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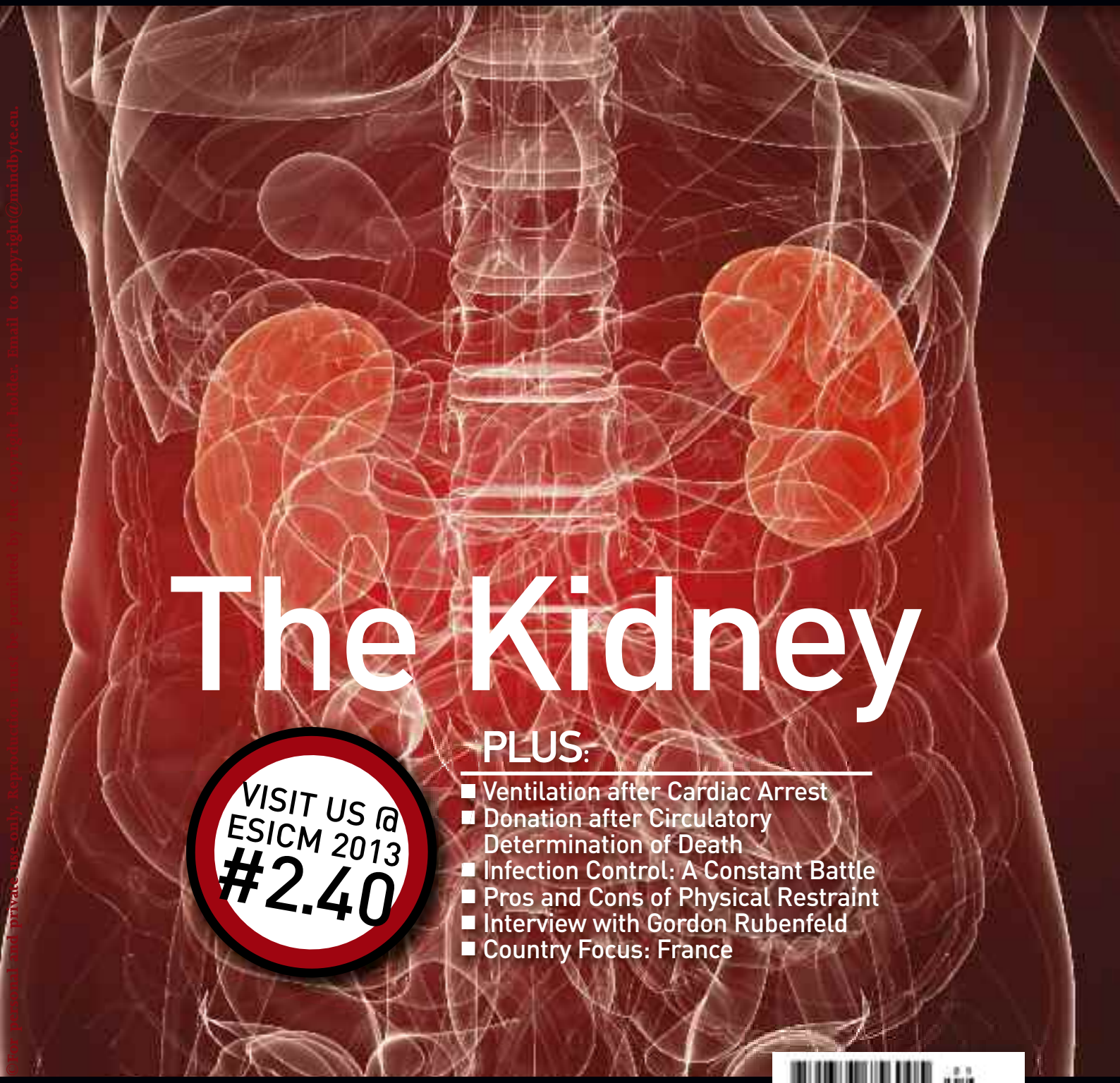

The Kidney

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THE KIDNEY

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In this issue our cover story focuses on one organ in particular, the kidney. As a commonly occurring complication in the ICU, acute kidney injury (AKI) has received much attention from intensive care clinicians in recent years. While there is more research to be done to combat this rapid-onset condition, our knowledge has increased over the last decade.

In the first article Profs. Lakhmir Chawla and John Kellum review biomarkers for AKI, including neutrophil gelatinase-associated lipocalin (NGAL) and urine output, noting that new discoveries along with reinvention of existing tools hold great promise. Despite inconclusive and sometimes controversial results from randomised controlled trials, interest in renal replacement therapy (RRT) is growing. Prof. Patrick Honoré and colleagues cover the state of RRT in 2013, with new insights on dosing, timing, modalities and membranes. The third article in our cover story, by Dr. Nakshatra Saxena, Prof. Ashita Tolwani and Dr. Keith Wille looks at anticoagulation in continuous renal replacement therapy, in particular the anticoagulants unfractionated heparin and regional citrate. Next, Dr. Manu Malbrain and colleagues provide an in-depth article on fluids and nutrition in AKI. In the final article in our cover story Drs. Max Bell and Johann Mårtensson discuss renal recovery after AKI, arguing that ICU management has a role in determining outcomes, and that for certain patients nephrology referral may minimise risk for end-stage renal disease or death.

In the Matrix section, Drs. Yudi Sutherasan and Iole Brunetti with Prof. Paolo Pelosi discuss ventilation after cardiac arrest. Optimising ventilation and gas exchange by protective ventilation, keeping normoxia and avoiding hypocapnia may play a role in improving outcome. They also consider transcranial Doppler as a new non-invasive monitoring tool. Next, Profs. Martí Manyalich and Ricard Valero and Dr. Jesús Carazo discuss organ donation after circulatory determination of death, which has come to the fore as demand for organs has increased. The final Matrix article is about the recently published results of the European Centre for Disease Prevention and Control's point prevalence survey on healthcare-associated infections and antimicrobial use in European hospitals.

Dr. Christina Jones, in the Management section, follows with a review of the arguments for and against the controversial practice of physical restraint of patients in the ICU.

Prof. Gordon Rubenfeld is interviewed for this issue, providing a perspective from Canada on critical care, including his views on the limitations of, and priorities for ICU research, and current challenges in the field.

ICU Management will be at the European Society of Intensive Care Medicine (ESICM) congress in Paris this month, and therefore France is the topic of our Country Focus. Dr. Yên-Lan Nguyen and Prof. Bertrand Guidet provide an overview of the state of critical care in France, observing that French intensivists are very active in clinical research. This activity is the subject of the article by Prof. Catherine Paugam-Burtz and Dr. Samir Jaber, which reviews recently published and completed clinical trials.

As always, if you would like to get in touch, please email **editorial@icu-management.org.**

Jean-Louis Vincent

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INDUSTRY AND RESEARCH NEWS

Pointless Treatment in Critical Care Costly, Say U.S. Researchers

Critical care treatment for patients that was perceived to be futile cost an estimated US$2.6 million at one academic medical centre during a three-month period, according to a study first published online last month in JAMA Internal Medicine. One in five patients in the study received treatment the physicians perceived as futile or potentially futile.

Thanh N. Huynh, of the David Geffen School of Medicine at the University of California, Los Angeles, and colleagues sought to quantify the prevalence and cost of treatment thought to be futile in adult critical care.

Researchers asked critical care specialists to identify patients they believed were receiving futile treatment in five intensive care units (ICUs) at an academic medical centre on a daily basis for three months.

Thirty-six critical care specialists assessed 1,136 patients, and judged that 904 (80 percent) never received futile treatment, 98 (8.6 percent) received probably futile treatment, 123 (11 percent) received futile treatment and 11 (1 percent) received futile treatment only on the day they transitioned to palliative care, according to the results.

"The most common reason treatment was perceived as futile was that the burdens grossly outweighed the benefits (58 percent). This reason was followed by treatment could never reach the patient's goals (51 percent), death was imminent (37 percent), and the patient would never be able to survive outside an ICU (36 percent)," according to the study results.

The average cost for one day of treatment in the ICU that was perceived as futile was US$4,004. For the 123 patients categorised as receiving futile care, hospital costs (ICU and subsequent non-ICU days) for the care that was thought to be futile totalled US$2.6 million, which was 3.5 percent of the total hospital costs for the 1,136 patients in the study, the results also indicate.

"In our health system, critical care physicians frequently perceived that they are providing futile treatment, and the cost is substantial. Identifying and quantitating ICU treatment that is perceived as futile is a first step toward refocusing care on treatments that are more likely to benefit patients," the authors conclude.

In an associated commentary Robert D. Truog of Harvard Medical School, Boston, and Douglas B. White of the University of Pittsburgh School of Medicine, urge caution in interpreting the findings. The study did not take into account opinions of other members of the clinical team or patients and families in judging if treatment was futile. In addition, the financial analysis did not include what would be saved if the futile treatments were not provided.

Truog and White go on to make recommendations for how clinicians in critical care units should conceptualise and respond to requests for treatment that they judge to be futile or wrong. They suggest using the term 'potentially inappropriate' rather than 'futile', and argue that, from an ethical and legal standpoint, these disputes are often more complicated than they seem. Clinicians' initial response to requests for treatments that they believe are wrong should be to increase communication with the patient or the patient's surrogate rather than simply refuse the request. Clinicians should pursue a fair process of dispute resolution rather than refusing unilaterally to provide treatment. "When disputes arise despite sustained efforts to prevent them, a stepwise procedural approach to resolving conflicts is essential," they conclude.

Source: JAMA

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Truog RD, White DB (2013 Sep 9) Futile treatments in intensive care units. JAMA Intern Med, doi:10.1001/jamainternmed.2013.7098 [Epub ahead of print]

Self-Guided Robotic Intubation Device Prototype to Be Trialled

Graduates of the Hebrew University of Jerusalem's Biodesign programme revealed in August a prototype robotic intubation device. GuideIN Tube automatically identifies the lungs using an infrared source and navigates toward it. The device was successfully tested on cadavers at the Hadassah Medical Center, and clinical trials will begin as soon as next year. The device targets a $3 billion market, which is expected to increase by 5 percent annually.

"I strongly believe that GuideIn Tube represents the future of intubation," said Dr. Elchanan Fried, director of the general intensive care unit in Hadassah Medical Center, and the group's clinical expert. "We really thought about the paramedic in the field", said Itai Hayut, the leading engineering student on the project. "We wanted something simple and compact that they could trust without fail. I think we hit it on all marks."

Biodesign is a multi-disciplinary, team-based approach to medical innovation, created by the Hebrew University of Jerusalem and Hadassah Medical Center in partnership with Stanford University.

Source: Hebrew University of Jerusalem via AlphaGalileo
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BIOMARKERS FOR ACUTE KIDNEY INJURY

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Acute kidney injury (AKI) is a syndrome of decreased renal function associated with an increased risk of chronic kidney disease (CKD) and death. Recent advances in the field promise to improve AKI diagnosis and treatment.

