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Anticoagulation therapy during ECMO: Scylla and Charybdis

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Keywords - ECMO, anticoagulation, bleeding, thrombosis

Extracorporeal membrane oxygenation (ECMO) has been widely accepted for life-threatening cardiac or pulmonary failure, even when occurring due to a cardiac arrest. Managing anticoagulation during ECMO is still challenging. The Extracorporeal Support Organisation (ELSO) database contains almost 90,000 ECMO runs, including almost 30,000 adults.[1] Of these ECMO runs, 16% are associated with thrombotic complications (pump malfunction, oxygenator clotting, infarction of the central nervous system (CNS) of the patient).[1] Of the reported ECMO runs, 40% are complicated by haemorrhagic events, such as haemorrhage of the gastrointestinal tract, surgical site bleeding, cannula site bleeding, pulmonary haemorrhage, or CNS haemorrhage.[1] CNS haemorrhage or CNS ischaemia occurs in approximately 6-10% of the ECMO runs.[1]

In this issue of the Netherlands Journal of Critical Care, Lancé and co-workers provide an excellent outline of anticoagulation management during ECMO.[2] This review describes why anticoagulation management differs in ECMO patients compared with other patients on the ICU who need anticoagulation. Also anticoagulation practice and anticoagulation monitoring is extensively described. As noted by the authors, there is still much debate on the optimal monitoring strategy during ECMO. Unfortunately, no randomised controlled trials have been performed to investigate the best anticoagulation strategy for ECMO patients. A concept for managing anticoagulation during ECMO is provided. The authors propose a safe sailing course between clotting and bleeding, guided by multiple parameters of haemostasis. In ECMO, no single parameter, including the activated partial thromboplastin time (aPTT), predicts clotting risk and/or bleeding risk.[3,4] Inflammation may shorten aPTT and consumption coagulopathy may prolong aPTT, which may lead to misinterpretation of heparin effects. Internationally, a growing number of centres use a multimodal approach, acknowledging the multifactorial process of anticoagulation, which is not captured by aPTT alone. This multimodal approach, however, is not based on evidence, but on expert opinion, as discussed in an expert round table conference in Rotterdam in 2016. Lancé et al. describe a multimodal approach to anticoagulation during ECMO that entails daily monitoring of multiple coagulation parameters. These tests include aPTT, aXa, platelet count and thromboelastometry (ROTEM®, including EXTEM, INTEM, FIBTEM and HEPTEM tests). In a patient with a normal bleeding and thrombosis risk, aXa levels would usually be maintained between 0.5-0.7 IU/ml, with a difference in clotting time between INTEM and HEPTEM of approximately 80 sec. This should correspond with an aPTT of approximately 60 sec. In a practical example, when aXa is 0.3 IU/ml, the clotting time difference between INTEM and HEPTEM is 30 sec, aPTT is 70 sec and platelet counts are declining, consumption coagulopathy could be suspected, perhaps due to heparin under-dosing. Then, despite elevated aPTT, increasing the heparin dose could be the appropriate therapeutic intervention. This example illustrates how monitoring of only the aPTT could lead to misinterpreting the coagulation status. As it is unpractical to monitor the whole anticoagulation status every six hours, usually the whole package is monitored once a day. After interpreting all the anticoagulation parameters, a new target aPTT is set and monitored every six hours, for the next 24 hours.

For monitoring of the coagulation status of the ECMO machine, D-dimers, fibrinogen and free haemoglobin concentration are measured. D-dimers >30 g/l for more than two days,[5] decrease of fibrinogen >50% or <1 g/l or a free haemoglobin concentration greater than 50 μmol/l could be an indication of clotting in the oxygenator or of an imminent blood clot in the pump head. The level of anticoagulation is dependent on many factors. Patients with high bleeding risk (for example trauma or postoperative patients) are maintained at a lower level of anticoagulation, whereas patients with a high thrombosis risk
(for example pulmonary embolism) are maintained at a higher level of anticoagulation. Ideally, bleeding risk or thrombosis risk is assessed on a daily basis. Anticoagulation should be achieved by the effect of heparin. Prolonged coagulation tests should be due to the effect of heparin, and not to a shortage of coagulation factors or an excess of anticoagulation proteins. The ECMO system also determines the anticoagulation threshold. Low ECMO flow or ECMO system characteristics may warrant adjustment of the targeted anticoagulation level. Of note, cannulas have been shown to cause endothelial trauma, leading to endothelial thrombosis resulting in occlusion of the inferior caval vein.\[6\]

Coagulation on ECMO is an evolving area, in which evidence is lacking. Most of the strategies are based on expert opinion. Although the review provided by Lancé and co-workers adds to the understanding of anticoagulation strategies during ECMO, much more research is needed, contributing to further improvement of outcome of ECMO therapy.

References

ECMO and anticoagulation: a comprehensive review

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Abstract
Since the last decade extracorporeal membrane oxygenation (ECMO) therapy has been widely accepted as the treatment of life-threatening cardiac and pulmonary failure. Maintaining homeostasis of the haemostatic system remains a major challenge. The choice of anticoagulants to inhibit continuous activation of coagulation by the non-endothelialised systems is still restricted. The most widely used agent is intravenous unfractionated heparin. Although one might expect monitoring of the anticoagulant level to be straightforward, the number of bleeding or thrombotic complications is still too high.

In this review, we report the impact of an extracorporeal circuit on the coagulation system and its complications. We describe the strategies for anticoagulation and possibilities of monitoring their effects. Finally, we give a view of the future developments in this specific field.

Introduction
Currently used extracorporeal circuits such as renal replacement therapy and extracorporeal membrane oxygenation (ECMO) – also called extracorporeal life support (ECLS) – belong to the standard therapy in the critically ill patient. These are prolonged forms of cardiopulmonary bypass (CPB), which derives from cardiac surgery where this method is used to maintain cardiac and respiratory function during cardiac surgery. However, there are several major differences between the techniques of which the duration of their use seems to be the most important. While CPB is commonly used for several hours, ECMO application lasts for up to several weeks.[1] The indication for ECMO covers different situations of heart failure and pulmonary failure which have been established for adults during the last decade. Particularly the use of venovenous (VV) ECMO for respiratory support has increased since the H1N1 pandemic in 2009 and reached a peak in 2012.[2] On the other hand, the incidence of venoarterial (VA) ECMO for circulatory support has shown a tremendous increase since 2013. Nevertheless, mortality levels during ECMO use remain high at 58% for VV-ECMO and 66% for VA-ECMO.[3]

As with any other artificial system, ECMO exposes the blood to a huge endothelial-free, foreign surface, which stimulates inflammation and coagulation, leading to a pro-thrombotic state. Many attempts have been made with anticoagulant medication to counteract coagulation activity, the most common practice being the use of unfractionated heparin (UFH) as a continuous infusion.

From a technical viewpoint, the development of modern hollow fibre oxygenators, biocompatible coatings for the tubing and oxygenators may decrease activation of coagulation. In addition, attempts to reduce the size of the system and thus the surface and applying high blood flow with a low chance of blood stasis are important developments.[4]

Nevertheless, the underlying disease also influences the haemostatic capacity. Due to this continuous activation, the coagulation eventually leads to exhaustion of platelets and coagulation factors, which could turn haemostasis into a bleeding tendency. This phenomenon is known from sepsis as slow disseminated intravascular coagulation (DIC).[5] On the other hand, it is known that inflammatory processes such as sepsis or autoimmune diseases, but also pregnancy and trauma, shift the haemostatic system to a hypercoagulable state which could result in thrombosis.

The aim of the current paper is to give an overview of the changes in the coagulation system, the current practice of anticoagulation, and its monitoring possibilities in the adult ECMO population. Finally, we review the haemostatic complications, such as thrombosis and bleeding, and future perspectives in this field.
Changes in the coagulation system

Shortly after blood comes into contact with the artificial surface of the CPB circuit, blood proteins, mainly albumin and fibrinogen, will stick to it. Over time, thrombospordin, fibronectin, von Willebrand factor (vWF) and even immunoglobulin E bind to the surface material. This protein layer serves as an anchor for platelets. Furthermore, platelets interact with vWF, which is activated by the high shear stress and aberrant flow pattern. Activated platelets bind via the GPIIb/IIIa receptors to the fibrinogen deposit. These activated platelets initiate coagulation by exposing tissue factor and coupling to factor VIIa (FVIIa). This is the initiation of coagulation as we understand it today, leading to activation of FX and finally resulting in a thrombin burst and conversion of fibrinogen to soluble fibrin, which will be transferred to an insoluble fibrin network by FXIIIa. Besides the coagulation system, the fibrinolytic system will be triggered to keep clot formation localised. This is reflected by the increasing D-dimer levels, which slowly rise over time. During a short-term two-hour contact with the CPB circuit nearly all the coagulation factors show reduced levels, except for FIX, which remains stable. Interestingly FVIII and vWF increase 24 hours after weaning from the circuit.

On the other hand, the contact activation system consisting of FXII, FXI, high-molecular-weight kallikrein (HMWK) and prekallikrein (PK), are activated by the foreign surface. FXII attaches to this surface and is converted to FXIa, which cleaves PK to release kallikrein. In turn, kallikrein splits bradykinin from HMWK. This system will activate coagulation by the intrinsic coagulation cascade, the immune response by the complement system and an inflammatory reaction by the kallikrein system, which also activates the fibrinolytic system. This crosstalk of coagulation and inflammation could cause vascular leakage and vasoplegic syndrome, which clinically can be seen as hypotension not responding to vasoactive drugs. Next to the pro-thrombotic state due to platelet and contact activation, the pro-inflammatory response, as described above, induces leukocyte, neutrophil, and monocyte involvement within the first 30 minutes after initiation, peaks within hours and then tapers down. The cells attach to the surface of the circuit and release their cytokines, including TNF-alpha and interleukin 6. The endothelial cells are again triggered to stimulate tissue factor (TF) generation and consequently contribute to thrombin formation via the FVII mediated extrinsic pathway.

Inevitably, some of the erythrocytes undergo haemolysis by extracorporeal circulation, resulting in free haemoglobin. In turn, free haemoglobin enhances the platelet-vWF interaction and promotes coagulation. Continuous activation of the coagulation system during ECMO therapy leads to consumption of coagulation factors and platelets. Indeed, many authors report a sustained drop in the platelet count of between 25-40% without signs of heparin-induced thrombocytopenia. Nonetheless, the low platelet count is not related to the duration of ECMO treatment but more to the pre-existing disease and platelet count before cannulation. Of note, the platelet count does not necessarily correspond with platelet function. Several papers have described deteriorated platelet function, due to ADP-receptor dysfunction in patients who were on CPB. Nevertheless, normal platelet function will be restored after discontinuation of the support. During ECMO application, platelets lose some of their receptors such as glycoprotein Ib (GPIb) and glycoprotein VI (GPVI), which are responsible for interaction with vWF (GPIb) and collagen (GPVI). While GPIb together with the reduced amount of large molecule vWF explain the acquired vWF syndrome, the reduction of collagen receptor activity contributes to the bleeding tendency in general. However, the relevance of acquired vWF syndrome which is mainly related to long-term use such as assist device implantation, is unclear. The association of acquired vWF syndrome with bleeding seems more clear in assist devices, which have different flow characteristics. Kalbhenn and co-workers showed in their cohort of 49 patients that 88% developed FXIII deficiency during the first seven days of VV-ECMO, while 80% developed vWF deficiency. Thrombocytopenia could be seen in only 55% and hypofibrinogenaemia in 40% of their patients. This is in agreement with Tauber and co-workers, who showed a loss of the high-molecular-weight vWF within the first 24 hours after ECMO initiation, which was accompanied by a drop in FVIII naturally protected from clearance by vWF. However, both factors increased to normal after cessation of the ECMO treatment independently of the indication, the route (VV-VA) or the kind of system used.

Independent of the decrease in these pro-haemostatic factors, the natural anticoagulant antithrombin (AT) decreases in the first days in about 50% of the cases, but it then returns to normal in the following period. The initial decrease might be explained by the infusion of UFH which binds to AT as a co-factor to inhibit coagulation. On the other hand, AT deficiency is associated with heparin resistance and a pro-thrombotic state, which might cause thrombotic complications in the first days of ECMO therapy. The levels of other natural anticoagulants, including protein C and protein S, are less well described during ECMO treatment. Currently, one can only reason from studies during CPB where the level of activated protein C increases during and after bypass. The early onset of this reaction has been related to improved haemodynamic stability. There are no reports on levels of protein S, the co-factor of protein C, during or after CPB or EMCO.

Interestingly, one contributor of the endothelial layer to anticoagulation - the glyocalyx - is disturbed by CPB. Koning et al. reported a decrease in the glyocalyx density after initiation of
CPB which sustained until the postoperative period. In contrast, patients undergoing cardiac surgery without CPB treatment (known as off-pump procedures) did not show signs of altered glycocalyx.[16] In ECMO therapy, a decrease in the glycocalyx density might contribute to the heparin-like effect which is described in patients on ECMO, even though these patients were not on heparin infusion. In more than half of the cases, the laboratory parameters show signs of heparinisation in terms of prolonged activated partial thromboplastin time (aPTT) and R-time in the thromboelastography (TEG). However, this report deals with post cardiac surgery patients in whom remaining heparin effects cannot be excluded completely.[17]

**Incidence of haemostatic complications**

The most common complications associated with ECMO are bleeding and thrombosis. Haemorrhage can be associated with an intervention (catheter placement) or with a previous operation. Thrombosis occurs mainly in VA-ECMO after cardiac surgery, due to a huge wound and long operation time combined with massive disturbance of the haemostatic system. On the other hand, exhaustion of the coagulation system and a continuous low level of fibrinolysis can lead to coagulopathic haemorrhage, which is present in 20-33% of the ECMO runs.[16] One contributor to this problem is chronic loss of small amounts of blood which needs replenishment with red blood cells (RBCs). However, this blood loss will be associated with a loss of coagulation factors and platelets. As a result, coagulation tests will show prolonged aPTT and ACT leading to the findings being misinterpreted as a heparin overdose, inducing a reduction of UFH which could end up in acute clotting of the system. Only direct testing of coagulation factor levels or viscoelastic testing is able to distinguish depletion of coagulation factors from heparin effect. Substantial bleeding occurs in more than 30% of the patients on ECMO. Nevertheless, the majority of the cases are non-life threatening (e.g. epistaxis or gastrointestinal bleeding). Of these bleeding events, 5-19% are reported to be life-threatening intracranial haemorrhages.[13] Transfusion of blood products is needed in about 56% according to a recent study.[19] Several authors have identified factors associated with bleeding. The most important factors are surgery prior to ECMO treatment, higher APACHE III score and coagulation abnormalities, while blood group 0 could also be associated with intensified bleeding.[19,20] RBC transfusion is frequently needed. The threshold to administer RBCs is suggested to be between 8 and 10 g/dl, but RBC trigger studies have not been performed in ECMO patients.[14] Likewise, thrombosis can be found in the ECMO system, but also during and more frequently after weaning from the device, presenting as deep vein thrombosis (DVT). Already in 2006, Rastan and co-workers suggested in an autopsy study that the true incidence of thromboembolic complications might be highly underestimated and contribute to morbidity and mortality.[21] It seems that the incidence of thrombosis is inversely related to the level of anticoagulation with the highest incidence in patients without anticoagulation.[22] Acute thrombosis of the oxygenator or tubing occurs in 35% of the cases, and must be followed by changing the system.[23] In contrast, a DVT will frequently be undiagnosed, even during continuous heparin infusion with an adequate aPTT target. In a study by Cooper and co-workers, the authors describe a nearly 20% incidence of DVT after decannulation of which only one patient showed symptoms.[24] In other retrospective analysis on 63 patients the incidence of venous thrombosis was 46%, while a small case series on 10 patients reported an incidence of upper extremity DVT of 80%. [25,26]

**Anticoagulation practice**

To prevent thrombosis in the patient and in particular in the ECMO system, but also to minimise bleeding risks, adequate anticoagulation strategies are indispensable (table 1). Up to the present day, UFH remains the main anticoagulant used for ECMO because of its rapid onset and the easy neutralisation with protamine. This was recently confirmed in a large survey where 96% of the responding centres reported UFH as their anticoagulant of choice.[18] Nevertheless, UFH administration around ECMO entails some caveats. Besides its unpredictable clinical effect, the use of UFH could cause what is known as...
heparin-induced thrombocytopenia (HIT) a life and limb threatening situation occurring in 5% of the patients in which an immediate stop of UFH infusion and switch to alternative anticoagulation strategies is required (e.g. direct thrombin inhibitors [DTIs]). However, the true incidence of HIT seems to be overestimated. In a publication by Glick et al. concerning a cohort of 119 patients undergoing ECMO treatment, the authors reported a clinical suspicion of 19%, with laboratory testing confirming HIT in only one patient.\cite{27}

Regarding the predictability of heparin effects, the negative charged long chains of the high-molecular-weight heparins are also found in UFH. Those chains bind easily to proteins and cellular structures, which explains the unpredictable inter-individual clinical effects reflected in the aPTT. As indicated above, heparin is not a uniform agent but more a mixture of glycosaminoglycans of different sizes and molecule masses. The primary anticoagulant function is based on heparin’s 1000-fold amplifying effect on the protein antithrombin (AT), due to the formation of a heparin-AT complex, which is a direct inhibitor of factor IIa (thrombin) and factor Xa. Further, factor Xa, IXa, and XIIa are inhibited in the same AT-dependent manner but at a much lower level. Immediately after AT is connected to one of the coagulation factors, heparin is dissociated from the complex and available for new AT enhancement. However, the mechanism of action depends on the size of the heparin molecules. The larger they are (such as in UFH), the stronger the interaction with FIIa and FXa. In contrast, the low-molecular-weight heparins (LMWH) bind more effectively to FXa.\cite{28} Although uncommon, there are publications on the use of LMWH to prevent clotting of the ECMO system.\cite{29}

Because of the described AT drop in the first few days after ECMO initiation, many attempts have been made to monitor and replace AT. However, none of the investigations showed benefit of AT replacement in terms of better haemostasis control. The only advantage might be a lower amount of heparin administration.\cite{30} Moreover, ‘heparin resistance’, which might be the target of AT therapy, is not completely attributable to low AT levels, but also depends on high platelet counts, previous heparin use, age above 65 and low haemoglobin levels.\cite{31}

A minority of ECMO centres use parenteral direct thrombin inhibitors (DTI) instead of UFH as their first choice. Mainly argatroban and bivalirudin are used upon indication (e.g. HIT). The main advantage of DTIs is that they bind directly and reversibly to thrombin, independent of AT levels, and they do not induce antibodies against platelets. In contrast to heparin’s antagonist protamine, there is no antidote available for argatroban and bivalirudin. The effects of both agents are mainly controlled by their short half-lives of 40 minutes and 30 minutes, respectively. While the synthetic arginine derivate argatroban is cleared by the liver, the clearance of the hirudin analogue bivalirudin relies on renal function. This is clinically relevant, because in case of impaired hepatic or kidney function, the half-life times will be prolonged resulting in overwhelming anticoagulation and bleeding. In a small retrospective study, Ranucci and co-workers showed that a bivalirudin-based protocol could be safely applied with lesser bleeding and a lower incidence of bleeding complications.\cite{32}

Similarly Sanfilippo et al. showed in a recent meta-analysis in 58 patients that bivalirudin could be safely used. However, these authors mentioned that the dosing protocols and monitoring regimens are highly diverse between the cases.\cite{33}

From a theoretical point of view, platelet inhibition might be useful and it could help in reducing activation of the coagulation, because platelets are the main initiators of coagulation. This could block the consumption of coagulation factors and platelets while enhancing the level of anticoagulation. However, only some smaller studies and case reports are described using this approach with various drugs.\cite{34}

The same holds true for alternative agents including citrate, nafamostat mesilate and FXII inhibitors, which are applied in experimental settings. Citrate anticoagulation is used during renal replacement therapy (RRT), as well as in cases of ECMO combined with RRT as an additional local anticoagulant. There are no studies describing citrate use for ECMO as a sole substance. A quite unknown synthetic serine proteinase inhibitor, nafamostat mesilate, was thought to inhibit coagulation, fibrinolysis and platelet activation with lower bleeding complications. In a published retrospective study comparing nafamostat with heparin, the authors failed to demonstrate this. In contrast, this drug was correlated with more bleeding and no significant difference on the incidence of thrombosis.\cite{35}

Finally, there are institutions which prefer not to use specific therapeutic anticoagulation, but prescribe a low-dose prophylactic LMWH without monitoring or adjusting because of the ECMO use.\cite{36} However, this is mainly the practice in cases of increased bleeding risk, e.g. after major surgery. Keeping in mind that insufficient anticoagulation is associated with higher thrombosis and intra-device clotting risk, a no-anticoagulation strategy cannot be advised as general practice in ECMO.\cite{36}

Monitoring coagulation during ECMO

Interestingly, most of the literature about ECMO covers a wide range of monitoring opportunities to guide and prevent inadequate dosing of the anticoagulants (table 2).

