (267/558; 48.0%).

**Conclusions:** QoL one year after ICU admission was significantly lower than in an age and gender matched control population. Marked variations were found across subgroups. The highest risk of mortality or a low QoL at one-year follow-up was found in patients with metastasized malignancy, chronic renal failure, and sepsis.
Editorial Board of the Netherlands Journal of Critical Care

A.B. Johan Groeneveld, Editor in Chief
Dept. of Intensive Care Medicine
Erasmus Medical Center
PO Box 2040
3000 CA Rotterdam

Jan Bakker, Section Editor
Hemodynamics
Dept. of Intensive Care Medicine
Erasmus Medical Center
PO Box 2040
3000 CA Rotterdam

Alexander Bindels, Section Editor
Endocrinology
Dept. of Internal Medicine
Catharina Hospital
Michelangeloalaan 2
5623 EJ Eindhoven

Bert Bosch, Section Editor
Pediatrics
Department of Pediatrics
Academic Medical Center
University of Amsterdam
Meibergdreef 9
1105 AZ Amsterdam

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

Wolfgang Buhre, Section Editor
Anesthesiology
Dept. of Anesthesiology
Maastricht UMC+
P. Debyelaan 25
6229 HZ Maastricht

Hans van der Hoeven, Section Editor
Mechanical Ventilation
Dept. of Intensive Care Medicine
Radboud University Nijmegen
Medical Centre
PO Box 9101
6500 HB Nijmegen

Can Ince, Section Editor
Physiology
Dept. of Physiology
Academic Medical Center
University of Amsterdam
Meibergdreef 9
1105 AZ Amsterdam

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

Nicole Juffermans
Section Editor
Hemostasis and Thrombosis
Dept. of Intensive Care
Academic Medical Center
University of Amsterdam
Meibergdreef 9
1105 AZ Amsterdam

Heleen Oudemans-van Straaten, Section Editor
Sepsis and inflammation
Dept. of Intensive Care Medicine
VU University Medical Center
PO Box 7057
1007 MB Amsterdam

Peter Pickkers, Section Editor
General
Dept. of Intensive Care Medicine
Radboud University Nijmegen
Medical Centre
PO Box 9101
6500 HB Nijmegen

Arjen Slooter, Section Editor
General
Dept. of Intensive Care Medicine
Gelse Hospital, location Lukas
PO Box 9014
7300 DS Apeldoorn

Jaap Tulleken, Section Editor
General
Dept. of Intensive Care Medicine
University Medical Center Groningen
PO Box 30001
9700 RB Groningen

Anton van Kaam, Section Editor
Neonatology
Dept. of Neonatal Intensive Care
Emma Children’s Hospital,
Academic Medical Center
University of Amsterdam
Meibergdreef 9
1105 AZ Amsterdam

Jozef Keseckiglu, Section Editor
Pulmonology
Dept. Of Intensive Care Medicine
University Medical Center Utrecht
PO Box 85500
3508 GA Utrecht

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

Maartje Nijsten, Section Editor
Surgery
Dept. of Intensive Care Medicine
University Medical Center Groningen
PO Box 30 001
9700 RB Groningen

Peter van der Voort,
Correspondence editor
Dept. of Intensive Care Medicine
Onze Lieve Vrouwe Gasthuis
PO Box 95500
1090 HM Amsterdam

International Advisory Board

Charles Gomersall
Dept. of Anaesthesia and Intensive Care
The Chinese University of Hong Kong, Prince of Wales Hospital
Hong Kong, China

Frank van Haren
A/ Professor, Australian National University Medical School
Department of Intensive Care Medicine
The Canberra Hospital
PO Box 11, Woden. ACT 2606
Canberra, Australia

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

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

Alun Hughes
Professor of Clinical Pharmacology
Imperial College London
South Kensington Campus
London, UK

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

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

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

Ravindra Mehta
Professor of Clinical Medicine
Associate Chair for Clinical Research
Department of Medicine
UCSD Medical Centre
8342, 200 W Arbor Drive
San Diego, USA

Xavier Monnet
Service de réanimation médicale
Centre Hospitalier Universitaire de Bicêtre
France

Jean-Charles Preiser
Dept. Intensive Care
CHU Liege – Domaine Universitaire
Liege, Belgium

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

Hannah Wunsch
Dept. of Anaesthesia
New York Presbyterian Columbia
New York, USA
The Netherlands Journal of Critical Care (Neth J Crit Care) is the official journal of the Netherlands Society of Intensive Care (Nederlandse Vereniging voor Intensive Care-NVIC). The journal has a circulation of about 1,750 copies bimonthly in the Netherlands and Belgium. High quality reports of research related to any aspect of intensive care medicine, whether laboratory, clinical, or epidemiological, will be considered for publication in the 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.

The journal is indexed by Embase, Emcare and Scopus. A Medline annotation is in preparation. The following manuscript types apply.