AKI is a serious complication of acute illness, typically occurring as a result of underlying conditions such as sepsis, and is independently associated with decreased survival. It has become increasingly clear that AKI is associated with development of end-stage renal disease (ESRD) and chronic kidney disease (CKD) (Ishani et al. 2011; Chawla et al. 2011; Hoste et al. 2010). Individuals fortunate enough to survive a significant episode of AKI are therefore at risk of developing CKD-related disease.

> *"These new markers provide clear and convincing evidence that AKI is indeed a very complex disorder"*

Our understanding of AKI has advanced over the past decade, with a unified definition and standard criteria for staging, a quantification of renal replacement therapy (RRT) dosing, and the emergence of biomarkers related to AKI. These new markers provide clear and convincing evidence that AKI is indeed a very complex disorder. A study by Paragas et al., which examined the expression of neutrophil gelatinase-associated lipocalin (NGAL) using a luciferase reporter assay, clearly showed a very specific signal in the kidneys in response to lipopolysaccharide (LPS), whereas similar reductions in glomerular filtration rate (GFR) from dehydration showed no such signal (Paragas et al. 2011). Although NGAL has been shown in multiple large cohort studies to be a biomarker for early AKI diagnosis and for AKI prognosis (Shemin and Dworkin 2011), NGAL is expressed in multiple organs and is thus not kidney specific. Understanding how non-kidney sources of NGAL impact the urinary NGAL signal and establishing the sources of NGAL in AKI is essential.

Paragas and colleagues (2011) conducted their novel experiment by creating a reporter mouse for NGAL. They inserted a double-fusion reporter gene that encoded luciferase-2 and mCherry (Luc2-mC) in the locus for NGAL (lcn-2). In so doing, the investigators could assess endogenous NGAL message in real time and assess in which organs the message was being transcribed. In separate experiments, mice were subjected to unilateral or bilateral renal ischaemic models and nephrotoxic injury with cisplatin. In addition, the investigators tested whether NGAL-Luc2-mC was activated in prerenal azotaemia and ascertained the portion of the nephron responsible for urinary NGAL (uNGAL) production in AKI. The investigators determined that the principal or exclusive source of uNGAL was the thick ascending limb and collecting ducts of the nephron. In addition, in the prerenal azotaemia model, serum creatinine level rose, but NGAL-Luc2-mC was not activated and no increase in uNGAL level occurred. These data show that uNGAL is an appropriate kidney injury specific biomarker despite not being exclusively expressed in the kidney.

Another study involving NGAL displayed the range in which AKI biomarkers can assist clinicians caring for patients with AKI. NGAL has been primarily thought of as a biomarker for early diagnosis of AKI (Shemin and Dworkin 2011), but utility of this and other biomarkers may be much broader. Using a large multicentre cohort of patients with community-acquired pneumonia, Srisawat and colleagues (2011) examined plasma of patients on the first day they experienced severe AKI (RIFLE Failure level). In this study, recovery was defined as being alive and neither requiring RRT during hospitalisation nor having a persistent RIFLE Failure level classification at hospital discharge. The investigators found that elevated plasma NGAL levels were associated with renal non-recovery. Although the absolute predictive value of pNGAL alone was only fair (area under the receiver operating characteristic curve 0.74), the reclassification of risk of not recovering renal function was increased by 17%. These data are most notable for two reasons. First, because AKI can cause CKD and ESRD, decisions regarding long-term care (for example, use of dialysis, vascular access, and follow-up) are often made in a piecemeal approach. If objective metrics coupled with clinical assessment can improve prognostic accuracy, a more informed decision can be made for sur-

vivors of AKI. Second, the association between plasma NGAL and renal non-recovery suggests that renal injury is ongoing, and even if a patient is undergoing dialysis therapies directed at mitigating ongoing injury may have a role in AKI treatment.

Within the advancing field of AKI, the oldest known biomarker is urine output. The precise utility of oliguria has been controversial, and within the Acute Kidney Injury Network (AKIN) staging system, there has been discussion on the precise definition of oliguria over time (for example, consecutive hours of oliguria versus average urine output over a period of time). To understand this further, Macedo and colleagues (2011) utilised high-fidelity urimeters to compare various definitions of oliguria in critically ill patients. In their study 317 patients had specialised high-accuracy urimeters placed on their urinary catheters in order to measure their urine output hourly. Serum creatinine was measured every 12 hours, and definitions of AKI based on urine output were compared with those based on serum creatinine. Urine output was classified in three ways: consecutive hours of oliguria (oligo6-cons), an average amount of oliguria over a fixed block of time (<3 ml/kg in the period from 6.00 am to 12.00 midday), or any episode of oliguria over a set period of time (<3 ml/kg for any 6-hour period). Of these variables, oligo6-cons was the most specific when compared with the AKIN stage I serum creatinine standard (sensitivity 34%, specificity 71%). The other two metrics, oliguria 6-hour fixed (oligo6-fixed) and oliguria 6-hour floating (oligo6-float), were more sensitive, but less specific (sensitivities 47% and 53%, and specificities 62% and 54%, respectively). Of the patients with oliguria for 6 hours, 79% of oligo6-cons advanced to AKIN stage II, while 64% of oligo6-fixed and 52% of oligo6-float advanced to AKIN stage II. Using the urine output definition of AKI increased the observed incidence of AKI to 52% as compared with an AKI incidence of 24% using serum creatinine definitions alone. The mortality rate of patients with AKI defined by urine output alone was comparable to that of patients with AKI defined by serum creatinine alone (8.8% versus 10.4%). Moreover, oliguria was a more sensitive marker of AKI, and tended to occur earlier than did change in serum creatinine. These data endorse current consensus Kidney Disease: Improving Global Outcomes (KDIGO) definitions (based on RIFLE - Risk, Injury, Failure, Loss, and End-stage kidney disease)/ AKIN - Acute Kidney Injury Network) that incorporate changes in both urine output and serum creatinine (Kidney Disease: Improving Global Outcomes 2012).

An alternative interpretation was offered by Ralib and colleagues (2013), who analysed records from 725 consecutive admissions to a general ICU over a 12 month period. For a 6-hour urine output collection they found a threshold of 0.3 ml/kg/h to have the greatest accuracy for predicting in-hospital mortality or dialysis. A threshold of 0.3 ml/kg/h exhibited hazard ratios for in-hospital and one-year mortality of 2.25 (1.40 to 3.61) and 2.15 (1.47 to 3.15) respectively after adjustment for age, body weight, severity of illness, fluid balance, and vasopressor use. By contrast, the 0.5 ml/kg/h threshold used by the KDIGO criteria was not as strongly associated with these outcomes (hazard ratios: 1.48 (0.89 to 2.45) and 1.43 (0.96 to 2.13)) and not statistically significant in this small cohort. However, it is our view that the urine output threshold should be set not on the basis of hazard ratios for mortality but to be a sensitive indicator for AKI. In any case a hazard ratio of 1.48 is clearly clinically important, even if the study by Ralib and colleagues (2013) was under-powered to detect it.

At the other end of the timeline, entirely new biomarkers are emerging. Munshi and colleagues (2011) reported a study where potential biomarker candidates were chosen from urinary excretion of injury-induced mRNAs. The investigators posited that the resulting proteins of these mRNAs might be good AKI biomarkers, and may offer pathogenic information in addition to diagnostic information. Munshi et al. (2011) quantified the urinary excretion of the mRNAs for one of these candidate proteins, monocyte chemoattractant protein-1 (MCP-1). The investigators conducted multiple preclinical studies wherein various forms of AKI were induced, and MCP-1 was compared with a

known representative AKI biomarker, NGAL. In the models of AKI, MCP-1 protein and mRNA increased more than corresponding increases in NGAL. Uraemia, without kidney injury, induced the NGAL gene, but not MCP-1, which suggests that MCP-1 may be more specific for AKI. These findings were tested in a candidate cohort of Acute Physiology and Chronic Health Evaluation (APACHE)-II-matched critically ill patients with and without AKI. In these patients, MCP-1 levels were significantly higher in those with AKI.

More recently, tissue inhibitor of metalloproteinases (TIMP)-2 and insulin-like growth factor-binding protein-7 (IGFBP7) were discovered and subsequently validated for their ability to predict the manifestation of moderate-severe (KDIGO stage 2-3) AKI within 12 hours (Kashani et al. 2013). Interestingly, not only do these biomarkers out-perform all other available AKI biomarkers, but their relationship to cell cycle arrest informs on a novel mechanism for AKI (Yang et al. 2010).

In our view, existing biomarkers such as NGAL and newly discovered biomarkers are beginning to shape clinical practice. This ongoing process of new discovery and reinvention of existing tools, including those as timeworn as urine flow, will advance the field further and we will eventually emerge with a set of tools that will not only help us diagnose AKI, but will also help us determine its cause, monitor its course and predict response to therapy. We eagerly await this bright future. ■

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L. S. Chawla declares associations with the following companies: Alere, Astute Medical.

J. A. Kellum declares associations with the following companies: Abbott, Alere, Astute Medical, Roche.

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RENAL REPLACEMENT THERAPY IN 2013 NEW INSIGHTS ON DOSING, TIMING, MODALITIES AND MEMBRANES

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Renal replacement therapy (RRT), particularly continuous veno-venous haemofiltration (CVVH), is increasingly used in the ICU. CVVH and derived modalities have become first-choice bedside techniques in the ICU for treatment of septic shock complicated by acute kidney injury (AKI). Despite controversial and inconclusive results emanating from randomised controlled trials, interest in continuous renal replacement therapy (CRRT) is growing steadily and even beyond its sole use in AKI. This article highlights some new insights and evolutions in the field of CRRT and RRT that may have direct or future impact on daily ICU practice, in particular, important issues such as dosing, time of initiation, and the introduction of novel highly-adsorptive dialysis membranes.

Renal Replacement Therapy in ICU Patients

What Dose?

Several large randomised controlled trials (RCTs) have focused on dose and intensity of renal RRT. In a landmark study Ronco et al. determined a haemofiltration dose of 35 ml/kg/h as most optimal for ICU patients (Ronco et al. 2010). An improved outcome was reported in patients undergoing daily rather than thrice weekly haemodialysis (Schiffl et al. 2002), suggesting that thrice weekly intermittent haemodialysis (IHD) was less convenient for treating AKI in an ICU setting. Another study showed better outcome when the convection dose was increased and dialysis combined with haemofiltration at doses matching those used by Ronco (Saudan et al 2006). In contrast, the VA/NIH Acute Renal Failure Trial Network showed that less intensive therapy (ie IHD thrice weekly, continuous veno-venous haemodiafiltration (CVVHDF) at 20 ml/kg/h or sustained low efficiency dialysis (SLED) for unstable patients) did as well as intensive therapy (ie daily IHD or CVVHDF at 35 ml/kg/h for unstable patients) (VA/NIH Acute Renal Failure Trial Network 2008). However, and despite the high quality of this large randomised study, more than 65% of the patients had already received IHD or SLED before randomisation. Interventions were started much later than commonly accepted, which may have worsened outcome in the intensive therapy group (Ronco et al. 2008; Cruz et al. 2008). In addition, the rather limited use of continuous therapy may have affected renal recovery rate (Prowle et al. 2010).