Traditionally, the effect of UFH on coagulation is assessed by aPTT which reflects the classical interpretation of the intrinsic pathway starting with FXII. A prolongation could be due to an acquired or inherited factor deficiency in this chain (FXII, FXI, FXIII, FIX, FX, FII and FV) but in some cases could also be due to other reasons, such as lupus anticoagulant or, of course, a drug effect. After its introduction by Rapaport and co-workers in 1961 it came clear that the assay reflects the intrinsic pathway
In this setting, the activated clotting time (ACT) is the monitoring during cardiac surgery to guide CPB. Plasma which is time consuming and renders it unfit for other hand, in this test the sample needs spinning to produce predictable because of its binding to plasma proteins. On the other hand, in this test the sample needs spinning to produce plasma which is time consuming and renders it unfit for monitoring during cardiac surgery to guide CPB.

In this setting, the activated clotting time (ACT) is the established ‘bedside’ whole blood test. Comparable to the aPTT, the ACT relies on contact activation. Depending on the device there are different activators available (kaolin, celite, glass beads or ellagic acid). Equally to the aPTT, the values may differ, implying similar assay problems as with the aPTT. Likewise, the ACT is also sometimes reported as a ratio (measured value/reference value). In contrast to the aPTT, the ACT is quite insensitive to low UFH dosages which are frequently used in ECMO settings.

Regarding accuracy, the anti-Xa assay seems to be the most reliable. This assay measures the inhibition of activated FX (FXa), the common pathway of the coagulation cascade. However, it is also time consuming and needs separate calibration for each type of heparin (UFH and each of the LMWHs). Similar to the aPTT, the anti-Xa assay underestimates the presence of UFH in case of free haemoglobin or bilirubin in the plasma.[38]

Because of their ability to reflect all aspects of haemostasis, viscoelastic tests (VETs) such as thromboelastography (TEG) or thromboelastometry (ROTEM) could be more informative than standard tests. Use of VETs is currently recommended in the Extracorporeal Life Support Organisation (ELSO) guidelines.[39]

Basically, these tests are based on activators of the classical coagulation cascades (extrinsic-tissue factor/intrinsic-kaolin, ellagic acid), but they also to some degree reflect platelet function as well as the breakdown of the clots, termed fibrinolysis. By adding inhibitors of heparin (heparinase) one can also confirm the effect of that drug by comparing one sample with and one without heparinase.

Although each assay has advantages and disadvantages, there is no consensus in the literature as to which of them is preferable in monitoring coagulation during ECMO therapy. Equipoise is reflected in the ELSO guideline, in which no uniform recommendation is given.[39] Most of the studies compare two tests in small, inhomogeneous cohorts. Activated PTT does not correlate well with ACT nor with anti-FXa. The same holds true the other way round. The explanation for this might be the variability between patients, thrombocytopenia and anaemia. The latter could influence the whole blood test more than the plasma tests, because they are independent of a cellular contribution. Even though viscoelastic tests might be a more accurate reflection of the in vivo conditions than other laboratory tests, the predictive value of the R-time, as the most cited parameter of the VETs, is low, with poor sensitivity and specificity for aPTT.[40] Therefore, many authors recommend a combination of these tests to increase the chance of being in the heparin target range. In recent studies about 11% of the ECMO centres utilised the anti-FXa to guide their heparin regimens and about 42% used the aPTT or the ACT while about 9% used the TEG or a combination of tests.[38,40,41]

Table 2. Monitoring coagulation

<table>
<thead>
<tr>
<th>Standard coagulation tests</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>aPTT (sec)</td>
<td>Well known Monitoring UFH Easy to interpret</td>
<td>Inter-laboratory variance (could be excluded by using ratio) Time consuming</td>
</tr>
<tr>
<td>ACT (sec)</td>
<td>Bedside method Easy to use Immediate results</td>
<td>Relatively insensitive to low doses of UFH Different devices with different reference ranges</td>
</tr>
<tr>
<td>Anti Xa assay (IU/ml)</td>
<td>Sensitive to UFH</td>
<td>Time consuming Needs calibration Free haemoglobin &amp; bilirubin could be underestimated</td>
</tr>
<tr>
<td>VETs (ROTEM/TEG)</td>
<td>Inhibit coagulation at starting point Might reduce platelet consumption</td>
<td>Poor specificity and sensitivity regarding therapy adjustment</td>
</tr>
<tr>
<td>Fibrinogen mg/l</td>
<td>Consumption marker</td>
<td>Increased in inflammatory situations Time consuming</td>
</tr>
<tr>
<td>D-dimer (mg/l)</td>
<td>Prognostic value for oxygenator failure</td>
<td>Time consuming Expensive</td>
</tr>
<tr>
<td>AT (%)</td>
<td>Heparin resistance (partial) Pro-coagulatory marker</td>
<td>Heparin resistance not completely relying on AT</td>
</tr>
<tr>
<td>Haemoglobin (g/dl)</td>
<td>Easy and fast</td>
<td>Not very relevant for coagulation</td>
</tr>
<tr>
<td>Platelet count 10^9/l</td>
<td>Easy and fast</td>
<td>No proven threshold Platelet count does not reflect platelet function</td>
</tr>
</tbody>
</table>

ACT = activated clotting time; aPTT = activated partial thromboplastin time; AT = antithrombin; ROTEM = rotational thromboelastometry; UFH = unfractionated heparin; TEG = thromboelastography; VET = viscoelastic test. of coagulation.[37] Principally this test seems ideal to monitor heparin therapy and in fact it is the current gold standard. However, several disadvantages for this aPTT assay are described. The most important factor seems to be the variability between different laboratories, which is due to the different commercially available reagents, and the use of different devices across the institutions. Also, some diseases interfere with the measurement, e.g. antiphospholipid antibodies (lupus antibodies) prolong the aPTT in most commercial assays while with the measurement, e.g. antiphospholipid antibodies (lupus antibodies) prolong the aPTT in most commercial assays while between different laboratories, which is due to the different commercially available reagents, and the use of different devices across the institutions. Also, some diseases interfere with the measurement, e.g. antiphospholipid antibodies (lupus antibodies) prolong the aPTT in most commercial assays while the patient shows a thrombophilic profile. Moreover, in patients with FXII deficiency, the aPTT will be prolonged without a change in haemostatic competence.

A way to exclude some uncertainties is to calculate the aPTT ratio, which is the measured value divided by the local reference value, which will not detect the effect of antiphospholipid antibodies. However, patient response to UFH is not easily predictable because of its binding to plasma proteins. On the other hand, in this test the sample needs spinning to produce plasma which is time consuming and renders it unfit for monitoring during cardiac surgery to guide CPB.

About 90-95% of the ECMO centres routinely monitor AT levels, targeting a value above 70%. When AT is below this target, AT substitution will be initiated. Although the heparin...
dose can be reduced following AT, there is no correlation with reduction in complications (bleeding or thrombosis). Assessment of platelet function during ECMO by modern point of care devices such as impedance aggregometry seems interesting. However, results depend on the platelet count, which hampers usefulness, as more than 50% of all ECMO patients show thrombocytopenia.42 Due to the consumption of coagulation factors, the fibrinogen level frequently decreases during ECMO therapy, requiring daily monitoring. For the same reason a whole blood count and particularly a platelet count is of interest, since both low haemoglobin but also low platelet count are associated with higher rates of coagulation abnormalities leading to sustained bleeding.

The assessment of D-dimers, as a marker for ongoing thrombosis and thrombolysis, could be of use in determining the urgency of changing the oxygenator. In a small study on 13 patients, the authors noticed a rise of D-dimers as a precursor of oxygenator failure. In another study, the same group suggested to monitor this parameter if there was suspicion of oxygenator malfunction. Nevertheless, an exchange of the oxygenator seems indicated if the oxygen transfer is impeded.43,44 While single coagulation tests do not correlate well with the clinical phenotype, a combination of different tests spread over the treatment period might improve treatment. This was shown in a recent meta-analysis where the prevalence of complications was lowest if an aPTT or strategy guided by combined test results was applied while the highest rate of complications was seen if there was no monitoring.22 In this light, many authors propose to combine, for example, the ACT with TEG/ROTEM. On the other hand, performing an assessment of AT and D-dimers on a regular basis to estimate the risk of thrombosis is also recommended, such as Ranucci and co-workers who combined ACT with TEG to improve the positive predictive value from 50% and lower for each single value to more than 70% in terms of being in target range for heparin.45

Similar to other medical challenges, a systematic approach with an evidence-based algorithm seems advisable during ECMO runs also checking other organ systems, such as renal and liver function.

Clinical approach
Before starting anticoagulation one should be familiar with the ECMO system. It is important to note whether the system is fully or partially coated. Next step is to create a system with a tubing long enough for practical purposes but short enough to reduce the contact surface. Both factors determine the prothrombotic activity of the system. Obviously, also the expected speed of the pump plays a major role. If the blood flow exceeds 2-2.5 l/min, the chance of thrombosis will decrease. On the other hand, one should consider technical modifications, such as building a shunt into the system, to enable a high flow. In the next step the patient’s comorbidities and current bleeding status should be considered; for example after major surgery or trauma the treatment could be started without anticoagulation and initiated after 24 hours. This is common practice after cardiac surgery if heparin during the operation is not antagonised. On the other hand, the patient’s medication is important. If this already includes an anticoagulant or an antiplatelet drug, the start with intravenous anticoagulants should be carefully monitored and increased stepwise. While this seems obvious, the underlying disease could also interfere with the haemostatic system. In some pro-thrombotic situations such as sepsis, autoimmune diseases or after child birth, the frequency of monitoring should be increased in the beginning of the ECMO run to adjust the dosage of anticoagulants. In cases with an increased bleeding tendency or potential bleeding in vital organs such as the brain, or during cerebrovascular accident or DIC it is wise to withhold anticoagulation until the risk is controlled. In most centres, the choice of agent is straightforward and will be UFH, because of the long experience and ease of use. It is difficult to determine the target of anticoagulation. Most centres target a certain aPTT/ACT level and adjust it according to the bleeding risk. This might be feasible, because thrombotic events could be more disastrous than bleeding situations. In the beginning, monitoring of the anticoagulation should be done frequently, but intensity could be reduced after reaching a stable situation (table 3). For example, monitoring of the aPTT in the starting period should be done every 2-4 hours until the target is reached and stable. In addition, daily assessment of INR, fibrinogen, AT and whole blood count should be done according to a protocol. If available, viscoelastic tests could be added to reflect the fibrinolysis (table 3).

Future perspectives
There are many possible future improvements in coagulation strategies for ECMO therapy which could reduce haemolysis and activation of the coagulation and immune system. From a technical viewpoint, minimising the circuit causes less surface

<table>
<thead>
<tr>
<th>Table 3. Suggested monitoring in UFH-treated patients (stable conditions)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Once daily</strong></td>
</tr>
<tr>
<td>Fibrinogen</td>
</tr>
<tr>
<td>MA-TEG/MCF-ROTEM</td>
</tr>
<tr>
<td>Lysis index</td>
</tr>
<tr>
<td>D-dimer</td>
</tr>
</tbody>
</table>

ACT = activated clotting time; aPTT = activated partial thromboplastin time; AT = antithrombin; MA-TEG = maximum amplitude thromboelastography; MCF-ROTEM: maximal clot firmness rotational thromboelastometry, R-time TEG: time to start amplification of clotting in thromboelastography, CT-ROTEM: clotting time in rotational thromboelastometry. |
blood contact and consequently decreased activation of the intrinsic coagulation cascade. The use of inner tube heparin coatings is already generally accepted, while attempts to use novel inhibitors of the FXII pathway could stabilise the contact activation system even more. Further improvement of inner circuit surface characteristics could stabilise flow patterns, which results in both less turbulence and less shear stress. This could possibly contribute to less platelet activation, less blood cell damage, and therefore decreased incidence of coagulation abnormalities. In terms of controlling the inflammatory aspects, studies should give more insights into the pathological mechanisms. This should be followed by tailored inhibition of the responsible mediators.

For practical purposes, it is important to clearly define the targets of the anticoagulation therapy (e.g. aPTT, ACT) associated with reduction of bleeding and thrombosis, after which a standardised strategy including choice of drug and methods for monitoring and dosing regimen to achieve this goal should be applied.

**Conclusion**

In the past 10 years, ECMO was established as a life-saving therapy in critically ill adult patients. Contact with the non-endothelialised surface of the extracorporeal circuit activates both the coagulation and the immune system, which could lead to overwhelming clotting in the system but also in the patient. Therefore, therapeutic anticoagulation is widely accepted. While the most frequent anticoagulant for this purpose remains UFH, the optimal test for monitoring is still a matter of debate. The current, a combination of both targets seems best which results in setting the laboratory target and adjusting it according to the bleeding risk. However, defining standards for daily practice is urgently needed.

Meanwhile new technical developments could improve the circuits and their biocompatibility. Finally, studies should elucidate the interaction of coagulation and inflammation to use the ECMO techniques with minimal impact on critically ill patients.

**Disclosures**

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**References**


Prevalence and predictors of acute kidney injury after cardiac surgery: A single-centre retrospective study in Qatar

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Keywords - cardiac surgery, cardiopulmonary bypass, acute kidney injury, prevalence

Abstract

Background: Despite modern advances in intensive care management, the incidence of acute kidney injury (AKI) continues to be high. This study was performed to characterise the predisposing factors impacting the development of AKI, and secondary outcomes among patients undergoing cardiac surgery.

Methods: In this single-centre retrospective study, AKI was defined according to the Acute Kidney Injury Network. Patients were divided into two groups: those without AKI (Group I, 544 patients) and those with AKI (Group II, 181 patients). Patients’ admission and outcome data were analysed.

Results: The patients’ mean age was 53±12 years, and 25% of the patients had AKI. The two groups were matched with regard to age, sex, body mass index (BMI), history of diabetes, and history of hypertension. Group II had a considerably higher additive EuroSCORE and lower ejection fraction than Group I. The lengths of ventilation, ICU, and hospital stay were significantly higher in Group II than I. Group II had a significantly higher incidence of postoperative atrial fibrillation and mortality rate than Group I. Interestingly, AKI was significantly more notable in Asians than in Arabs. A total of 1.9% of patients required renal replacement therapy. The independent risk factors for AKI in our population were the additive EuroSCORE, time of cardiopulmonary bypass, low postoperative haemoglobin level, postoperative white cell count, and total amount of blood loss.

Conclusion: Cardiac surgery-induced AKI is highly prevalent and prognostically fundamental. Management options targeting treating preoperative anaemia, shortening cardiopulmonary bypass time, and reducing red blood cell transfusion may help to prevent this complication.

Background

Acute kidney injury (AKI) is one of the most prevalent complications following cardiac surgery, especially in patients undergoing cardiopulmonary bypass (CPB). AKI prolongs the postoperative stay, in turn causing increased use of hospital resources. Despite recent evolution of perioperative care in cardiac surgery patients, AKI remains a common complication. The reported incidence of AKI after cardiac surgery varies from 5% to 31%. The demand for renal replacement therapy (RRT) in this population ranges from 1% to 5% of patients and is associated with increased postoperative morbidity and mortality. Patients who develop AKI are prone to an increased hospital stay, higher mortality rates, and greater use of resources, all of which are more pronounced in patients requiring RRT.

Patient-related risk factors for the evolution of AKI after cardiac surgery include cardiogenic shock requiring treatment with an intra-aortic balloon pump (IABP), total circulatory arrest, left main disease, peripheral vascular disease, diabetes mellitus, chronic obstructive pulmonary disease, deteriorated left ventricular function, the need for emergency surgery, and renal insufficiency. The known procedure-related risk factors after cardiac surgery include the aortic cross-clamp (ACC) time, CPB time, haemolysis, and haemodilution.

Multifactorial mechanisms of the development of AKI after cardiac surgery have been proposed, including renal autoregulation impairment secondary to a low intraoperative mean arterial blood pressure below the limits of autoregulation and generation of free haemoglobin and iron from the haemolysis that occurs during CPB, which predisposes patients to ischaemic kidney injury. Rhabdomyolysis has also been described as a possible cause of AKI after cardiac surgery.
Other possible causes of AKI include a systemic inflammatory response secondary to contact of blood ingredients with the synthetic surface of the CPB circuit, ischaemia-reperfusion injury, and Gram-negative endotoxaemia.[13,16]

**Aim of this work**
The prevalence and predictors of AKI after cardiac surgery have been infrequently evaluated in the Gulf area. Therefore, this study was performed to identify the prevalence and predictors of postoperative AKI in adults undergoing cardiac surgery using CPB in the state of Qatar.

**Methods**

**Study design and assessments**
This single-centre retrospective study was conducted during a 3-year period (October 2011 to October 2014) in a 12-bed cardiothoracic intensive care unit (ICU) of a tertiary hospital in Qatar. The ethics committee at Hamad Medical Corporation approved this study (reference number 15094/15), and informed consent was waived for all patients enrolled in this study. However, all study data were maintained anonymously. The exclusion criteria included patients who require RRT, either dialysis or transplantation, which defines pre-existing end-stage renal disease,[17] age of <18 years, aortic dissection repair surgery, off-pump cardiac surgery, and death within 24 hours postoperatively. We evaluated 836 patients who underwent cardiac surgery during the study duration; of these, 725 patients were eligible for enrolment in the study.

The following data were recorded for all patients: age, sex, weight, height, body mass index, history of diabetes or hypertension, type of surgery, length of anaesthesia, CPB time, ACC time, utilisation of vasopressors and inotropes, EuroSCORE, preoperative anaemia (defined as a haemoglobin level of <12 g/dl and <13 g/dl for women and men, respectively, according to the World Health Organisation),[18] time interval between coronary angiography and surgery, time interval between recent myocardial infarction (MI) and surgery, preoperative ejection fraction, preoperative glycosylated haemoglobin, preoperative blood urea nitrogen (BUN) concentration, preoperative serum creatinine concentration, preoperative international normalised ratio (INR), preoperative platelet count, cardiogenic shock and use of IABP, postoperative serum creatinine concentration, postoperative BUN concentration, peaked postoperative white blood cell (WBC) count within first 60 hours, total blood loss, total blood transfusion, rates of re-exploration and readmission to the cardiothoracic ICU, and rate of AKI development.

The outcome variables included the length of mechanical ventilation (LOV), length of stay in the ICU (LOS_ICU), length of stay in the hospital (LOS_hosp), postoperative atrial fibrillation, and the patients’ need for RRT. Dendrite Clinical Systems (London, UK) were used to retrieve these data.

