Netherlands Journal of Critical Care

Bi-monthly journal of the Dutch Society of Intensive Care

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Antibiotic resistance and selective decontamination of the digestive tract: a never-ending story?

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Keywords – Selective decontamination digestive tract, antibiotic resistance, antimicrobial resistance, intensive care

Over the years, a pivotal point in the acceptance and application of selective decontamination of the digestive tract (SDD) has been the possible emergence of antibiotic resistance. This has led to low acceptance of SDD especially in areas with a high endemicity of resistant bacteria. Furthermore, the increasing world-wide clinical prevalence of multi-resistant gram-negative bacteria leads to increasing scrutiny of antibiotic usage especially in prophylactic settings. SDD, and its less invasive counterpart, selective oropharyngeal decontamination (SOD), constitute a prophylactic regime aimed at preventing ventilator associated pneumonias (VAP) in the intensive care unit (ICU). Ever since the introduction of SDD, staunch debate has been in place on the harm (i.e. potential increase in antibiotic resistance) versus benefit (i.e. decrease in VAP and attributable morbidity and mortality) ratio of this treatment. Studies over the years have provided ample evidence that SDD, and to a lesser degree SOD, constitute means of significantly decreasing morbidity and mortality in the ICU. In contrast to general beliefs, de Longe et al. have reported for the first time that SDD resulted in a decrease in the resistance of bacteria colonizing the digestive tract in ICU patients. However, the major caveat is that the majority of studies that prove the efficacy of SDD were performed in areas of low baseline incidence of resistance. To address concerns on increasing antibiotic resistance secondary to the use of SDD, several analyses have been performed in the past that shed some light on this issue. In this issue of the Netherlands Journal of Critical Care, Muskiet analyses the evidence regarding the development of antibiotic resistance related to the use of SDD in the ICU. In his extensive description of the current literature on the subject, no conclusive substantiation of the worries regarding potential harm of long-term use of SDD can be found. On the contrary, the review elaborates on the somewhat counterintuitive finding that institution of SDD seems to result in lower rates of antibiotic resistance. Several factors could attribute to this phenomenon of which the absolute reduction in the load of potentially pathogenic micro-organisms is probably the predominant factor. Currently available data do not seem to show a worrisome trend in time regarding the development of antibiotic resistance. Could it therefore be possible to close the book on the everlasting debate regarding the potential harm of SDD? Is it time to consider this treatment as standard-of-care in ICUs worldwide, bearing in mind the proven efficacy of SDD in preventing VAPs and their attributable morbidity and mortality? Not likely, and this is probably for the better. Outside the well investigated setting of the Netherlands, with a relatively low level of antibiotic resistance, SDD and SOD remain controversial treatments. If there is ever to be a closure of the debate on efficacy versus suggested side-effects, definitive studies on this issue need to be initiated. These studies need to focus on several key issues as follows. Does the seemingly present absence of major resistance problems as a result of long-term SDD use in areas of low endemicity of antibiotic resistance manifest itself also in areas of high endemicity of antibiotic resistance? Is the bactericidal potential of high enteral concentrations of antibiotics in the gut enough to overcome high acquisition rates of resistant gram negative pathogens? Furthermore, what are the effects of SDD in high endemicity areas on the acquisition rate of colistin resistance, with colistin being a key-component of the SDD-regime and also often a last resort antibiotic against resistant gram-negative bacteria? And finally, what happens after cessation of SDD on the general ward? Is there a price for the rigorous suppression of gram-negative bacteria in the ICU and could there be an increase in colonization and re-colonization with resistant gram-negative bacteria after patient discharge from the ICU? Further studies need to focus on the issues outlined above before we can safely close the book on the controversy regarding SDD and antibiotic resistance.
References


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Development of antibiotic resistance related to selective decontamination of the digestive tract

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Keywords – Selective digestive tract decontamination, selective decontamination gut, selective decontamination digestive tract, selective decontamination gastrointestinal tract, antibiotic resistance, antimicrobial resistance

Abstract

Purpose: To discuss the relevant studies on selective decontamination of the digestive tract (SDD) in intensive care unit (ICU) patients regarding the occurrence of antibiotic-resistant bacteria.

Findings: Since the introduction of SDD as a preventive infection measure in the ICU, there have been concerns about inducing antimicrobial resistance. Earlier studies proved that SDD reduces infections without a convincing clinical increase in resistant bacteria, but were not designed to assess this potential problem. In recent years, large prospective studies that were also designed to investigate the occurrence of resistant bacteria during SDD have shown a decrease in antibiotic-resistant Gram-negative bacteria. Increases of resistant Gram-positive bacteria and the increase of colistin resistance during SDD in a setting with an outbreak of extended spectrum beta lactamase producing Klebsiella pneumoniae have been reported.

Conclusion: SDD reduces colonization, infection and mortality. No convincing overall increase of antimicrobial resistance can be attributed to the use of SDD. The use of SDD in ICUs with low levels of antibiotic resistance can be justified.

Introduction

It has long been recognized that ICU patients are susceptible to infections, such as respiratory tract infections due to mechanical ventilation. Many of these infections are caused by aerobic Gram-negative bacteria originating from the digestive tract. These nosocomial infections can increase morbidity, mortality and healthcare costs. In the late nineteen-sixties, seventies and early eighties, studies initially performed on mice and later in neutropenic leukaemia patients showed that anaerobic flora played an important role in preventing colonization with aerobic flora. Therefore, the hypothesis was postulated that secondary infections could be prevented by the prophylactic eradication of potential pathogenic bacteria.

Most infections in ICU patients have an endogenous source with the patient’s own oropharynx and digestive tract as the main source of infection. Colonization of the oropharynx and digestive tract with aerobic Gram-negative bacteria precedes nosocomial infections. Selective digestive tract decontamination (SDD) was introduced as a measure to prevent colonization with Staphylococcus aureus, Gram-negative bacteria and yeasts while leaving anaerobic microflora unchanged. This can be accomplished by the administration of non-absorbable antibiotics to selectively decontaminate the digestive tract and reduce the load of potentially pathogenic bacteria while keeping the anaerobic flora intact. Different SDD strategies have been proposed to prevent secondary infections including adding systemic antibiotics as pre-emptive treatment for infections during the patient’s first few days on the ICU. The first study published on SDD in ICU patients reported a study in trauma patients. The result of this trial was a significant reduction in colonization and infection. Since then, many studies, reviews and systematic reviews have been published that address the effectivity and safety of SDD in ICU patients. Several studies using only the oropharyngeal part of the SDD, the so-called SOD (Selective Oropharyngeal Decontamination), have suggested comparable results to SDD in reducing ventilator associated pneumonia (VAP).

Although there is evidence that SDD and SOD can reduce morbidity and mortality in ICU patients, both these interventions are not widely applied outside the Netherlands. This can be partly explained by the fear of inducing antibiotic resistance in bacteria. A prophylactic, mostly systemic use of antibiotics is associated with increasing antibiotic resistance. Antibiotic resistance is increasing worldwide and thus becoming more of a problem. This increase depends on time and place, the use of antibiotics and the prevalence of different species of bacteria.
The goal of this review is to collect and analyse the evidence regarding the development of antibiotic resistance related to SDD use in the ICU. A Pubmed search was performed for relevant articles published from 1960 until 2013 using the search strategy shown in Table 1. Additionally, a cross reference search of selected articles was conducted. A historic perspective has been used to show the developments during the last three decades since the first publications on the use of SDD in ICU patients.

Early studies
In the early eighties, Stoutenbeek and colleagues performed the first study in an ICU administrating SDD to 119 trauma patients after earlier successful application of this technique as a measure for preventing infection in neutropenic leukaemia patients. The SDD-regime consisted of decontaminating the oropharynx and the digestive tract with non-absorbable antibiotics (tobramycin, colistin and amphotericin B) next to systemic administration of cefotaxim during the first four days to treat upcoming infections. In this study, the infection rate decreased from 80% in the retrospective studied control group, to 16% in the treatment group. According to the author, the occurrence of resistant microorganisms was rare, but numbers were not reported.

Randomized clinical trials performed by Unertl et al., Kerver et al., and Ulrich et al. also showed a decrease in infections with Gram-negative bacteria. Mortality was either decreased or unchanged with equal length of stay in the ICU and duration of mechanical ventilation. Unertl et al. showed that the overall occurrence of resistant pathogens did not increase during SDD when compared with the control group and that no therapeutic problems were posed for the few infections caused by resistant Gram-positive bacteria. No emergence of multiple resistant bacteria was recorded by Kerver et al. during his study. Ulrich et al. used a regime of polymyxin E, norfloxacin and amphotericin B along with systemic trimethoprim until decontamination was achieved. Colonization and overgrowth of resistant micro-organisms did not occur. These studies were performed with relatively small groups and were not designed to assess antimicrobial resistance.

In the nineteen-nineties, Rodriguez-Roldan et al. performed the first randomized, double-blind controlled study in Spain in which SDD was compared to a control group. SDD was used without the systemic administration of antibiotics, but concomitant infections were treated with parenteral antibiotics in both groups. The pattern of resistance did not differ between groups, but the groups were very small (13 vs. 15 patients). Up until this time, most studies had been performed with historical control groups. Aerdt et al. designed a prospective, blinded, randomized trial where a treatment group (TG) consisting of participants on SDD with systemic administration of cefotaxim was compared to two control groups. These two control groups did not receive SDD but received different antibiotic regimes (ampicillin/piperacillin (A/P) vs. cefuroxime plus gentamycin (C/G)) in cases where an infection was suspected. People in the TG were less frequently colonized by Gram-negative bacteria in the oropharynx (TG 0 vs. A/P and C/G >80%) and stomach (TG 24% vs. A/P 94% and C/G 90%), acquired less respiratory tract infections, and had a lower infection related mortality. This was a study with low mortality rates and small numbers of included patients, so it was underpowered to permit conclusions regarding mortality. The development of resistance against the antibiotics used for prophylaxis was not observed. After a limited number of patients had taken part, this study was discontinued because of significant differences in colonization and infection between the treatment and control groups, in favour of the treatment group.

In 1992, Hammond et al. reported the results of her study in South-Africa, a region with a high incidence of resistant microorganisms. There was no significant difference between the SDD and placebo groups in infections overall but there was a reduction of infections with Enterobacteriaceae in the SDD group. In this study, mortality, lengths of stay in hospital and ICU stay were similar. Hammond found a significant increase in methicillin resistant Staphylococcus aureus (MRSA) and that the application of SDD was more expensive. She later published a study that evaluated the long term effects of SDD on the development of antimicrobial resistance. A comparison was made between isolates in the previous year, during and after the use of SDD with systemic antibiotics. In the SDD group, a reduction was found for the resistance to third generation cephalosporins, the incidence of MRSA infections remained unchanged and there was no increase in microorganisms resistant to aminoglycosides. No long term effects on antimicrobial resistance could be attributed to the use of SDD.

Other studies around that time showed that SDD led to lower rates of infections and colonization with resistant microorganisms. However, there were still concerns about the costs and clinicians were reluctant to implement SDD as oropharyngeal colonization with Gram-positive bacteria
increased. Nonetheless, there were fewer infections with Gram-negative bacteria and no selection of resistant Gram-positive or Gram-negative bacteria occurred in SDD groups.