More convincing data regarding dose finding for treatment of AKI in the ICU emerged from the RENAL trial, which demonstrated no beneficial effect of CVVHDF at 40 ml/kg/h as compared with 25 ml/kg/h (RENAL Replacement Therapy Study Investigators 2009). Hence, consensus exists that CRRT dose in septic AKI should be 25 ml/kg/h with no additional benefit from a dose increase. Most experts recommend avoiding undertreatment and delivering at least 25 ml/kg/h of fluid exchange. In practice, this implies prescribing 30-35 ml/kg/h to compensate for predictable (changing bags, nursing etc.) or unpredictable (surgery, filter clotting etc.) treatment interruptions (Vesconi et al. 2009).

> *"Convincing evidence for the ideal moment to start haemofiltration in critically ill patients with AKI is still awaited"*

Two recently published trials activated the debate on ideal haemofiltration dose in septic AKI. The IVOIRE study compared haemofiltration doses of 35 and 70 ml/kg/h in patients with septic shock, AKI and multiple organ failure. No difference in mortality at 28 and 90 days was observed, yet global

mortality was comparable (39% at 28 days and 52% at 90 days) to the RENAL study cardiovascular sequential organ failure assessment (SOFA) score 3 and 4 subgroups despite inclusion of more severely ill patients (Joannes-Boyau, Honoré et al 2013). Zhang et al. compared doses of 50 and 85 ml/kg/h in septic patients with AKI, and also found no difference in mortality (Zhang et al. 2012). Mortality was higher than in the IVOIRE study, which could be perhaps explained by a more rapid inclusion (24 hours versus ± 7 days) and start of haemofiltration (at RIFLE Injury level) in the IVOIRE trial (Honoré et al. 2011). Taken together, 25 ml/kg/h must remain the standard delivered dose, in particular in septic shock. An earlier start-up time in septic AKI seems desirable, but its benefit remains to be proven.

When to Start?

Until recently AKI was ill-defined, which precluded stratification according to degree of renal impairment. Nowadays, the RIFLE (Risk, Injury, Failure, Loss, and End-stage kidney disease), Acute Kidney Injury Network (AKIN) and Kidney Disease: Improving Global Outcomes (KDIGO) classifications of AKI have become universally accepted (Levey et al. 2013). These criteria not only alert clinicians to the presence of AKI, but also promote early intervention. However, convincing evidence for the ideal moment to start haemofiltration in critically ill patients with AKI is still awaited. Bouman et al. found no effect of time to start haemofiltration on outcome of cardiac surgery patients, but their study was insufficiently powered and the patient population too selective (Bouman et al. 2002). Late initiation of CRRT was found to worsen outcome of AKI after major abdominal surgery (Shiao et al. 2009). A recent meta-analysis confirmed a beneficial effect of initiating CRRT at an early stage (Seabra et al. 2008). Early CRRT may also benefit patients with ARDS undergoing extracorporeal membrane oxygenation (Ricci et al. 2010; Santiago et al. 2009). In contrast, a French trial demonstrated that starting CRRT before fulfillment of AKI criteria might harm the patient (Payen et al. 2009). The IVOIRE trial suggested starting CRRT at RIFLE Injury level (or AKIN stage 2) for treatment of AKI accompanying septic shock (Honoré et al. 2011). Finally, fluid overload refractory to diuretics may trigger early initiation of CRRT in ICU patients without AKI (Ricci et al 2010). Ideally, a decision to start CRRT should be based on a composite index, including variables such as disease severity (e.g. SOFA score), AKI level (based on RIFLE, AKIN or KDIGO criteria), degree of fluid overload, time from ICU admission, and eventually specific biomarkers (Kashani et al. 2013).

> *"CRRT is the preferred first-line therapy in haemodynamically unstable patients with AKI"*

Which Modalities and Membranes?

CRRT and related techniques are attractive not only for treatment of AKI, but also for use in various ICU conditions not primarily associated with AKI (e.g. haemodynamic instability, hepatorenal syndrome, raised intracranial pressure, acute or severe fluid overload, and persistently positive fluid balance). Yet, the Hemodiafe study, comparing IHD with CVVHDF in ICU patients, showed that both techniques performed equally well in terms of patient outcome (Vinsonneau et al. 2006). However, a recent meta-analysis confirmed better control of haemodynamics and fluid balance by CRRT (Bagshaw et al. 2008). In addition, the PICARD group showed that CRRT was more efficacious for fluid removal in AKI patients with severe fluid overload than any intermittent or semi-continuous method (Bouchard et al. 2009). Based on aggregated results of the ATN (VA/NIH Acute Renal Failure Trial Network 2008) and RENAL (RENAL Replacement Therapy Study Investigators 2009) trials, most opinion leaders recommend CRRT as the most appropriate approach in vasopressor-dependent ICU patients with AKI (Prowle et al. 2010; Schneider et al. 2013).

One important reason to embrace CRRT in this context was the observation that a majority of shock patients receiving IHD evolved towards chronic dialysis (Prowle et al. 2010). This ominous finding was recently underpinned by a meta-analysis (Schneider et al. 2013), which showed that initial IHD was associated with higher rates of dialysis dependence than CRRT in 3,500 AKI survivors, regardless of whether haemodynamic instability was present or not. More robust RCTs are awaited to solve this controversial issue.

Current research is focusing on novel dialysis membranes that can eliminate a wide spectrum and/or large amounts of unbound mediators during CRRT, such as the AN69 ST (surface treated), SEPTEX, PMMA (polymethylmetacrylate), and AN69 OXIRIS membranes (Honoré et al. 2013). The AN69 Oxiris and PMMA membranes enable capturing of endotoxin and many cytokines (Hirasawa et al. 2010). The AN69 ST membrane is also a potent cytokine scavenger. In particular, it adsorbs the high mobility group box 1 protein, a highly inflammatory upstream cytokine that is not removed by convection (Yumoto et al. 2011). Finally, the high-porosity SEPTEX membrane was shown to beneficially influence haemodynamics in unstable septic patients treated with CVVH (Morgera et al. 2006).

Polymyxin (PMX) B column haemoperfusion is a specific form of high-surface selective membrane therapy (Cruz et al. 2009). A recent clinical study using this treatment modality showed improvement of haemodynamics and mortality (Cruz et al 2009). Given their very large surface (at least 500 and up to 10,000 m^2), adsorptive columns and sorbents are commercialised as cartridges that can run with a haemoperfusion device (Honoré et al 2013). Apheresis or selective plasma exchange are other treatment options, but data regarding their use in sepsis are scarce. The cytokine filter CytoSorb effectively eliminates most inflammatory mediators with the exception of endotoxin and IL-10 (Quintel 2012).

Conclusions and Perspectives

With time, CRRT has evolved from a pure AKI treatment to a more sophisticated therapy in terms of indication, dosing and timing. Optimising CRRT filtration dose has a proven positive effect. An ultrafiltration rate of at least 25 ml/kg/h, adjusted for pre-dilution and downtime, is required for treatment of septic

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ANTICOAGULATION IN CONTINUOUS RENAL REPLACEMENT THERAPY

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- Anticoagulation is necessary for continuous renal replacement therapy (CRRT) as it prevents clotting of the circuit and helps deliver an adequate dialysis dose.
- Unfractionated heparin is the main anticoagulant used, although regional citrate anticoagulation is gaining wider acceptance.

Introduction

Continuous renal replacement therapy (CRRT) is the favoured modality of renal replacement therapy for haemodynamically unstable patients with acute kidney injury (AKI) in the intensive care unit (ICU). Its main disadvantage is clotting of the extracorporeal circuit, leading to decreased solute clearance and inadequate metabolic, acid-base, and volume control (Tolwani and Wille 2009). To combat this problem, anticoagulation is typically used with CRRT. The perfect anticoagulant should provide optimum anticoagulation, be easily reversible, have a short half-life, and have negligible systemic effects.

There are various anticoagulants that can be used for CRRT, including systemic unfractionated heparin, regional heparin (in conjunction with protamine sulphate), low molecular weight heparin, regional citrate, thrombin antagonists, and platelet inhibiting agents. Of these, unfractionated heparin and regional citrate are more commonly used and will primarily be discussed here. For the other methods of anticoagulation, larger prospective studies and standardised protocols are needed to determine the best application of these agents.

Heparin

Unfractionated heparin is the most common anticoagulant used worldwide. Reasons for its mainstream use include relatively lower cost, wider availability, and easy reversibility with protamine sulphate. Unfractionated heparin inhibits factors IIa and Xa by potentiating antithrombin III. The anticoagulant effect is monitored by measuring activated plasma prothrombin time (aPTT), with typical protocols targeting the aPTT in the extracorporeal circuit 1.5 to 2 times control. However, heparin use in sepsis may be limited by the fact that the very substrate it acts upon, antithrombin III, may be depleted. Furthermore, heparin can result in several undesired effects, such as bleeding and heparin induced thrombocytopaenia (HIT) (Hirsh et al. 2001). Thrombocytopaenia is common in critically ill patients, and this may preclude use of systemic heparin as well.

The major complication of heparin is an increased risk of bleeding due to systemic anticoagulation. Erratic heparin pharmacokinetics in the setting of renal failure can predispose to bleeding despite normal aPTT levels, and the mortality from anticoagulation-related bleeding may be as high as 15% (Greaves 2002; van de Wetering et al. 1996). Low molecular weight heparins such as nadroparin and enoxaparin have been used in conjunction with CRRT to provide a more reliable anticoagulation response (van der Voort et al. 2005; Journois et al. 1990). Typical protocols for CRRT recommend target anti-Xa levels of 0.25 to 0.35 units/mL. These agents have less plasma protein binding, and so pharmacokinetic parameters are more predictable. Nevertheless, low molecular weight heparins are more expensive, require anti-Xa measurements for titration of anticoagulation, accumulate in renal failure, and can lead to systemic bleeding.

To minimise the systemic effects of heparin, regional anticoagulation can be delivered using unfractionated heparin and protamine sulphate by administering heparin pre-haemofilter and protamine sulphate post-haemofilter, thus restricting anticoagulation to only the circuit. However, protamine sulphate may have negative systemic effects, such as hypotension and anaphylaxis, and the protocols that use regional heparin anticoagulation are difficult to standardise (Horrow 1985).

Regional Citrate Anticoagulation

Given the challenges with heparin, use of regional citrate anticoagulation (RCA) for CRRT has increased. Regional citrate limits anticoagulation to the extracorporeal circuit and serves as a substrate for metabolism to bicarbonate by mainly the liver.