**Outcome definitions**
The primary outcome was the diagnosis of AKI in the entire patient population. With reference to the Acute Kidney Injury Network definition, AKI was defined as an acute (≤48 hours) deterioration in the renal functions, with an absolute increase in the serum creatinine concentration of ≥0.3 mg/dl (26.4 μmol/l) or an increase of ≥50% (1.5-fold from baseline).[19] The secondary outcome measures were the LOV, LOS_ICU, and LOS_hosp. Based on the presence of AKI, patients were divided into two groups: those with and without AKI.

**Statistical analysis**
Normally distributed continuous variables are presented as mean ± standard deviation, and skewed variables are presented as median (interquartile range). The patients were divided into two groups based on the presence of AKI. The groups were compared using parametric tests, nonparametric tests, or the chi-square test as appropriate. A p value of ≤0.05 was considered to indicate statistical significance. Correlations of log AKI were first examined by single-variable linear or logistic regression and presented as the non-adjusted coefficient and 95% confidence interval. Factors with a p value of ≤0.05 by single-variable regression analyses were included in a multivariable linear regression model, presented as the adjusted coefficient with 95% confidence interval. Multivariable logistic regression modelling was carried out to validate the adjusted combinations of the measured perioperative variables with the AKI threshold. Statistical analysis was performed using SPSS software (version 22; IBM Corp., Armonk, NY, USA).

**Results**
During the study period (October 2011 to October 2014), 836 patients underwent cardiac surgery. After patient selection according to the preset exclusion criteria, 725 patients were enrolled in the study (figure 1). A total of 181 (25%) patients had AKI. Fourteen patients (1.9%) received postoperative RRT in the hospital. The patients’ mean age was 53±12 years, and the patients were predominantly male (n=649, 89.5%) (table 1). Both study groups were matched with regard to age, BMI, preoperative hypertension, diabetes, preoperative use of angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers (table 2).

The following preoperative risk factors were significantly different between the two groups according to univariate analysis: the additive EuroSCORE, preoperative WBC count, preoperative BUN concentration, and ejection fraction (table 2). In conjunction with previous risk factors, we found the following preoperative factors to be significantly different between the two groups: atrial fibrillation, anaemia, and IABP (table 2).

The duration between the onset of MI and cardiac surgery was significantly different between the two groups. We found...
that patients who developed a recent MI within the first 30 days were more liable to develop AKI. Urgency and ethnicity were significantly different between the two groups. Among intraoperative risk factors, the CPB time, ACC time, lowest haematocrit on CPB, and anaesthesia time were significantly different between the groups. The transfusion variables were also significantly different (table 3).

The LOV, LOS$_{ICU}$ and LOS$_{hosp}$ were significantly higher in the AKI group, with a higher incidence of postoperative atrial fibrillation (table 3). Multivariate logistic regression analysis demonstrated that the additive EuroSCORE, preoperative BUN concentration, recent MI, CPB time, lowest haematocrit on CPB, lowest postoperative haematocrit, and total blood loss were independent predictors of AKI (table 4).

Discussion

The key findings of this study are as follows. First, many variables may precede AKI. Second, AKI is a common cause of morbidity and mortality after cardiac surgery and occurred in 25% of the present cohort; additionally, 1.9% of the study population required RRT. Third, a high WBC count was associated with AKI development.

Results in the context of previous studies

Among the clinical predictors of AKI, we found several independent risk factors including the additive EuroSCORE, preoperative BUN concentration, recent MI, CPB time, lowest haematocrit on CPB, lowest postoperative haematocrit, and total blood loss during the first 48 hours. All of these were also identified in previous studies.

Some authors found a significant increment in the incidence of AKI when the time from coronary angiography to surgery was ≤5 days, and they recommended postponing cardiac surgery for at least 5 days after coronary angiography. Similarly, using univariate analysis we found a high incidence of AKI within 5 days after coronary angiography. This was not in agreement with the study conducted by Moulton et al., who did not find an association between coronary angiography and deterioration of postoperative renal function.

Preoperative or intraoperative use of an IABP was considered to be a risk factor for AKI in the present study, which is in agreement with previous studies. Furthermore, we found that the relationship among preoperative anaemia, red blood cell transfusion, and AKI was statistically significant, which is in accordance with the results obtained by Karkouti et al. in 2009. They found that association of anaemia preoperatively and red blood cell transfusions perioperatively were strongly associated with AKI.

Karkouti et al. found that surgical re-exploration after cardiac surgery was considered to be a risk factor for the development of AKI, which is consistent with our retrospective data. In 2014, Kandler et al. found that AKI was independently associated with increased mortality after cardiac surgery, which is also in agreement with the results obtained in the current study.

We found that neither diabetes mellitus nor hypertension showed any predictive value for the development of AKI.

Table 1. Description of the studied group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>725</td>
<td>19</td>
<td>85</td>
<td>53±12</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>725</td>
<td>14.5</td>
<td>51.9</td>
<td>27±5</td>
</tr>
<tr>
<td>Creatinine (µmol/l)</td>
<td>725</td>
<td>32</td>
<td>152</td>
<td>97.1±60.1</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>720</td>
<td>20</td>
<td>70</td>
<td>49.6±10.2</td>
</tr>
<tr>
<td>Additive EuroSCORE</td>
<td>717</td>
<td>0</td>
<td>22</td>
<td>4.1±2.9</td>
</tr>
<tr>
<td>Preoperative BUN (mmol/l)</td>
<td>725</td>
<td>1.8</td>
<td>19.7</td>
<td>5.8±2.8</td>
</tr>
<tr>
<td>Preoperative serum creatinine</td>
<td>725</td>
<td>32.0</td>
<td>286.0</td>
<td>91.6±60.8</td>
</tr>
<tr>
<td>(µmol/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPB time (min)</td>
<td>725</td>
<td>29</td>
<td>364</td>
<td>120.2±48.3</td>
</tr>
<tr>
<td>ACC time (min)</td>
<td>675</td>
<td>0</td>
<td>251</td>
<td>76.4±37.2</td>
</tr>
<tr>
<td>Lowest HCT on CPB (%)</td>
<td>725</td>
<td>16.2</td>
<td>35.7</td>
<td>25.9±3</td>
</tr>
<tr>
<td>Total blood loss in first 48 hours</td>
<td>725</td>
<td>50.0</td>
<td>11,400.0</td>
<td>1027±918</td>
</tr>
<tr>
<td>Total PRBCs transfusion (units)</td>
<td>725</td>
<td>0.00</td>
<td>49.00</td>
<td>2.5±4.2</td>
</tr>
<tr>
<td>Total FFP transfusion (units)</td>
<td>725</td>
<td>0.00</td>
<td>16.00</td>
<td>0.6±1.7</td>
</tr>
<tr>
<td>Peaked 36-60 h postoperative WBCs (10³)</td>
<td>725</td>
<td>3.90</td>
<td>35.00</td>
<td>13.2±5.2</td>
</tr>
<tr>
<td>Lowest postoperative HCT (%)</td>
<td>725</td>
<td>18.60</td>
<td>42.00</td>
<td>25±2.7</td>
</tr>
<tr>
<td>LOV (hours)</td>
<td>725</td>
<td>2</td>
<td>449</td>
<td>14±38</td>
</tr>
<tr>
<td>LOS$_{ICU}$ (days)</td>
<td>725</td>
<td>5</td>
<td>151</td>
<td>35.1±30.6</td>
</tr>
<tr>
<td>LOS$_{hosp}$ (days)</td>
<td>725</td>
<td>1</td>
<td>72</td>
<td>2.6±3.8</td>
</tr>
</tbody>
</table>

Figures are numbers or mean ± standard deviation. BMI = body mass index; BUN = blood urea nitrogen; CPB = cardiopulmonary bypass; ACC = aortic cross clamp; HCT = haematocrit; PRBCs = packed red blood cells; FFP = fresh frozen plasma; WBCs = white blood cells; LOV = length of mechanical ventilation; LOS$_{ICU}$ = length of stay in intensive care unit.
data were close to those from the study by Lopez-Delgado et al. where diabetics comprised only 10% of the patients who suffered or were at risk of AKI; however, the same group found that 67.5% of the AKI study population had hypertension. We tend to operate at a younger age where hypertension may not be fully established; the mean age in our study was 53±12 years, in comparison with Lopez-Delgado’s cohort which had a mean age of 67.7 ± 9.8.[28]

In another review article by Shin et al., the authors identified the potential risk factors for cardiac surgery-induced AKI to include anemia, ischemic reperfusion, CPB, and use of aprotinin but...
they did not mention diabetes or hypertension as risk factors.[29] In contrast, some authors[20-22] considered diabetes mellitus and hypertension to be independent risk factors for AKI. Impaired left ventricular function was a significant risk factor for AKI after cardiac surgery in the current study, which is compatible with previous studies.[21,23] Chew et al.[22] and Fernandes et al.[30] investigated ethnic predisposition in AKI after cardiac surgery. They found that ethnicity is an independent risk factor for the development of AKI after cardiac surgery and showed that Malays and Indians have a higher risk of developing postoperative AKI than do the Chinese. They assumed that ethnicity strikes a role in the development of atherosclerosis, coronary heart disease, and associated complications, including AKI. We addressed the same concept in our study and found that AKI was more prevalent in the Asian than Arab population.

Although many predictive risk factors were recognised in the current study, most of them can be considered potentially modifiable (recent MI, time difference between coronary angiography and surgery, preoperative IABP, perioperative anaemia, total blood loss, red blood cell transfusion, and CPB duration). Therefore, if a patient recently developed MI, it may be beneficial if cardiac surgery is delayed for >30 days post-MI; for patients who recently underwent coronary angiography, it is advised to delay the surgery for more than 5 days post-angiography as long as this does not affect the patient’s outcome. Patients who are at high risk and in need of prolonged surgery would benefit from less invasive surgery to reduce the CPB time, thus reducing the incidence of AKI. The total blood loss and red blood cell transfusion, when blood conservation strategies are followed, will minimise the risk of AKI and thus the effect of perioperative anaemia. A novel, unexpected, and interesting finding of this study compared with previous studies is the significant correlation between the peaked 36-60 hour postoperative WBC count and the development of AKI after cardiac surgery in the multivariate logistic regression analysis. One pathogenetic mechanism of AKI is ischaemic kidney injury, which may develop due to the systemic inflammatory response that follows cardiac surgery.[31] WBCs as an inflammatory marker usually peak 36 to 60 hours after CPB.[31] To the best of our knowledge, the relationship between the postoperative WBC count and AKI has not been studied before. Only the relationship between the postoperative WBC count and atrial fibrillation was evaluated by Lamm et al. in 2006. They found that the postoperative WBC count independently predicted the development of postoperative atrial fibrillation.[32] We could not attribute the high WBCs to steroid administration in our study. The protective effect of steroids has been addressed in many randomised clinical trials;[33,34] however, we do not routinely administer steroids after cardiac surgery as the evidence is not strong enough to support the possible side effects.[35]

### Conclusion

Cardiac surgery-induced AKI is highly predominant. Strategies targeting modifiable risk factors for AKI may reduce the incidence of AKI post cardiac surgery. The association of high WBCs with AKI needs to be confirmed in other cohorts.

### Acknowledgment

This work would not have been possible without all levels of support given by many individuals in our organisation. The authors are thankful to all members of the Cardiothoracic Surgery Department of Hamad Medical Corporation, Qatar, for providing the help needed during the duration of the study. The authors also thank all members of the academic health system in the medical research department of Hamad Medical Corporation for their unlimited support throughout this study.

### Disclosures

The authors declare that they have no competing interests. The study was funded by Hamad Medical Corporation. The Medical Research Centre in Hamad Medical Corporation funded the publication of this manuscript.

### Availability of supporting data and materials

The datasets supporting the conclusions of this article are available on request to the corresponding author Dr. Samy Hanoura (e-mail: sehounura73@yahoo.com), after permission from the Medical Research Centre.
References

Use of cardiopulmonary bypass and full heparinisation in patients with an asymptomatic intracranial aneurysm

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Keywords - cardiopulmonary bypass; intracranial aneurysm; risk assessment; subarachnoid haemorrhage

Abstract

Introduction: The overall prevalence of unruptured intracranial aneurysms is 3.2%. The rupture risk of an intracranial aneurysm during cardiopulmonary bypass requiring full heparinisation is unknown.

Patients and Methods: Rupture risk was assessed using data from a trial in which dexamethasone was compared with placebo in 4482 patients undergoing cardiac surgery with cardiopulmonary bypass.

Results: Not a single haemorrhagic stroke occurred during surgery and only one patient had a subarachnoid haemorrhage three weeks after cardiac surgery.

Discussion: Although the actual prevalence of intracranial aneurysms in the study population is unknown, based on patient characteristics, it is likely that the incidence is not below the average of 3.2% of the general population. So probably at least 143 patients with an intracranial aneurysm underwent surgery with full heparinisation without any rupture.

Conclusion: Cardiopulmonary bypass with heparinisation is not a risk factor for rupture of an intracranial aneurysm. An unruptured intracranial aneurysm should not hinder lifesaving surgery for which cardiopulmonary bypass is required.

Figure 1. CT angiography of the candidate (Case 1) for lung transplantation showing an aneurysm at the left middle cerebral artery (arrow)
a ruptured aneurysm of the right middle cerebral artery, from which she fully recovered. The ruptured aneurysm was surgically clipped, but an asymptomatic additional aneurysm of the left middle cerebral artery remained. Recent CT angiography showed an aneurysm with a 4 by 4 mm dome and a 2 mm neck, which was stable over time (figure 1).

Case 2
A 56-year-old woman was screened for lung transplantation, because of severe lung emphysema. She had a history of hypertension and quit smoking when she was 50 years of age. Two years ago, she had a left-sided craniotomy for clipping of an unruptured middle cerebral artery bifurcation aneurysm. A small asymptomatic left-sided internal carotid artery aneurysm remained with a maximal diameter of 2.5 mm, which stayed stable over time according to follow-up CT angiographies.

Both patients are being considered for bilateral lung transplantation, which may require cardiopulmonary bypass with full heparinisation; final inclusion on the waiting list has been postponed to perform a risk assessment for perioperative aneurysm rupture.

Patients and methods
The study was approved by the appropriate Ethics authority. Written informed consent was obtained from all subjects, both from participants of the randomised clinical trial described below as well as from the patients described in the introduction. The study was registered before patient enrolment at Trial Registration clinicaltrials.gov; Identifier: NCT00293592.

The prevalence of unruptured intracranial aneurysms in the general population is 3.2%. In our randomised clinical trial on dexamethasone in 4482 patients undergoing cardiac surgery with cardiopulmonary bypass and full heparinisation (DECS trial), we followed patients during the first year after surgery for major morbidity including stroke.

Results
None of the participants had a haemorrhagic stroke during cardiac surgery. Only one of the 4482 patients had an aneurysmal subarachnoid haemorrhage during follow-up, but this occurred three weeks after cardiac surgery when the patient was already home. In our study population, 143 persons are expected to harbour an intracranial aneurysm. If we assume that the subarachnoid haemorrhage in the participants of the trial was still somehow related to the procedure, the cardiopulmonary bypass associated risk for aneurysm rupture would be 1/143 or 0.7% (95% confidence interval 0.1-4.9%). However, the patients were followed for one year, and a risk of rupture of 0.7% per year is comparable with the natural history of intracranial aneurysms.

Discussion
We found no indication that cardiopulmonary bypass with full heparinisation is a risk factor for rupture of an intracranial aneurysm.

A limitation of our study is that the exact prevalence of intracranial aneurysm in participants of the DECS trial is unknown. In the meta-analysis by Vlak et al. that forms the basis of our analysis, the overall estimated prevalence of 3.2% (95% CI 1.9-5.2) is calculated for an average study population that was without comorbidity, consisted of 50% men, and had a mean age of 50 years. However, both age above 50 (prevalence ratio 2.2; 95% CI 1.3-3.6) and atherosclerosis (prevalence ratio 1.7; 95% CI 0.9-3.0) increase the risk for harbouring an intracranial aneurysm. Our study population had a mean age of 66 years with risk factors for cardiovascular disease so it is unlikely that the prevalence of intracranial aneurysm is lower than estimated for the general population.

According to a meta-analysis in 4705 patients totalling 6556 unruptured aneurysms, the overall risk of rupture was assessed to be between 0.6% and 1.3% per patient-year at risk. If the single subarachnoid haemorrhage in our study, three weeks after cardiac surgery, was related to the procedure, the cardiopulmonary bypass associated risk for aneurysm rupture would be estimated at 0.7% per patient at risk, which is comparable with the natural history of aneurysm rupture. However, based on the numbers of this meta-analysis and our study, the sample size for an unrelated matched cohort study exceeds 6000 per arm, so even in our large study population of 4482 patients, the results must be interpreted with caution.

The risk of aneurysm rupture during cardiopulmonary bypass procedures with full heparinisation has not yet been studied. We could only find one case report describing aneurysm rupture during neurosurgical clipping under the protection of hypothermic cardiac arrest with use of femoro-femoral cardiopulmonary bypass and heparinisation, but this occurred after neurosurgical dissection of the aneurysm and active external cooling to 32 °C.

Although surgical clipping and endovascular coiling have shown to be effective in the prevention of rebleeding of symptomatic aneurysms (i.e. after aneurysmal subarachnoid haemorrhage), their use for the treatment of asymptomatic aneurysms is not clear, since benefit of treatment cannot be seen until a follow-up of several decades. Meta-analyses on patients with unruptured intracranial aneurysms showed that the occurrence of an unfavourable outcome one year after treatment is not negligible and in general more frequent after clipping (6.7%) then after coiling (4.8%).

Treatment should be considered for unruptured aneurysms in patients under 60 years of age, and possibly for aneurysms...
Bypass and heparinisation with an asymptomatic aneurysm larger than 7 mm in diameter in older patients, without comorbidity. The decision for or against intervention is actually more complex, as this further depends on other risk factors for spontaneous rupture, the risk of the intervention, life expectancy and comorbidity. The risk of rupture of the aneurysm is composed of patient-related (age, hypertension, race) and aneurysmal-related (size, location, previous rupture) factors.\[11\]

In conclusion, the risk of rupture of a small asymptomatic intracranial aneurysm located in the anterior circulation is relatively low while complications of treatment can be serious. Cardiopulmonary bypass is not a risk factor for rupture of an intracranial aneurysm, as illustrated by the absence of subarachnoid haemorrhage in any of our 4482 patients during cardiac surgery with full heparinisation. An unruptured intracranial aneurysm should not hinder life-saving surgery for which cardiopulmonary bypass is required. Our patients are scheduled for bilateral lung transplantation. As median survival for double-lung transplantation is 7.4 years (source: www.ishlt.org) and in our institution more than 10 years and aneurysm treatment risk exceeds the aneurysm rupture risk for this period, we do not plan to perform aneurysm repair in these patients.

**Funding**

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors; however we did extract information from our previously published study, which was supported by the Netherlands Organization for Health Research and Development (ZonMw), grant number 80-82310-98-08607 and the Dutch Heart Foundation, grant number 2007B125.

**References**

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A 72-year-old female was admitted to the ICU after an emergency angiography for an intracranial haemorrhage, as a complication of an uneventful elective aneurysm coiling of the anterior cerebral artery. Her past medical history consisted of hypertension, non-insulin dependent diabetes and hypothyroidism. On admission to the ICU a routine chest X-ray was ordered, which showed an unusual contour in the right hemithorax.

What is your diagnosis?

Answer
You will find the answer on page 28 of this issue.