In the second half of the nineteen-nineties, several authors did report an increase in the resistance associated with the use of SDD. These reports varied from a trend towards more resistance to gentamicin and to polymyxin in the SDD group to an increase of colonization (not infection) with multi-resistant coagulase negative Staphylococci (CNS) and an increase in tobramycin-resistant microorganisms. Lingnau et al. reported a shift towards Gram-positive microorganisms, an increase and outbreak in MRSA and an increase in ciprofloxacin resistance of CNS after the introduction of SDD in ICU patients. He also reported on the control of the MRSA outbreak by implementing hygienic measures. These consisted of a change of protocols for hand washing, disinfection and room cleaning protocols, adopting the use of plastic gowns, barrier nursing techniques and motivating nursing staff by educating them on the transmission routes of bacteria. The incidence of pneumonia and mortality increased prior to the above-mentioned hygiene measures but decreased to relatively low values after these measures had been implemented and a decrease in the incidence of MRSA, methicillin-resistant Staphylococcus epidermidis (MRSE), ciprofloxacin-resistant Staphylococcus aureus and ciprofloxacin-resistant Staphylococcus epidermidis was seen concomitantly.

Recent studies

Around the beginning of the millennium, a few reviews and meta-analyses were published that actually investigated the occurrence of antibiotic resistance associated with the use of SDD. Bonten et al. summarized the findings of 27 prospective randomized studies and six meta-analyses in 2000. Although these studies were difficult to compare due to differences in the application of SDD (SDD or SOD alone) and differences in the antibiotics used, he concluded that SDD is associated with a decrease in the numbers of ventilator-associated pneumonias, but not with improved patient survival, reductions in the duration of ventilation or ICU stay or reductions in antibiotic use. He further stated that the use of SDD is associated with the selection of microorganisms that are intrinsically resistant to the antibiotics used but that studies in the main have been too small and too short to adequately investigate whether SDD will lead to the development of antibiotic resistance.

Concerns were raised over the fact that the increasing use of antibiotics during the last sixty years had led to an increase in antibiotic resistance and that SDD might contribute to further increase of antibiotic resistance. In contrast, Zandstra & van Saene came to the conclusion that the eradication of the reservoir of abnormal bacteria located in the gut by topical non-absorbable antibiotics appears to significantly reduce morbidity, mortality and resistance. His conclusions were to a great extent based on the review of randomized trials by d’Amico et al., cited earlier.

The results of SDD trials have depended on the regime used and the environment where SDD is applied. In regions where the incidence of resistance was low, there was either no difference in the occurrence of resistant microorganisms or there was a decrease in colonization of Gram-negative microorganisms resistant to ceftazidime, ciprofloxacin, imipenem, polymyxin E or tobramycin. Leone et al. evaluated the effect of SDD on antimicrobial resistance in multiple trauma patients over a six year period. In SDD patients and in control patients, the resistance of Enterobacteriaceae, Pseudomonas aeruginosa and Acinetobacter to beta-lactamines and aminoglycosides was the same. He observed a relative overgrowth of Gram-positive cocci and an increase in MRSE but no increase in MRSA.

The use of oropharyngeal or enteral vancomycin during SDD to eradicate Staphylococcus aureus gave rise to the fear of selecting vancomycin-resistant enterococci (VRE). De la Cal et al. investigated whether enteral vancomycin could eradicate MRSA in an endemic setting in Spain. They found that the incidence of MRSA significantly decreased from 31% to 2%. There was an outbreak of VRE during SDD which was self-limiting. Staphylococcus aureus intermediate sensitive to glycopeptides was not observed. About the same time, Silvestri et al. performed a randomized trial to assess the impact of oropharyngeal application of vancomycin on MRSA carrier rates and lower airway infections as well as the emergence of VRE. The study showed that topical oropharyngeal vancomycin was effective in preventing ICU-acquired lower airway infections and preventing secondary carriage due to MRSA in long-term ventilated patients receiving SDD. Neither VRE nor vancomycin-intermediate Staphylococcus aureus was isolated during the study period or in the following year. These studies had a relative short duration.

In 2006, Heininger et al. assessed the distribution of bacterial species and antimicrobial resistance in an ICU during long-term (five years) use of SDD and compared this to national German data. MRSA remained stable in this study, aminoglycoside- and betalactam-resistant Gram-negative rods did not increase and the incidence of Pseudomonas resistant to aminoglycosides was lower compared to the mean incidence nationwide.

The relative frequency of enterococci and CNS was higher in the SDD group and this might be of concern.

In 2009 a Cochrane review was published. After the examination of 36 trials, the conclusion was that although there were differences in the SDD regime, differences in patient characteristics, differences in the risk of respiratory tract infection and in the risk of mortality in control groups, there was an overall significant reduction in respiratory tract infections and mortality in patients treated with both topical and systemic antibiotics. Patients treated with topical...
antibiotics alone showed reduced incidence of respiratory tract infections but not of mortality. According to the authors of that review, the risk of resistance of antibiotics was appropriately explored only in the trial published in the Lancet in 2003 by de Jonge which did not show any such effect. SDD remained controversial because of conflicting results regarding the occurrence of antibiotic resistance associated with SDD use. To quantify the effects of both SDD and SOD on patient outcome and antibiotic resistance in Dutch ICUs, de Smet et al. designed a cluster-randomized multi-centre study with cross-over design to compare both strategies mutually and to standard care. Systemic administration of ceftazidime during the first four days of admission was part of the SDD regime. Thirteen ICUs participated in this study which enrolled almost 6000 patients and was the largest randomized controlled trial conducted up to that time. This study showed that SDD reduced mortality by 3.5 percentage points and that SOD reduced mortality by 2.9 percentage points compared to standard care. Besides the reduction in mortality, the need for systemic antibiotics decreased in both treatment groups. With regard to antibiotic resistance, the prevalence rates for antibiotic-resistant Gram-negative bacteria were lower during SDD and SOD when compared to standard care and lower during SDD when compared to SOD. SDD and SOD were not associated with increased selection or induction of antibiotic resistance for the antibiotics used for SDD and SOD in the short term.

Nevertheless, Oostdijk et al. reported that SDD and SOD can have marked effects on bacterial ecology in the ICU. Analysing the data from the point-prevalence shown in the previously mentioned study from de Smet et al., she concluded that SDD and SOD lead to an increase in ceftazidime-resistant Gram-negative bacteria. In addition, a considerable rebound effect of ceftazidime resistance in the intestinal tract after discontinuation of SDD was observed in this study. Prevalence rates significantly increased as compared with before and during intervention. Shortcomings of this study were the fact that many patients were only briefly on the ICU (while not using SOD or SDD) and the incidence of antibiotic resistance on the non-ICU hospital wards was unknown. The second shortcoming was the different combinations of ICUs pre, per and post intervention. In contrast, Oostdijk’s findings are partly consistent with the results of a five year prospective cohort study conducted in Spain by Ochoa-Ardilla et al., which showed an increase in ceftazidime-resistant (and imipenem-resistant) P. aeruginosa during SDD. But this study also demonstrated a reduction in the incidence of P. aeruginosa resistant to tobramycin, amikacin and ciprofloxacin and a stable incidence of resistant Enterobacteriaceae. The total incidence of antibiotic-resistant bacteria remained stable so the author concluded that long-term use of SDD is not associated with an increase in acquisition of resistant flora. But although the total incidence remained stable, some specific resistant strains might pose a problem. Oostdijk et al. also analysed the rates of colistin resistance during SDD and SOD as this had not been accurately determined. She concluded that during persistent intestinal carriage of Gram-negative bacteria and during intestinal colonization with tobramycin–resistant Gram-negative bacteria, the risk of acquiring colistin resistant Gram-negative bacteria and conversion rates to colistin resistance increased. But the overall risk of acquisition of colistin resistant Gram-negative bacteria and conversion rates to colistin resistance were low. In line with the findings of Oostdijk et al., Halaby et al. reported an increase of colistin resistance in extended spectrum beta lactamase producing Klebsiella pneumoniae in one ICU in the Netherlands where SDD had been used to control an outbreak.

Another study by de Smet et al. assessed the effectiveness of SDD and SOD for the prevention of respiratory tract colonization and bacteraemia with highly resistant microorganisms in patients after three days on the ICU. Compared with standard care, SDD reduced the rate of acquired highly resistant microorganisms by 38% and SOD by 32%. SDD was associated with a 62% reduction in acquisition rate of cephalosporin-resistant Enterobacteriaceae compared with standard care and SOD. The development of bacteraemia acquired in ICUs caused by highly resistant microorganisms was 59% less frequent with SDD than with standard care and 63% less frequent for SDD than with SOD. The author concluded that widespread use of SDD and SOD in intensive-care units with low levels of antibiotic resistance is justified.

Discussion and Conclusion

During the last sixty years, the prevalence of antibiotic-resistant bacteria has increased and is associated with the use of antibiotics. The change in ecology and notably the global emergence of multi-resistant Gram-negative bacteria is worrisome. Since the 1980s, it has become clear that there is an increase in Gram-negative bacteria producing extended spectrum beta lactamases. Nowadays, Gram-negative bacteria are capable of producing carbapenemases able to hydrolyze carbapenems. It is thus becoming more important to prevent an increase in resistance and to prevent infections with these microorganisms in ICU patients. One of these preventive measures is SDD, which reduces mortality, reduces acquisition of antibiotic-resistant Gram-negative bacteria and can control an outbreak of multi-resistant Enterobacteriaceae colonizing the respiratory and intestinal tract. Oostdijk et al. showed that the eradication of intestinal carriage of Gram-negative bacteria led to a lower incidence of bacteraemia, so probably eradication of resistant bacteria reduces both cephalosporin-resistant Enterobacteriaceae colonization pressure and thereby the risk of bacteraemia.
SDD probably lowers the incidence of antibiotic resistance by reducing the bacterial load and by reducing the total amount of systemic antibiotics used,25,41,42 but should be used with great care and superb surveillance in surroundings with higher antibiotic resistance levels. Other important measures such as rational prescribing of antibiotics and strict hygiene measures remain essential. Together they can reduce the chance of transmitting resistant bacteria. In hospitals in the United States, where MRSA prevalent rates are high, universal decolonization with chlorhexidine has been shown to lead to lower MRSA carrier rates and fewer bloodstream infections, as demonstrated by Huang.43

Most evidence in favour of SDD arises from the Netherlands and it is not clear whether the results obtained here can be extrapolated to other regions of the world, especially those with a higher baseline incidence of resistance. Yet, studies in South Africa, Spain and France do show similar results,16,17,31 although the amount of evidence in regions with high MRSA and VRE prevalence is limited. De Jonge published a review in 2005 where he stated that SDD can lower resistance in low MRSA prevalence circumstances, and suggested that more studies are needed to investigate this in regions with higher prevalences of MRSA.44 A recently published systematic review and meta-analysis by Daneman et al. in 2013, reported that the perceived risk of long-term harm related to selective decontamination cannot be justified by available data.45

There are still some unclear issues that deserve to be unravelled. Cost-effectiveness of the use of SDD has only been shown in one study,66 and more studies on even longer term effects of SDD and SOD on patient and ICU bacterial ecology need to be performed, certainly in surroundings with high levels of antibiotic resistance. These matters will be subjects for research in the near future. In order to investigate this properly, more has to be done than just the surveillance and screening of ICU patients for resistant bacteria alone. For example, a comparison should be made with patients in general hospital wards to get an impression of the development of overall bacterial resistance patterns.

Acknowledgements
The author thanks Professor de Smet for her support in preparing this manuscript.