Citrate is delivered into the blood at the beginning of the CRRT extracorporeal circuit. It binds ionised calcium and prevents clotting by making free calcium unavailable to the coagulation cascade. A post-haemofilter ionised calcium level less than 0.35 mmol/l in the extracorporeal circuit, which corre-

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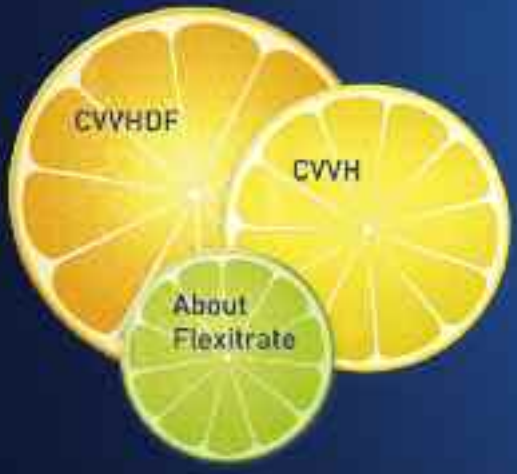

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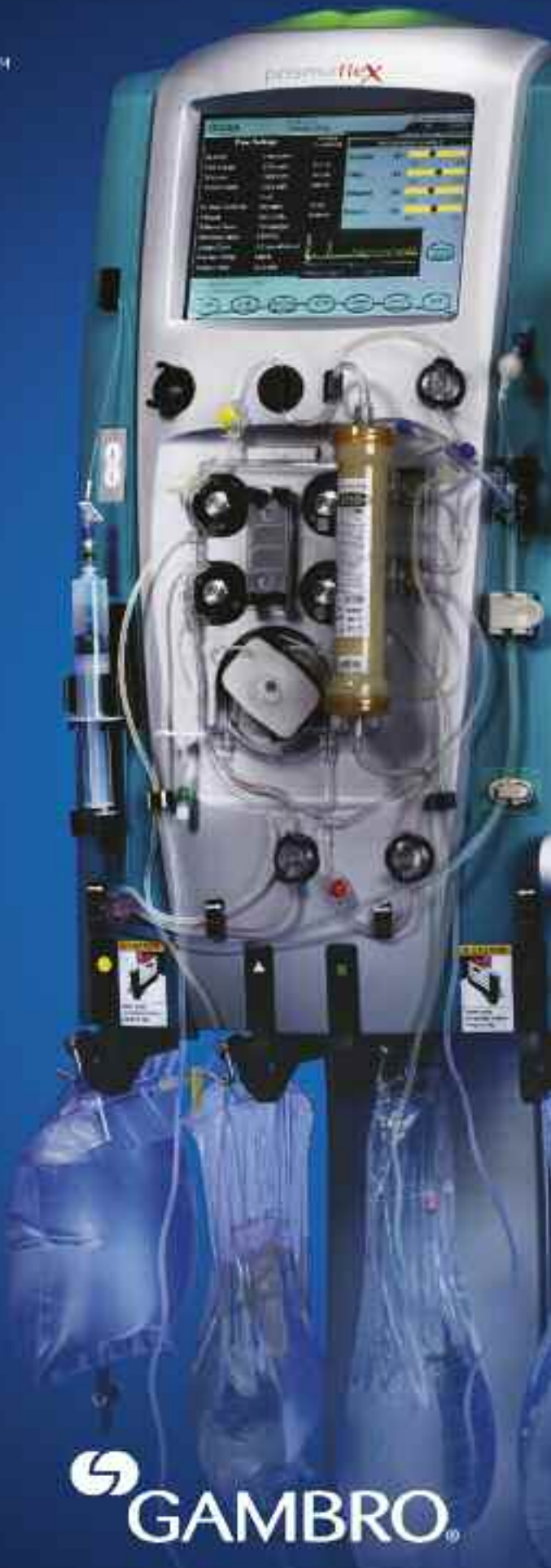

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lates with a citrate blood concentration of 4-6 mmol/l, has been shown to adequately inhibit anticoagulation (Calatzis et al. 2001). As some of the calcium-citrate complex is filtered across the haemofilter and lost in the effluent or ultrafiltrate during CRRT, a systemic calcium infusion is necessary. The remainder of the calcium-citrate complex enters the systemic circulation of the patient, where it is diluted and metabolised by the liver to bicarbonate, releasing ionised calcium back to the circulation. By maintaining normal levels of ionised calcium in the systemic circulation, anticoagulation is limited only to the circuit.

While RCA has several advantages, disadvantages include metabolic alkalosis, hypernatraemia from the use of commercially available hypertonic citrate solutions (such as 4% Trisodium Citrate, and 2.2% Anticoagulant Citrate Dextrose Solution), and hypocalcaemia. It is therefore necessary to frequently monitor acid-base status, electrolytes, and ionised calcium in the systemic circulation. Citrate accumulation may occur in patients who cannot metabolise citrate, such as those with liver failure or severe lactic acidosis, leading to severe hypocalcaemia and metabolic disorders (Meier-Kriesche et al. 2001). The use of citrate as an anticoagulant in these patients may be contraindicated. Predictive models using citrate kinetic parameters have been developed to assess the risk of citrate accumulation in patients with AKI undergoing CRRT (Zheng et al. 2013).

The use of citrate as a regional anticoagulant for CRRT was first reported in 1990 (Mehta et al. 1990). Despite its introduction over two decades ago and the experience gained since then, citrate is yet to become the mainstream anticoagulant used with CRRT. Obstacles to wider citrate use include a lack of safe citrate formulations for CRRT (commercially available CRRT solutions have high concentrations of sodium and citrate, which increase the risk of metabolic complications), cumbersome protocols, and lack of Food and Drug Administration approval in the United States (Tolwani and Wille 2012) .

Comparing Heparin to Regional Citrate Anticoagulation

To date, there have been six randomised controlled trials comparing low molecular weight heparin or unfractionated heparin to citrate during CRRT. In the largest trial, by Oudemans-van Straaten et al., 200 patients on continuous venovenous haemofiltration (CVVH) were randomised to citrate or the low molecular weight heparin nadroparin (Oudemans-van Straaten et al. 2009). Citrate was administered at a dose of 3 mmol/l blood flow, without monitoring of post-haemofilter ionised calcium. Safety was significantly better in the citrate group with only two patients requiring a change in anticoagulation regimen versus 20 patients in the nadroparin group. Patients in the nadroparin group developed more metabolic alkalosis, hyponatraemia, and lactic acidosis. In the citrate arm, fewer patients developed chronic dialysis dependence, and 3-month mortality was lower. To explain the beneficial effects of citrate on patient and kidney survival, the authors theorised that, by binding calcium, citrate reduces calcium-induced release of pro-inflammatory mediators. In another large trial, by Hetzel et al., 174 patients with AKI on mechanical ventilation were randomised to systemic heparin or RCA (Hetzel et al. 2011). Enrolled patients received pre-dilution CVVH, and while citrate use did not improve survival, it did lead to longer filter patency and a lower risk of bleeding.

Wu et al. conducted a meta-analysis that included all six randomised controlled trials of citrate anticoagulation (Wu et al. 2012). They found no significant difference in circuit life, incidence of metabolic complications, or incidence of HIT between heparin and regional citrate for CRRT. Fewer bleeding events occurred in the citrate arm. The authors concluded that RCA was safe and effective, provided that proper protocols for citrate with CRRT were in place. In a separate meta-analysis that included the same six randomised trials, Zhang et al. found that circuit life was prolonged by 23 hours with citrate, as compared to heparin (Zhang and Hongying 2012). They also reported fewer bleeding events in the citrate group.

Conclusion

While studies have demonstrated that fewer bleeding events occur with citrate use, there is conflicting data about its efficacy in terms of circuit survival time, frequency of metabolic complications, and patient and kidney survival. Unfractionated heparin is currently the most common anticoagulant used with CRRT; however, RCA is gaining acceptance. Future work involving citrate should include standardisation of citrate protocols and solutions to lessen the incidence of bleeding and metabolic complications. ■

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FLUIDS AND NUTRITION IN ACUTE KIDNEY INJURY

This article focuses on the impact of fluid and nutrition administration on kidney function. It discusses the deleterious effects of accumulating fluid overload leading to kidney oedema and worsening kidney function, and provides advice on how to adapt nutrition in the different stages of AKI, with or without RRT. Finally, information on the cardio-abdominal-renal syndrome (CARS) is provided, since AKI seldom comes alone.

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Introduction

It is important for a patient with chronic kidney disease that he or she knows what to eat in order to prevent further disease progression. Similarly, it may also be equally important for the ICU patient admitted with septic shock that we as ICU physicians adapt our treatment in order to prevent the development of AKI or its progression from an oliguric to anuric state.

Fluids and AKI

It is beyond the scope of this review to discuss the effects of different replacement and resuscitation fluids like crystalloids, starches or albumin on kidney function. Recent randomised controlled clinical trials (6S, CRYSTMAS and CHEST) could not demonstrate a benefit for colloids over crystalloids (Perner et al. 2012; Guidet et al. 2012; Myburgh et al. 2012a). This re-opened the debate as to whether hydroxyethyl starches 130/0.4 are safe to use, especially in septic patients with AKI (Haase and Perner 2012). Colloids seem to be related to increased risk for AKI and longer duration of RRT (Guidet et al. 2012; Schortgen et al. 2001; Cittanova et al. 1996; Brunkhorst et al. 2008). The VISEP study on the other hand did not show a statistical significant difference (Brunkhorst et al. 2008). The largest CHEST trial showed no difference in outcome between crystalloids versus colloids, but crystalloids were associated with less AKI and less RRT, although the risk for renal failure was the same (Myburgh et al. 2012b). It remains to be proven whether these observations can be extrapolated also to the newer balanced starches.

More important is the impact of fluid overload on end organ function (Malbrain et al. 2012, Malbrain and Van Regenmortel 2012). In patients with septic shock and capillary leak, fluid administration will lead to accumulation of second and third space fluids, especially if the patient does not transgress spontaneously from the ebb to flow phase of shock (Malbrain 2013). End-organ oedema may then lead to organ dysfunction, while the combination of ascites, intestinal oedema, and ileus may lead to increased intra-abdominal pressure (IAP), which in turn can worsen kidney function by reduction of renal plasma flow and decreased glomerular filtration rate (GFR) (De Laet, Malbrain et al. 2007). Even in the absence of overt intra-abdominal hypertension (IAH), renal interstitial oedema alone might impair renal function. As an encapsulated organ, the kidney is affected by fluid congestion and raised venous pressures with a disproportionate elevation in intracapsular pressure, which leads to a decrease in renal blood flow and GFR (Prowle et al. 2012). Many other studies and reviews focus on the same relation between fluid overload and IAH or AKI (Bouchard and Mehta 2009; Prowle and Bellomo 2013; Prowle and Bellomo 2010; Butcher and Liu 2012; Cordemans et al. 2012). After the initial early resuscitation phase a conservative fluid management strategy seems advocated (Murphy et al. 2009). No randomised controlled study exists to show that a positive fluid balance is beneficial in AKI or during acute illness in general. However, a recent meta-analysis showed consistent deleterious effects (on morbidity and mortality) of a positive cumulative fluid balance within the first week of ICU stay (Malbrain et al. 2012). Since the only way to give nutritional support is via the enteral or parenteral route, nutrition and fluid administration cannot be separated from each other.