Figure 1. Chest x-ray
CASE REPORT

Upside down you’re turning me: inverted Takotsubo pattern cardiomyopathy

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Keywords - Intensive Care, Takotsubo cardiomyopathy, pheochromocytoma, paraganglioma

Abstract
We present the case of a 17-year-old male paraganglioma patient who presented in shock to our emergency department. During workup, an inverted Takotsubo pattern cardiomyopathy was identified. Treatment consisted of blocking catecholamine synthesis as well as supportive care with inotropic medication and high flow nasal cannula oxygen administration. The case is described in detail and the phenomenon of inverted type Takotsubo cardiomyopathy is discussed.

Introduction
Paraganglioma is a neuroendocrine tumour of the autonomic nervous system, which produces catecholamines. The term pheochromocytoma is reserved for paraganglioma located in the adrenal medulla. Pheochromocytomas are rare tumours, which classically present with symptoms of hyperactivity of the sympathetic nervous system, such as paroxysmal hypertension, palpitations, headaches and anxiety. Paraganglioma and pheochromocytoma have been known to cause reversible cardiomyopathy.[1] Takotsubo cardiomyopathy is a clinical syndrome of transient left ventricular dysfunction in the absence of obstructive coronary disease. It is named after a Japanese octopus trap, ‘tako-tsubo’.[2] In the clinical presentation, patients may present with symptoms and ECG abnormalities similar to an acute coronary syndrome. On echocardiography, typical findings include ballooning of the cardiac apex and a hyperdynamic base.

Case report
A 17-year-old man presented to the emergency room with a painful left knee. During a minor incident, in which he slipped when opening the front door, he had fallen on his knee. His previous medical history was significant for a large (about 200 cm³) para-aortic paraganglioma caudal to his left kidney, which had unfortunately metastasised to his bones. Bone metastases were present in his skull, thoracic lamina, costa, left illum and both femurs. He had undergone a surgical procedure five months prior to presentation, which was intended to resect the neuroendocrine active tumour in the left sympathetic trunk. On arrival to the emergency department, he received 60 µg of fentanyl and his left leg was immobilised using a vacuum splint. The patient was afebrile with a blood pressure of 160/100 mmHg, a heart rate 140 beats/min, a respiratory rate of 20 breaths/min and an oxygen saturation of 91% on a non-rebreathing mask.

Investigations
Laboratory examination revealed a leucocytosis of 31 x 10⁹/l. Arterial blood gas analysis showed a pH of 7.25, pO₂ 13.8 kPa, pCO₂ 5.9 kPa and a lactate level of 1.9 mmol/l. ECG showed sinus tachycardia, an inverted T wave in lead aVL and upsloping ST segments in leads V3-V5 (figure 1). Chest radiography showed consolidation in the right lower lobe. The X-ray of his left thigh showed a fracture of the proximal femur.

Diagnosis and treatment
For haemodynamic monitoring and treatment, the patient was admitted to our medium care unit. Because of a worsening hypoxaemia, high flow nasal cannula oxygen was initiated. Our initial working diagnosis was blood loss due to a fracture of the femur resulting in tachycardia, with hypotension. However, severe bleeding in his femur was not observed. Surprisingly, the troponin level was elevated (1.58 µg/l, normal range: 0.000-0.050 µg/l). At the time of admission the metanephrine/creatinine ratio was significantly increased. By indexing urinary metanephrine levels by urinary creatinine levels, errors of underestimating or overestimating metanephrine excretion can be avoided.[3] A transthoracic echocardiogram was performed, showing hypokinesia of the basal segments with hyperkinesia of the apical segments in an inverted Takotsubo-type pattern (figure 2; online video file 1). Milrinone was started at a dose of 0.25 µg/kg/min to support left ventricular function. Metirosine
Inverted Takotsubo pattern cardiomyopathy

was started to inhibit catecholamine synthesis. After 1 day, the milrinone was stopped and alpha blockage with doxazosin was started. The patient was transferred to the ward for further medical treatment. Eight days later, the transthoracic echocardiogram was repeated, showing a good ventricular function with no residual regional wall motion abnormalities (online video file 2). The patient was discharged home after two weeks with continuation of the doxazosin therapy and was subsequently re-admitted for elective surgery for osteosynthesis of the pathological femur fracture.

Discussion

Takotsubo cardiomyopathy was first described in Japan in 1991, including transient left ventricular dysfunction with apical ballooning and a hyperkinetic base of the heart.[1] Cardiac enzymes are usually slightly elevated and the ECG may show elevated ST segments and/or T wave inversion.[6] There is no significant coronary stenosis on coronary angiography. According to the Mayo Clinical Diagnostic Criteria, the diagnosis of Takotsubo cardiomyopathy requires all of the following criteria: (1) transient hypokinesia, akinesia, or dyskinesia of the left ventricular mid-segments with or without apical involvement; the regional wall motion abnormalities extend beyond a single epicardial vascular distribution; a stressful trigger is often but not always present, (2) absence of obstructive coronary disease or angiographic evidence of acute plaque rupture, (3) new electrocardiographic abnormalities (either ST-segment elevation and/or T-wave inversion) or modest elevation in cardiac troponin, (4) absence of pheochromocytoma or myocarditis.[2,5] Although the exact pathophysiological mechanism behind the development of Takotsubo is unknown it is well recognised that it frequently occurs in patients suffering from intense emotions, hence its nickname 'broken heart syndrome'. The working hypothesis is that catecholamine surges during these emotional states are mechanistically important.[2,3,4]

In contrast to a regular Takotsubo cardiomyopathy, the subtype of an inverted or reversed Takotsubo cardiomyopathy is characterised on echocardiography by a hyperkinetic apex and a dynamic base.[2,6] This specific type is much less prevalent, occurring in about 2% of patients in the International Takotsubo Registry study.[7] Although an inverted type of Takotsubo is therefore quite rare, it has been reported in all patient groups. However, it seems to be preferentially reported in pheochromocytoma patients.[2,4,6]

There are different hypotheses to explain the different patterns. One hypothesis is the different anatomical distribution of beta-1 and beta-2 adrenoceptors in the myocardium in different individuals or regional anatomic differences in catecholamine sensitivity. Other theories include coronary vasospasm and transient microthrombi.[6] In inverted Takotsubo cardiomyopathy related to pheochromocytoma, there are persistently higher levels of catecholamines compared with the transient normalising levels of catecholamines in normal variant Takotsubo cardiomyopathy, which may influence the specific form of cardiomyopathy observed.[5] The inverted Takotsubo cardiomyopathy seems to occur more often in pheochromocytoma patients but may be seen in non-affected patients as well. In those patients, it has been observed that younger individuals (median age of 50 years) have a higher incidence of inverted type Takotsubo as compared with the patients with normal variant Takotsubo cardiomyopathy, which usually presents around the sixth decade.[5] Both types seem to predominantly affect females.[2,5]

Taken together, we describe a patient with a paraganglioma who presented with a rare and unexpected Takotsubo variant. Although this variant of inverted Takotsubo has been described in these patients before, the mechanistic explanation for this association remains to be elucidated. It is, however, of great importance to be aware of the association of pheochromocytomas and Takotsubo cardiomyopathy and realise that in these patients an upside down pattern Takotsubo may be encountered.

Disclosures

All authors declare no conflict of interest. No funding or financial support was received.
Inverted Takotsubo pattern cardiomyopathy

References


Online you’ll find the videos mentioned in the text.

**Video file 1:** Transthoracic echocardiogram (parasternal short axis view at basal, mid and apical level): hypokinesia of the basal segments with hyperkinesia of the apical segments in an inverted-Takotsubo type pattern

https://www.njcc.nl/njcc-17-68-chin-choi-video-1

**Video file 2:** Transthoracic echocardiogram repeated after eight days (parasternal short axis view at basal, mid and apical level): good ventricular function with no residual wall motion abnormalities.

https://www.njcc.nl/njcc-17-68-chin-choi-video-2
Research News

Is reconnection to mechanical ventilation for one hour after a successful spontaneous breathing trial recommended in order to reduce reintubation rate in critically ill patients?

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Keywords - mechanical ventilation, spontaneous breathing trial, rest, post-extubation respiratory failure

Article
Reconnection to mechanical ventilation for 1h after a successful spontaneous breathing trial reduces reintubation in critically ill patients: a multicentre randomized controlled trial. Published in Intensive Care Medicine, November 2017.[1]

Why was this research done?
Spontaneous breathing trials (SBT) are used to identify extubation readiness. Still, extubation failure and the need for reintubation after a successful SBT remain common and is associated with higher mortality.[2] Optimal technique and duration of a SBT are subject of debate. However, circumstantial evidence indicates that a period of ventilator reconnection after a SBT may reduce extubation failure.[3,4]

What was the research question?
To determine whether one hour of rest after a successful SBT would reduce post-extubation respiratory failure and reintubation rate. Primary outcome was reintubation within 48 hours of extubation. Secondary objectives included ICU mortality, hospital mortality, ICU length-of-stay and hospital length-of-stay.

How was this investigated?
The study was a multicentre randomised controlled trial conducted in Spain. Adult patients receiving invasive mechanical ventilation for at least 12 hours were randomised after successfully completing a SBT to be either extubated directly (control group) or reconnected to the ventilator for a one hour’s rest before extubation (rest group). The SBT was performed according to local clinical protocols and the technique and duration varied among centres. Reintubation or use of noninvasive ventilation (NIV) after extubation remained at the discretion of the physicians. Patients were followed up until hospital discharge or death.

Main findings
In total, 470 patients were randomised. Reintubation within 48 hours after extubation was more common in the control group than in the rest group (24% vs. 10%; p<0.001). Rescue NIV was applied more often in the control group than in the rest group (14% vs. 5%; p=0.71).

After concluding the study, it was realised that the sample size had been miscalculated; this should have been 1372 patients.

Conclusion and consequences for daily practice
The authors conclude that one hour of rest after a successful SBT prevents reintubation and extubation failure within 48 hours after extubation. The strengths of the study include the multicentre design and pragmatic approach to weaning techniques. The limitations include that the study was underpowered, even for the primary endpoint, absence of a reasonable physiological explanation for the improved outcome in the rest group, and frequent use of NIV in extubation failure. Given the limitations of this study we do not recommend to routinely reconnect patients to the ventilator ‘for rest’ after a successful SBT.

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

References
ANSWER TO PHOTO QUIZ

An unusual finding on a chest X-ray

Keywords - accessory lobe, azygos lobe

The azygos lobe

The azygos lobe, first described by Heinrich Wrisberg in 1877, is a rare, but normal anatomic variant of the right upper lobe. It is found in 1% of anatomic specimens and approximately 0.4% of chest radiographs. The azygos lobe is not a true accessory lobe as it does not correspond to a distinct anatomical bronchopulmonary segment. The anomaly is formed by a persisting lateral position of the azygos vein during embryological development, which separates the dome of the pleura into two compartments. As a result, the right upper lobe is split in two, with the medial side presenting the accessory azygos lobe. Clinical importance is limited to possible diagnostic difficulties, as the accessory lobe may be mistaken for a bulla, abscess, pulmonary node or lung mass in case of a consolidated azygos lobe. Also thoracic surgery may prove more difficult in the presence of an azygos lobe. Physicians need to be aware of this normal variant when interpreting a chest X-ray or when preparing for thoracic surgery.

References

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Figure 2. Computed tomography of the chest
BOOK REVIEW

Me and my ICU
A book illustrating professionals working on the ICU

Frank Muller: Ik en mijn IC

Photographer and former ICU nurse Frank Muller spent about 20 day, evening and night shifts on a number of ICUs in the Netherlands, taking pictures of all the activities. The photographs relate to events taking place on a regular day on the ICU, framing the day from dawn to night fall.

For ten years, Muller worked as an ICU nurse. Seventeen years ago he decided to trade this profession for a career in photography. This book is his own initiative, born out of respect for his former ICU colleagues. Muller thinks that generally speaking, people are unfamiliar with the work we do. With the book, he intended to highlight our daily activities. This book, which besides photographs also contains interviews with doctors, nurses and supporting services, tells the story of ICU care from the viewpoint of those working there.

When I asked what struck him most after all those years of absence, he told me that he was surprised by the level of structure and organisation. As an example, he mentioned a case of cardiopulmonary resuscitation that he witnessed. Caregivers all had clear tasks, acted according to protocol, and worked together. In short, there was no chaos. This professional approach does not mean that ICU care has become impersonal, according to Muller. In contrast, also the attention for the needs of a patient has evolved towards a patient-centred care approach, in which also psychological needs are considered.

Appetite for further reading? The book can be ordered via info@zorginbeeld.nl for € 37.50 (including shipping costs).

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**Translational studies into the immunomodulatory effects of norepinephrine and alternative vasopressors**

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**Background:** Sepsis-induced immunoparalysis, a phenomenon characterized by a severely suppressed state of the immune system which may render patients unable to combat infections, has been increasingly recognized as the overriding immune dysfunction in sepsis in recent years. Norepinephrine is the cornerstone vasopressor for patients with septic shock, however, in vitro evidence indicates that norepinephrine exerts anti-inflammatory effects. Therefore, norepinephrine could inadvertently compromise host immunity and alternative vasopressors such as phenylephrine or vasopressin might hold an advantage in this respect. However, in vivo data on the immunomodulatory effects of vasopressors are largely lacking. Herein, we performed a proof-of-principle study in healthy volunteers challenged with endotoxin (lipopolysaccharide [LPS]) to assess the effects of norepinephrine and alternative vasopressors on the systemic immune response in humans in vivo. For further mechanistic unraveling, complementary experiments in mice were performed.

**Methods:** Forty healthy male volunteers were randomized to a 5-hour intravenous infusion of norepinephrine (0.05 μg/kg/min), phenylephrine (0.5 μg/kg/min), vasopressin (0.04 IU/min), or saline (n=10 per group). One hour after the start of vasopressor/saline infusion, all subjects were intravenously challenged with 2 ng/kg LPS. Hemodynamic alterations and plasma cytokine levels were assessed. Murine studies were performed in C57BL/6j mice that received continuous intravenous infusion of norepinephrine (5 μg/kg/min) or placebo (PBS) for 3 or 24 hours via micro-osmotic pumps, after which they were intravenously challenged with 5 mg/kg LPS or saline and sacrificed 90 minutes later. Effects on plasma cytokine levels and neutrophilic ROS production were assessed.

**Main Results:** In humans, infusion of norepinephrine and phenylephrine increased blood pressure before LPS administration, but did not prevent LPS-induced hypotension. Norepinephrine and phenylephrine profoundly enhanced LPS-induced plasma concentrations of the anti-inflammatory cytokine IL-10, while attenuating levels of the pro-inflammatory chemokine IP-10. Furthermore, trends towards lower concentrations of other pro-inflammatory mediators (MCP-1, IL-8, GM-CSF) were observed for these vasopressors, most notably for norepinephrine. Vasopressin did not affect levels of any of the cytokines measured. In mice, norepinephrine also profoundly increased plasma IL-10 levels, whereas it significantly decreased concentrations of virtually all pro-inflammatory mediators via a post-transcriptional mechanism. Furthermore, norepinephrine attenuated the PMA-induced oxidative burst in circulating neutrophils.

**Conclusion:** Norepinephrine infusion causes a distinct shift towards an anti-inflammatory cytokine profile during systemic inflammation, which was not observed for vasopressin. These results may signify that norepinephrine contributes to the development of immunoparalysis in septic shock patients, and that vasopressin might represent an alternative with less untoward immunologic effects.

**The safety, tolerability and pharmacokinetics/-dynamics of the selective anti-adrenomedullin antibody Adrecizumab during experimental human endotoxaemia**

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**Background:** Adrenomedullin (ADM) is an important regulator of endothelial barrier function and vascular tone. ADM plasma levels are increased in sepsis and correlate with disease severity and mortality; therefore may represent a novel treatment target. Adrecizumab is a high-affinity non-neutralizing antibody against the N-terminus of ADM. Adrecizumab reduced catecholamine requirements and vascular leakage in preclinical studies of sepsis and systemic inflammation, while improving blood pressure, renal function, and survival. A first in man study demonstrated excellent safety and tolerability. We investigated the safety, tolerability and pharmacokinetics/-dynamics of Adrecizumab in healthy volunteers after induction of systemic inflammation.

**Methods:** Healthy male volunteers participated in a randomized, double-blind, placebo-controlled phase I study. Subjects were randomized into four groups (n=6 each): 0.5, 2, or 8 mg/kg Adrecizumab, or placebo. All subjects received bolus administration of 1 ng/kg of LPS, followed by continuous infusion of 1 ng/kg/hour of LPS for 3 hours to induce systemic inflammation. Study medication infusion was initiated one hour after the LPS bolus administration and lasted for one hour. Several clinical, biochemical, pharmacokinetic/-dynamic and haematological safety parameters were monitored for 90 days.

**Results:** LPS administration resulted in a systemic inflammatory response, illustrated by a plasma TNF-α increase already prior to drug administration, increased body temperature and heart rate, and decreased blood pressure. Adrecizumab showed an excellent safety and tolerability profile. No serious adverse events occurred. Study drug administration did not result in relevant changes in vital signs. Apart from transient clinically insignificant laboratory abnormalities, 26 adverse events (AEs, 9 possibly related, 17 unrelated) were reported. The percentage of AEs in Adrecizumab groups was similar to the placebo group, implying no relation to Adrecizumab. AEs were transient and did not require intervention. PK analysis showed proportional increases of peak Adrecizumab plasma concentrations with increasing dosages (Figure 1), a small volume of distribution (~100 ml/
kg), a low clearance rate (~0.2 ml/h/kg) and a terminal T_{1/2} of ~14 days.

Adrecizumab infusion elicited a pronounced and long-lasting increase of total plasma ADM levels (Figure 2), while concentrations of the prohormone fragment MR-proADM remained unchanged, showing that de novo synthesis of ADM was not influenced. Adrecizumab did not influence the clearance of circulating cytokines. Reported endotoxin-induced symptoms were less pronounced and resolved earlier in Adrecizumab-treated groups compared to placebo.

**Conclusion:** Administration of Adrecizumab is safe and well-tolerated in humans during systemic inflammation. These findings pave the way for further investigation of Adrecizumab in sepsis patients.

**Methods:** We performed a double-blind placebo-controlled randomized study in 30 healthy male volunteers who were intravenously challenged with bacterial endotoxin (LPS) twice (a bolus of 1 ng/kg followed by continuous administration of 1 ng/kg/hr during 3 hours). The two endotoxin challenges were separated by a week. Subjects were randomized into three groups, a prophylaxis group (80mg ASA daily for a 14-day period starting 7 days before the first LPS challenge), a treatment group (80mg ASA daily for the 7-day period in-between both LPS challenges), and a control group that was challenged with LPS twice but received a placebo.

**Results:** Upon the first challenge, prophylactic use of ASA enhanced TNFα plasma concentrations by 50% compared with the control group (p=0.02, Figure 1). The development of endotoxin tolerance was illustrated by a severely blunted plasma cytokine response upon the second LPS challenge in the control group (decrease in AUC of TNFα: 58±11%, p=0.003; IL-6: 73±11%, p=0.004; IL-8: 65±10%, p=0.003; IL-10: 56±11%, p=0.003; MCP-1: 38±11%, p=0.007; MIP-1α: 48±5%, p=0.001; MIP-1β: 55±11%, p=0.01). ASA prophylaxis did not result in altered cytokine levels during the second LPS challenge compared with the control group. ASA treatment resulted in enhanced plasma levels of TNFα (+53%, p=0.02, Figure 1), IL-6 (+91%, p=0.03) and IL-8 (+42%, p=0.02) upon the second LPS challenge compared with the control group, whereas plasma levels of the key anti-inflammatory cytokine IL-10 were lower compared with the control group (-40%, p=0.003). This pro-inflammatory phenotype in the treatment group was accompanied by a decrease in peak urinary prostaglandin E metabolite levels (-33%, p=0.01).