References
Development of antibiotic resistance related to selective decontamination of the digestive tract


Extracorporeal membrane oxygenation and its evidence in adults

Extracorporeal membrane oxygenation (ECMO) has been deployed for more than 40 years, first as a therapeutic option for circulatory shock and later also for the worst cases of acute respiratory distress syndrome (ARDS). However, as far as we know, no randomised trials have been performed that demonstrate the efficacy of ECMO for circulatory support. ECMO for respiratory support was found not to be superior to conventional treatment in two randomised controlled trials in the nineteen-nineties.1,2 Consequently, its use has long been restricted to neonates and small children. Due to major technological improvements in ECMO machines and catheters,3 ECMO has regained interest and the number of published case series has increased since the beginning of this century. Especially during the H1N1 pandemic, a dozen case series of patients who failed on conventional ventilation and were saved by ECMO therapy were published.4-8 In addition, a randomised trial was performed in which treatment in specialised ARDS centres (with ECMO capability) was compared to treatment in centres without ECMO capability.9 The study demonstrated a mortality benefit for patients treated in specialised ECMO centres. However, the study received criticism as it was the centres and not the treatment modalities that were compared. Moreover, in a recent propensity matched case-control study, ECMO did not demonstrate a survival benefit in H1N1-induced ARDS patients.10 Therefore, while ECMO is used as rescue therapy in certain centres, a survival benefit of ECMO is still lacking. Hopefully the recently started multicentre international randomised study, which will test the efficacy of early veno-venous-ECMO in patients with severe ARDS (EOLIA trial), will clarify this topic.

Physiology of ECMO

In veno-arterial extracorporeal membrane oxygenation (vaECMO), blood is drained from the caval vein and after oxygenation blood is returned into the femoral artery. Blood flow through the ECMO system is mostly around 4-7 l/min and is thus capable of taking over the complete circulation, even when cardiac output is nil due to severe cardiac failure. vaECMO is suitable for circulatory support and less suitable for respiratory support, especially in patients with preserved native cardiac output.

Veno-venous extracorporeal membrane oxygenation (vvECMO) drains blood from the inferior caval vein and returns oxygenated and decarboxylated blood in the right atrium via the superior caval vein. Without native gas exchange in the lung, vvECMO can achieve an arterial saturation of 90%. The arterial saturation depends on blood-oxygen saturation in the drainage canula, haemoglobin concentration, and the ratio blood ECMO flow / native cardiac output (figure 1). Decarboxylation does not require a high ECMO blood flow as blood solubility of CO₂ facilitates a more rapid diffusion and higher clearance through the membrane lung. Therefore, CO₂ removal is primarily a function of the fresh gas flow through the membrane, provided a minimal ECMO blood flow of 1 l/min to allow complete clearance of the patient’s CO₂ production.

Which patients should receive vvECMO?

Determining which patients should receive vvECMO therapy is still very difficult. Historically, oxygenation failure, assessed by a Murray score or oxygenation index, is used to decide whether to start vvECMO therapy. The Extracorporeal Life Support Organisation (ELSO) states that vvECMO can be considered with a PaO₂/FiO₂<150 mmHg and a Murray score 2-3, which represents an estimated mortality risk >50%.11 vvECMO is indicated with a PaO₂/FiO₂<80 mmHg and a Murray score 3-4, representing an estimated mortality risk of 80%. Moreover, CO₂ retention due to asthma with a PaCO₂>80 mmHg or the inability to achieve plateau pressure (Pplat) <30 mbar is also an indication for vvECMO, as well as severe air leak syndromes. Ventilation longer than one week at high settings...
Figure 1a and 1b. Arterial oxygenation depends on ECMO blood flow and native cardiac output and venous saturation. In this figure, venous saturation is 50%. In the left figure, high native cardiac output (10 l/min) with and ECMO blood flow of 4.5 l/min results in a large amount of blood not going through the oxygenator and results in a low arterial saturation. In the right figure, cardiac output is lower, resulting in a higher arterial saturation. These figures are under the assumption of an absent recirculation.

Table 1. The ECMOnet score.12

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<th>Bilirubin (umol/l)</th>
<th>PreECMO Hospital LOS (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2.5</td>
<td>0</td>
<td>&lt;3</td>
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<td>2.6 - 11.1</td>
<td>0.5</td>
<td>4 - 7</td>
</tr>
<tr>
<td>11.2 - 19.6</td>
<td>1</td>
<td>8 - 11</td>
</tr>
<tr>
<td>19.7 - 28.2</td>
<td>1.5</td>
<td>&gt;11</td>
</tr>
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<td>28.3 - 36.7</td>
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<td>Hematocrite (%)</td>
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<tr>
<td>&gt;36.7</td>
<td>2.5</td>
<td>&gt;40</td>
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<tr>
<td>Creatinine (umol/l)</td>
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<td>1</td>
</tr>
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<td>&lt;64</td>
<td>0</td>
<td>31 - 35</td>
</tr>
<tr>
<td>45 - 70</td>
<td>0.5</td>
<td>&lt;31</td>
</tr>
<tr>
<td>71 - 97</td>
<td>1</td>
<td>MAP (mmHg)</td>
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<tr>
<td>98 - 123</td>
<td>1.5</td>
<td>&gt;90</td>
</tr>
<tr>
<td>124 - 150</td>
<td>2</td>
<td>61 - 90</td>
</tr>
<tr>
<td>151 - 176</td>
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<td>&lt;60</td>
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<tr>
<td>177 - 203</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>&gt;203</td>
<td>3.5</td>
<td></td>
</tr>
</tbody>
</table>

MAP = mean arterial pressure, regardless of vasopressor use, LOS = length of stay.

(FiO₂>90% or Pplat>30 mbar), major immunosuppression (absolute neutrophil count < 400/m³) and recent CNS bleeding are considered relative contraindications. Furthermore, an increased mortality risk with increasing age should be considered (no specific age criteria are set), weight >125 kg, non-fatal co-morbidities and bridging to lung transplant can be a relative contraindication because of the limited number of donors.

Who should be excluded from vvECMO: predicting mortality while on vvECMO

As the criteria for withholding a patient from vvECMO therapy were based on expert opinion, the ECMOnet score has recently been developed, based on historical data.12 The aim of the ECMOnet score is to identify predictors of mortality in patients treated with vvECMO in referral centres. The dataset contained 60 patients (82% H1N1 patients) and the validation set contained 74 patients (81% H1N1 patients). Using multivariate analysis, five significant predictors for death were identified (table 1). An ECMOnet score >4.5 had an area under the curve of 0.69 in the receiver-operator-characteristics (ROC) of the validation set with a sensitivity of 51% and a specificity of 76% for survival on ECMO therapy.

Experience in the Erasmus Medical Center

Since 2004, 122 adults in the EMC have been treated with ECMO: 9 patients received vaECMO during cardiopulmonary resuscitation (ECPR), 60 patients received vaECMO mainly due to ischemic cardiomyopathy and 54 vvECMO mainly due to bacterial or viral pneumonia (figure 2). The survival rate was 38%, 63% and 67%, respectively, and this was in accordance with the ELSO registry data. Figure 3 shows that the survival rate has decreased after vvECMO therapy during the last few years. However, the ECMOnet score increased, indicating that more severely ill patients have been treated over the years. Whilst patients were receiving vvECMO, the causes of death on the ICU were multiple organ failure (n=4), intracerebral haemorrhage (n=4), massive bowel ischemia (n=2), cardiac arrest (n=2) and lack of respiratory improvement (n=2). Patients on the vvECMO frequently had renal failure, requiring renal replacement therapy (36%). Severe complications of vvECMO were intracerebral bleeding, which occurred in 7% of patients, cardiac tamponade and myocardial infarction, which occurred in 5% of patients. These severe complications required immediate neurosurgical or cardiothoracic intervention. These data may illustrate the severity of illness in vvECMO patients and the need for neurosurgical and cardiothoracic backup in an ECMO centre.

In the beginning, our indications for vvECMO were very strict and limited. In 2009, only patients with mono-organ failure were candidates for vvECMO treatment. One year later, also
young patients with systemic diseases were included and the need for renal replacement therapy was no longer a contraindication. In 2011, patients with septic shock were included for vvECMO. Thereafter, a patient with haemorrhagic shock due to trauma was included for vvECMO. Due to massive lung bleeding the patient was planned for vvECMO, but as the patient developed a cardiac arrest during the preparation phase, vaECMO was successfully instituted during resuscitation. In 2012, patients were receiving lung transplantation while on vvECMO. Recently, even duration of mechanical ventilation was no longer considered a contraindication. This is illustrated by the case of a young man with pneumosepsis, ventilated with peak pressures between 35 and 40 mbar (PEEP 10 mbar) for 37 days who underwent a successful vvECMO run for treatment of severe air leaks.

When analysing the power to predict mortality using the ECMOnet score in patients treated in the Erasmus MC, the ECMOnet score has the same area under the curve of 0.69, but with a higher optimal cut-off value of >6.5.13 In the Erasmus MC, an ECMOnet score above 6.5 has a sensitivity of 50% and a specificity of 80% for predicting mortality in patients on vvECMO. In our patients, the oxygenation index and APACHEII had an area under the curve of 0.54 for both variables.

Over the years, the ECMOnet score firmly increased in our centre, but mortality remained stable. As stated above, the indications for vvECMO expanded over the years and patients were found to be progressively more ill. Figure 3 shows the progression of the ECMOnet score over the years in patients treated in the Erasmus MC and with the survival rate. Most likely, increasing expertise and the introduction of protocols has lead to the relative increase in survival. In addition, bleeding complications have decreased dramatically due to percutaneous insertion of cannulas being carried out by an experienced team on the intensive care unit. Furthermore, a lower degree of anticoagulation is now accepted which results in a lower risk of bleeding complications. Just as in our intubated ICU patients, deep sedation of ECMO patients appeared to be superfluous and patients are now treated awake on ECMO, whenever possible. When they have a single, double lumen cannula in the internal jugular vein (Figure 4 and 5) and are awake on ECMO, patients receive physiotherapy and are mobilised. Mobilisation on vvECMO reduces mortality in patients awaiting lung transplantation.14,15 Due to our

Figure 2. Number of adult patients per year treated with extracorporeal membrane oxygenation (ECMO) in the Erasmus MC. va-ECMO= veno-arterial ECMO, vv-ECMO= veno-venous ECMO, ECPR= ECMO during cardiopulmonary resuscitation.

Figure 3. Number of patients/year treated with veno-venous extracorporeal membrane oxygenation (vv-ECMO). Numbers above bars is the mean annual ECMOnet score. Number in the bars is the percentage of ICU survivors.

Figure 4. Patient with methotrexate pneumonitis on full veno-venous extracorporeal membrane oxygenation, awake and cycling.
experience in the last five years, we strongly believe that ECMO should be centralised in expert centres where severe complications can be immediately be treated.

ECMO and transport
Patients on ECMO can be transported.16,17 49 of the 101 patients who received ECMO were transported to the Erasmus MC to receive ECMO. Recently, we have started ECMO transport with our mobile intensive care units (MICU). The MICU Zuidwest Nederland is equipped with its own ECMO machine integrated on the trolley and 18 cases of transport of adults on ECMO have been done (figure 6), of which one was initiated by the MICU team in the referring hospital. Up until now, no complications during transportation have been reported.

The team caring for ECMO patients
The ELSO has made guidelines for ECMO centres.18 These guidelines mainly describe the minimal preconditions to which a centre has to comply and the training preconditions of each team member involved in ECMO care. The minimal preconditions of ECMO care are that it should be delivered in tertiary centres, located in geographic areas that can support an absolute minimum of 6 ECMO cases per year, and are actively involved in the ELSO registry.