> *"The recommendations for nutritional support can at best be described as open for discussion and debate"*

Nutrition and AKI

• Nutrition and Kidney Disease

As the aetiology and severity of AKI is diverse and can be either prerenal vs renal vs postrenal, with or without pre-existing chronic kidney disease, with or without RRT, the recommendations for nutritional support can at best be described as open for discussion and debate. The Acute Dialysis Quality Initiative recommended expressing the severity of AKI with the RIFLE criteria (Bellomo et al. 2004), which assess the severity (risk of renal dysfunction, injury to the kidney, and failure of kidney function) and outcome (loss of function and end stage renal disease) in AKI.

The recommendations below are based on the ESPEN Guidelines and recent reviews (Cano et al. 2009; Cano et al. 2006; Toigo et al. 2000a, 2000b; Berbel et al. 2011; Fiaccadori and Cremaschi 2006; Fiaccadori et al. 2008).

• Normal Energy Expenditure

The human body should be seen as a metabolic engine that needs organic fuels. These fuels (lipids, carbohydrates and proteins) are combusted in combination with oxygen and produce heat, Kcal and waste. The energy yield differs from 9.1 kcal/g for lipids, 4 kcal/g for protein and 3.75 kcal/g for glucose. Normal nutritional requirements (daily energy expenditure) can be calculated by different formulas:

BEE (Basal Energy Expenditure) kcal/24 hr

- Men = 66 + (13.7 x weight) + (5.0 x height) − (6.7 x age)
- Women = 655 + (9.6 x weight) + (1.8 x height) − (4.7 x age)

REE (Resting Energy Expenditure)

- REE = 1.2 x BEE

EE in critical illness:

- EE should always be measured, or calculated, and then corrected depending on the concomitant condition;
- In most cases it does not exceed 1.3 x BEE, though it may reach 1.5-1.7 x BEE in some cases.

In practice we use simplified computations: 25-35 kcal/kg ideal body weight (in AKI, the dry weight should be used as these patients are often hyperhydrated or have overt oedema), depending on activity and stress (more than 40 kcal/kg/day are seldom used and are potentially dangerous):

Caloric requirements: 70% from carbohydrates and 30% from fats
Protein requirements: 0.8 to 1.2 g/kg/day in normal metabolism, 1.2 to 1.8 g/kg/day in hypercatabolism

To cope with periods of starvation the body has organised endogenous fuel stores. Energy stores can last up to 10 days depending on the rate of catabolism. Carbohydrate stores (90 g with an energy yield of 900 kcal) are limited, and daily intake is needed for adequate central nervous system function. In periods of starvation fat and protein from breakdown of adipose tissue (15 kg with an energy yield of 141,000 kcal) and muscle (6 kg with an energy yield of 24,000 kcal) become the main sources of calories.

• Metabolic Alterations in Acute Illness

Different metabolic alterations can be observed in patients with septic shock and AKI. First, due to the hypermetabolic state the EE changes and becomes proportional to the amount of stress. The presence of AKI by itself (in the absence of critical illness) does not seem to affect REE; as such, EE in AKI is determined mainly by the underlying condition. Studies in chronic kidney disease yield conflicting results, varying between increased, normal, or even decreased REE. Second, while the kidneys play an important role in glucose homeostasis in healthy individuals, the underlying critical illness and the loss of kidney function by itself may contribute to altered carbohydrate metabolism in AKI. Third, stress diabetes can develop, resulting in hyperglycaemia and insulin resistance, while gluconeogenesis increases mainly due to the action of catabolic hormones such as glucagon, epinephrine, and cortisol. The normal suppressive action of exogenous glucose and insulin on hepatic gluconeogenesis, and peripheral glucose utilisation in insulin-dependent tissues (muscle and fat) are decreased. Fourth, while the malnutrition of starvation is due to deficits in essential nutrients that can be corrected with nutrient intake, malnutrition in AKI and other critical illnesses is due to a disease-induced abnormal nutrient processing. Nutrient intake alone may not correct the malnutrition. The underlying disease that results in abnormal nutrient processing must be equally addressed. Fifth, while in healthy subjects 5% of glucose is metabolised to lactate, this may rise up to 85% in critically ill patients, leading to nutrient toxicity. Sixth, critical illness is accompanied by protein catabolism and net negative nitrogen balance. The increased protein synthesis is unable to compensate for the higher proteolysis. In the acute phase, this catabolic response may be beneficial, providing amino acids for hepatic gluconeogenesis (supplying substrate for vital tissues such as the brain and immune cells), and for synthesis of proteins involved in immune function and in the acute-phase response. However, the sustained hypercatabolism in the chronic phase of critical illness results in a substantial loss of lean body mass and in muscle weakness and decreased immune function. Protein catabolic rates may go up to 1.3 and 1.8 g/kg per day. Protein catabolism also accelerates the increases of serum potassium and phosphorus.

• Who Needs Nutritional Support in AKI, When and What Route?

Nutritional support is limited to patients with unmet nutrient requirements, documented inadequate oral intake, unpredictable return of GI function, or a prolonged period of bowel rest. In general these are the more severe cases that also need RRT; the conservatively treated (non-dialysed) patients usually present with a milder course. No data exists investigating the effect of nutritional support versus starvation in the latter group of patients with mild AKI. In a study comparing higher calorie total parenteral nutrition (PN) to lower calorie total PN the extra nutritional support did not improve estimated nitrogen balance, protein catabolic rate, or urea generation rate, but increased serum triglycerides, glucose, insulin need and nutritional fluid administration (Li et al. 2010). Moreover, urea nitrogen appearance was higher in the high nitrogen intake group than in the low nitrogen intake group. Meta-analyses comparing enteral nutrition (EN) with PN did not show any difference in mortality, although there seem to be fewer infectious complications associated with EN (maybe due to lower incidence of hyperglycaemia) (Gramlich et al. 2004). Early EN may have beneficial effects by triggering gut immunity, while delay of EN may promote a pro-inflammatory state. Failure of EN is associated with gut atrophy and a higher incidence of infection. Changes in gut integrity

start within six hours, resulting in a 24 to 48 hour window of opportunity (Zaloga 1999; McClave et al. 2002). Despite the beneficial effect of EN, EN fed critically ill patients often do not meet their nutritional targets, especially during the first days of ICU stay. Although adequate early nutrition is easier via the parental route, there is still a lot of controversy about the timing of the initiation (early vs late) of PN in critically ill adults in whom caloric targets cannot be met by EN alone, especially after the publication of the results of the EPaNIC trial (Casaer et al. 2011). Casaer et al. found that there was no significant difference in mortality between late initiation and early initiation of PN among patients in the ICU who were at risk for malnutrition, despite the use of early EN plus micronutrients in a protocol that prevented hyperglycaemia. However, withholding of PN until day eight was associated with fewer ICU infections but a higher degree of acute inflammation. Late initiation of PN was also associated with a shorter duration of mechanical ventilation, a shorter course of RRT and a shorter ICU stay, despite a slight increase in hypoglycaemic episodes (Casaer et al. 2011). Unlike the EPaNIC trial, which compared semi-starvation for one week to early glucose load followed by hypercaloric low protein PN within 48 hours, Heidegger et al. started the intervention on day four to maximise the potential for EN delivery, in keeping with ESPEN guidelines (Heidegger et al. 2013). Moreover, as opposed to the EPaNIC trial, their EN group was a true control group demonstrating cumulative increasing energy deficit (indirect calorimetry): 77±25% energy target vs. 104±16% (group with supplemental PN), and their population was composed exclusively of patients with a real indication of nutritional therapy, ie failure of EN on day three.

• What Amount of Calories Should be Used in AKI?

Overfeeding should be avoided at all times, since this may result in hyperglycaemia, excess lipid deposition, azotaemia, excess carbon dioxide CO_2 production with difficult weaning from the respirator and infectious complications. Although not based on solid evidence, recent recommendations suggest a non-protein energy supply of 25 to 30 kcal/kg/day in men and 20 to 25 kcal/kg/day in women (Casaer et al. 2008). The proposed proportions of non-protein energy supply are 70% to 75% of carbohydrate and 25% to 30% of fat. Recent trials have renewed interest in hypocaloric feeding, and showed that combining normal protein with reduced caloric supply (caloric intake of between 33% and 66% of the target) resulted in fewer infectious complications and reduced ICU length of stay (Casaer et al. 2011; National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network 2012; Rice et al. 2011; Arabi et al. 2011. The use of indirect calorimetry is recommended.

• What Amount of Proteins Should be Given in AKI?

The goal is to improve protein synthesis and nitrogen balance. Although negative nitrogen balances are associated with the worst outcomes, there are no randomised studies comparing different protein or nitrogen intakes with regard to clinical outcomes in ICU patients. Although the ideal amount is still debated, a protein intake of between 1.2 and 1.6 g/kg/day (0.16 to 0.24 g nitrogen/kg/day) is usually recommended. Because many nonessential amino acids (NEAA) are not readily synthesised or increasingly used in critically ill patients, the combination of essential and nonessential amino acids is supposed to be superior. The optimal EAA:NEAA ratio has not yet been established, and can range from

2:1±4:1. If more than 0.4±0.5 g/kg/day are supplied, the addition of NEAA is mandatory. Composition of the amino acid mixture should be tailored to meet the specific metabolic requirements of uraemia (histidine, taurine, tyrosine).

• Should we Use Specific Nutritional Components in AKI?

Glutamine is the most abundant amino acid in the body, and is an important fuel for cells of the immune system. In stress situations, concentrations of glutamine decrease and it becomes a 'conditionally' essential amino acid. Although still controversial, some guidelines recommend enteral and parenteral supplementation (Fiaccadori and Cremaschi 2009). Antioxidant micronutrients (vitamins and trace elements) play a key role in metabolism, immune function, and antioxidant processes. Because critically ill AKI patients have increased oxidative stress their antioxidant micronutrients are deficient and thus should be supplemented. Selenium, zinc, vitamin E, and vitamin C show promising effects on infectious complications and/or mortality in ICU patients. Recommended vitamin C in AKI varies between 30 to 100 mg but should probably not exceed 50mg/day, because inappropriate supplementation may result in secondary oxalosis. Vitamin A should probably be avoided because of the possibility of accumulation, as reported in chronic renal failure, and signs of toxicity should be carefully monitored.

Immunonutrients are nutrients with an immune-modulating effect and include glutamine, arginine, nucleotides, and omega-3 fatty acids. Arginine is a precursor of nitric oxide synthesis, and may be detrimental in critically ill patients with severe sepsis or septic shock. A systematic review aggregating the results of randomised controlled trials and meta-analysis of enteral supplementation of omega-3 fatty acids (fish oil) in patients with acute respiratory distress syndrome demonstrated that enteral formula enriched with fish oils significantly reduces mortality and ventilator days and tended to reduce ICU length of stay (Heyland and Dhaliwal 2005; Heyland et al. 2001). A role for exogenous omega-3 fatty acids in human renal protection is, at this moment, purely speculative. Cocktails of several immunonutrients and antioxidants (containing glutamine, arginine, nucleotides, and omega-3 fatty acids) in critically ill patients, however, showed no difference in clinical outcome with standard EN (Heyland et al. 2013).

• What Can we Recommend During Continuous RRT (CRRT)?