**Conclusion:** Low dose ASA partially reverses the development of in vivo endotoxin tolerance in humans. These findings may partly explain the beneficial effect of ASA in sepsis patients and might provide rationale for use of ASA in patients with sepsis-induced immunoparalysis.

**Figure 1:** Plasma TNFa levels upon the first (C1) and second (C2) endotoxin challenge (mean±SEM). The grey block depicts the endotoxin administration period.

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**Acetylsalicylic acid reverses endotoxin tolerance in vivo in humans: a randomized placebo-controlled study**

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**Background:** Sepsis is a major health care burden with increasing incidence and high mortality rates. A severely suppressed state of the immune system known as immunoparalysis is increasingly recognized as the overriding immune dysfunction in septic patients. Experimental studies have demonstrated that acetylsalicylic acid (ASA) exerts pro-inflammatory effects, and epidemiologic data show that prehospital use of low dose ASA is associated with improved sepsis outcome. However, it remains to be determined whether ASA can reverse immunoparalysis. We investigated whether ASA prophylaxis and/or ASA treatment prevents or reverses in vivo endotoxin tolerance induced by experimental human endotoxemia (a model for sepsis-induced immunoparalysis).

**Methods:** A double-blind placebo-controlled randomized study in 30 healthy male volunteers who were intravenously challenged with bacterial endotoxin (LPS) twice (a bolus of 1 ng/kg followed by continuous administration of 1 ng/kg/hr during 3 hours). The two endotoxin challenges were separated by a week. Subjects were randomized into three groups, a prophylaxis group (80mg ASA daily for a 14-day period starting 7 days before the first LPS challenge), a treatment group (80mg ASA daily for the 7-day period in-between both LPS challenges), and a control group that was challenged with LPS twice but received a placebo.

**Results:** Upon the first challenge, prophylactic use of ASA enhanced TNFα plasma concentrations by 50% compared with the control group (p=0.02, Figure 1). The development of endotoxin tolerance was illustrated by a severely blunted plasma cytokine response upon the second LPS challenge in the control group (decrease in AUC of TNFα: 58±11%, p=0.003; IL-6: 73±11%, p=0.004; IL-8: 65±10%, p=0.003; IL-10: 56±11%, p=0.003; MCP-1: 38±11%, p=0.007; MIP-1α: 48±5%, p=0.001; MIP-1β: 55±11%, p=0.01). ASA prophylaxis did not result in altered cytokine levels during the second LPS challenge compared with the control group. ASA treatment resulted in enhanced plasma levels of TNFα (+53%, p=0.02, Figure 1), IL-6 (+91%, p=0.03) and IL-8 (+42%, p=0.02) upon the second LPS challenge compared with the control group, whereas plasma levels of the key anti-inflammatory cytokine IL-10 were lower compared with the control group (-40%, p=0.003). This pro-inflammatory phenotype in the treatment group was accompanied by a decrease in peak urinary prostaglandin E metabolite levels (-33%, p=0.01).

**Conclusion:** Low dose ASA partially reverses the development of in vivo endotoxin tolerance in humans. These findings may partly explain the beneficial effect of ASA in sepsis patients and might provide rationale for use of ASA in patients with sepsis-induced immunoparalysis.

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**Neuroleptic malignant syndrome-like reaction in a patient with gamma-butyrolactone withdrawal.**

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**Introduction:** There is little medical information available about γ-butyrolactone (GBL) dependence or withdrawal. GBL is an industrial solvent that is rapidly absorbed and metabolized to γ-hydroxybutyrate (GHB). We describe an ICU patient with a GBL withdrawal syndrome in...
which dantrolene was used to treat hyperthermia and rhabdomyolysis.

**Case:** A 31-year-old man with a history of GBL abuse was admitted to the ICU with severe agitation and psychotic symptoms. He was hospitalized 2 days earlier for an ankle fracture resulting in GBL withdrawal symptoms. Due to severe agitation he was treated with antipsychotics and high dose benzodiazepines. Because of resulting respiratory depression he was intubated and mechanically ventilated. Despite high levels of benzodiazepines, propofol, sufentanil, quetiapine and GHB 12 x 2250 mg orally it was difficult to achieve deep sedation. Clinical titration of therapeutic GHB to match our patient’s daily GBL intake was challenging because of severe gastric retention the first five ICU days. Physical examination revealed only tachycardia and high fever (39.9°C). Initial laboratory measurements revealed: CK 939 IU/L, urea 10.3 mmol/L, creatinine 106 µmol/L. In the first days following body temperature rose to 41.5°C and CK level up to 33,360 IU/L. We diagnosed a GBL withdrawal syndrome. Malignant hyperthermia was ruled out in the absence of generalized rigidity. To prevent further deterioration the patient was cooled therapeutically to temperatures under 39°C. Despite adequate treatment elevated levels of CK persisted. On day 7 dantrolene in a dosage of 4mg/kg/day was started off-label to treat hyperthermia and rhabdomyolysis. During treatment temperature normalized and CK levels declined dramatically within 2 days. Dantrolene could be stopped four days after initiation with no further need for benzodiazepines, propofol and sufentanil. The patient awoke with no agitation and could be weaned from the ventilator.

**Conclusion:** Existing literature suggests the use of high dose benzodiazepine as a first-line treatment. In our case we observed poor effect to high doses of benzodiazepines. Recent studies have found GBL and its analogues possesses high affinity for a specific form of extrasynaptic GABA-A receptors that are insensitive to benzodiazepines. Also, some GBL withdrawal symptoms are similar to those of neuroleptic malignant syndrome and the use of antipsychotics might worsen patients neurological condition. As all conventional treatment options failed we started dantrolene off-label. A literature search for the use of dantrolene in treatment of hyperthermia and rhabdomyolysis due to GBL/GHB withdrawal revealed no hits.
Methods: We retrospectively reviewed data of discharged patients from the ICU in our hospital between 2000 and 2014. Patients with incomplete NEWS, age < 16 years or patients discharged for palliative care were excluded. NEWS was calculated using parameters validated by the ICU nurse at 6 a.m. on the day of discharge. Individual NEWS variables and total NEWS were compared between readmissions and non-readmissions within 72 hours. Mann-Whitney U test was used for continuous variables, Chi-square test for binary and categorical variables.

Results: 8745 patients were included in the study. Patients were 68% male and on average 66 years old. Most patients were admitted for elective cardio-thoracic surgery (61%) or medical reasons (20%). The readmission rate was 4% (n = 333). Most readmissions were caused by cardiovascular failure (18%) or infection/sepsis (13%). In the readmitted patients respiratory frequency and heart rate at discharge were significantly higher than in non-readmitted patients (Table 2). Compared to non-readmitted patients, readmitted patients had significantly more often an isolated red score (31% versus 21%), a higher NEWS (4.6 versus 4.0) and more NEWS ≥ 7 (20% versus 12%). Patients with a NEWS ≥ 7 at discharge had a higher readmission rate than NEWS < 7 (6.6% versus 3.5%). A NEWS ≥ 7 had a sensitivity of 20% (68/333) and a specificity of 89% (7457/8412) for readmission.

Conclusion: NEWS at ICU discharge is higher in readmitted patients than in patients without readmission. Also, patients with an isolated red score at discharge have higher readmission rates. Nevertheless, since the discriminative value of both elements is too low to predict ICU admission, further research is needed on this topic.

References:
3. A V, P, or U

Table 1: NEWS parameters and readmission ≤ 72h

Table 2: The National Early Warning Score

<table>
<thead>
<tr>
<th>PHYSIOLOGICAL PARAMETERS</th>
<th>&lt;76</th>
<th>76-79</th>
<th>80-83</th>
<th>84-87</th>
<th>≥88</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory rate, bpm</td>
<td>≤10</td>
<td>11-20</td>
<td>21-25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>60-69</td>
<td>70-79</td>
<td>80-89</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP</td>
<td>≤90</td>
<td>91-100</td>
<td>101-110</td>
<td>111-129</td>
<td>130-220</td>
</tr>
<tr>
<td>Oxygen Saturation</td>
<td>≤91</td>
<td>92-93</td>
<td>94-95</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Core Temperature</td>
<td>≤35.5</td>
<td>35.6-36.0</td>
<td>36.1-38.0</td>
<td>38.1-39.0</td>
<td>≥39.1</td>
</tr>
<tr>
<td>V, P, or U AVPU</td>
<td>V</td>
<td>P, N</td>
<td>U</td>
<td>N</td>
<td>N</td>
</tr>
</tbody>
</table>

Subarachnoid haemorrhage as a complication of invasive pneumococcal disease after total knee replacement

C.J.A. van der Poort, D. Ramnarain, J.P. Peluso, J.A.H. van Oers

Elisabeth-TweeSteden Hospital, Intensive Care, Tilburg, Netherlands

Introduction: Invasive pneumococcal disease can cause severe complications, especially in elderly. We present the case of a patient with septic pneumococcal arthritis causing meningitis, hydrocephalus and subarachnoid haemorrhage (SAH).

Case description: A 69 year-old man, that has had total knee replacement ten years ago, was admitted to a regional hospital with a septic arthritis of the left knee. The knee was surgically drained and flucloxacillin was started. One day after admission, the patient developed a headache, nuchal rigidity and neurological deterioration. A lumbar puncture was performed with a high opening pressure of 40 cm water. Cerebrospinal fluid (CSF) showed elevated protein concentration, high leucocyte cell count with high polymuclear cell count and low glucose, indicating bacterial meningitis.

CSF, joint and blood cultures showed S.Pneumoniae and continuous intravenous administration of benzylpenicillin, 12 million IU/24 hours was started. Computed Tomography (CT)-scan showed hydrocephalus and the patient was referred to our neurosurgical centre for additional diagnosis and continuous external lumbar drainage. At arrival, blood pressure was 170/130 mmHg and pulse rate 170 beats/minute, due to atrial fibrillation. There was no fever at that point. Auscultation of the chest did not show any abnormalities. Echocardiography showed no signs of endocarditis. Glasgow Coma Scale (GCS) score was E4M5V2. Despite drainage of CSF by an external lumbar drain (ELD) the patient deteriorated overnight to a GCS score of E1M4V1. A new CT-scan (Fig. 1) showed SAH with an aneurysm of the superior cerebellar artery and an increased hydrocephalus. The ELD was replaced by an external ventricular drain (EVD). The patient developed high fevers. Blood cultures remained negative. Despite optimal therapy, the patient’s condition deteriorated. After 12 days of intensive treatment, medical care was withdrawn after which the patient died.
Discussion: Our patient developed invasive pneumococcal disease after total knee replacement, causing pneumococcal meningitis. Intracerebral haemorrhage is seen in 9% of pneumococcal meningitis. SAH in patients with meningitis may be induced by vessel erosion, due to vasculitis or aneurysm formation, associated with an inflammatory response in the subarachnoid space due to meningitis. Although post-mortem evaluation of the brain was not performed, our hypothesis is that our patient developed hydrocephalus and meningitis causing vasculitis, which induced rupture of the aneurysm of the superior cerebellar artery, resulting in SAH.

Effect of bronchoscopy on gas exchange and respiratory mechanics in critically ill patients with atelectasis: an observational cohort study

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¹VUmc, Intensive Care, Amsterdam, Netherlands; ²Noordwest Ziekenhuisgroep, Anesthesiology, Alkmaar, Netherlands

Background: Atelectasis is frequently encountered in critically ill patients with respiratory failure and may lead to complications. Literature on this topic focused on the effects of bronchoscopy on re-expansion of the collapsed pulmonary region on chest X ray and short term evaluation of gas exchange. Results are conflicting and effects on respiratory mechanics are largely missing. The aim of the present study is to evaluate the effect of bronchoscopy on gas exchange and respiratory mechanics in intensive care unit patients with atelectasis.

Methods: Retrospective, observational, single-centre cohort study in patients undergoing bronchoscopy for atelectasis in the ICU of a tertiary University hospital from January 2011 till July 2015. Response to bronchoscopy was deemed clinically relevant based on improvement of oxygenation, as defined by increase of the ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO₂/FiO₂ ratio) > 20 and improvement of ventilation, defined as decrease of > 2 mmHg in partial pressure of CO₂ in arterial blood (PaCO₂). Longitudinal changes in continuous outcome variables on gas exchange and respiratory mechanics after bronchoscopy were examined at 1, 12 and 24 hours post bronchoscopy.

Results: We included 88 patients undergoing 101 bronchoscopies for atelectasis. Bronchoscopy was beneficial in most patients by improving oxygenation (76%), ventilation (59%) or both (49%) for at least 24 hours (Table 1). Patients with a low baseline recording of PaO₂/FiO₂ ratio and high baseline recording of PaCO₂ seemed to benefit most. A statistically significant increase in PaO₂/FiO₂ ratio was seen after 1, 12 and 24 hours post bronchoscopy (resp. mean difference compared to baseline 29.94mmHg, 49.56mmHg, 48.51mmHg). As for the arterial- end tidal CO₂ difference, the decrease was seen after 12 hours and 24 hours post bronchoscopy (resp. mean difference compared to baseline -2.70mmHg and -3.55mmHg). In addition, a significant improvement was found in dynamic compliance (median difference to baseline -8.5 ml/cmH₂O), Peak pressure (Ppeak) and driving pressure (Pdriving) (median difference to baseline -2 cmH₂O), with positive effects lasting for up to 24 hours. When performing a subgroup analysis on pressure control ventilated patients these observed differences persisted or became even larger (Table 2). Lastly, bronchoscopy was safe, since only mild complications were seen in 13% of patients.

Conclusions: In conclusion, bronchoscopy for atelectasis is beneficial in most ICU-patients, in terms of improved oxygenation, ventilation and respiratory mechanics, whereas these positive effects lasted for at least 24 hours. In addition, bronchoscopy is safe in these patients.

Table 1. Indication, main findings, interventions during bronchoscopy and associated outcome and side effects

<table>
<thead>
<tr>
<th>Findings during bronchoscopy and on chest X ray (CXR)</th>
<th>Number of atelectatic lobes on CXR*</th>
<th>97 (96)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>60 (59)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>31 (31)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>6 (6)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of obstructed (secondary) bronchi found during bronchoscopy</th>
<th>101 (100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>33 (33)</td>
</tr>
<tr>
<td>1</td>
<td>30 (30)</td>
</tr>
<tr>
<td>2</td>
<td>25 (25)</td>
</tr>
<tr>
<td>3</td>
<td>10 (10)</td>
</tr>
<tr>
<td>&gt;3</td>
<td>3 (3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type of bronchoscopic intervention</th>
<th>Intervention performed (suctioning of secretion and BAL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchial lavage</td>
<td>20 (20)</td>
</tr>
<tr>
<td>Suctioning of secretion (without or without obstruction of bronchi)</td>
<td>81 (80)</td>
</tr>
<tr>
<td>Suctioning of secretion with obstruction of bronchi</td>
<td>68 (67)</td>
</tr>
<tr>
<td>Intervention performed (suctioning of secretion and BAL)</td>
<td>90 (89)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome and side effects</th>
<th>Improvement on chest X ray</th>
<th>Improvement in oxygenation</th>
<th>Improvement in ventilation</th>
<th>Improvement in both oxygenation and ventilation***</th>
<th>Bronchoscopy reported safe</th>
<th>Complications†††</th>
<th>Desaturation between 80-90%</th>
<th>Discomfort requiring more sedation</th>
<th>Hypotension due to sedation</th>
<th>Arrhythmia</th>
<th>Values are N (%) unless otherwise stated</th>
</tr>
</thead>
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<tr>
<td>Bronchoscopy reported safe</td>
<td>101 (100)</td>
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<td></td>
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<td></td>
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<tr>
<td>Complications†††</td>
<td>13 (13)</td>
<td></td>
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<td></td>
<td></td>
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<td>Desaturation between 80-90%</td>
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<tr>
<td>Discomfort requiring more sedation</td>
<td>1 (1)</td>
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<tr>
<td>Hypotension due to sedation</td>
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<tr>
<td>Arrhythmia</td>
<td>1 (1)</td>
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*Four missing, atelectasis were seen on CT scan
†Clinical improvement oxygenation defined as increase of PaO₂/FiO₂ ratio > 20 (11, 12)
‡Clinical improvement ventilation defined as decrease of PaCO₂ > 2mmHg (13)
§Mild complications not requiring early termination of bronchoscopy, no severe complications found
Table 2. Results of bronchoscopy on gas exchange and respiratory mechanics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Outcome</th>
<th>Difference to baseline</th>
<th>p-value</th>
<th>Subgroup analysis</th>
<th>Difference to baseline</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaO2/FiO2 ratio overall</td>
<td>Baseline</td>
<td>254 (150)</td>
<td>38.4 (5.3)</td>
<td>36.3 (6.5)</td>
<td>0.052</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1 hour</td>
<td>254 (150)</td>
<td>38.4 (5.3)</td>
<td>36.3 (6.5)</td>
<td>0.052</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>2 hours</td>
<td>254 (150)</td>
<td>38.4 (5.3)</td>
<td>36.3 (6.5)</td>
<td>0.052</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>4 hours</td>
<td>254 (150)</td>
<td>38.4 (5.3)</td>
<td>36.3 (6.5)</td>
<td>0.052</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>12 hours</td>
<td>254 (150)</td>
<td>38.4 (5.3)</td>
<td>36.3 (6.5)</td>
<td>0.052</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>24 hours</td>
<td>254 (150)</td>
<td>38.4 (5.3)</td>
<td>36.3 (6.5)</td>
<td>0.052</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Arterial pH</td>
<td>Baseline</td>
<td>37.5 (7.6)</td>
<td>37.5 (7.6)</td>
<td>0.052</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>1 hour</td>
<td>37.5 (7.6)</td>
<td>37.5 (7.6)</td>
<td>0.052</td>
<td>&lt;0.001</td>
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<td>0.052</td>
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</tbody>
</table>

Determination of tobramycin serum concentrations in ICU patients treated with selective decontamination of the digestive tract: a prospective study

H. Dijkstra1, J. De Zee2, M. van Hulst1, M. Luinstra1, N. Holman1

1Martini Hospital, Clinical Pharmacy, Groningen, Netherlands; 2University of Groningen, PharmacoTherapy-Epidemiology-Economics, Groningen, Netherlands

Background: Selective decontamination of the digestive tract (SDD) is used in intensive care units to prevent nosocomial infections. The antibiotics used are considered safe as they are not absorbed from the gastrointestinal tract. However, literature shows that tobramycin serum levels have been detected in critically ill patients [1,2]. The aim of this study is to evaluate the extend of systemic absorption of tobramycin. The secondary aim is to identify risk factors that may contribute to an increased risk of absorption of tobramycin.

Methods: The study performed was a single-centre observational prospective cohort study. Inclusion criteria were: admission on the ICU and administration of SDD. Exclusion criteria were: admission to the burn ICU, parental or pulmonary tobramycin up to 72 hours prior to SDD treatment and patients not receiving SDD four times per 24 hours. Depending on the duration of stay, tobramycin serum concentrations were determined on the 3th, 7th, 10th and 14th day after the start of SDD. Patients without measurable tobramycin levels were defined as non-cases, whereas patients with measurable tobramycin levels were defined as cases.

Results: Six of 45 patients (13%) had detectable tobramycin levels, of which none had a high level (≥ 1.0 mg/L). The prevalence of sepsis (P = 0.03), abdominal sepsis (P = 0.002), impaired renal function (P <0.001), CVVH (P <0.001) and the use of a suppository (P <0.001) was significantly higher in the case group. The duration of treatment in general (P = 0.008) and of the SDD suspension (P = 0.008) was also longer in the case group.