According to the ELSO guidelines, the ICU should be staffed with experienced intensivists and experienced intensive care nurses. These intensivists and nurses must have followed a certification and re-certification programme containing didactic lectures, simulation sessions and bedside training, ending with an exam. Team members not involved in ECMO management for >3 months should be required to go through a re-certification programme. Moreover, support staff from the permanent hospital staff should include a:

- Cardiologist
- Cardiovascular surgeon
- General surgeon
- Cardiovascular perfusionist
- Anaesthesetist
- Neurosurgeon
- Radiologist.

The adult intensive care unit of the Erasmus MC has put much effort into complying with these valuable guidelines. A training programme has been instituted as follows: a full day basic course is given to all staff, nurses and ICU-fellows containing lectures and an extensive simulation programme. Moreover, all team members receive a short hands-on training on every type of ECMO machine once every three months. This training mainly aims at practising the emergency procedures for each type of ECMO machine and all the alarms/screens. Fully ECMO trained physicians are immediately available at the bedside 24/7. At first glance, it might seem odd that the ECMO requires such an intensive training scheme. Other machines such as renal replacement, hemodynamic monitoring machines, echo machines do not require such training procedures. The reason for such intensive training is that an ECMO machine is a life-saving machine that is rarely used. In a normal intensive care setting, only two machines are considered to be immediately life-saving – the ventilator and infusion pumps. Frequent, very extensive training procedures with these machines are not required as the exposure by staff to these machines is large. For ECMO machines however, exposure is limited and malfunction of these machines may cause cardiac arrest in few seconds, for example, with vaECMO and (in our experience) also with vvECMO. Therefore, extensive training and a solid collaboration with the above named support specialties is crucial for a successful ECMO programme according to the ELSO guidelines.
Future Perspectives: How do we organise ECMO care in the Netherlands?

Paediatric ECMO has a long tradition in the Netherlands and is well organised. The Netherlands have two paediatric ECMO centres, one of them being the Children’s Hospital of the Erasmus MC which has performed approximately 700 ECMO runs, with very good outcome. The adult ECMO however, has not yet been organised. Funding for adult ECMO is still unclear and which centres will be designated to perform ECMO is also unclear. Due to the lack of organisation, intensive care units tend to rent an ECMO machine and give it a go. This situation is comparable with Germany, where ECMO centres are appearing all over the place, most of them being low volume ECMO centres. It is supposed that the reason for this is the good reimbursement for ECMO treatment in Germany, and debate is going on in the larger German ECMO centres on how to tackle this problem. In contrast, in Sweden, ECMO care is strictly regulated where only the Karolinska institute provides ECMO treatment. This centre is a centre of excellence known in the ELSO registry and is famous throughout the world due to its high quality care and innovations.

In our view, Dutch ECMO centres should primarily comply to the ELSO guidelines, thus being a tertiary centre, with the capability of performing cardiothoracic surgery and neurosurgery. These ELSO guidelines also prescribe an extensive training programme with simulation and a hands-on training every three months for the whole team (physicians and nurses). Centres complying with the ELSO guidelines should subsequently be reimbursed on the basis of real costs. For our centre, we aim at a minimum of 20 ECMO runs annually to maintain the experienced team19–21 and to pay off the investment of the extensive training programme.

Conclusion

Extracorporeal membrane oxygenation is a rarely used therapy that is regaining interest. Formulating the indications for ECMO and the best therapy during ECMO is still highly dynamic. Due to these rapid developments of a rarely used therapy and due to the relatively high complication rate, ECMO is best used in selected, specialised centres. The most important preconditions for ECMO centres is a large base of specialists, including a cardiovascular surgeon and a neurosurgeon and a solid training programme with a basic course including simulation and a refresher course every three months for the whole team.

Conflict of interests

D. Reis Miranda en D. Gommers have received fees from NovaLung GmbH.

Table 2. The experience of veno-venous extracorporeal membrane oxygenation (vveCMO), veno-arterial ECMO (vaECMO) and initiation of ECMO during cardiopulmonary resuscitation (ECPR). For vaECMO, most patients are in principle candidates for heart transplantation. Therefore, bridge to transplant patients are categorized by their underlying disease.

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<tr>
<th>Underlying disease</th>
<th>ICU survivors</th>
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<td>VAECMO</td>
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<td></td>
</tr>
<tr>
<td>Ischemic</td>
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<td>6</td>
</tr>
<tr>
<td>Post thoracic surgery</td>
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<td>8</td>
</tr>
<tr>
<td>Transplant failure</td>
<td>5</td>
<td>4</td>
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<td>Myocarditis</td>
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</tr>
<tr>
<td>VV ECMO</td>
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<tr>
<td>Bacterial</td>
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<td>7</td>
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<tr>
<td>Viral</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Bridge to transplant</td>
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<td>1</td>
</tr>
<tr>
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<tr>
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<td>Total</td>
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<td>45</td>
</tr>
</tbody>
</table>

References


Complications following oesophagectomy, a review with future perspectives

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Keywords – Oesophagectomy, gastric tube reconstruction, complications

Abstract
Oesophagectomy with gastric tube reconstruction is a complex, high-risk surgical procedure. Despite improvements in surgical techniques and perioperative care, the postoperative course is often complicated. The two most frequent and important complications following oesophagectomy are anastomotic failure and pulmonary morbidity.

Along with surgical methods, microvascular blood flow is an important factor in the development of anastomotic failure. Location of the anastomosis, tissue supportive techniques and early detection of anastomotic leakage may contribute to a decrease in morbidity.

The pathogenesis of pulmonary complications is multifactorial. Prolonged systemic inflammatory response syndrome responses are associated with pulmonary complications. The cholinergic anti-inflammatory pathway may play a role in this inflammatory response and future research in this direction is necessary in the search for better care.

In our opinion, only clinical pathways that include early extubation, fluid management, pain management and early mobilization and nutrition, are providing opportunities for fewer postoperative pulmonary complications. However, clinical pathways succeed only if surgeons, anaesthetists and intensivists feel they are part of the treatment process and take responsibility as a team for all complications.

Introduction
Oesophagectomy with gastric tube reconstruction is a complex and high-risk surgical procedure. Despite improvements in surgical techniques and perioperative care, the postoperative course is often complicated. Complications following oesophagectomy can be divided into two categories, firstly surgical and secondly medical. Unlike any other oncological or gastro-intestinal operation, oesophagectomy is associated with numerous non-surgical complications. It is unclear why patients are more vulnerable following oesophagectomy than patients following, for example, a pneumonectomy or pancreatic surgery.

The complexity, morbidity and in-hospital mortality rates have led to national and international discussion for the need for centralization of oesophageal surgery. Although complication rates are similar in lower and higher volume hospitals, it is more likely that high volume centres treat complications more successfully. An increase in volume of this procedure has led to a better understanding and regulation of the infrastructure of the management of patients. The introduction of clinical pathways may help improve the infrastructure surrounding patients following oesophagectomy and also improve complications.

In the following section we discuss the two most frequent and important complications following an oesophagectomy: anastomotic failure and pulmonary morbidity.

Gastroesophageal anastomotic failure
For an acceptable quality of life for patients after radical curative oesophageal resection, continuity of the gastrointestinal tract is necessary. Of all the conduits (colon, jejunum and stomach) gastric tube reconstruction is the one used most often internationally. The gastric tube is constructed by ligating the left and right gastric arteries, the short gastric arteries and the left gastroepiploic artery. These are then fashioned along the greater curvature of the stomach. The fundus side of the gastric tube depends on the right gastroepiploic arterial arcade for arterial supply. In the literature, leakage of the gastroesophageal anastomosis occurs in 0% to 35% patients. The wide range is partly due to the various definitions used for anastomotic leakage. In a recent review of 80 articles on complications following gastric tube reconstruction, 25 different definitions were used for anastomotic leakage.

Compromised microvascular blood flow of the gastric tube, as a result of ligation of the main arteries, is thought to be an important factor in the pathogenesis of anastomotic failure. By vascular conditioning due to endovascular coiling or
laparoscopic clipping of the depending arteries prior to gastric tube reconstruction, stimulation of collateral perfusion of the gastric tissue might be achieved. These techniques are currently being evaluated in research protocols. Large series, and therefore results on outcome, have not yet been published. Other studies have tried to improve arterial circulation by creating vascular anastomosis of the short gastric vessels with vessels in the neck. A remarkable observation was made in the improvement of microcirculation after creating only the venous anastomosis, suggesting that venous congestion plays an important role. This corresponds with our observation, where at the end of gastric tube reconstruction, the fundus of the stomach often has a bluish colour instead of a pale colour. As an impaired arterial blood supply would lead to a pale appearance of the tissue, whereas venous congestion gives a darker colour of the tissue, we underscribed the hypothesis of venous congestion (figure 1).

By using a combination of laser Doppler flow and reflection spectrophotometry to measure microvascular blood flow and microvascular oxygenation, we studied the microvascular blood flow during gastric tube reconstruction. We measured an increase in microvascular haemoglobin concentration and gradual decrease in microvascular haemoglobin saturation. According to our hypothesis this would be expected to occur in the presence of venous congestion. Another argument for a role for venous congestion was that after application of topical nitro-glycerine on the gastric fundus, the gastric microvascular blood flow increased. These results roused our curiosity on the relation between tissue perfusion pressure and venous congestion of the gastric tube. We created a gastric tube reconstruction in a pig model and we used nor-epinephrine to increase mean arterial pressures from 50 to 110 mmHg. In a second group, nor-epinephrine was combined with intravenous nitro-glycerine, in a dosage to keep the central venous pressure below 10 mmHg (figure 2). We observed that the combination of nor-epinephrine and nitro-glycerine provides a more improved microvascular perfusion of the gastric conduit than nor-epinephrine alone. This observation supports our hypothesis of a role for venous congestion in impaired gastric blood flow following gastric tube reconstruction.

The position of the gastroesophageal anastomosis in relation to microcirculation and the limits of the right gastroepiploic arterial arcade seem to be important. In 1946, Ivor -Lewis introduced a technique with an intrathoracic anastomosis of a gastric conduit and the rest of the oesophagus. Unfortunately, leakage of the intrathoracic anastomosis, led to infection of the mediastinum with fatal consequences. Therefore, a technique with a cervical anastomosis was developed. In case of leakage of the cervical anastomosis, drainage to the outside of the neck is often a proper and manageable solution with no great clinical consequences. However, to create a cervical anastomosis a longer and more poorly circulated conduit is necessary. This in return will lead to a greater risk for anastomotic failure. Although most cervical anastomosis leakages are drained to the outside, some may leak into the chest and create infections of the mediastinum as well. Due to the availability of better diagnostic tools, minimal invasive techniques for the management of leakage, and the lower expected incidence of anastomotic failure, the intrathoracic anastomosis has become a procedure of renewed interest in the Netherlands. However, an intrathoracic anastomosis is only suitable for tumours in the lower oesophagus and not for carcinoma in the higher oesophagus and recent analysis failed to provide evidence as to which type of anastomosis is of more benefit to patients. In the treatment of anastomotic leakage, aggressive surgical re-exploration with additional drainage, total parenteral nutrition, nasogastric decompression and broad-spectrum antibiotics are effective, but lead to a prolonged ICU and hospital stay. Occasionally anastomotic repair and reinforcement of the anastomosis with muscle flaps is necessary; the results, however, are poor. To seal anastomotic leakage, recently self-expanding metal or plastic stents in combination with effective drainage seem to be a viable option. However, dislocation of these stents remains a problem.