The effect of CRRT on EE and protein catabolic rate is probably small and not clinically relevant. Blood-membrane contact during RRT may induce a protein catabolic effect, but this may be of debatable nutritional significance. The exact metabolic fate of the administered amino acids is unknown. They could be used for the synthesis of 'beneficial' proteins or burnt for energy, but they could also join the inflammatory mediator pool (oil on the fire). The daily amino acid losses with RRT may reach between 10 and 15g (0.2 g/kg/day) especially with high flux dialysers (and this loss should be integrated by artificial nutrition). On the other hand, extracorporeal losses of lipoproteins are not to be expected. Higher amino acid intake (2.5 g/kg/day) may improve nitrogen balance in comparison with lower intake (1.2 g/kg/day), while requiring more aggressive haemofiltration. Other factors like blood pump rate and type and rate of substitution fluid may also play a role, therefore the optimal nutritional support strategy for patients with AKI requiring CRRT remains a matter of great controversy.

What about CARS?

We already mentioned the importance of comorbidities (like congestive heart failure) in the development of AKI. Within this respect, the abdominal compartment can be seen as the missing link in the pathophysiology of acute decompensated heart failure (ADHF) and worsening kidney function or cardio-renal syndrome. Indeed, increased IAP, as an extreme marker of abdominal congestion, is correlated with renal dysfunction in ADHF. Recent studies showed that raised IAP is prevalent in advanced heart failure with reduced ejection fraction and correlates with impairment of renal function (Mullens et al. 2008a). However, IAH defined as > 12 mmHg is less frequent and frank ascites is rare. Importantly, medical treatment resulting in a decrease of IAP ameliorates renal function and in cases of persistent high IAP, ultrafiltration might be beneficial (Mullens et al. 2008a, 2008b). Notably, while organ dysfunction in the intensive care literature has only been described when IAP exceeds 12 mmHg, patients with ADHF already develop worsening renal function with a much lower IAP (Mullens et al. 2008a). This might suggest that the underlying reserve of the kidneys to counteract increased IAP is limited in this setting. It is also vital to emphasise that, although the degree of renal dysfunction is probably correlated with the degree of elevated IAP, there can be a wide range of IAPs in relation to serum creatinine levels at presentation (Verbrugge et al. 2012). While we can only speculate why this discrepancy exists, it is clear that other mechanisms including coexisting systemic congestion, pre-existing renal insufficiency, as well as drugs used during the treatment of ADHF, probably play a role (Verbrugge et al. 2013). Absolute increases in blood or interstitial volume are not implied in every episode of ADHF (e.g. 'flash' lung oedema in diastolic heart failure). This implies that vascular redistribution is another important mechanism for elevated cardiac filling pressures. The splanchnic vasculature normally contains about 25 % of the total blood volume, a large part of which can quickly be recruited to the circulatory system through elastic recoil of the splanchnic veins and sympathetically-mediated venoconstriction (Verbrugge et al. 2012; Verbrugge et al. 2013). Because of the extensive orthosympathic innervations of abdominal capacitance veins, more blood is probably distributed to the effective circulation in states of increased sympathetic nerve system activation such as ADHF. Therefore, the term Cardio-Abdominal-Renal Syndrome (CARS) was recently coined to emphasise the potentially important role of the abdominal compartment and splanchnic vasculature in the pathophysiology of AKI and worsening chronic kidney disease in ADHF. Because fluid resuscitation may lead to fluid accumulation with second and third compartment spacing, especially in oliguric and anuric AKI, the presence of AKI carries the potential for further increase in IAP which in turn can

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worsen AKI itself especially if underlying morbidity like ADHF co-exists.

Conclusions

Energy needs in patients with AKI should be measured via indirect calorimetry, and should be fully covered after day four, as this will result in fewer infections, more AB-free days, shorter duration of mechanical ventilation and eventually shorter duration of RRT. In general, however, there is not enough evidence to support the effectiveness of nutritional support for AKI and further high quality randomised studies are required to provide reliable evidence of the effect and safety of nutritional support in AKI. Meanwhile, the ESPEN Guidelines should be followed, or at least clinical common sense, and we suggest using the gut if available! In non-dialysed AKI use low protein and adequate carbohydrates. For dialysed AKI patients, although no strong evidence is available, physiologic arguments favour nutritional support. If there is failure of EN, EN combined with supplemental PN should be used. If PN is to be used, commercially available all-in-one three chamber bags are convenient either for central or peripheral vein administration. Fluid accumulation should be avoided and IAP needs to be measured. In case of worsening heart and kidney function, think of CARS! ■

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RENAL RECOVERY AFTER ACUTE KIDNEY INJURY

Renal recovery after acute kidney injury is affected by co-morbidities as well as ICU treatment. Nephrology referral for at risk patients may be a way to minimise risk for end-stage renal disease or death.

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Introduction

Acute kidney injury (AKI) complicates around 20% of hospitalisations, and is associated with morbidity and mortality (Uchino et al. 2006; Wang et al. 2012). In-hospital mortality rates of more than 50% for patients on renal replacement therapy (RRT) are common (Hoste and Schurgers 2008). The most recent studies report lower, albeit still high, 90-day mortality rates: 34% for critically ill patients with AKI and 39% for the subgroup requiring RRT (Nisula et al. 2013).

20,000 cardiac surgery patients without pre-existing CKD, rose progressively with increasing rise in creatinine (Heung and Chawla 2012). These findings were supported by a recent meta-analysis: the risk of developing CKD rose with mild, moderate and severe AKI when compared with no AKI (adjusted HR 2.0, 3.3 and 28.2, respectively) (Coca et al. 2012). Moreover, in a Veterans Affairs database study of diabetic patients, Thakar et al. demonstrated how AKI patients, as compared to non-AKI patients, were significantly more likely to develop CKD stage 4 (HR 3.56, 95% CI 2.76-4.61).

"We as intensivists seem to lack knowledge regarding long-term kidney morbidity and/or fail to act in the best interest of our AKI survivors"

With a focus on morbidity, a US study from 2012 demonstrated that only 8.5% of AKI survivors were referred to nephrologists and that severity of AKI did not affect referral rates (Siew et al. 2012). This ignores the fact that the recovery phase of AKI may represent the best opportunity to intervene in the negative outcomes of AKI (Chawla 2011). Most major cardiovascular events during a stay in hospital or in the intensive care unit (ICU) will trigger a cardiology referral. However, we as intensivists seem to lack knowledge regarding long-term kidney morbidity and/or fail to act in the best interest of our AKI survivors.

This review therefore details two post-ICU consequences for AKI survivors, namely chronic kidney disease (CKD) and end-stage renal disease (ESRD). More specifically, we seek to assess the risk factors associated with AKI survivors progressing to CKD/ESRD and to examine if interventions during the ICU stay may have an impact on long-term morbidity.

Co-morbidities or Intrinsic Factors Affecting Long-Term Outcome

The link between AKI and the development of CKD has been shown in numerous investigations. Heung and Chawla looked at dose-response, and showed that the risk of CKD, in over

Interestingly, patients with multiple episodes of AKI had a more than twice-fold risk for CKD for each additional AKI hit (HR 2.02, 95% CI 1.78–2.30) (Thakar et al. 2011).

Looking at aggravating factors for patients in the ICU we see a number of non-surprising findings. Advanced age, presence of diabetes mellitus and decreased baseline estimated glomerular filtration rate have been identified as risk factors for the progression to advanced stage CKD in studies on AKI survivors (Amdur et al. 2009; Ishani et al. 2009; Lo et al. 2009; Wald et al. 2009). Adding to that panel of risks, a low serum albumin concentration is a strong predictor of poor long-term renal outcome (Chawla et al. 2011).

ICU Treatment

Besides the baseline risks detailed above, are there interventions when the patient is in the ICU that have an effect on the long-term outcome? Avoiding nephrotoxic agents if possible, considering alternatives to radio contrast procedures and ensuring adequate volume status and perfusion pressures are obvious steps to take. Having stated that, we acknowledge that the last part, "ensuring adequate volume status and perfusion pressures" are easy statements on paper but hard to gauge in the clinical reality in which we operate.

Interventions that we can try to analyse include: modality, timing and dose of renal replacement therapy (RRT). Furthermore, we can look into fluid removal management in AKI patients.

RRT Modality

If a patient needs RRT, multiple studies point to the fact that modality is important. In short, it seems that continuous renal replacement therapy (CRRT) holds a long-term outcome benefit over intermittent RRT (IRRT) in the ICU setting. A large systematic review and meta-analysis from 2013 identified 23 studies: seven randomised controlled trials (RCTs) and 16 observational studies involving 472 and 3,499 survivors respectively (Schneider et al. 2013). Pooling RCTs showed no difference in the rate of dialysis dependence among survivors (relative risk (RR) 1.15 [95 % CI 0.78–1.68]). However, pooled analyses of observational studies indicated a higher rate of dialysis dependence among survivors who initially received IRRT as compared with CRRT (RR 1.99 [95 % CI 1.53–2.59]).

Timing of RRT

When to start RRT has been the subject of debate. In the absence of life-threatening derangements associated with kidney failure (metabolic acidosis, hyperkalaemia, uraemia, and/or fluid overload), there is limited evidence to guide clinicians on when to initiate RRT in the critically ill patient with AKI. Some data suggest that earlier RRT initiation may attenuate kidney-specific and non-kidney organ injury from acidaemia, uraemia, fluid overload, and systemic inflammation (Clark et al. 2006; Matson et al. 2004). This could potentially translate into improved survival and earlier recovery of kidney function (Matson et al. 2004). A meta-analysis from the University of Alberta and the Harvard School of Public Health did shed some light on this issue (Karvellas et al. 2011): 15 unique studies (two randomised, four prospective cohort and nine retrospective cohort) were analysed, and early RRT initiation was associated with reduced mortality compared to late initiation (pooled OR 0.45; 95% CI, 0.28 to 0.72, P < 0.001). Five studies (of seven reporting data) described a higher rate of kidney recovery to dialysis independence at hospital discharge for patients receiving early RRT. Pooled analysis of these seven studies showed a non-significant summary estimate favouring early RRT (OR 0.62, 95% CI 0.34 to 1.13).

Dose of RRT

The RRT dose has not been shown to have an effect on mortality or the rate of renal recovery in the two large RCTs on the subject (VA/NIH Acute Renal Failure Trial Network 2008; RENAL Replacement Therapy Study Investigators 2009). However, please note that these studies did not detail fluid removal as a determinant of dose. Instead they viewed dose as an *a priori* determined level of high or low intensity, where patients could be treated both with IRRT and CRRT (VA/NIH Acute Renal Failure Trial Network 2008) or CRRT-only effluent flow based on body weight, either 40 ml/kg/h or 25 ml/kg/h (RENAL Replacement Therapy Study Investigators. 2009).