Conclusion: Potential risk factors for detectable tobramycin levels are (abdominal) sepsis, impaired renal function and CVVH, the use of a SDD suppository and duration of treatment. Further research is necessary so that the SWAB guideline can provide more information about the necessity and frequency of measuring tobramycin serum levels, the risk factors for detectable levels and how to handle detectable or high tobramycin levels.

References:

Postoperative nausea and vomiting in the critical care unit: opportunity for improvement

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UMC Groningen, Critical Care, Groningen, Netherlands

Background: Postoperative nausea and vomiting (PONV) is one of most frequent side effect after anesthesia, occurring in 30% of unselected patients and up to 70% of “high-risk” patients [1]. Postoperative patients admitted to the critical care unit are at high risk for PONV mostly due to prolonged thoracic or abdominal surgery. PONV is a complex physiologic phenomenon involving multiple neurophysiologic pathways with both central and peripheral receptor mechanisms. As PONV may be effectively reduced by adherence to standards, it can also be used as a marker for quality of care.[2]

Universitair Medisch Centrum Groningen (UMCG) has a protocol for the treatment of PONV. Aim of our study is to investigate the documentation and treatment of PONV in our critical care department.

Methods: All patients who were admitted to the critical care unit at the UMC between 1 January 2017 and 31 March 2017 after elective or emergency surgery were considered eligible for the study and were sequentially screened. Patients included were those involving all main...
surgical specialties. Medical and nursing charts were screened for remarks considering PONV as well as prescription data for antiemetic medication during the first 48 hours, or until discharge.

**Results:** 289 patients were included in the study. 25 patients were identified during preoperative screening as high risk for PONV and received prophylactic medication intraoperatively. 64 were not screened due to emergency surgery. 202 (69.8%) patients had documentation on PONV in their medical (31.4%), nursing (173;85.6%) or both (26;12.8%) charts. A total of 85 (29.4%) patients experienced PONV for which 65 (76.4%) received medication. In 87 (30.1%) patients no documentation on PONV was registered, 5 (5.7%) of these patients received PONV medication.

**Conclusion:** The most striking result of the present study is that routine documentation of PONV seems to be insufficient. The registered incidence in the present study was lower than reported in other studies with high-risk patients. This study suggests that PONV is inadequately documented in the critical care department and prevalence might be underestimated, resulting in possible undertreatment of patients with PONV. Increased awareness and documentation should be a concern in the critical care department.

**References:**

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**P 08**

**Caregivers' perceptions towards communication with mechanically ventilated patients: The results of a multicenter survey**

C.E. IJssennagger1, S. Ten Hoorn1, A. van Wijk1, J.M. van den Broek2, A.R. Girbes1, P.R. Tuinman1

1VUmc, ICI, Amsterdam, Netherlands, 2Zaans Medisch Centrum, IC, Zaandam, Netherlands

**Background:** It is well-studied that mechanically ventilated (MV) patients often experience difficulties with communication. However, the opinions of health care professionals on this subject remain unknown. Moreover, communication with MV patients is becoming increasingly important since intensive care (ICU) guidelines aim to reduce the use of sedatives, thus it is expected that more patients will be awake and have communication needs. The purpose of this study was to investigate ICU health care providers' perception towards communication and associated problems with MV patients. The primary aim was to quantify the extent of the problem and to determine its effect on patient care and job satisfaction.

**Methods:** A multicenter survey study was conducted among nurses, residents and intensivists of 15 ICUs in the Netherlands using an online questionnaire.

**Results:** Communication difficulties were experienced in half of the interactions with MV patients, resulting in daily loss of valuable time for 43% of the professionals. Job satisfaction was negatively affected in 43% of the participants, primarily with feelings of unfulfillment (76%) and frustration (72%). Negative effects on patient care were psycho-emotional care (91%), above general care (80%), symptom assessment (73%), plan-of-care (72%) and end-of-life care (72%). To facilitate communication, one-third of respondents reported to regularly use augmentative and alternative communication methods, but the most effective and preferred method remained the use of basic gestures. In addition, half of respondents indicated to be dissatisfied with their personal communication skills with MV patients. Over 75% of the caregivers never received training in communication with MV patients, while most of them would like to receive training in the future.

**Conclusion:** In half of the interactions with MV patients, health care professionals experience communication difficulties. These difficulties frequently lead to negative effects on job satisfaction and even more important patient care according to the responders. These results emphasize the need for improvements such as the development of communication protocols, skills training and continued research into new communication methods.

**References:**

**Table:** Data are presented in N (%), *median and [IQR] with a total of 457 respondents.
Self-reported attitude and practice regarding sleep optimization during ICU admission

F.M. van Iersel, M.S. Schinkelshoek, D.J. van Westerloo
LUMC, Intensive Care, Leiden, Netherlands

Background: Patients in the ICU are known to suffer from disrupted sleep (1). Poor sleep is associated with important adverse physical consequences for patient outcome. Taken together, sleep disruption is a significant problem in the ICU setting and it is widely believed that improvements in the quality and quantity of sleep during critical illness would improve care and outcome. We investigated the beliefs and clinical practice of ICU health care workers regarding sleep optimization in critically ill patients.

Methods: In an academic teaching hospital in the Netherlands, ICU physicians and nurses were invited to complete an 18-question questionnaire about sleep. In total 104 ICU workers (64% of invitees, 90 nurses and 24 physicians) responded to our questionnaire.

Results: In total, 90% of the respondents believed that sleep deprivation in the ICU is a major concern especially (as 80% stated) in patients admitted to the ICU for longer than 1 week. An astounding 91% of ICU workers was convinced that improving sleep will lead to a shorter ICU admission time. However, only 38% felt that sleep optimization gets enough attention in daily practice and only 42% was convinced that sound and light minimization during the night is adequate. 65% of respondents felt that patients are frequently disturbed during the night by interventions that might very well have been postponed until morning. Although 65% of respondents stated that a bad nights sleep is included in the handover to the day shift only 48% said that the day shift then usually makes a plan to improve sleep for the following night. With regard to sleep medication, 65% of ICU workers stated that benzodiazepines work well although 53% of respondents state that usually the effect wears off after three nights. In these cases, 65% of respondents felt that starting continuous IV sedation was appropriate.

Conclusions: The large majority of ICU workers acknowledge the potential adverse effects of sleep deprivation in the ICU and feel this should be improved. In sharp contrast, the majority of ICU workers is also convinced that in actual clinical practice, sleep optimization does not get enough attention form ICU workers.

As a result of this questionnaire, quantitative and qualitative sleep scores were introduced in our ICU that are discussed during rounds on a daily basis. Additionally, new interventions and medications to improve sleep were introduced and ICU workers were educated with regard to continuous sedation.

Reference:

Metabolic acidosis with elevated lactate due to auto-intoxication.

S.H. Cuijpers, J. van Rosmalen, D. Ramnarain, J. van Oers
ETZ Elisabeth–Twee steden, Intensive Care, Tilburg, Netherlands

Introduction: Auto-intoxication happens quite frequently and often needs Intensive care admission. We present a case of a patient with an auto-intoxication and a metabolic acidosis with elevated lactate.

Case: A 48-year-old woman, with a history of DM2, presented at the emergency department after she was found unconscious at home. Several empty medication strips with ibuprofen, metformin, Panadol and bromazepam were found. With a GCS of 3 she had to be intubated, and mechanical ventilation was started. She was haemodynamically stable and further physical examination revealed no abnormalities. Laboratory studies are described in table 1. Arterial blood gas analyses showed a severe metabolic acidosis, pH<6.75 with a high anion gap of 29,4 mmol/l [Na+ - (Cl- + HCO₃⁻)] [N 8-16 mmol/l] and immeasurable high lactate, >31 mmol/l. As the patient was not in shock and there were no signs of tissue hypoxia, no signs of hepatic failure and no significant levels of paracetamol and metformin in the serum we could not explain the elevated lactate. Her history of auto-intoxication and an osmol gap of 39 mOsmol/kg [measured serum osmol 331 minus calculated osmol (2 x Na+) 292] suggested an co-intoxication with other toxins. Therefore the patient’s family was send home to search for clues of a possible ingestion. They found a bottle of ethylene glycol behind the heater. Toxicological screening of serum showed an ethylene glycol level of 242mg/l. Screening for ethanol, methanol, aspirin and toluene were all negative. The patient developed mild acute kidney injury, GFR 34 ml/min. The patient was admitted to the ICU and ethanol infusion and haemodialysis were initiated. Her renal failure recovered completely. After 2 days she could be extubated and discharged from the ICU.
Discussion: Ethylene glycol is a non-toxic liquid, but due to metabolites, can cause severe organ damage. The toxic effects occur from an ingestion of 200mg/kg or a serum level of 200mg/L. Ethylene glycol is metabolized in the liver by alcohol dehydrogenase to glycolic acid which is metabolized to glyoxylic acid and oxalic acid, which causes acute kidney injury. Glyoxylic acid is the major metabolite that causes the metabolic acidosis. The molecular structure of glycolic acid and to a lesser extend glyoxylic acid is similar to lactate and can cause a false high elevated lactate concentration due to analytical interference. Our hospital uses a ABL 90 FLEX plus blood gas analyser, which cannot differentiate between high lactate or ethylene glycol metabolites.

Table 1: Laboratory Results

<table>
<thead>
<tr>
<th>Substance</th>
<th>Reference</th>
<th>Day 2</th>
<th>Day 1</th>
<th>Day 1</th>
<th>Day 1</th>
<th>Day 1</th>
<th>Day 1</th>
<th>Day 1</th>
<th>Day 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloride</td>
<td>97-107 mmol/L</td>
<td>113</td>
<td>102</td>
<td>101</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>49-99 mmol/L</td>
<td>142</td>
<td>173</td>
<td>109</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethanol</td>
<td>promile</td>
<td>-0.1</td>
<td>1.8</td>
<td>1.5</td>
<td>1.0</td>
<td>0.2</td>
<td>1.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethylene glycol</td>
<td>mg/L</td>
<td>242</td>
<td>162</td>
<td>150</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactate</td>
<td>0.5-1.6 mmol/L</td>
<td>&gt;31.0</td>
<td>&gt;31.0</td>
<td>&gt;31.0</td>
<td>&gt;31.0</td>
<td>18.0</td>
<td>13.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potassium</td>
<td>3.5-5.0 mmol/L</td>
<td>5.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum-pH</td>
<td>7.35-7.45</td>
<td>&gt;6.75</td>
<td>&gt;6.87</td>
<td>&gt;7.13</td>
<td>&gt;7.30</td>
<td>&gt;7.28</td>
<td>&gt;7.54</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium</td>
<td>134-145 mmol/L</td>
<td>146</td>
<td>151</td>
<td>158</td>
<td>156</td>
<td>145</td>
<td>142</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urea</td>
<td>2.5-4.6 mmol/L</td>
<td>10.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arterial CO2</td>
<td>8-14 mmol/L</td>
<td>29.4</td>
<td>51.2</td>
<td>38.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**Entreatable Professional Activities of Intensive Care Medicine (EPAsICM): The next step towards excellence in intensive care medicine training**

E.A.P. van Bockel¹, P.A. Walstock¹, W.N.K.A. van Mook², M.S. Arbous³, R. Tepaske⁴, J.D. van Hemel³, M.C.A. Müller⁴, J.E. Tulleken⁴

¹UMCG, ICU, Groningen, Netherlands, ²MUMC, IC, Maastricht, Netherlands, ³LUMC, IC, Leiden, Netherlands, ⁴AMC, IC, Amsterdam, Netherlands

**Background:** We present Entrustable Professional Activities of Intensive Care Medicine (EPAsICM) as a new workplace based assessment tool in the competency based training of intensivists. Entrustable Professional Activities (EPAs) are activities to be entrusted to a trainee once he has attained sufficient competence. EPAs emphasise the role of trust between trainees and supervisors.

The Competency Based Training in Intensive Care Education (CoBaTrICE) program took the first step developing common standards of ICM training. Entrustable Professional Activities (EPAs) are to be entrusted to a trainee once he has attained sufficient competence. EPAs emphasise the role of trust between trainees and supervisors. The program was developed as an appealing workplace based assessment tool to support the development of EPAs. EPAsICM are a first step in implementing EPAsICM in the Dutch ICU training program.

**Methods:** We present EPAsICM as a new and helpful tool for assessing competence of trainees of ICM. We have developed EPAsICM that represent the final products of ICM training. EPAsICM are descriptors of what intensivists actually do in practice and the grading scale aligns with daily judgement of trainees of ICM. EPAsICM emphasise the role of trust in assessing trainees. Further studies are needed and planned to learn more about implementation of this new workplace assessment tool as well as about content validity, interrater variability and generalisability across other countries.

**Results:** The expert panel agreed on 15 typical ICU clinical problems or situations as EPAsICM. Together these EPAsICM cover the competencies of CoBaTrICE and CanMEDS. The grading system is a 5-point entrustment scale based on the amount of supervision a trainee needs. Implementation of EPAsICM in the Dutch ICU training program started in April 2017 as a pilot project, and was fully implemented in September 2017.

**Conclusion:** We present EPAsICM as a new and helpful tool for assessing competence of trainees of ICM. We have developed EPAsICM that represent the final products of ICM training. EPAsICM are descriptors of what intensivists actually do in practice and the grading scale aligns with daily judgement of trainees of ICM. EPAsICM emphasise the role of trust in assessing trainees. Further studies are needed and planned to learn more about implementation of this new workplace assessment tool as well as about content validity, interrater variability and generalisability across other countries.

Table 1: List EPAsICM

<table>
<thead>
<tr>
<th>EPA ICIM</th>
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</thead>
<tbody>
<tr>
<td>1. Prooperative management care of surgical patient</td>
</tr>
<tr>
<td>2. Consultation and triage of potential ICU patients</td>
</tr>
<tr>
<td>3. Management of patient with sepsis</td>
</tr>
<tr>
<td>4. Management of patient with acute abdominal condition</td>
</tr>
<tr>
<td>5. Management of patient with cardiogenic shock and/or cardiovascular disorders</td>
</tr>
<tr>
<td>6. Management of patient with massive bleeding</td>
</tr>
<tr>
<td>7. Management of patient with complex ventilation and oxygenation problems</td>
</tr>
<tr>
<td>8. Management of patient with altered consciousness</td>
</tr>
<tr>
<td>9. Management of patient with acute (chronic) liver failure</td>
</tr>
<tr>
<td>10. Management of trauma patient</td>
</tr>
<tr>
<td>11. Management of patient with acute renal failure</td>
</tr>
<tr>
<td>12. Management of patient with renal failure</td>
</tr>
<tr>
<td>13. Management of patient with metabolic disturbance</td>
</tr>
<tr>
<td>14. Management of long stay ICU patient</td>
</tr>
</tbody>
</table>

Table 2: Supervision levels (abbreviated)

<table>
<thead>
<tr>
<th>Grading scale: Supervision level</th>
</tr>
</thead>
<tbody>
<tr>
<td>I Direct supervision</td>
</tr>
<tr>
<td>II Proactive supervision</td>
</tr>
<tr>
<td>III Responsive supervision</td>
</tr>
<tr>
<td>IV Postponed supervision</td>
</tr>
<tr>
<td>V Provide supervision</td>
</tr>
</tbody>
</table>

* Trainee remains under final responsibility of supervisor

**Table 1:** Laboratory Results

**Table 2:** Supervision levels (abbreviated)
A multidisciplinary approach at the emergency department to admit potential organ donors for end-of-life care to the intensive care unit


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Background: In 2014, we performed a cohort study in which we found that initiation of end-of-life care in acute settings outside Intensive Care Units (ICUs) results in under-recognition of potential organ donors, particularly in patients with an acute devastating brain injury admitted to the emergency department (ED). (1) The aim of the present study is to implement a novel multidisciplinary approach for organ donation at the ED in order not to miss potential organ donors.

Methods: In a prospective intervention study, we implemented this approach in six hospitals in the Netherlands. The approach was used in patients admitted to the ED with a devastating brain injury. The decision to withdraw life sustaining treatment was made at the ED in patients without contra indications for organ donation, an ICU admission for end-of-life care was considered. This was communicated accordingly with the family. Every ICU admission for end-of-life care was evaluated. Interviews were conducted with emergency physicians, neurologists and ICU physicians according to a standardized questionnaire. This standardized interview focused on medical decisions that were made and difficulties arising during hospitalization.

Results: From 1 January 2016 to November 2017 data were collected on the number of patients admitted to the ED with acute brain injury in six hospitals. In total, 50 potential organ donors were admitted to the ICU for end-of-life care. Donation was either requested in the ED (12%), ICU (78%), neurology department (4%), or donation was not requested (6%). Out of 48 donation requests, 26 families (51%) consented to donation. This led to 21 successful organ transplantations. In four of these 21 patients family points raised during the interviews with professionals were: explaining the end-of-life care. Donation was either requested in the ED (12%), ICU (78%), neurology department (4%), or donation was not requested (6%). Out of 48 donation requests, 26 families (51%) consented to donation. This led to 21 successful organ transplantations. In four of these 21 patients family consent was obtained to intubate them and initiate invasive mechanical ventilation solely for the purpose of organ donation. The most important points raised during the interviews with professionals were: explaining the non-therapeutic ICU admission to the family, the location where donation should be requested (ED/ICU), suitability for organ donation and utility of ICU resources.

Conclusion: A close collaboration between the ED, neurology department and ICU is necessary and achievable in order not to miss potential organ donors in patients with acute brain injury with a futile prognosis in the ED.

Reference

Sedation with midazolam and the influence of increasing age in ICU patients

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1Martiniziekenhuis, Klinische farmacie, Groningen, Netherlands, 2State university Groningen, Farmacy, Groningen, Netherlands

Background: Midazolam is used as a sedative in critically ill patients on the intensive care unit (ICU). A main advantage of midazolam is its rapid onset of action. Midazolam is mainly metabolized in the liver by the co-enzyme CYP450-3A4 into 1-hydroxymidazolam and both are equally pharmacologically active drugs. After conjugation of 1-hydroxymidazolam into midazolam-glucuronide (10% activity) it is eliminated by the kidney. In the elderly midazolam accumulation can result in severe adverse effects, due to increased sensitivity to benzodiazepines.

The aim of the present study is to evaluate in patients with increasing age the midazolam dose by continuous infusion to obtain a sedation level of RASS ≤ -2.

Methods: In this retrospective study we included adult patients (≥18 years of age), admitted to the ICU in the Martini Hospital Groningen who were mechanically ventilated and sedated with continuous infusion of midazolam for at least 48 hours. After 24 hours of sedation (estimated time to reach steady state midazolam plasma levels), the mean dose of midazolam over a second time period of 24 hours (whilst RASS during the whole 24 hours was at least ≤ -2) was calculated. Exclusion criteria were the use of other sedatives, administration of CYP3A4 inhibitors or inductors, and cerebral comorbidity. Correlation between age and mean midazolam dose was calculated. Results Data of 53 patients were evaluated. Finally data of 37 patients were included in the analysis. In table 1 patient characteristics are summarized. In Figure 1 Age and midazolam dosage to obtain RASS ≤ -2 ( R2 0.305, p 0.001) are shown.

Discussion: In our population, older age correlated with a decrease in administered dose of midazolam to obtain RASS ≤ -2. In a study of Bremer et al. also lower midazolam infusion rates were required to achieve sedation in patients older than 70 years as compared to patients younger than 50 years of age. Midazolam clearance is influenced by both liver and kidney function. Impairment of these functions in elderly ICU patients is likely. Therefore it is suggestive that the reduced dose requirement of midazolam is due to both increased sensitivity and accumulation. Careful dosing of midazolam is advocated in ICU patients of increasing age.