**Pulmonary morbidity**

Oesophagectomy is highly associated with pulmonary complications. In a recent review postoperative pneumonia was reported in 57% of the studies. Similar to anastomotic leakage, there are many different definitions of pneumonia. Almost all definitions of post-oesophagectomy pneumonia use a combination of radiologic infiltrates, positive culture of sputum, fever, increased white blood count and clinical suspicion for which antibiotics were started. The incidence of pulmonary complications is associated with age, operation duration, proximal tumour location and...
During a transthoracic oesophagectomy procedure, one lung is collapsed to allow surgical exposure to the oesophagus. This leads to atelectasis and local contusion of the lung. Prolonged duration of procedure predisposes patients undergoing one lung anaesthesia, to increased atelectasis and respiratory complications. Systemic inflammatory response due to surgical trauma of the other lung, can lead to bilateral lung oedema and acute lung injury. Several inflammatory markers including interleukins, tumour necrosis factor and neutrophil endothelial markers are likely to cause persistent injury to the alveolar-capillary barrier function which leads to a shift and accumulation of fluids in the extra vascular space and this induces pulmonary oedema. Minimal invasive oesophagectomy, may reduce the pulmonary complications, leading to a reduced length of ICU and hospital stay.

There is emerging evidence that next to the influence of surgical techniques, anaesthetic management also directly influences the incidence of pulmonary complications. Early extubation has been shown to reduce pulmonary complications. However, to achieve successful early extubation, effective postoperative analgesia is required. Although subject for debate, thoracic epidural analgesia is recommended to intravenous opiates to achieve effective analgesia during oesophagectomy. Epidural analgesia provides pain relief, reduces respiratory complications, reduces ICU stay and possibly the mortality rate following oesophagectomy. There is also a beneficial effect of epidural analgesia on the surgical stress response and associated immune function in oesophagectomy. Effective thoracic epidural analgesia increases tissue oxygenation during abdominal surgery and might improve gastric blood flow following oesophagectomy. Regarding all these arguments we still encourage epidural analgesia for oesophagectomy.

The relation between perioperative fluid management on pulmonary complications following major surgery is well documented. In order not to compromise gastric tube perfusion, perioperative hypotension usually was treated with administration of fluid, thereby avoiding the use of vasoactive medication. As a result, the net fluid balance at times increased in the first 24 hours. In some cases net fluid balance reached up to 10 L. Clinical trials investigating the effect of restrictive fluid management found a reduction in postoperative complications. However, studies using a goal directed fluid management also claim better results. Unfortunately, local differences have led to diverse standards of fluid management; the restrictive treatment in one study is called liberal in the next study. Looking specifically at oesophagectomy patients, several studies favour fluid restriction. We have shown in a clinical study that a reduction in administered fluids can reduce pulmonary complications following oesophagectomy without an increased incidence of anastomotic leakage.

It is surprising that only a few studies have been performed that look at perioperative ventilation strategies aimed at reducing pulmonary morbidity. The use of protective mechanical ventilation using low tidal volume during the one lung ventilation reduces the interleukin-6 levels. High levels of interleukin-6 are associated with adverse outcome following surgery and protective ventilation improves postoperative lung function and results in earlier extubation. Prolonged perioperative hypoxemia and haemodynamic instability are associated with higher occurrences of pulmonary complications, e.g. acute lung injury and adult respiratory distress syndrome. Incorrectly positioned double lumen tubes during oesophagectomy have also been noted as a serious contributor to perioperative morbidity. To avoid double lumen tubes or bronchus blockers, we studied the feasibility of two-lung high frequency ventilation. We concluded that two-lung high frequency ventilation is a usable ventilation strategy, although there is no effect on postoperative pulmonary complications.

**Figure 2.** Microvascular blood flow (MBF) measurements on gastric pylorus, corpus and fundus at increasing MAP levels. Data represent mean ± SEM; # P<0.05 vs CTRL, b P<0.05 vs baseline, ^ P<0.05 vs MAP 50, $ P<0.05 vs MAP 60.
**Inflammatory pathways**

In the previous paragraphs we described the two most important complications following oesophagectomy. In both complications there is a role for the systemic inflammatory response syndrome (SIRS). However, what are the effects of SIRS on morbidity following oesophagectomy?

Increased surgical stress parameters (blood loss/body weight and operation time) correlates with the duration of SIRS, or the number of positive criteria for SIRS post-surgery. Morita described the mechanism of an increased inflammatory response post-oesophagectomy in a two hit model. The first hit is the result of great surgical stress, the necrosis and infection around the poorly circulated gastric oesophageal anastomosis, which in return results in the second hit, acute lung injury. The influence of preoperative neoadjuvant chemoradiotherapy is associated with prolonged or severe SIRS parameters. However, neoadjuvant chemoradiation does not appear to increase postoperative morbidity or mortality post-oesophagectomy. There is growing evidence for several agents to reduce SIRS. For example, steroids are recommended in Japanese guidelines. More recently a neutrophil elastase inhibitor was demonstrated to reduce postoperative pneumonia following oesophagectomy. Increased plasmatic cytokine levels are characteristic for post-oesophagectomy patients and especially for post-oesophagectomy patients with postoperative infection including pulmonary infection. Detection during the first 48 h of SIRS criteria, high plasma pro-inflammatory cytokine levels (interleukin 6, tumour necrosis factor alpha) and impairment of PaO₂/FiO₂ predicts the onset of pulmonary complications. Additionally, increased C-reactive protein concentration (CRP) levels in the early postoperative period, are associated with the occurrence of postoperative complications and increased one year mortality. The production CRP in the liver is stimulated by pro-inflammatory cytokines.

It has been shown that the vagus nerve plays a prominent role in inflammation through the cholinergic anti-inflammatory pathway. The vagus nerve down-regulates inflammation by decreasing the release of tumour necrosis factor (TNF)-α by macrophages. Activation of the vagus nerve releases acetylcholine in the vicinity of macrophages within the reticulo-endothelial system, leading to the inhibition of cytokine release. Stimulation of the vagus nerve results in decreased cytokine release, whereas vagotomy results in an increase in cytokine release. In a recent study, trauma patients who underwent vagotomy developed septicemia eight times more often than the matched control patients. Therefore, the presence of an intact vagus nerve and gut innervation will decrease the post-injury inflammatory response. In both trans hiatal and or transthoracic oesophagectomy, acute vagotomy is performed thus deactivating the cholinergic anti-inflammatory pathway. In oesophagectomy, where a cervical anastomosis is applied, both the vagus nerves are dissected in the upper mediastinum. However, in oesophagectomy with an intrathoracic anastomosis, the higher branches of the vagus nerve are preserved.

In this context, vagal sparing oesophagectomy might play a role in the prevention of post-operative complications. Vagal sparing oesophagectomy is a well-known technique, first described by Akiyama in 1994. The goal of vagal sparing oesophagectomy is to increase quality of life by preserving postoperative gastric emptying and prevent patients from developing the dumping syndrome and diarrhoea. In later studies, this technique was found to be clinically associated with lower mortality and morbidity. In vagal sparing oesophagectomy the oesophagus is stripped (inverted) out of the mediastinum. Only a highly selective vagotomy is performed on the gastric-oesophageal junction and the colon is used as an oesophageal substitute. However, vagal sparing oesophagectomy is only possible in a limited group of patients. These include patients with: end-stage benign oesophageal disease, Barrett’s oesophagus with high-grade dysplasia, or multifocal oesophageal cancer limited to the lamina propria.

There is growing evidence that the cholinergic anti-inflammatory response can be stimulated by nutrition. Nutrition should specifically include dietary lipids, these activate the autonomic nervous system through the afferent vagal nerve and lead to the release of neuro-endocrine hormones. Thus, nutrition may be used as therapy to prevent excessive inflammation. However, randomized controlled trials are necessary to collect evidence for this interesting hypothesis in the clinical setting from thousands of different individuals, our patients.

**Conclusion**

Although mortality following oesophagectomy has decreased during the last few decades because of improvements in surgical and perioperative care, the procedure is still associated with high morbidity. Anastomotic failure and pulmonary complications are the most frequent complications. Tissue supportive strategies may reduce the incidence of anastomotic leakage by stimulating the microvascular blood flow of the gastric conduit. Clinical pathways and minimally invasive surgical techniques may influence the rate and severity of pulmonary complications.

The role of SIRS and the cholinergic anti-inflammatory pathway in the pathogenesis of pulmonary complications post-oesophagectomy is a challenging subject for future research. The concentration of highly complex care leads to more experience in the treatment of complications and the development of new multi modal pathways. However, clinical pathways succeed only if surgeons, anaesthesists and intensivists feel that they are part of the process and take responsibility as a team for all complications that occur.
References

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Verkorte productinformatie Mycamine® 50 mg/100 mg (januari 2013)

Samenstelling: Mycamine® 50 mg/100 mg poeder voor oplossing voor infusie (in natriumvorm). De toe te dienen hoeveelheid na reconstitutie is 10 mg/ml en 20 mg/ml; resp. (in natriumvorm).

Farmacotherapeutische groep: Overige antymycotica voor systemisch gebruik, ATC-code: J02AX05.

Therapeutische indicaties: Behandeling van invasieve en niet-invasieve, behandeling van oesofageale candidose. Bij patiënten voor wie intravenezale therapie geschreken is. Profylaxe van Candida infectie bij patiënten die allergische hematoopoëtische stemcelltransplantatie ondergaan of van wie wordt verwacht dat ze aan neutropenie lijden gedurende 10 dagen of langer. Andere (non-invasieve en invasieve) behandeling van invasieve candidose.

Patienten die Mycamine in combinatie met sirolimus, nifedipine of itraconazol ontvangen, dienen nauwkeurig te worden geobserveerd. De therapietoediening moet worden gestopt als de laesies verergeren. In dit geval dient nauwlettend te worden gevolgd of er geen versnelde verspreiding optreedt en er doent een niet-herstelbare laesie ontstaan. Indien de laesies des te meer aanwassen wordt een overgang tot een substitutetherAPIA of een andere antymycotica medicatie aanbevolen. De risico’s, met een scherpe controle op mogelijke toxiciteit van amfotericine B-desoxycholaat. Micafungine met amfotericine B-desoxycholaat is alleen toegestaan wanneer de voordelen duidelijk opwegen tegen de risico’s.
CASE REPORT

Legal issues in patient management of intoxicated patients: a case of auto-intoxication by intravenous pentobarbital injection

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Keywords – Barbiturates, pentobarbital, intoxication, suicide, legal issues, withdrawal of life support

Abstract
We present a case report of a 79-year-old woman who injected herself with pentobarbital. After admission to hospital, laboratory examination revealed a lethal serum concentration of pentobarbital (33 mg/L; toxic serum level > 10 mg/L) in the patient. This case of a pentobarbital overdose illustrates that legal issues, such as the authenticity of a written patient statement, have to be considered in decisions on the continuation or discontinuation of curative care.

Introduction
Barbiturates are drugs with sedative and anti-convulsive properties. Barbiturates can be classified into three groups: a) ultra-short-acting (for example thiopental), b) short-acting (for example pentobarbital) and long-acting barbiturates (for example phenobarbital). In Western countries, barbiturates are considered obsolete agents for medical treatment. However, phenobarbital is still prescribed as an anti-epileptic drug. Thiopental and pentobarbital are clinically applied for the induction of narcosis and for lowering the intracranial pressure. In addition, barbiturates are used in various veterinary settings. Barbiturates act by suppressing the central nervous system, resulting in severe sedation or coma in cases of overdose. In cases of intoxications, suppression of the central nervous system, hypotension, hypothermia, coordination disorders, respiratory failure and coma are the major clinical symptoms. Both miosis and mydriasis are observed in patients who have been poisoned with barbiturates.