Fluid Management

As stated above, fluid therapy aiming to improve renal perfusion and oxygen delivery remains a cornerstone in the management of patients with, or at risk of, AKI. Current evidence suggests that early goal-directed correction of hypovolaemia with fluids improves renal outcome (Oliveira et al. 2008) and survival (Oliveira et al. 2008; Rivers et al, 2001) in septic patients. Evidence from observational studies, however, indicates that a prolonged and uncritical fluid therapy, causing fluid accumulation, might negatively impact recovery from AKI. The results from these studies highlight the importance of timing of RRT initiation as well as the delivered dose, not in terms of molecular clearance but rather measured as the extent of fluid removal.

Hayes and co-workers investigated 76 RRT-treated children in a paediatric ICU, focusing on the percentage fluid overload (%FO) at RRT initiation and outcome (Hayes et al. 2009). Forty-two children survived to hospital discharge, and these patients had significantly lower %FO (7.3%) at RRT initiation than non-survivors (22.3%). Although RRT was successfully discontinued in all survivors without preexisting ESRD and with complete follow-up data (n = 37), those with a %FO of >20% spent a longer time on the RRT machine as compared to children with a %FO of <20% (median 8 vs. 26 days, p = 0.0038).

Heung and co-workers found similar results when they studied 170 adult patients treated with RRT for AKI (Heung et al. 2012). The primary endpoint was recovery of adequate renal function to discontinue dialysis for at least two weeks within one year after dialysis initiation. Thirty-six percent of patients met the renal recovery criterion. Renal recovery was highly associated with survival, as 71% of patients who met this criterion were alive at one year. In contrast, only 15% of patients who did not recover their renal function were alive at this time. Multivariate Cox proportional hazard modelling was used to identify variables independently associated with renal recovery. A higher baseline serum creatinine, one or more major comorbidities, time between nephrology consultation and RRT initiation and use of vasopressors were all independently associated with a decreased likelihood of renal recovery. For fluid overload, each 1% increase in %FO at RRT initiation was associated with 3% decreased likelihood of renal recovery at one year.

In the study by Bouchard and colleagues, the effect of fluid overload on renal recovery was less consistent (Bouchard et al. 2009). Their study comprised 618 AKI patients from five academic centres in North America. Fluid overload was defined as a percentage of fluid accumulation >10% over baseline weight at hospital admission. Fluid overload at dialysis initiation was not related to dialysis independence at hospital discharge. Neither was fluid overload at AKI diagnosis associated with recovery of kidney function, as defined by a serum creatinine ≤44 µmol/l or ≤20% above baseline. Patients with fluid overload at the time of their peak creatinine were, however, significantly less likely to recover renal function than patients without fluid overload.

The importance of a negative fluid balance during RRT on mortality and renal recovery was recently highlighted in a post-hoc analysis of the data from the RENAL study (RENAL Replacement Therapy Study Investigators 2012). The authors showed not only that a negative mean daily fluid balance during RRT was associated with a nearly 70% reduction

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DONATION AFTER CIRCULATORY DETERMINATION OF DEATH

A NEW OLD FRIEND

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Organ transplantation has become a successful therapy for end-stage organ failure thanks to major advances in fields as essential as immunosuppression, transplant technology and intensive care.

Introduction

Although first transplants were carried out from asystolic donors, since the introduction of the brain-death concept that followed the declaration of the Ad Hoc Committee of Harvard Medical School in the 1960s and the agreement of criteria for the diagnosis of brain death, heart-beating donors have become the main source of organs for transplantation. Despite many countries having reached maximum numbers of organ transplants, due to the efforts to optimise donation programmes in brain death, growing organ demand added to the epidemiological change in profile of the brain dead donor are leading to a feared situation of organ shortage and higher waiting lists.

Transplant teams have searched for alternative sources of organs for two decades. Living donation and reactivation of old programmes of donation after circulatory determination of death (DCDD) have contributed to mitigating this misfortune and expanding the donor pool.

Traditionally donors from a DCDD program have been considered as marginal donors because warm ischaemia time (WIT) following cardio-circulatory arrest (CCA) has important deleterious effects on organ viability. However, this problem has radically changed in recent years thanks to a better understanding of mechanisms involved in ischaemia-reperfusion injury. In this way, protective strategies against these insults that inevitably occur in these organs have been included in DCDD protocols. Actually long-term outcomes of DCDD are similar to brain-dead donation (BDD).

Terminology and Classification

DCDD is defined as donation that takes place after death has been confirmed by using circulatory criteria. Terminology applied to DCDD in the world has evolved over the years. Currently, we can find DCDD as other terms in the literature: non-heart-beating donation (NHBD) as opposed to heart-beating donation (HBD) or brain-dead donation (BDD), or donation after cardiac death (DCD). It is emphasised that the person's death is not determined by the irreversible loss of cardiac function, but by the irreversible loss of circulatory (and respiratory) function.

At the First International Workshop on NHBD held in Maastricht in 1995 four types of DCDD donors were clearly defined (Koostra et al. 1995):

I. Dead on arrival: patients who suffer a CCA are declared dead at an out-of-hospital site and brought to the hospital without any attempts of resuscitation.

II. Unsuccessful resuscitation: resuscitation attempts are made, but they are unsuccessful.

III. Awaiting cardiac arrest: patients with end-stage diseases such as irreversible brain damage, end-stage musculoskeletal disease, or severe spinal cord injury in whom withdrawal of life-sustaining therapy is considered and when it occurs, the subsequent CCA is awaited.

IV. Cardiac arrest in brain-dead patient: brain death is declared prior to an unanticipated CCA due to haemodynamic disturbances or the catecholamine storm during the brainstem herniation.

DCDD categories III and IV are classified as controlled DCDD (cDCDD), because CCA is always witnessed by a medical team and sometimes it can be expected and the transplant team can prepare for the procurement process. DCDD categories I and II are considered uncontrolled DCDD (uDCDD), because CCA is unexpected and the medical or transplant team is unaware of it.

Traditionally DCDD has been subdivided according to these Maastricht criteria, which are still widely used internationally. However, sometimes it is recognised that this classification is not accurate, and it does not reflect the DCDD reality held in clinical practice. In fact, DCDD has been classified in different ways by transplant teams, and the importance of discerning between CCA that takes place inside the hospital and outside it has been highlighted in uDCDD (Detry et al. 2012).

Donors can also be classified according to the phase of the donation process in which the person suffering the cessation of circulatory function remains. This classification has been recently published by the World Health Organization (WHO) within the Critical pathways for or-

gan donation as part of an initiative to address the common challenges and make recommendations on how to maximise deceased donation (including BDD and DCCD) (Domínguez-Gil et al. 2011). The pathways provide clear definitions for potential, eligible, actual, and utilised donors, allowing better national and international comparisons to be made.

Warm Ischaemia Time

Knowledge of warm ischaemia time (WIT) as accurately as possible is critical to assess the viability of these organs for transplantation, because the ischaemia resulting from CCA induces a damage which may result in a reduced graft function in the recipient. In addition, there is large evidence that warm ischaemia exacerbates the deleterious effects of cold ischaemia.

In uDCDD WIT is defined as the time between witnessed circulatory arrest and the initiation of organ preservation manoeuvres. It is widely accepted that it should be less than 120-150 minutes and the time between CCA and initiation of cardiopulmonary resuscitation should be less than 15-30 minutes (Fondevila et al. 2007; Sánchez-Fructuoso et al. 2006) .

In cDCDD there is not worldwide consensus on the definition of WIT, but the interval of time between extubation (as the definitive withdrawal of treatment) until the initiation of preservation manoeuvres is the most commonly used (referred to as total WIT). But currently many of us prefer to register WIT as the time since the onset of a significant hypoperfusion (the first episode in which is recorded systolic blood pressure ≤ 60 or ≤ 50 mmHg determined by invasive arterial monitoring and/or oxygen saturation ≤ 80% determined by pulse oximetry) up to preservation manoeuvres (referred to as functional or true WIT) (Manara et al. 2012). Most transplant teams accept a maximum functional WIT of less than 60 minutes, although this time may be restricted to 30 minutes for a specific organ or donor.

Determination of Death

The determination of death is a critical phase in the process of donation, where professionalism, respect for fundamental ethical principles and transparency must be guaranteed. DCDD donors are declared dead using circulatory-respiratory criteria. Since the resumption of DCDD programmes an ongoing debate about the methods used for determination of both cessation of functions and its irreversibility has been established.

Cessation of circulatory functions is recognised by indirect measures of circulatory arrest (absence of heart sounds, pulse, blood pressure, respiratory effort). In a clinical setting of DCDD the use of confirmatory tests may be required in accordance with national or hospital protocols. Irreversibility is recognised by persistent cessation of function during an appropriate period of observation, but in the DCCD setting it is critical because it must be minimised to avoid an unnecessary increase of the WIT. This period, the so-called 'no touch' or 'hands off' period is stipulated as five minutes in Spain, but it can range from two to 20 minutes. This debate arises from the publication of some cases of autoresuscitation (spontaneous return of circulation) after failed attempts of CPR. A recent systematic review of autoresuscitation in DCDD donors showed no cases when invasive treatment was withdrawn (Bernat et al. 2010; Bernat et al. 2006).

Organ Preservation Techniques

In cDCDD, the most often used technique for preservation of abdominal organs consists of a laparotomy and cannulation of the aorta to start the cold flush, also called 'super-rapid technique'. In uDCDD, chest compressions and ventilation are restored while the femoral vessels are cannulated after declaration of death in order to perform a normothermic regional perfusion (NrP), which involves maintaining blood temperature at 37°C with a heat exchanger. An alternative technique is total body cooling, maintaining the blood temperature at 15°C. Both systems have demonstrated the ability to reverse warm ischaemia injury, but the use of NrP changes the period of CCA (warm ischemia) into a period of preconditioning (ischaemic preconditioning) (Fondevila et al. 2007; Net et al. 2005). This technique reduces the incidence of delayed graft function compared to in situ perfusion.

After retrieval, organs must be preserved until the moment of the transplantation. Static cold storage (CS) has been traditionally used for all the organs. Nevertheless, various studies have focused their attention on organ preservation through the use of pulsatile perfusion machines (PM) until transplantation in the recipient. These studies have demonstrated an improvement in graft function in ischaemically damaged organs (Jochmans et al. 2011). This preservation technique reduces vascular resistances increased by the ischaemic insult and facilitates the elimination of erythrocyte residues from the microcirculation. PM is widely used in kidneys. Newly, an isolated liver PM has been developed, and it works in normothermia in order to add a period of normothermic recirculation ex vivo (Hessheimer et al. 2012).

Outcomes from DCDD

The outcomes are usually acceptable as long as the selection criteria of the DCDD donor are strict (age, NrP for a maximum of 240 minutes) The short- and mid-term outcomes of transplanted kidneys retrieved from DCDD donors are similar to those of kidneys retrieved from DBD donors (Wadei et al. 2013). In the case of livers, there is a higher incidence of primary graft failure and also a higher incidence of biliary duct complications (mainly intrahepatic ischaemic-type biliary strictures). Some of these recipients require retransplantation (Suárez et al. 2008). In the case of lungs, some studies have shown that the long-term patient and graft survival rates after DCDD donor lung transplantation are equivalent or better to those after BDD (de Antonio et al. 2007).