**Structured abstracts**

All manuscripts should be submitted with structured abstracts as described below. No information should be reported in the abstract that does not appear in the text of the manuscript. Manuscripts should include an abstract of no more than 300 words using the following headings: Background and objectives, Design, Methods and results and Conclusions. For the sake of brevity, parts of the abstract may be written as phrases rather than complete sentences.

**Background and objectives**

State the precise primary objective of the review. Indicate whether the review emphasizes factors such as cause, diagnosis, prognosis, therapy, or prevention and include information about the specific population, intervention, exposure, and tests or outcomes that are being reviewed.

**Design**

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

**Methods and results**

Summarize here accurately, although concisely, summarize how you will proceed in learning the answer to the objective. Also provide the main outcomes of the study.

**Conclusions**

The conclusions and their applications (clinical or otherwise) should be clearly stated, limiting interpretation to the domain of the review.

**Original articles/reviews**

Articles should describe original investigations that have been brought to an acceptable degree of completion. Articles should not exceed 3000 words. The editorial board also welcomes review papers which should also not exceed 3000 words.

The manuscript should be clear in outline (with subheadings) for maximum clarity. Only a limited number of figures (coloured figures are encouraged without extra charge) and tables may be included; double presentations in the form of figures and tables should be avoided. The text should follow the IMRAD format and contain an abstract, introduction, materials and methods, results, discussion section and references. The abstract should not exceed 250 words and should be structured. Authors should provide a minimum of three keywords, a running title, and list not more than 30 references for original articles and 70 references for review articles.

**Case Reports**

The text of a case reports should also include an abstract, introduction, case report/case history, discussion section, legends for figures and references. The abstract should not exceed 250 words and may be unstructured. The journal kindly requests authors to provide a minimum of three keywords and to list not more than 30 references.

**Clinical Images**

A clinical image should contain one or two pictures and a short case history, and should preferably not be referenced. The legend to the image should succinctly present relevant clinical information, including a short description of the patient’s history, relevant physical and laboratory findings, clinical course, response to treatment (if any), and condition at last follow-up. The journal kindly requests authors to provide a minimum of three keywords.

**General information**

The original manuscript and two copies (or electronic file) are to be submitted to the editor in chief at the NVIC office by e-mail (see below). The manuscript must be accompanied by a cover letter stating the following: the complete mailing address, email address, telephone number and fax number of the corresponding author, and if it is a resubmission, the previous Neth J Crit Care number and year. Receipt of the manuscript will be acknowledged in writing within 14 days. If this is not the case, authors are requested to check. The language of the journal is British English. Authors who are unsure of proper English usage will have their manuscript checked by someone proficient in the English language.

**Layout**

Paragraphs starting immediately under headings and subheadings should begin at the left margin. Subsequent paragraphs should be indented. All text should be double spaced, on one side of the paper and with a wide margin. The manuscript pages, including references and legends, must be sequentially numbered throughout.

**Tables**

Tables are to be numbered independently of the figures with Arabic numbers, with headings and kept separate from the text.

**Figures**

Figures must also be numbered with Arabic numbers and kept separate from the text. Legends must be given on a separate sheet. Schematic line drawings are preferred. Figures already published elsewhere cannot usually be included, except in survey articles. Colour figures can be published. Short, clear legends make additional description in the text unnecessary. The desired placement of figures and tables can be marked in the margins of the manuscript sheets. Figures should be provided in electronic format TIFF or better.

**References**

Only articles cited in the text are to be listed. They are to be arranged in order of appearance in the text .... and numbered consecutively. Only the reference number should appear in the text. Include all author names (unless there are seven or more, in which case abbreviate to three and, add ‘et al.’), and page numbers.

**Copyright**

Copyright ownership is to be transferred in a written statement, which must accompany all manuscript submissions and must be signed by all authors. The agreement should state, “The undersigned authors transfer all copyright ownership of the manuscript (title of article) to the Netherlands Journal of Critical Care. Authors must disclose any potential financial or ethical conflicts of interest regarding the contents of the submission. Any relevant papers that may be considered as duplicating in part the current submission should be reported.”
How to submit
Submit manuscript directly to: Editorial office e-mail: nethjcritcare@nvic.nl

Proofs
The corresponding author will receive proofs by e-mail. Corrected proofs must be returned within 48 hours of receipt.