We present an interesting pentobarbital overdose case of a woman admitted to our hospital. In this case we had to deal with legal questions before discontinuation of curative care was permitted and a procedure of a non-natural death was started. The questions included doubt on the authenticity of a suicidal note and, how this woman had access to a pentobarbital solution and, consequently, if she had indeed injected herself.

Case history
A 79-year-old woman was found by her general practitioner at home in a coma. A 100 mL brown bottle without label, containing about 2-3 mL of an unknown viscous liquid and crystals were found near the patient, together with a syringe (figure 1). A small injection mark and purple spot were observed on her left elbow.

On admission to the hospital emergency department, she had no heart action. The patient was resuscitated. After return of spontaneous circulation, the patient was admitted to the ICU. Her Glasgow coma score was E1-M1-V1. She was in cardiogenic shock with a sinus bradycardia. Both pupils were slightly dilated. Blood and urine samples were collected for toxicology screening. In these samples, the presence of barbiturates was demonstrated as described below.

The initial therapy in the ICU was mechanical ventilation, therapeutically induced hypothermia (32-34°C), and administration of dopamine and norepinephrine. Several hours

Figure 1. Bottle, containing an unknown mixture with precipitated crystals.
after the initiation of this therapy the patient’s family arrived. The family produced a statement that included a prohibition to treat her in times of coma. At that time it was not immediately clear whether, on legal grounds, the treatment should be continued or discontinued. Treatment was continued overnight so that the legal consequences of treatment discontinuation could be further explored. The next morning the patient showed characteristics of clinical brain death. Typical brain death characteristics in this patient were the absence of stem reflexes and apnoea. Also an iso-electric EEG was observed. After approval by the public prosecutor, mechanical ventilation was stopped according to the wish of the patient. The patient died because of apnoea within a few minutes. Thereafter, the routine procedure for non-natural death was followed.

### Toxicology investigations

After admission to hospital, blood and urine samples were collected for toxicology screening. Toxicology investigations were performed on blood and urine samples and on a bottle found at her house.

#### Bottle

The bottle contained 2-3 mL of a viscous alkaline liquid mixture with precipitated crystals. Liquid and crystals were investigated by Fourier Transform Infrared Spectroscopy using a Nicolet Avatar 370 DTGS apparatus (Thermo Fischer Scientific, Madison, USA), equipped with a toxicology library and by a HPLC-diode array detection with library (Systematic Toxicological Identification Procedure, STIP, \(^\text{5,6,7}\)) as described below. Toxicology screening of the liquid and crystals in the bottle indicated the presence of ethanol, propylene glycol and a barbiturate-like compound. The STIP analysis revealed the presence of pentobarbital in the bottle. The pH of the mixture in the bottle was 11. This can be attributed to the presence of the pentobarbital in the form of sodium salt. The pentobarbital concentration of the liquid in the bottle was 16g/100 mL. This corresponds with a concentration of pentobarbital in the form of the sodium salt of 17\% (g/v).

#### Patient

A comprehensive screening was performed on urine- and serum samples. Considering the clinical state of the patient, the serum was screened for the presence of ethanol, paracetamol, salicylates and metoprolol. The urinary toxicology screen was done by immunochemistry (Emit, 2000, Siemens Healthcare Diagnostics Inc., Newark, DE 19714, USA). STIP was performed allowing identification and quantification of toxic compounds. \(^\text{5,6,7}\) A Shimadzu CLASS-VP V 6.12 SP4 HPLC system was used equipped with a Microsphere C18 column (30 cm x 4.6 mm). The mobile phase was a mixture (1000 mL) of acetonitril (Lichrosolv) (470 mL) and water (530 mL), containing phosphoric acid 85\% (approximately 400 \(\mu\)L), triethylamine 146 \(\mu\)L, adjusted to pH 3.30 with a 10\% (g/v) potassium hydroxide solution. The column temperature was 55\^\circ\text{C}, the flow rate was 0.6 mL/min and the detection took place at 205 nm. The retention times in minutes were: phenobarbital 3.8; butobarbital 4.4; secobarbital 7.4; pentobarbital 5.9 and thiopental 11.5. Calibration curves were constructed by adding known amounts of pentobarbital and MMPH (5-(p-methyl-phenyl)-5-phenylhydantoin) as internal standard to methanol or serum.

The toxicology screen did not reveal traces of cocaine, heroin, methadone, amphetamines, cannabis, benzodiazepines, paracetamol, salicylates and metoprolol. The urinary toxicology screen clearly indicated the presence of barbiturates, corresponding with the findings in the bottle found at the patient’s house. Only a low level of ethanol was found in her blood (0.14 g/L). STIP analysis confirmed the presence of pentobarbital in the woman’s blood and revealed that the serum pentobarbital level was 33 mg/L. Therapeutic ranges of pentobarbital in serum are between 1-10 mg/L. Serum levels above 10 mg/L can cause coma and levels above 30 mg/L as observed in the present case are usually lethal. \(^\text{1,2,3}\)

### Discussion

This case demonstrates that legal issues have to be carefully considered in cases of drug overdoses. Legal issues may influence patient management as illustrated in our ICU patient who had injected herself with a lethal amount of pentobarbital. In this case, it was possible to estimate the amount of pentobarbital present in the body and the minimal volume of the pentobarbital mixture that the patient had injected into herself. The volume of distribution (Vd) of pentobarbital is 1 L/kg.\(^9\) The woman’s weight was approximately 70 kg, resulting in a Vd of pentobarbital of approximately 70 L. The estimated amount of pentobarbital in the body at the time of sampling was approximately 2.1 grams. In the present case of a presumed auto-injection with a concentrated pentobarbital solution of 16 g/100 mL, it is possible to calculate that at least 13 mL of a possibly veterinary pentobarbital solution has been injected.

Interestingly, other cases have shown the death of individuals after auto-injection with similar doses of pentobarbital.\(^3,9\) For instance, Romain et al. describe a 51-year old man who was found dead who also had a purple spot at the site of injection. The concentration of the injected pentobarbital mixture was 21.7 mg/L and the estimated amount of injected pentobarbital was approximately 1.6 g.\(^9\)

In our case, after admission to hospital, the physicians were informed about a written statement that included the patient’s refusal to be treated in a case of coma. At that point it was not clear whether discontinuation of treatment would be legally allowed. Until it was clear whether curative or palliative care should be provided by the ICU, the treatment was continued.
overnight. The next day, the patient showed the critical condition of brain death, including an iso-electric EEG, which may have been induced by the pentobarbital.

An important legal issue of the present case is the authenticity of the patient’s written statement including her refusal to be treated for a coma. A written statement of refusal orders a physician to respect the wish of the patient by abstaining or omitting medical treatment. In the specific case of a patient attempting suicide and with a written statement for abstaining treatment, refusal of treatment has to be respected.

In the Netherlands, several laws regulate patient rights. According to article 7:450 paragraph 3 of The Dutch Medical Treatment Contract Act (WGBO), a written statement of refusing treatment made by a patient of 16 years or older, has to be respected and is legally enforceable.10 This is in agreement with the general rule in article 7:450 paragraph 1 (WGBO) which implies that treatment without permission cannot take place. However, there are some exceptions to this general rule. If there are so called ‘serious grounds’, a physician is not required to obey the written declaration of the patient (article 7:450 paragraph 3 (WGBO)).10 Such serious grounds may include uncertainty of the authenticity of the statement itself, doubts about the authenticity of the signature and doubts about the interpretation of the statement.

Only in cases where there are serious grounds, a physician is not required to obey the patient’s written declaration of abstaining treatment. The physician should confirm that a declaration of refusal has been written. Given the profound effects, it is desirable that any written statement is genuine, has a signature, is dated and is unambiguous. It should be noted that all of these requirements are not obliged by law or regulations per se.12

In the present case, the written statement of refusal came to light a few hours after the patient was hospitalized. In such cases it is very hard and often unclear what the physician should do. According to the WGBO, a physician is required in case of an emergency to act and treat the patient as stated in article 466 paragraph 2 (WGBO).10 The general practitioner of this patient indeed confirmed that the patient had signed a legal statement. Furthermore, the public prosecutor also stated that discontinuation of the treatment was legal. The procedure for a non-natural death was started and since it was concluded that she injected herself no further legal investigations were initiated.

Conclusions

This case of a pentobarbital overdose clearly demonstrates that legal issues have to be taken into account in patient management, especially when decisions on continuation or discontinuation of curative care for intoxicated patients are being made.

References


Acknowledgment

The authors thank Dr. M.E. Attema-de Jonge for her valuable contribution in critically reading and editing the manuscript.
Acetazolamide induced hyperammonaemia: a case report and review of the literature

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Keywords – Acetazolamide induced hyperammonaemia, metabolic alkalosis

Abstract
Nonhepatic hyperammonaemia is a rare disorder in the ICU. We describe a patient who developed hyperammonaemia after the administration of acetazolamide. Acetazolamide is a frequently used drug in the ICU for the correction of metabolic alkalosis. Acetazolamide-associated hyperammonemia may develop due to interference with the breakdown of ammonia through the urea cycle and through inhibition of the renal excretion of ammonia. Possible treatment options for hyperammonemia have been reviewed. Although the frequency of acetazolamide-induced hyperammonemia is unknown in ICU patients, it is a condition that must be considered when patients treated with acetazolamide show unexplained changes in consciousness.

Introduction
Metabolic alkalosis is a common acid-base disorder in ICU patients and is associated with adverse cardiovascular, pulmonary and metabolic effects.1-3 By increasing the excretion of bicarbonate, acetazolamide might facilitate discontinuation from mechanical ventilation. Acetazolamide is frequently used in the ICU, and is generally considered to have a favourable safety profile. We describe a patient with severe and recurrent hyperammonaemia upon administration of acetazolamide. We further discuss the literature regarding the underlying mechanisms and treatment options for this condition.

Case
A 73-year-old man was transferred from another hospital to our ICU for analysis of difficult weaning after multiple thoracotomies for pleural empyema. He had a medical history of myocardial infarction, coronary artery bypass surgery with diminished left ventricular function and chronic renal failure with an endogenous creatinine clearance of 60 ml/min. Upon admission, a CT scan of the chest revealed pleural effusions with multiple loculations and adhesions and the patient underwent a rethoracotomy for evacuation of the infected material. During his ICU stay, he developed generalized oedema and was treated with furosemide which resulted in a metabolic alkalosis with a bicarbonate of 44.9 mmol/l. Acetazolamide in a dose of 500 mg daily was started for correction of the alkalosis and to facilitate weaning. On the third day after the start of acetazolamide, his level of consciousness gradually decreased from alert and communicative to stuporous without signs of lateralization. Laboratory analysis revealed a high blood ammonia concentration of 110 µmol/l without signs of liver failure. At that point in time his renal function temporarily decreased to an endogenous creatinine clearance of 37 ml/min. There were no signs of portal hypertension. Because no other medication could be implicated, acetazolamide was stopped and the patient was treated with lactulose to decrease the production and absorption of ammonia in the intestine. The patient regained his normal consciousness after the ammonia level had decreased to normal values in the days that followed. After two weeks, acetazolamide was recommenced in a dosage of 500 mg/day. Again the ammonia concentration increased from 39.9 to 60.4 µmol/l, with no signs of liver or kidney failure. During both episodes, no other metabolic derangements were found that could explain his decreased level of consciousness. After cessation of the acetazolamide and treatment with lactulose, the ammonia concentration decreased and his level of consciousness returned to normal. Ultimately, after 62 days on our ICU, active treatment was withdrawn because of persistent weaning failure.