References:
Reducing administrational burden: a core set of quality indicators for effective quality improvement and efficient accountability

M. Zegers, R.J. Verhage, J.G. van der Hoeven
Radboudumc, Intensive Care, Nijmegen, Netherlands

Background: Healthcare professionals suffer from the amount of quality indicators they register. Moreover, they do not perceive all quality indicators as meaningful for patient care or quality improvement. The aim of this study, part of Experiment ZIRE (zinvolle registratie), was to select a core set of indicators for effective quality improvement and efficient accountability in the Intensive Care Unit (ICU).

Methods: In 2017, we conducted a two-phase adapted Delphi study in four hospitals with 34 experts: 13 ICU physicians, 11 ICU nurses and 10 ICU survivors and relatives from the FCIC (Family and Patient Centered Intensive Care), the Dutch foundation for ICU survivors and relatives. We identified all quality parameters regarding the ICU (n=122). We asked participants to indicate the relevance of each quality parameter for quality improvement (round 1). Subsequently, the participants discussed the results of round 1 and determined the final core set of quality parameters in three focus group interviews (round 2).

Results: The participants selected a core set of 16 parameters (see table 1).

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Table 1: core set of indicators for quality improvement in the ICU

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Reported by</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Team climate</td>
<td>Health care professional</td>
<td>SMR/ ICU-mortality</td>
</tr>
<tr>
<td>Safety culture</td>
<td></td>
<td>ICU-readmissions within 48 hours</td>
</tr>
<tr>
<td>CRM-compliance</td>
<td></td>
<td>Complications: delirium and delirium</td>
</tr>
<tr>
<td>NVIC quality visitation</td>
<td></td>
<td>Learn and improve after serious incidents</td>
</tr>
<tr>
<td>Experiences of ICU survivors and relatives from post-ICU clinic visits</td>
<td>Patient and Relative</td>
<td>Quality of life of ICU survivors 5 years after ICU admission</td>
</tr>
<tr>
<td>Questionnaire experiences relatives Complaints</td>
<td></td>
<td>Quality of life of relatives Physical, mental and cognitive problems 5 years after ICU admission (e.g. fatigue, frailty, anxiety, depression, PTSD, loss of memory)</td>
</tr>
<tr>
<td>Socio-economic impact (e.g. resumption of work)</td>
<td></td>
<td>Cost-effectiveness of ICU care (quality of life versus costs)</td>
</tr>
</tbody>
</table>

Prominent aspects of the core set were experiences and short and long term outcomes reported by ICU survivors, such as physical, mental and cognitive problems after ICU admission.

Interestingly, also experiences and mental problems reported by relatives were part of the core set.

Conclusion: In conclusion, healthcare providers, ICU survivors and relatives selected a core set of 16 parameters for effective quality improvement and efficient accountability in the ICU. In 2018 and 2019, the effect of using a core set of parameters on patient outcomes will be evaluated.

Our hypothesis is that registering less quality indicators will lead to more room for quality improvement and ultimately to better outcomes and experiences for patients and relatives.

Experiment ZIRE is part of ‘Innovation Place Cure’, initiated by the Dutch Ministry of Health. They facilitate the exemption for supplying mandatory quality indicators.
Limited usefulness of the 4T-score for pre-test probability in patients with confirmed heparin-induced thrombocytopenia during extracorporeal life support

T.S.R. Delnoij, Y. Henskens, E. Pragt, R. Lorusso, S. Oei, M. van de Poll, J.E.M. Sels

MUMC, Intensive Care, Maastricht, Netherlands

Abstract: Extracorporeal life support (ECLS) requires the use of heparin to prevent clotting and thrombosis. Type 2 heparin-induced thrombocytopenia (HIT) is a rare but life-threatening complication. The frequently used (ELISA) screening test has a low specificity and requires confirmatory testing. The 4T-score is clinically used to determine the pretest probability and increase specificity of the screening test. The 4T-score accounts for Thrombocytopenia, Timecourse of thrombocytopenia, Thrombotic sequelae, and other probable causes of Thrombocytopenia. Cut-off values for the 4T-score are ≤3, ≤5 and ≤8 (low, intermediate and high probability respectively). However, thrombocytopenia is very common and the applicability of the 4T-score in these patients is unknown. We sought to evaluate the usability of the 4T-score to detect HIT in ECLS patients.

Methods: 271 consecutive patients receiving ECLS treatment in our institution from 2007-2017 were evaluated. We identified all patients in which a HIT screening test was performed and calculated the 4T-score for these patients. HIT was confirmed by a heparin-induced platelet aggregation assay (HIPAA). Mann-Whitney U test was used for statistical analysis

Results: In 20 patients (7.3%) a HIT screening test (ELISA) was performed. Of these, 4 (1.4%) were confirmed as positive with a HIPAA. All confirmed HIT patients had a positive screening test. A positive screening test had a positive predictive value of 80% for the diagnosis of HIT. Surprisingly, the mean 4T-score was identical in patients with a positive and a negative HIPAA (3.5 (2.5) vs 3.2 (1.7); p=0.44).

Conclusion: In this cohort of ECLS patients the usual cut-off values for the 4T-score had a low sensitivity to diagnose HIT. Thrombocytopenia during ECLS should raise suspicion of HIT and may warrant confirmatory testing even when 4T-score is low.

Outcome of patients with acute pancreatitis requiring ICU treatment in a tertiary referral hospital

L.M. Kropman

Maastricht UMC+, Intensive Care, Maastricht, Netherlands

Abstract: Mortality of acute necrotizing pancreatitis is very high. When organ failure occurs and ICU treatment is indicated mortality rates exceeding 60% have been reported. In the last decade, management of necrotizing pancreatitis has evolved to a multimodal multidisciplinary treatment. The need for specific expertise has increased the number of referrals of patients to centers with specific expertise. Aim of this study was to evaluate clinical outcome of patients with acute pancreatitis admitted to our ICU with a special emphasis on referred patients.

Methods: We retrospectively analysed all adult patients with acute pancreatitis admitted to our ICU in a tertiary referral centre for pancreatic surgery (approximate adherence 180000 people) from 2012 to 2017. We evaluated demographics, clinical data on admission, number of therapeutic interventions (e.g. CT-guided drainage, video-assisted retroperitoneal drainage (VARD)) and clinical outcome. Statistical tests used were Mann-Whitney U-test and chi-square test.

Results: We identified 43 patients, of which 18 patients were admitted from our own adherence area (non-referred group=NRG) and 24 were referred from regional hospitals (referred group=RG). One patient transferred from outside our region was excluded from the analysis. Based upon admission numbers from our own adherence area we calculated an incidence of 2:100000 per year (18:180000/5 years). In referred patients (RG) median duration of hospital admission at the moment of transfer was 9.5 (IQR 9.25) days, median ICU admission 2 (IQR 27) days. For the entire cohort in-hospital mortality was 28.6%, ICU mortality 9.5%. More therapeutic interventions were performed in referred patients (CT-guided drainage: 7/18 (38.9%) in the NRG vs 17/24 (71%) in the RG. p= 0.26). Referred patients had a significantly longer ICU stay (median 28 days (IQR 33.8) vs. 6.5 days (IQR 17.3), p=0.02). There was no significant difference in hospital mortality between referred and non-referred patients (25% versus 33% respectively, p=0.55).

Conclusion: In conclusion, ICU admission for acute pancreatitis has a relatively low incidence and high mortality. Transfer of patients to tertiary care seems to occur preferentially when a therapeutic intervention is warranted or when long ICU stay is expected. Referred patients stayed longer in the ICU than non-referred, but no significant differences in mortality were found in this small cohort. Further research is needed to see whether earlier referral to high volume centers could improve outcome of patients with acute pancreatitis requiring ICU treatment.
A rare case of pulmonary and abdominal tuberculosis in a young immunocompetent patient with fatal outcome

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Diakonessenhuis, Intensive Care, Utrecht, Netherlands

Introduction: Tuberculosis (TB) is an infectious disease developing in only 10-15% of the patients infected with the bacillus Mycobacterium tuberculosis. An immunocompromised status is a major risk factor for developing disease. TB typically affects the lungs, but can affect any other part of the body. Extrapulmonary tuberculosis represented 15% of the incident cases in 2016, with abdominal tuberculosis being even more rare. We report on disseminated tuberculosis with intestinal perforation in a young immunocompetent patient.

Case report: A 44-year old male who recently travelled to India, with no medical history, presented to our Emergency Department because of coughing, hiccups and weight loss (10 kg in a couple of weeks). Physical examination showed a cachectic tachypneic patient (22 breaths/minute). The chest X-ray revealed extensive bilateral consolidations (Figure 1A). Within 12 hours clinical deterioration occurred with respiratory insufficiency and a decreased level of consciousness, for which the patient was admitted to the Intensive Care Unit. Invasive mechanical ventilation and broad-spectrum antibiotics (ceftriaxone, metronidazole and gentamicin) were started. A CT-scan of the thorax and abdomen showed extensive bilateral cavitating pulmonary consolidations, intraperitoneal free air and fluid, with an aberrant appearance of the terminal ileum suspected for perforation (Figure 1D). Subsequent emergency laparotomy revealed three lesions of the ileocecal region and ileocecal resection was performed. Histopathology showed necrotizing granuloma. Sputum was positive on auramine staining and PCR for M. tuberculosis was positive. HIV testing was negative. Tuberculostatics (moxifloxacin, rifampicine, isoniazide, ethambutol) were started. Despite treatment, multiple organ failure rapidly developed and because of progressive severe respiratory failure, he was transferred to an university hospital for veno-venous extracorporeal membrane oxygenation. However, refractory septic shock with hepatic, renal and respiratory failure persisted. Hereupon treatment was discontinued and the patient died soon afterwards.

Discussion: TB is rare in the Netherlands, with 5.1 incident cases per 100.000 inhabitants of which only 0,9% (n=8) died due to the disease#_edn1. Intestinal perforation is an uncommon complication of abdominal TB due to the reactive thickening of the peritoneum and subsequent adhesion formations with surrounding tissues. A high level of suspicion is necessary to identify TB in Dutch daily practice. This was present in our case, however, despite immediately started maximum treatment our patient died within 48 hours after admission. This case shows that even young and immunocompetent patients can have a fulminant course of disseminated TB with uncommon complications leading swiftly to death.

#_ednref1 RIVM Tuberculose in Nederland 2015

Figure 1: A:extensive consolidations B:cavitating consolidations C:intraperitoneal free air D:aberrant appearance of terminal ileum suspected for perforation

Uncommon complications of FESS: meningitis and secondary intracranial hemorrhages

R.H. van der Schatte Olivier, M.J. van Dam
UMCU, Anesthesiology, Utrecht, Netherlands

A 35-year old male patient with a medical history of hepatitis B without clinical sequelae was transferred to our hospital with suspected meningitis after functional endoscopic sinus surgery (FESS) two days earlier. On admittance at the emergency department the patient was disoriented, agitated and scoring E3M5V3 on the Glasgow Coma Scale (GCS). That night, while continuing antibiotic therapy, his clinical situation deteriorated with
a right hemiparesis and deterioration of the GCS to E3M5V1. The cranial CT-scan showed multiple intraparenchymal hemorrhages with a significant midline shift and uncal herniation for which an emergency decompressive hemicraniectomy (DHC) left was performed. Postoperatively the patient was admitted to the intensive care unit. Approximately 12 hours after surgery his left pupil became dilated and unresponsive to light. A second CT-scan showed a subtle increase of the midline shift with unchanged hemorrhages (photo).

Without other neurosurgical options, sedation was continued and osmotic therapy started by means of intermittent hypertonic saline (HTS 3%) aiming for a serum value between 155 and 160 mmol/L. Soon after the first bolus of HTS the left pupil, though still dilated, responded to light again. CT-scans on day 3 and 4 demonstrated a subtle improvement of the midline shift and, as possible portes d’entree, lesions of the ethmoid sinus and the medial orbital wall were identified (both 3mm). HTS-therapy was stopped when his left pupil was still dilated but remained responsive to light. Thromboprophylaxis was started. At day 6 sedation was stopped. Scoring E4M6V3 with a right hemiparesis he was successfully extubated and discharged to the medium care.

Now, approximately one year later, after extensive rehabilitation, he lacks fine motor skills of the right arm and hand. Furthermore he has complaints of polyposis nasi for which he will soon undergo FESS.

Discussion: Meningitis and intraparenchymal bleeding though extremely rare are major complications after FESS. This patient suffered not only from meningitis and intraparenchymal hemorrhages but also from a persisting midline shift and a light unresponsive pupil after DHC. Intermittent HTS-therapy was successfully initiated since his pupil soon was light responsive again and on CT-scan a slight decrease of midline shift was objectivated. Although the response to HTS was quite direct, it is not excluded that other factors may also have influenced his recovery.

Reference:

A pathognomonic clinical presentation of the inferior caval vein syndrome

K.H.J. Bos 1,2, C. van der Leij 3, R. de Graaf 7, C.H. Wittens 4, L.M. Kropman 1,2, S.F.M. Heuts 7, R.G.H. Driessen 1,2, M.J.H. Ariës 1,2

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Clinical presentation: A 52-year old male presented to our emergency department with respiratory distress after collapse. His medical history revealed mental retardation and heavy smoking. The patient was clinically in severe shock, with a combined respiratory and metabolic acidosis and an arterial blood saturation of 87%. He was unable to move his legs. Before further diagnostics could be organized, the patient was intubated, intravenous fluids were administered and vasopressors and antibiotics were started.

Diagnostic modalities: On clinical examination, a marble-like discoloration of the abdomen and the lower extremities was observed with signs of severe venous congestion (figure 1). A remarkable sharp line was found a few centimeters below the umbilicus marking the congestion. Transthoracic echocardiography revealed hyperdynamic but empty ventricles without pericardial effusion. On contrast-enhanced Computed Tomography of the thorax and the abdomen, no signs of aortic dissection, pulmonary emboli, or malignancies were found. However, the inferior caval vein (IVC) was thrombosed with suggestions of local compression at the level of the 4th lumbar vertebra by retroperitoneal collections (Figure 2). Subsequently, the caudal part of the IVC and the femoral veins were evidently enlarged. Additional abdominal echocardiography demonstrated evidence of a hyper-echogenic thrombus in the IVC. The patient was admitted to the intensive care unit with a diagnosis of severe distributive shock and paraparesis caused by an acute inferior caval vein syndrome.

Intervention/Therapy: Urgent invasive contrast venography (Figure 3A+B) and subsequent emergency thrombectomy was performed in our hybrid operating room with additional venous recanalization using a 24x159mm Sinus XL Flex stent (Optimed Medical Instruments GmBH, Ettingen, Germany).

Outcome: Post-procedural angiography demonstrated an excellent result without signs of remaining thrombi or contrast stasis (Figure 3C). The marble-like discoloration, the congestion of the lower body and the paraparesis resolved immediately. All supportive measures could be ceased. Discharge to the regular ward followed on the first postoperative day. Additionally imaging modalities excluded gastro-intestinal and urogenital malignancies. Laboratory findings were negative for tumor markers. Invasive diagnostic biopsy of the retroperitoneal collection revealed a large amount of small thrombosed collateral veins. The patient was discharged on the sixth postoperative day with start of oral anticoagulants. Two weeks postoperatively, Magnetic Resonance Venography revealed patency of the stent with a significant decrease of peri-caval vein thrombosis. There were no signs of pathological lymph nodes or malignancy (Figure 4). At present
no cause (except the heavy smoking) was found for the local (probably acute on chronic) thrombosis.

Figure 1: Findings on clinical examination with marble-like discoloration of the abdomen and lower extremities with evidence of venous congestion till umbilicus

Figure 2: Preoperative contrast-enhanced Computed Tomography revealing an inferior caval vein syndrome caused by retroperitoneal collections.

Acute mitral valve regurgitation presenting as diffuse alveolar hemorrhage: A case report

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A 56-year-old male, with a history of juvenile rheumatoid arthritis, attended the emergency department for acute dyspnea and fever. On examination, the temperature 38.3°C, SpO2 of 96% after 4L of O2 by nasal cannula with a breathing frequency of 22/min; lower lung field crackles and rales were notable. Cardiac examination revealed a 2-3/6 systolic murmur loudest at the apex. The patient was admitted and treated for a pulmonary infection using amoxicillin. The laboratory test showed leucocytes count 10.0×10^9/L, hemoglobin 6.2 mmol/L, platelet count 96×10^9/L, normal kidney function, and electrolytes. His chest X-ray showed bilateral infiltrates. However, the clinical condition deteriorated presenting with hemoptyis and epistaxis, for which he was transferred to the critical care unit and short after required prone position ventilation after which he was transferred to our tertiary critical care unit.

The differential diagnosis on admittance consisted of (a)typical infections, viral and fungal pathogens, immunological (granulomatosis with polyangiitis) and cardiovascular diseases. Blood and urine cultures remained negative as well as tests for influenza, legionella, HIV. Serologic studies included a positive antineutrophilic cytoplasmic antibody, myeloperoxidase negative, proteinase-3 negative and no dysmorphic erythrocytes. ENT endoscopy showed no signs of granulomatosis with polyangiits and a bronchoscopy with bronchoalveolar lavage showed diffuse alveolar hemorrhage. A transthoracic echocardiogram (TTE) showed normal cardiac function with a pathologic mitral valve compatible with Barlow’s disease without significant regurgitation. A transesophageal echo (TEE) was performed showing severe mitral regurgitation and an immobile aortic bicuspid leaflet with minimal regurgitation. Right heart catheterization showed a pulmonary artery pressure of 65/35/45 mmHg (systolic/diastolic/mean); pulmonary capillary wedge pressure (PCWP) of 31 mmHg, with a substantial V-wave (figure 1), right atrial pressure of 5 mmHg, RV: 40/20 mmHg (systolic/diastolic).

After multidisciplinary review, the patient was accepted for a mechanical double valve replacement which was complex although without complications. No alveolar hemorrhage was seen during cardiopulmonary bypass. The patient had a prolonged recovery in the critical care unit due to acute kidney failure but recovered completely.

The clinical findings were highly suggestive of diffuse alveolar hemorrhage syndrome, presenting with classical symptoms with a rather abrupt onset of dyspnea, fever, cough and eventually hemoptyis. Diagnosing the underlying cause remained challenging. Our case provided little diagnostic evidence in laboratory findings or blood cultures. The TTE showed no evident mitral regurgitation stressing the need for TEE which demonstrated a severe regurgitation.

Figure 1: V-wave as expression of severe mitral valve regurgitation
Case series: subarachnoid hemorrhage resembling myocardial ischemia on electrocardiogram after cardiac arrest

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AMC, Intensive Care, Amsterdam, Netherlands

Subarachnoid hemorrhage (SAH) is observed in approximately 25% of out of hospital cardiac arrest patients. Post-resuscitation electrocardiogram can show ST-segment changes suggesting myocardial ischemia. Advanced cardiac life support guidelines suggest immediate coronary angiography when myocardial ischemia is suspected on electrocardiogram. We describe two patients, who presented with an out of hospital cardiac arrest with ST-segment changes suggesting cardiac ischemia, and were diagnosed with a SAH.

A 53 year old male, with no medical history, was presented to the emergency department after an out of hospital cardiac arrest. The electrocardiogram showed potential myocardial ischemia. A coronary angiogram was performed with no visible coronary stenosis. The brain computed tomography (CT) performed thereafter showed a massive SAH. The CT angiogram of the brain showed no vascular perfusion of intracranial vessels. Consequently, further supportive treatment was regarded futile. The patient died rapidly after ceasing vital support.

A 50 year old female, with a medical history of colitis ulcerosa, was presented to the emergency department after an out of hospital cardiac arrest. After arrival at the emergency department an coronary angiography was performed because of potential myocardial ischemia on the electrocardiogram. During coronary angiography, no occluded coronary vessels were seen. Initial differential diagnosis was a Tako Tsubo cardiomyopathy, reversible myocardial ischemia following coronary spasm, passing thrombus or other electrical cardiac pathology. She was admitted to the ICU and treated with targeted temperature management. On brain CT, made 3 days after admission, a SAH was seen. A superior cerebellum artery aneurysm was successfully coiled the next day. After 3 weeks she was discharged from hospital and recovered completely.