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

General guidelines on house style
• The title of manuscript should be in typeface Times New Roman, size 12. With the exception of the first word and proper nouns, initial capitals are not used in the title.
• The names of departments should be in typeface Times New Roman, size 12.
• The names of hospitals should be written in English.
• Generally, abbreviations should not be used in the title (see Table of standard abbreviations) for exceptions.
• The corresponding author need only provide their e-mail address on the title page.
• Please provide a minimum of three keywords and a running title.
• In addresses write The Netherlands. In running text, the Netherlands.
• The abstract should be written in the structured format (with the exception of case reports).
• Unstructured abstracts should take the form of a single paragraph.
• The abstract should be bold typeface Times New Roman, size 12.
• Headings must be in bold.
• Non-standard abbreviations (see Table of standard abbreviations) should always be explained and their use kept to a minimum.
• Please use British English spelling, except in titles of institutions that have chosen to use US spelling, e.g. Academic Medical Center, Amsterdam.
• The journal uses British English spelling, e.g. aetiology, oestradiol, anaemia, haemorrhage, oesophagus, practice (noun), practise (verb), fetus. This should be used consistently. Use z spellings, e.g. anaemia, haemorrhage, oesophagus, practice (noun), practise (verb). English.
• Generally, organizations and groups of people take single verbs, e.g. the team has researched.
• ± is a mathematical symbol and should not be used in a non-mathematical context to mean approximately or about.
• Avoid “he” as a general pronoun. Make nouns and pronouns plural, use “they”. If this is not possible then use “he or she”.
• Drugs should be referred to by their English language non-proprietary names, e.g. not fosfomycin but phosphomycin.
• Brackets. In English, information in brackets is not crucial to the meaning of the sentence and may be omitted without detracting from its meaning. The Dutch convention of using brackets to contain information crucial to the sentence should not be applied, e.g. (immuno) histology should be written as immunohistology and histology, (un) sterile gloves as sterile or unsterile gloves.
• Apostrophe. In English the apostrophe is used to indicate possession or omission, e.g. the patient’s notes, not to form a plural, e.g. ECG’s should be ECGs.
• “False friends.” Please be aware that although some words sound like they have the same meaning they do not, e.g. adequate is not always synonymous with adequate (adequate = toereikend), e.g. “Bij 98% werd technisch adequate wervelmorfometrie verricht” becomes “In 98% spinal morphometry was technically successful.” “Klachten” may not universally be translated as “complaints”; please use “signs and/or symptoms” where appropriate.
• The gender of an author is not specifically reported. Do not use Ms or Mrs in front of Professor or Doctor.
• Spell check your article before submission using UK English (references keep original spelling).
• Abbreviating names. Use initials only J Smit not Joh Smit.
• Numbers under 10 are spelled out except for measurements with a unit (10 mmol/l) or age (4 weeks old), or when in a list with other numbers (5 mice, 6 rats, 12 gerbils).
• When referring to tables or figures in the text use a capital letter, e.g. see Table 2.
• Quotation marks – please use double, not single, inverted commas. For reported speech, Full stops go inside quotation marks.
• Avoid “he” as a general pronoun. Make nouns and pronouns plural, use “they”. If this is not possible then use “he or she”.
• Drugs should be referred to by their English language non-proprietary names, e.g. not fosfomycin but phosphomycin.
• Brackets. In English, information in brackets is not crucial to the meaning of the sentence and may be omitted without detracting from its meaning. The Dutch convention of using brackets to contain information crucial to the sentence should not be applied, e.g. (immuno) histology should be written as immunohistology and histology, (un) sterile gloves as sterile or unsterile gloves.
• Apostrophe. In English the apostrophe is used to indicate possession or omission, e.g. the patient’s notes, not to form a plural, e.g. ECG’s should be ECGs.
• “False friends.” Please be aware that although some words sound like they have the same meaning they do not, e.g. adequate is not always synonymous with adequate (adequate = toereikend), e.g. “Bij 98% werd technisch adequate wervelmorfometrie verricht” becomes “In 98% spinal morphometry was technically successful.” “Klachten” may not universally be translated as “complaints”; please use “signs and/or symptoms” where appropriate.
• The gender of an author is not specifically reported. Do not use Ms or Mrs in front of Professor or Doctor.
• Spell check your article before submission using UK English (references keep original spelling).
• Abbreviating names. Use initials only J Smit not Joh Smit.

Table of abbreviations

| AID | acquired immune deficiency syndrome |
| ALI | acute lung injury |
| ARDS | adult respiratory distress syndrome |
| APACHE | acute physiology 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 |
| ECMO | extracorporeal membrane oxygenation |
| EEG | electroencephalogram |
| ELISA | enzyme-linked immunosorbent assay |
| ETCO2 | end-tidal carbon dioxide |
| HCU | 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 | positive end expiratory pressure |
| PET | positron emission tomography |
| SARS | severe acute respiratory syndrome |
| SIRS | systemic inflammatory response syndrome |
| SOFA | sequential or organ failure assessment |
| SPECT | single-photon emission ct |
| TIA | transient ischemic attack |
| TRALI | transfusion-related acute lung injury |
Ecalta®
Als medicatieveiligheid telt

- Geen klinisch relevante geneesmiddelen interacties1-5
- Geen dosisaanpassing in verband met gewicht, lever- en nierfunctiestoornissen1-5