Discussion
Ammonia is continuously produced during normal metabolism, mainly in the gut, as a by-product of protein digestion and bacterial metabolism. Smaller amounts of ammonia are produced in the kidney, where it is essential for the maintenance of the normal acid-base homeostasis. Ammonium is synthesized in the proximal tubule where
it facilitates the renal excretion of H+ ions. Plasma concentrations of ammonia in the systemic circulation are low, due to an efficient detoxification and elimination process. Hyperammonaemia develops if the ammonia load is high, if portal blood from the intestines bypasses the liver or when there are disturbances in the normal urea cycle. Hepatic failure is the most common cause of acute severe hyperammonemia in adult ICU patients. Non-hepatic hyperammonaemia is a less recognized cause of hyperammonaemia in ICU patients. It can result from increased ammonia production that exceeds the liver’s excretory capacity, resulting for instance from increased protein metabolism as seen after gastrointestinal haemorrhage and steroid use. Ammonia production can also increase after infection with urease splitting bacteria or after urinary diversion when (urease-producing) bacteria in the colon degrade the nitrogenous compounds excreted in the urine with formation and adsorption from ammonia into the systemic circulation. Decreased ammonia elimination is caused by portosystemic shunting, or interference with the normal urea cycle. Ammonia is metabolized in the liver to urea through the urea cycle. This hepatic urea synthesis is controlled by a large number of enzymatic processes and is important for both the removal of the toxic ammonium ions and for the removal of bicarbonate.

Acetazolamide may induce hyperammonaemia in two ways. First, carbonic anhydrase activity is essential for hepatic urea synthesis from ammonium ions. Carbonic anhydrase inhibitors such as acetazolamide can inhibit this urea synthesis. This inhibition of urea synthesis occurs proximally in the urea cycle, at a step prior to citrulline formation, thus causing hyperammonaemia. Acetazolamide can also interfere with the normal production and excretion of ammonia from the kidney. Normal kidney cells produce free ammonium ions that are either excreted into the urine or released into the renal vein. The release of ammonia into the renal vein represents a major source of the normal ammonia concentration in blood. Acetazolamide acts through changes in the acid-base balance and by a direct effect on the kidney. The total amount of ammonia produced by the kidney and its partition into the renal vein or the urine is modified in response to the acid–base balance, potassium status and kidney function. Acidosis induces an increase in the total kidney ammonia production and a significant rise in the urinary excretion of ammonia. In contrast, metabolic alkalosis is associated with a marked reduction in urinary ammonium excretion and a rise in the ammonium released into the kidney’s venous blood. In the kidney, carboxic anhydrase is located on the brush border of the tubular cells, where it promotes hydrogen ion loss and reabsorption of bicarbonate. Acetazolamide mainly acts on the proximal tubule of the kidney and induces a metabolic acidosis by inhibiting bicarbonate re-uptake. Acetazolamide also reduces the urinary excretion of ammonium by shifting the ammonia from the urinary compartment to the renal vein, thus further contributing to the hyperammonaemia – as seen in our patient. As acetazolamide is mainly excreted by the kidney, patients with renal failure are at risk for acetazolamide accumulation resulting in hyperammonaemia.

Untreated hyperammonaemia can result in encephalopathy, brain oedema and intracranial hypertension, with high morbidity and mortality rates in ICU patients. Ammonia is metabolized by astrocytes to form glutamine. Increased intracellular glutamine concentrations act as an active osmolyte causing movement of water into the astrocytes, inducing swelling of the astrocytes and brain oedema. Ammonia also changes GABA-mediated neurotransmission which reduces the normal level of consciousness. During the course of hyperammonaemic encephalopathic neuroinflammatory processes, disruption of the blood-brain-barrier and oxidative stress may also contribute to the brain damage.

The first step in the treatment of hyperammonaemia is the identification and correction of the precipitating cause. Laxatives such as lactulose and other non-absorbable disaccharides are generally used as first line treatment in most institutions. Scientific evidence for the use of non-absorbable disaccharides is poor. One systematic review found no significant effect of non-absorbable disaccharides on acute or chronic hepatic encephalopathy when compared to placebo. Antibiotics such as vancomycin and neomycin reduce ammonia absorption from the gut by decreasing bacterial ammonia production in the intestinal tract and can be used as
Acetazolamide induced hyperammonaemia: A case report and review of the literature

Acetazolamide is a frequently used drug that may induce hyperammonaemia by interfering with the urea cycle and renal ammonium handling. Hyperammonaemia must be considered in ICU patients with unexplained changes in consciousness who are treated with acetazolamide.

REFERENCES

Abstract

ICU admission due to serotonin syndrome (SS) is well described in the literature. However, development of SS during ICU admission has not been reported to date. We present a patient in whom SS was suspected during ICU admission. SS may be induced by either increased serotonergic activity or by lowering the cerebral serotonin sensitivity threshold. SS is not easily recognized, especially in ICU populations because it can easily be confused with clinical deterioration or other drug-related toxidromes. SS is a potentially fatal clinical syndrome, which requires rapid diagnosis and timely treatment. This case demonstrates the need to consider SS in the differential diagnosis of ICU patients with unexplained hyperthermia and signs of autonomic dysregulation, who are treated with serotonergic active medication.

Introduction

Serotonin syndrome (SS) is a potentially life-threatening condition caused by absolute or relative serotonergic overstimulation in the central nervous system. SS may be induced by either increased serotonergic activity or by lowering the cerebral serotonin sensitivity threshold. Diagnosing SS depends on clinical observation since laboratory analysis and imaging do not provide the specific information needed for this condition. Symptoms can vary widely, but include changes in mental status and behaviour, motor system changes and autonomic instability, including hyperthermia. SS symptoms show overlap with symptoms found in neuroleptic malignant syndrome (NMS), sepsis and delirium. Diagnosing serotonin syndrome during an intensive care unit (ICU) admission is even more challenging, because crucial symptoms may be lacking (e.g. absence of muscle rigidity and hyperreflexia in cases of critical illness polyneuromyopathy) or mistaken for clinical deterioration. Correct and timely diagnosis followed by rapid treatment, however, is crucial, since a significant proportion of SS cases (17%) lead to a worse outcome, with a mortality rate of up to 0.2%. SS is mostly seen as a result of inadvertent interactions between serotonin-active drugs and/or intentional self-poisoning. We describe a patient who was suspected of SS during ICU admission, whilst continuing a medication regime that included citalopram and amitriptyline.

Case report

A fifty-five year old somnolent male was admitted to the Department of Internal Medicine of a large academic teaching hospital in the Netherlands. The patient was admitted with a suspected recurrent gastrointestinal perforation and intentional opioid overdose. The patient’s psychiatric history revealed long-term alcohol abuse, generalized anxiety disorder, recurrent depressive disorder, auto-mutilation and several attempts of intentional self-poisoning. His medical history indicated circular colonic ulcers (due to abuse of non-steroidal anti-inflammatory drugs), insulin dependent diabetes mellitus, hypertension and asthma. Earlier in the same year, the patient had been admitted to the ICU on two separate occasions, due to severe community acquired pneumonia (CAP) and abdominal sepsis as a result of gastrointestinal perforation.

Medications upon admission consisted of amlodipine 10 milligrams once daily, metoprolol 50 milligrams twice daily, pantoprazol 40 milligrams twice daily, citalopram 20 milligrams three times daily, amitriptyline 50 milligrams three times daily, oxazepam 10 milligrams twice daily, ferrous fumarate 200 milligrams three times daily, vitamin B complex forte once daily, morphine 10 milligrams four times daily and novo rapid. No allergies were reported.

Prior to ICU admission, the patient was treated with naloxone, resulting in mild recovery of his somnolent status. Psychotropic drugs were continued, based on the pre-admission dosing.
regimen. Additional investigations showed no signs of gastrointestinal perforation. Worsening of the hypoxaemia, however, despite maximal oxygen therapy, required ICU admission for the third time in one year. After endotracheal intubation, mechanical ventilation was initiated. The chest X-ray showed consolidation of the left lower lobe. Recurrent CAP was suspected and treated with ceftriaxone 2 grams once daily and ciprofloxacin 400 milligrams twice daily was initiated. During the first week of his ICU stay, the patient suffered from refractory bronchospasm, requiring muscle relaxation and permissive hypercapnia. The patient then showed signs of intrapulmonary shunting and was made a computed tomographic (CT) scan of the pulmonary arteries was made, showing a massive pulmonary embolism in the right pulmonary artery. The prophylactic dose of dalteparin was increased to a therapeutic one. After two weeks of respiratory support, the patient’s clinical condition improved. As a result of severe muscle weakness, a percutaneous tracheostomy was performed. Despite low inflammatory markers (8*10^6 leukocytes /ml and C-reactive protein (CRP) 30 mmol/l), the patient developed a persistent fever up to 40 degrees Celsius, in combination with refractory hypertension, tachycardia, agitation and anxiety. Biochemical analysis showed a hyponatremia (131 mmol/L), most probably caused by the syndrome of inappropriate antidiuretic hormone secretion. Three weeks after ICU admission, the patient experienced an episode of clonic seizures. A CT scan of the brain revealed no abnormalities. Delirium, NMS, SS, anticholinergic syndrome (ACS) and viral meningitis were considered in the differential diagnosis. The Naranjo scale was used to estimate the probability of an adverse drug reaction (ADR) due to serotonin-active drugs. The Naranjo scale is a ten-item questionnaire designed for determining the likelihood of whether an ADR is actually due to the drug rather than the result of other clinical factors. Probability is assigned via a score termed definite (>9 points), probable (5-8 points), possible (1-4 points) or doubtful (0 points). The Naranjo score in our case was 5 points, which does not actually prove the patient’s clinical condition was caused by an adverse reaction of a combination of citalopram and amitriptyline, but made a SS very likely. Citalopram was withdrawn, the amitriptyline dose was gradually tapered off and oxazepam 50 mg three times daily was initiated. Serum concentrations of amitriptyline, nortriptyline, citalopram and desmethylicitalopram were low (21 μg/ml, <10 μg/ml, 15 μg/ml and < 10 μg/ml respectively). No other serotonergic medication was initiated during ICU admission. Twenty-four hours after withdrawal of citalopram, the patient’s agitation and anxiety diminished significantly. Hypertension, tachycardia and hyperthermia declined progressively, and returned to normal within the next six days. Seven days after the first suspicion of SS, the patient had completely recovered and could be transferred back to the Department of Internal Medicine.

Discussion
Serotonin syndrome is a complexity of symptoms which is probably caused by changes in the sensitivity of the serotonin receptor system in the brain stem and spinal cord. SS is mostly caused by a combination of serotonin-active drugs, resulting in serotonergic overstimulation (table 1). However, case reports of selective serotonin reuptake inhibitor (SSRI) poisoning, have indicated that severe toxicity can occur and deaths have been reported following massive single ingestions, although this is exceedingly rare. The exact incidence of SS is unknown due to a lack of good quality studies. Mackay et al., estimated the incidence of SS for nefazodone at 0.4 per 1000 users, SS is therefore marked as an uncommon disorder. Eighty-five percent of general physicians are not aware of its existence. In addition, in the absence of specific laboratory tests and imaging characteristics, SS can only be diagnosed by clinical observation and might therefore be easily overlooked. The incidence of SS may become more significant with the increasing prescription of antidepressants in general and SSRIs in particular.