Electrocardiogram changes are frequently seen in patients with SAH and can mimic myocardial ischemia. This may result in misdiagnosis and administering of anti-coagulation agents, which may lead to devastating consequences in patients with SAH. Post-resuscitation electrocardiogram can be used as a predictive tool to determine which patients need an immediate brain CT. The combination of 4 characteristic ECG changes; narrow QRS complex, atrial fibrillation, ≥ 4 ST-segment depressions and prolonged QTc interval (> 460 ms) have a high negative predictive value in identification of SAH.

References:

Hemofilter failure in continuous renal replacement therapy due to hypertriglyceridemia

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Erasmus MC, Intensive Care, Rotterdam, Netherlands

Continuous renal replacement therapy (CRRT) is a widely used therapy in critical care units for patients with kidney failure. To provide the best therapy it is important to have as little downtime as possible. This could be influenced by the survival time of the circuit. There are a lot of known factors, which can be influenced; such as the method of anticoagulation, blood flow, filtration fraction and hematocrit level. In our case, we had an unexpected cause of shortened hemofilter life.

A 67-year old patient diagnosed with a high risk pre-B immunophenotype of acute lymphoblastic leukemia received chemotherapy and allogeneic stem cell transplantation. He got respiratory insufficient by an engraftment syndrome, for which he got intubated and admitted to our ICU. He was sedated with propofol mg/kg/hour; he already received total parenteral nutrition (TPN) for 15 days. One day later we started CRRT because of acute kidney failure. Despite regional anticoagulation using citrate, we had a filter failure after 15 minutes, after restarting there was another failure in 30 minutes. The filter showed a yellow, greasy substance (see Fig. 1). His blood triglyceride concentration was 8.55 mmol/L (see Graph 1). We immediately stopped his TPN and propofol infusion. At a triglyceride level of 3.32 mmol/L, we restarted his CRRT without any problems. In addition, we replaced his propofol with midazolam and started fat-free TPN.

This case report teaches us that the use of propofol and TPN together could lead to hypertriglyceridemia. Earlier case reports by Kazory et al 1 and Bassi et al 2, suggested that severe hypertriglyceridemia might promote a procoagulant state, which could explain the shortened filter survival time. In case of a shortened filter survival time you should consider hypertriglyceridemia, especially if you observe a yellow, greasy substance in your system. It is relatively simple tested and can be dissolved easily.

References:

Figure 1. The yellow, greasy substance in the CRRT machine
Introduction: Previous research has shown that the endothelial glycocalyx and microcirculation are damaged during cardiopulmonary bypass (CPB) [1] and subsequently recover shortly after CPB is stopped. However, the exact temporal behavior of this damage and its subsequent recovery are unknown.

Aim: To study the temporal behavior of endothelial glycocalyx damage during CPB for cardiovascular surgery.

Methods: We included 13 patients undergoing coronary artery bypass graft (CABG) surgery with the use of CPB. Endothelial glycocalyx thickness was assessed using a sidestream dark field imaging (SDF) camera with Glycocheck software. This software assesses the thickness of the perfused boundary region (PBR) of microvessels with a diameter of 5-25 µm. The PBR is inversely proportional to the endothelial glycocalyx.

We measured glycocalyx thickness after induction of anesthesia (T1), immediately after commencement of CPB (T2), immediately after cessation of CPB (T3) and 2 hours after admission at the ICU (T4). In 9 of the 13 patients we also measured the day before surgery (T0). Results are presented as mean (std) and statistical significance was determined using mixed model analysis (p<0.05 was considered significant).

Results: There was no significant difference between PBR at T0 and T1, excluding an effect of anesthesia on the endothelial glycocalyx thickness. Mean PBR in all patients at T1 was 1.78 (0.24) µm, at T2 2.23 (0.23) µm, at T3 2.21 (0.17) µm and at T4 1.99 (0.19) µm. The increase from T1 to T2 was significant (p<0.001)

In all patients we observed glycocalyx damage at onset of CPB (T2 with respect to T1), p<0.001 (Fig 1). Further analysis revealed two groups. In six patients we observed a high peak in PBR at T2 with subsequent decrease during CPB, indicating recovery of glycocalyx during CPB. In the other 7 patients we observed a lower initial peak, followed by a continuing increase of PBR and decrease only after cessation of CPB (Fig 2).

Conclusion: In conclusion, these preliminary findings show that glycocalyx damage is seen right after onset of CPB. A subset of patients already show (partial) recovery of glycocalyx during CPB while others show recovery only after cessation of CPB. We are currently investigating the determinants and clinical implication of the latter observation.
Adherence to recommended care for antibiotic use in ICU patients: a retrospective case record study

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1Canisius Wilhelmina Ziekenhuis, Intensive Care, Nijmegen, Netherlands, 2Radboudumc, Intensive Care, Nijmegen, Netherlands, 3AMC, Onderzoeksafdeling, Amsterdam, Netherlands

Abstract: BACKGROUND: The burden of antimicrobial resistance in healthcare settings is especially prevalent at the intensive care unit (ICU) (1). It is important that physicians and nurses appropriately use antibiotics and adhere to antibiotic use recommendations to conserve currently available antibiotics. METHODS: A retrospective analysis of patients' medical and nursing records was conducted between 2013 and 2016 to study the adherence to antibiotic use recommendations, defined as quality indicators. Two sets of quality indicators were studied in the ICU of one general teaching hospital in the Netherlands: (1) quality indicators for appropriate antibiotic use at the ICU, and (2) quality indicators on Selective Digestive tract Decontamination (SDD) use (2). RESULTS: A total of 150 patients were included. The highest adherence rate was found for the antibiotic use recommendation ‘stop third generation cephalosporin therapy as part of SDD after four days’ (44/46; 95.7%). The lowest adherence rate was found for the antibiotic use recommendation ‘doubling of SDD dose if so required by protocol’ (10/38; 26.3%). CONCLUSION: This study showed that more than 89% of the patients received the recommended care for obtaining surveillance cultures and stopping third generation cephalosporin therapy as part of SDD. There is room for improvement on the adherence to performing blood cultures and determining blood levels in time when therapeutic drug monitoring is indicated. Especially doubling the dose of SDD if required by protocol warrants attention. The quality indicators tested in this study can be used by hospital antibiotic stewardship teams to determine where to set priorities to improve antibiotic use in ICU patients.

References:

Table 1: Adherence to antibiotic use recommendations

<table>
<thead>
<tr>
<th>NICE quality indicators</th>
<th>Definition</th>
<th>Numerator</th>
<th>Denominator</th>
<th>Target value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Perform blood cultures at start of antibiotic therapy</td>
<td>95/126</td>
<td>75.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2) Determine blood levels in time when TDM is indicated</td>
<td>8/11</td>
<td>72.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3) Obtain surveillance cultures when SDD is applied</td>
<td>61/66</td>
<td>92.4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Quality indicators

<table>
<thead>
<tr>
<th>Quality indicators</th>
<th>Definition</th>
<th>Numerator</th>
<th>Denominator</th>
<th>Target value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Quality indicators for antibiotic use at the ICU</td>
<td>100 patients days or 100 admissions at ICU</td>
<td>100%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2) Perform blood cultures at start of antibiotic therapy</td>
<td>Percentage of patients in whom at least two sets of blood cultures were performed before or at start of empiric antibiotic therapy as an ICU</td>
<td>44/46</td>
<td>95.7%</td>
<td></td>
</tr>
<tr>
<td>3) Determine blood levels in time when TDM is indicated</td>
<td>Percentage of patients in whom blood levels were obtained within 48 hours when TDM was indicated at ICU</td>
<td>8/11</td>
<td>72.7%</td>
<td></td>
</tr>
<tr>
<td>4) Obtain surveillance cultures when SDD is applied</td>
<td>Percentage of patients in whom surveillance cultures were obtained within 48 hours after start of mechanical ventilation at ICU</td>
<td>61/66</td>
<td>92.4%</td>
<td></td>
</tr>
<tr>
<td>5) Doubling of SDD dose if required by protocol</td>
<td>Percentage of patients in whom the dose of SDD was doubled when one of the surveillance cultures obtained the throat, peritoneal, or respiratory tract shows gram-negative bacteria within 48 hours after start of mechanical ventilation at ICU</td>
<td>10/38</td>
<td>26.3%</td>
<td></td>
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<tr>
<td>6) Appropriate administration of SDD paste</td>
<td>Percentage of patients in whom within 60 min of SDD paste was given four times daily during an episode of mechanical ventilation when SDD was applied at an ICU</td>
<td>44/46</td>
<td>95.7%</td>
<td></td>
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Table 2: Quality indicators (source: Guideline SDD)

<table>
<thead>
<tr>
<th>SDD quality indicators</th>
<th>Definition</th>
<th>Numerator</th>
<th>Denominator</th>
<th>Target value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Obtain surveillance cultures in time</td>
<td>Total number of patients in whom surveillance cultures were obtained at the throat, peritoneum, and respiratory tract shows gram-negative bacteria within 48 hours after start of mechanical ventilation at ICU</td>
<td>95/126</td>
<td>75.4%</td>
<td></td>
</tr>
<tr>
<td>2) Obtain two surveillance cultures per week</td>
<td>Total number of patients in whom at least two sets of surveillance cultures were obtained within 48 hours after start of mechanical ventilation at ICU</td>
<td>61/66</td>
<td>92.4%</td>
<td></td>
</tr>
<tr>
<td>3) Doubling of SDD dose if required by protocol</td>
<td>Total number of patients in whom the dose of SDD was doubled when one of the surveillance cultures obtained the throat, peritoneal, or respiratory tract shows gram-negative bacteria within 48 hours after start of mechanical ventilation at ICU</td>
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<td>44/46</td>
<td>95.7%</td>
<td></td>
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We wholeheartedly thank the reviewers for their hard work, thereby keeping up the standards and quality of the Neth J Crit Care.
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Editorials are always commissioned by the Editors and comment on one or more articles in the same issue of the Journal or to a subject with high news value. Editorials should not exceed 1500 words and may include up to 15 references. Editorials have a maximum of 3 authors and no abstract. Please provide 2-3 key words.

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The text of a case report should include an abstract, introduction, case report/case history, discussion, tables and figures (2 in total), and references. The main text may be up to 2000 words; the abstract should not exceed 150 words and may be unstructured. Please provide a minimum of 3 keywords and a list of not more than 30 references. Please include an informed consent statement from the patient described in the case.

Clinical problem-solving

These manuscripts consider the step-by-step process of clinical decision-making. Information about a patient is presented to an expert clinician or clinicians in stages (indicated by boldface type in the manuscript) to simulate the way such information emerges in clinical practice. The clinician responds (in regular type) as new information is presented, sharing his or her reasoning with the reader. The text should not exceed 2500 words, and there should be no more than 15 references. Please include an informed consent statement from the patient described in the case.

Research news

Research news should be a review of a manuscript which has appeared in the past two months. It contains sections on why this study was done, the research question, how this was investigated, conclusions and the impact of the study on clinical practice. The text should not exceed 800 words with a maximum of 5 references. Contributions for this section will be commissioned; however, inquiries about contributions can be sent to a.p.vlaar@amc.uva.nl.

Clinical images

A clinical image should contain one or two pictures with a legend and a short case history, and should preferably not be referenced. The manuscript should succinctly present relevant clinical information, including a short description of the patient’s history, relevant physical and laboratory findings, clinical course, response to treatment (if any), and condition at last follow-up. Please provide a minimum of 3 keywords. The text should not exceed 500 words. Please include an informed consent statement from the patient described in the case.

Photo quiz

In this section relevant images for critical care medicine (e.g. flow and pressure curves of mechanical ventilation or haemodynamic indices, radiological images or laboratory results) will be accompanied by a short introduction of the context. The introduction will be followed by ‘what is your diagnosis?’. The answer will include a brief discussion of the literature. A photo quiz should not exceed 500 words and contain no more than two figures, and five references conform the Vancouver style. Abbreviations of measurements should be quoted in SI units.

Book reviews

A book review should not exceed 300 words. Please mention in the header: title, author, edition and year. Scan the cover in high resolution (300 dpi/1 mb) and send with the text. With an online review, the cover can usually be downloaded. Details with the cover: title, author, edition, year, publisher, number of pages, price and ISBN number. Conclude with the name and affiliation(s) of the reviewer.

Letters to the editor

Letters to the editor provide an opportunity to present results of scientific value where a short format is most appropriate. They should not exceed 1000 words, 5 references and 1 figure or table.

Correspondence

Correspondence provides an opportunity to debate published articles. This should not exceed 500 words, 5 references and 1 figure or table. Correspondence is sent to the authors for rebuttal, and a final decision on publication is made at the end of this process, by the editor.

General information

Each manuscript should be accompanied by a cover letter stating the following: the complete postal address, email address and telephone number of the corresponding author and, if it is a resubmission, the previous Neth J Crit Care number and year. The language of the journal is British English. Authors who are unsure of proper English usage should have their manuscript checked by someone proficient in the English language. All text should be double spaced. The manuscript pages, including references and legends, should be sequentially numbered throughout.
General guidelines on house style
- The title of the manuscript should be in typeface Times New Roman, size 20.
- With the exception of the first word and proper nouns, initial capitals are not used in the title.
- The names of departments should be in typeface Times New Roman, size 12.
- The names of hospitals should be written in English.
- Write 'the Netherlands', without capitalising the t.
- Generally, abbreviations should not be used in the title (see ‘Table of standard abbreviations for exceptions’).
- The corresponding author only provides his/her email address on the title page.
- Please provide a minimum of three keywords and a running title.
- The abstract of original and review articles should be written in a structured format.
- Unstructured abstracts should take the form of a single paragraph.
- Headings must be in bold. Use no more than two levels of headings.
- Paragraphs starting immediately under headings and subheadings should begin at the left margin. Subsequent paragraphs should be indented.
- Non-standard abbreviations (see ‘Table of standard abbreviations’) should always be explained and their use kept to a minimum.
- Use British English spelling – except in titles of institutions that have chosen to use US spelling, e.g. Academic Medical Center, Amsterdam. Examples: anaemia (instead of anemia), oesophagus (instead of esophagus), litre (instead of liter), colour (instead of color), labelling (instead of labeling), practice (noun), and practise (verb). This should be used consistently. Use the s-form spelling, e.g. minimisation, re-registration.
- Do not use full stops in initials, abbreviations and academic titles.
- References are numbered sequentially in the text and placed in square brackets after the punctuation. [...] Genus names should be written in italics, e.g. Staphylococcus aureus, S. aureus.
- Numbers spelled out except for measurements with a unit (10 mmol/l) or age (4 weeks old), or when in a list with other numbers (5 mice, 6 rats, 12 gerbils).
- When referring to tables or figures in the text, use italics; do not use a capital letter, e.g. see table 2.

Tables
Tables are to be numbered independently of the figures with Arabic numbers and are uploaded as separate documents.
- Tables should be laid out in Word, using the table function. Other tables (e.g. in pdf format or PowerPoint) will not be accepted.
- Do not use internal horizontal or vertical lines.
- Do not use spaces, tabs or hard returns in tables.
- Each piece of data must be contained in its own cell.
- Numbers and percentages are presented in the same cell.
- Tables should always be cited in the text in consecutive numerical order.
- For each table, supply a title explaining the components of the table.
- Any abbreviations used in the table must be defined in a legend.
- Tables should not exceed the printed area of the page (174 x 234 mm).

Figures
Figures should also be numbered with Arabic numbers and are uploaded in separate documents. Legends should be given in the document that contains the text, references, and tables. Authors wishing to include figures or tables that have already been published elsewhere are required to obtain permission from the copyright owner and provide evidence that such permission has been granted when submitting their paper. Colour figures can be published. Short, clear legends make additional description in the text unnecessary. Figures should be provided in electronic format (TIFF or JPEG).

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References
Neth J Crit Care uses the Vancouver style of referencing. Only articles cited in the text are to be listed. They should be arranged in order of appearance in the text and numbered consecutively. Only the reference number should appear in the text between brackets. [...] Include all author names (unless there are more than six, in which case abbreviate to three and add ‘et al’), and page numbers. Use the Medline abbreviation for names of journals.


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All papers are subject to a peer-review system handled by the editors. Authors are encouraged to resubmit, when invited, the revised paper within two weeks after the editorial decision. The changes made in the revised paper should be highlighted and the manuscript accompanied by a letter with a point-to-point rebuttal.

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The corresponding author will receive proofs of accepted papers by email. Corrected proofs should be returned within 48 hours of receipt.

Production process
Decisions of the editors are final. All material accepted for publication is subject to copyediting. The Neth J Crit Care reserves the right to edit for house style, clarity, precision of expression, and grammar. Authors review these changes at the proof stage but must limit their alterations in the proof to correcting errors and to clarifying misleading statements.

Table of commonly used abbreviations

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS</td>
<td>acquired immunodeficiency syndrome</td>
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<tr>
<td>ALI</td>
<td>acute lung injury</td>
<td></td>
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<tr>
<td>ARDS</td>
<td>adult respiratory distress syndrome</td>
<td></td>
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<tr>
<td>APACHE</td>
<td>acute physiology and chronic health evaluation</td>
<td></td>
</tr>
<tr>
<td>BIPAP</td>
<td>biphasic positive airways pressure</td>
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<tr>
<td>ECCU</td>
<td>coronary care unit</td>
<td></td>
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<tr>
<td>COPD</td>
<td>chronic obstructive pulmonary disease</td>
<td></td>
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<tr>
<td>CPAP</td>
<td>continuous positive airway pressure</td>
<td></td>
</tr>
<tr>
<td>CT</td>
<td>computed tomography</td>
<td></td>
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<tr>
<td>ECG</td>
<td>electrocardiogram</td>
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<tr>
<td>ECMO</td>
<td>extracorporeal membrane oxygenation</td>
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<tr>
<td>EEG</td>
<td>Electroencephalogram</td>
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<tr>
<td>ELISA</td>
<td>enzyme-linked immunosorbent assay</td>
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<tr>
<td>ETCO2</td>
<td>end-tidal carbon dioxide</td>
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<td>HIV</td>
<td>human immunodeficiency virus</td>
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<td>IC</td>
<td>intensive care</td>
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<tr>
<td>ICU</td>
<td>intensive care unit</td>
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<td>IM</td>
<td>intramuscular</td>
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<tr>
<td>INR</td>
<td>international normalised ratio</td>
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<tr>
<td>IPPV</td>
<td>intermittently positive pressure ventilation</td>
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<tr>
<td>IV</td>
<td>Intravenous</td>
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<tr>
<td>MAP</td>
<td>mean arterial pressure</td>
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<tr>
<td>MODS</td>
<td>multiorgan dysfunction syndrome</td>
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<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
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<tr>
<td>PACU</td>
<td>post anaesthesia care unit</td>
<td></td>
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<tr>
<td>PEEP</td>
<td>positive end expiratory pressure</td>
<td></td>
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<tr>
<td>PET</td>
<td>position emission tomography</td>
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</tr>
<tr>
<td>SARS</td>
<td>severe adult respiratory syndrome</td>
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<tr>
<td>SI RS</td>
<td>systemic inflammatory response syndrome</td>
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<tr>
<td>SOFA</td>
<td>sequential organ failure assessment</td>
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<tr>
<td>SPECT</td>
<td>single-photon emission computed tomography</td>
<td></td>
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<tr>
<td>TIA</td>
<td>transient ischaemic attack</td>
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<tr>
<td>TRALI</td>
<td>transfusion-related acute lung injury</td>
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</tbody>
</table>

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