The main indication for prescribing SSRIs is major depression. SSRIs are, in addition, frequently prescribed for anxiety disorders, eating disorders, chronic pain, posttraumatic stress disorder and depersonalization disorder. Serotonin-active drugs are not regularly prescribed in the ICU department. Intensivists have therefore little experience with the serious side effects of these drugs. In addition, diagnosing SS in an ICU population is hampered by the clinical condition of the patient, for instance, absence of muscle rigidity and hyperreflexia in

Table 1. Serotonin-active drugs.

<table>
<thead>
<tr>
<th>Class</th>
<th>Drugs</th>
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</thead>
<tbody>
<tr>
<td>Antidepressants</td>
<td>MAOIs (e.g. tranylcypromine, moclobemide), TCAs (e.g. amitriptyline, nortriptyline), SSRIs (e.g. citalopram, paroxetine), SNRIs (duloxetine, venlafaxine), bupropion, nefazodone, trazodone, lithium</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>risperidone, olanzapine, quetiapine, aripiprazole, ziprasidone</td>
</tr>
<tr>
<td>Opioids</td>
<td>tramadol, pethidine, fentanyl, pentazocine, buprenorphine, oxycodone, hydrocodone, meperidine</td>
</tr>
<tr>
<td>CNS stimulants</td>
<td>phentermine, diethylpropion, amphetamine, sibutramine, methylphenidate, methamphetamine, cocaine</td>
</tr>
<tr>
<td>Antimigraines</td>
<td>triptans (e.g. sumatriptan, rizatriptan, zolmitriptan)</td>
</tr>
<tr>
<td>Psychodelics</td>
<td>MDMA, MDA, 5-Methoxy-diisopropyltryptamine, LSD, (S)-ketamine</td>
</tr>
<tr>
<td>Anti-emetics</td>
<td>ondansetron, granisetron, metoclopramide, erythromycin</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>L-Dopa, valproate, buspirone, linezolid, dextromethorphan, chlorpheniramine, ritonavir</td>
</tr>
</tbody>
</table>

MAOIs: mono-amino-oxidase inhibitors, TCAs: tricyclic antidepressants, SSRIs: selective serotonin reuptake inhibitors, SNRIs: selective norepinephrine reuptake inhibitors, MDMA: 3,4-methylenedioxymethamphetamine (Ecstasy), MDA: 3,4-methylenedioxymethamphetamine, LSD: lysergic acid diethylamine, L-dopa: levodopa.
cases of critical illness polynuromyopathy. Underdiagnosing SS in the ICU-setting might therefore be a significant problem. In our case, the patient was prescribed a combination of high dose citalopram (an SSRI) and amitriptyline (a tricyclic antidepressant (TCA)) for severe generalized anxiety disorder. Either combining proserotoninergic drugs (as in this case citalopram and amitriptyline) or adding co-medication involved in inhibiting their metabolism, may result in SS.22 Case reports have even shown SS with monotherapy of low dose citalopram or normal dose amitriptyline.23,24 Since serum levels of citalopram and amitriptyline were low and metabolic interacting drugs (ciprofloxacin) had been stopped long before the onset of symptoms, SS in this case was probably caused by an altered level of the cerebral serotonin sensitivity threshold. Although the most plausible diagnosis for symptoms occurring three weeks after ICU submission was SS, the differential diagnosis is much more extensive. Table 2 shows a practical guide to help differentiate psychotropic drug-related disorders from more common ICU related syndromes (e.g. sepsis and delirium).25-29

We would like to point out that SS should be included in the differential diagnosis in ICU patients who use serotonergic active medication and present with unexplained hyperthermia and signs of autonomic dysregulation.

**Conclusion**

Diagnosing SS in ICU populations is challenging because the syndrome is relatively unknown, diagnosis depends solely on clinical observation and the clinical condition of ICU patients often means that symptoms are suppressed. The recognition

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**Table 2. Symptoms of psychotropic drug-related disorders and common intensive care related syndromes.**

<table>
<thead>
<tr>
<th></th>
<th>Del.</th>
<th>NMS</th>
<th>SS</th>
<th>ACS</th>
<th>SI</th>
<th>MH</th>
<th>MG/EC</th>
<th>Sepsis</th>
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</thead>
<tbody>
<tr>
<td><strong>Autonomic disturbances</strong></td>
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<td>Tachycardia</td>
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<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
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<td>-</td>
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<tr>
<td>Diaphoresis</td>
<td>+/−</td>
<td>+</td>
<td>+</td>
<td>−</td>
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</table>

*: likely manifestation, +/-: possible manifestation, −: unlikely manifestation
* antipsychotic agents (e.g. haloperidol)
** increased white blood cell count, elevated creatine phosphokinase, and decreased serum bicarbonate concentration.
of SS, however, is crucial because if it goes unrecognized it can lead to elevated morbidity and mortality. Changes in pharmacodynamics and pharmacokinetics in ICU populations may probably render patients more susceptible to SS. We would like intensivists to increase their awareness of SS in patients who continue to be given serotonergic active drugs. We advise consulting a psychiatrist and a clinical pharmacist in cases where serotonin-active drugs are prescribed, to discuss the risks, benefits, continuation or withdrawal of this type of medication on an individual basis.30,31

References

Clinical fluid therapy in the perioperative setting

Edited by Robert Hahn

Given that both hypoperfusion of organs as well as fluid overloading greatly affect a patient’s postoperative course, careful titration of fluids is mandatory. However, due to a lack of scientific data, controversies about the amount, type and goal of fluid therapy remain. In this book of 21 chapters, which are all narrative reviews, some of these issues are discussed.

A rule of thumb is given as to how much fluid should be infused in several types of surgery, including orthopedic, gastrointestinal and vascular surgery. Open surgery requires a larger amount than laparoscopic procedures. Most research in major abdominal surgery has focused on restrictive vs. liberal fluid therapy. The summary of results seems to favour a more restrictive approach.

Several meta-analyses are discussed on the choice of crystalloids or colloids as the preferred type of fluid for the perioperative patient. It is noted that dextran reduces haemostatic potential and starches can induce anaphylactic reactions. Otherwise, no definite directions as to which type of fluid should be used is given. Of note, the literature discussed in this book does not include recent trials which have compared starches with crystalloids in several patient populations, which mostly show a higher mortality in patients resuscitated with starches.

The goal of fluid infusion is to maintain ‘adequate tissue perfusion’, but how this goal should be reached is not clear. Goal directed therapy can include non-invasive analysis of arterial or pulse oximetry wave forms or invasive monitoring of cardiac output with a pulmonary artery catheter or echocardiography. Using these techniques to guide the amount of fluids seems to reduce morbidity in high risk surgical patients, but their implementation is still a challenge.

Several other patient conditions are also discussed in this book. For example, it is noted that the tolerance to acute haemodilution due to blood loss is high. Although the choice of resuscitation fluids is also not clear in this setting, it is generally agreed that blood transfusion can often be avoided. This does not hold true for uncontrolled haemorrhage, in which fluids contribute to further haemodilution. In this case, blood products may be a reasonable alternative.

Besides suggestions for clinical practice perioperatively, the book provides background information on the principles of cardiac output measurements as well on the physiology of body fluid compartments and fluid compositions, which are of interest to any doctor who prescribes fluid therapy to patients.

N.P. Juffermans
# Conferences

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<th>Date</th>
<th>Event</th>
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<td>CRRT 2014 – the 19th International Conference</td>
<td>San Diego, California</td>
<td>E-mail: <a href="mailto:nicole@res-inc.com">nicole@res-inc.com</a> <a href="http://www.crrtonline.com">http://www.crrtonline.com</a></td>
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<td></td>
<td>Acute Kidney Injury: Controversies, Challenges and Solutions</td>
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<td>13-14 March</td>
<td>VIC Echografiecursus</td>
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<td>18-21 March</td>
<td>34th International Symposium on Intensive Care and Emergency Medicine</td>
<td>Brussels Meeting Center (Square)</td>
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<td>3-4 September</td>
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<td>18-19 September</td>
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<td>27 September – 1 October</td>
<td>LIVES 2014, the 27th ESICM Annual Congress</td>
<td>Barcelona, Spain (CCIB)</td>
<td><a href="http://www.esicm.org/events/next-congress/sthash.mKg9FHCV.dpuf">http://www.esicm.org/events/next-congress/sthash.mKg9FHCV.dpuf</a></td>
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<td>17-18 November</td>
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Editorial board changes

In keeping with the idea that the leadership for the Netherlands Journal of Critical Care should change after a few years of service, we have decided to change the members of the editorial board a little. Obviously, we wholeheartedly thank the board members so far who have spent some of their precious time in guiding the journal’s review process and in helping the journal to take shape. The contributions of these members has been very valuable. We would like to welcome the new members and hope they will show enthusiasm for making future improvements to the journal including an on line submission system and wider indexing.

Graag nodigen wij uw intensivecareafdeling uit om deel te nemen aan een kwaliteitsvisitation in 2014. Voor beschikbare data en aanvullende informatie kunt u contact opnemen met het NVIC secretariaat via e-mail: secretariaat@nvic.nl, of per telefoon: 030-6868761.
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.

**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.


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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.”
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

¹ Productinformatie: zie elders in deze uitgave, 11-MMC-03
² Productinformatie: zie elders in deze uitgave, 11-MMC-03
How to submit
Submit manuscript directly to: Editorial office e-mail: nethejcritcare@nvic.nl

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

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tion is subject to copyediting. The original manuscript will be dis-
carded 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
mislaking statements.
For guidelines on the NJC’s house style see website

General guidelines on house style
• The title of manuscript should be in typeface Times New Roman,
size 12.
• 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 held 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, oestra-
diol, anaemia, haemorrhage, osseous, practice (noun), practise
(diary), fetus. This should be used consistently. Use a-spellings, e.g.
minimise, organization (Oxford spelling).
• Do not use exclamation marks except in direct quotes from other
sources.
• Non-full stops in initials, abbreviations and academic titles.
• Reference numbers go after commas and full stops, before semeio-
tons and colons.
• Quotation marks – please use double, not single, inverted commas
for reported speech. Full stops go inside quotation marks.
• Date names should be in italics, e.g. Staphylococci aureus, S.
aureus.
• Numbers under 10 are spelled out except for measurements with a
unit (10 mmol/l or age 16 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.

Guidelines on writing style for Dutch-speaking authors
• Following English language convention prof. dr. should be written as Professor.
• The gender of an author is not specifically reported. Do use Ms
or Mrs in front of Professor or Doctor.
• Spell check your article before submission using UK English (refer-
ences keep original spelling).
• Abbreviating names. Use initials only J Smit not Job Smit.
• 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-propio-
tary 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 detract-
ing from its meaning. The Dutch convention of using brackets to
contain information crucial to the sentence should not be applied,
e.g. (immun) histology should be written as immunohistology and
histology, latex sterile gloves as sterile or unsterile gloves.
• Apostroph. In English the apostrophe is used to indicate posses-
sion 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.
“By 98% werd technisch adequate uitoefening 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.
• ± is a mathematical symbol and should not be used in a non-math-
ematical context to mean approximately or about.
• Generally, organizations and groups of people take single verbs, e.g.
the team has researched.

Table of abbreviations

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<td>ARDS</td>
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<td>acute physiology and chronic health evaluation</td>
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<td>arterial blood pressure</td>
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<td>systemic inflammatory response syndrome</td>
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<td>TIA</td>
<td>transient ischemic attack</td>
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<td>TRALI</td>
<td>transfusion-related acute lung injury</td>
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</table>

NOTEER ALVAST IN UW AGENDA!
Wereldwijd meer dan 1 miljoen patiënten met Mycamine behandeld!¹

Hoog gebruiksgemak
• Geen significante drug-drug interacties²
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Voor alle leeftijden (0-99)²