Conclusions

Worldwide implementation of DCDD programmes has mitigated the shortage of organs, with acceptable outcomes becoming an alternative to BDD. Further improvements in preservation techniques are needed to increase the organs for transplantation retrieved from potential DCDD donors. ■

For full references, please send a request to **editorial@icu-management.org**

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HOSPITAL MANAGEMENT IN TIMES OF CRISIS:

CONSTRAINTS, CHALLENGES AND OPPORTUNITIES

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(MERGERS, JOINT VENTURES, OUTSOURCING, HUMAN RESOURCE MANAGEMENT, FINANCIAL RESOURCES)
- Two 30-minute lectures (14.00 - 15.00)
- Poster Session - presentation (15.00 - 15.30)
- Break (15.30 - 16.00)
- Two 30-minute lectures (16.00 - 17.00)
- 45-minute roundtable (17.00 - 17.45)

RECEPTION HOSTED BY THE CITY OF LUXEMBOURG
(Evening)

Friday, 29 November 2013

BUSINESS PROCESS RE-ENGINEERING
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- Two 30-minute lectures (09.00 - 10.00)
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- Two 30-minute lectures (10.30 - 11.30)
- 45-minute roundtable (11.30 - 12.15)

NEW BUILDINGS, NEW LOGISTICS, NEW TECHNOLOGIES
- Two 30-minute lectures (14.00 - 15.00)
- Poster Session: awards ceremony (15.00 - 15.15)
- Break (15.15 - 15.45)
- Two 30-minute lectures (15.45 - 16.45)
- 45-minute roundtable (16.45 - 17.30)

GALA DINNER AT CASINO 2000, Mondorf-les-Bains (L)
(Evening)

INFORMATION

VENUE
The Congress will be held in Luxembourg business centre, at the prestigious Conference Centre (Luxembourg/Kirchberg). The building is located 5 min from downtown Luxembourg and is well connected by public transport.

OFFICIAL LANGUAGES
The official congress languages will be English/German/French. All presentations will be in one of these three languages.

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REGISTRATION
Online registration for attendees and accompanying persons will begin on 1 March 2013 via the congress website:
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VENTILATION AFTER CARDIAC ARREST

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Post-cardiac arrest syndrome is associated with high morbidity and mortality not only from poor neurological outcome but also from respiratory dysfunction. Optimising ventilation and gas exchange by protective ventilation, keeping normoxia and avoiding hypocapnia may play a relevant role in improving outcome. Furthermore, transcranial Doppler (TCD) can be considered as a new non-invasive monitoring tool.

Introduction

For decades, physicians have focused on how to improve outcome in post-cardiac arrest patients. They have used several methods to optimise neurological recovery such as therapeutic hypothermia, control of seizure and blood sugar during the 'golden period' after return of spontaneous circulation (ROSC). However, non-neurological post-cardiac arrest syndrome is another issue that should be of concern.

Not only neurological dysfunction but also cardiovascular dysfunction and respiratory impairment have an impact on mortality. However, there are few data in terms of ventilator strategy in patients after cardiac arrest. In this review, the authors aim to describe the outcome of organ failure after cardiac arrest, the effect of protective ventilation, the goal of gas exchange and a non-invasive method for cerebral blood flow monitoring.

In their recent large prospective cohort study for evaluating outcome of patients with mechanical ventilation, in 1998, 2004 and 2010, Esteban et al. demonstrated that intensive care unit and in-hospital mortality are decreased over time. However, the incidence of cardiac arrest in this group rose from 2% to 5% despite a decrease in the incidence of congestive heart failure (CHF) from 10% to 6-8%. The mortality in patients with cardiac arrest was still between 44-48% (Esteban et al. 2013).

Roberts et al. (2013a) reported that the highest cardiovascular and respiratory specific Sequential Organ Failure Assessment (SOFA) scores were associated with in-hospital mortality in 203 post-cardiac arrest patients, in which the majority of causes of cardiac arrest were pulseless electrical activity and asystole initial rhythm. The respiratory SOFA score is the degree of oxygen impairment. In an animal experimental model, Wang et al. (2013) have demonstrated that dead space, airway resistance and lung elastance are increased after ROSC. The previously mentioned findings represent the value of haemodynamic and respiratory optimisation during the post-cardiac arrest period.

> *"Although current evidence suggests protective ventilation in patients without preexisting lung injury, there is no sufficient data in terms of optimal tidal volume to decrease lung injury and mortality in post-cardiac arrest after ROSC"*

Outcome and Organ Failure After Cardiac Arrest

After cardiac arrest, mortality and bad neurologic consequences become the major concern. Therapeutic hypothermia improves neurological outcome and decreases the mortality rate (Nolan et al. 2010). Several studies have demonstrated that neurological abnormalities mainly impact on worse clinical outcome. Glasgow-Pittsburgh Cerebral Performance Categories and prognostic biomarkers such as serum neuron-specific enolase (NSE) and S100B are known as predictors for neurological outcome (Rana et al. 2012; Rana et al. 2011).

Protective Mechanical Ventilation

Inappropriate mechanical ventilator settings can be harmful to the lungs even in non-pre-existing lung injury. The mechanisms of ventilator-induced lung injury are as follows: 1) overstretching from high tidal volume (VT); 2) repeated recruitment and de-recruitment of unstable lung units (Whitehead and Slutsky 2002) and; 3) peripheral

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airway collapse at low end expiratory lung volume from cyclic open and closing of peripheral airway (Pelosi and Rocco 2007). In an animal experimental model low VT ventilation with positive end expiratory pressure (PEEP) showed a favourable outcome in terms of decreased lung inflammation compared to high VT without PEEP (Curley et al. 2011; Pelosi and Rocco 2011). In clinical investigations, a recent meta-analysis has demonstrated that low VT ventilation in patients without preexisting lung injury is associated with lower incidence of acute respiratory distress syndrome, overall mortality and pulmonary infection. The authors suggest avoiding VT more than 10 ml/kg even with no lung injury (Serpa Neto et al. 2012).

Although current evidence suggests protective ventilation in patients without preexisting lung injury, there is no sufficient data in terms of optimal tidal volume to decrease lung injury and mortality in post-cardiac arrest after ROSC. Further study should be warranted in the future.

On a physiologic basis, the application of PEEP might worsen haemodynamic status in patients with either acute myocardial infarction or CHF. However, some evidence suggests that PEEP can decrease oxygen demand, increase oxygen delivery and decrease intracardiac lactate production (Wiesen et al. 2013). According to the principle of heart-lung interaction, positive pressure ventilation (PPV) has a positive effect on haemodynamic parameters, namely decreased left ventricular (LV) preload and LV afterload from decreased intra-thoracic transmural pressure (Pinsky, 2005). The PPV can reduce metabolic demand and decrease hypoxaemic-induced pulmonary vasoconstriction. Furthermore, PEEP aggravates the shifting of fluid from alveoli and interstitial space back to the circulation (Fernandez Mondejar et al. 1996). Several prospective studies have demonstrated that PEEP can improve pulmonary capillary wedge pressure, cardiac index, stroke index and ability to wean from mechanical ventilation (Jubran et al. 1998; Lenique et al. 1997). Furthermore, application of PEEP at level 5-8 cmH_2O in non-hypoxaemic patients can reduce the incidence of ventilator-associated pneumonia (Manzano et al. 2008). The optimal level of PEEP in post-cardiac arrest patients with cardiogenic shock is still debated, depending on the volume status. Cardiac output monitoring should be warranted during initiation of PEEP (Wiesen et al. 2013).

The role of O_2 and CO_2

In a multicentre cohort study of 120 hospitals in the United States, Kilganon et al. (2011) demonstrated that in non-traumatic cardiac arrest adult patients with hyperoxia defined by arterial oxygen tension (PaO_2) more than 300 mmHg was associated with decrease in survival to hospital discharge compared with either normoxia or hypoxia. In addition, exposure to hyperoxia increased the risk of death (OR 1.8 95% confidence interval 1.2–2.2) after adjusting the model for propensity score. Likewise, hypoxia less than 60 mmHg is associated with mortality. However, the authors did not mention the optimal level of PaO_2 and ventilator setting (Kilgannon et al. 2010). The same group demonstrated that each 100 mmHg increase of PaO_2 was associated with a 24% increase in risk of death (Kilgannon et al. 2011). The 100% oxygen supplement after ROSC caused the increase of NSE level compared to the 30% oxygen supplement in the patients who were not treated with therapeutic hypothermia (Kuisma et al. 2006).

The increase of oxidative stress activity by oxidative impairment of mitochondrial respiration is proposed as the main mechanism that causes worsening of brain injury by neuronal damage, particularly during one hour after ROSC (Pilcher et al. 2012; Neumar 2011). We recommend titrating oxygen and keeping pulse oximetry between 94% and 98% (Nolan et al. 2010) or PaO_2 between 60-100 mmHg instantly after ROSC. During CPR, there are insufficient data about the optimised level of oxygen (Nolan et al. 2010).

Mild hypercarbia can improve cerebral perfusion by cerebral vasodilatation concomitant with decrease of cerebral lactate. It has a protective effect to neurons in terms of seizure threshold and oxidative stress. However, arterial carbon dioxide tension ($PaCO_2$) more than 100 mmHg causes further brain injury (Zhou et al. 2010). Hypocarbia is associated with decrease of cerebral perfusion and neuronal injury (Pynnonen et al. 2011; Tolner et al. 2011). In a recent cohort study, hypocapnia ($PaCO_2$<35mmHg) was associated with worse clinical outcome compared to normocapnia ($PaCO_2$ between 35 and 45 mmHg) and hypercapnia ($PaCO_2$>45). Additionally Schneider et al. (2013) have reported that hypercapnia is associated with the greater chance of discharge home. However, $PaCO_2$ ≥ 50 mmHg is associated with poor neurological outcome defined by cerebral performance category ≥ 3 at discharge. Therefore, we recommend keeping $PaCO_2$ between 35 and 45 mmHg in adults after cardiac arrest (Roberts et al. 2013b). However, only 55% of cardiac arrest patients after successful on-site resuscitation achieve $PaCO_2$ of 35-45 mmHg during mild therapeutic hypothermia (Falkenbach et al. 2009).

In paediatric cardiac arrest, a retrospective cohort study demonstrated that neither PaO_2 > 200 mmHg nor < 50 mmHg are associated with worse outcome (Bennett et al. 2013). The level of $PaCO_2$ <30 mmHg and > 50 mmHg are associated with poor outcome with OR of 2.71 (95% CI 1.04-7.05) and 3.27 (95% CI 1.62-6.61) respectively (Del Castillo et al. 2012).

Doppler as an Adjunctive Tool For Non-Invasive Cerebral Blood Flow Monitoring

Since in patients with brain injury and post anoxic-ischaemic encephalopathy PEEP can increase intracranial pressure (Videtta et al., 2002), and therapeutic hypothermia can decrease CO_2 production (Polderman, 2004), that may have the consequence of worsening cerebral blood flow. Ventilator settings will need to be changed during induced hypothermia and during the rewarming phase. Physicians need a specific guided tool for monitoring cerebral blood flow (CBF).

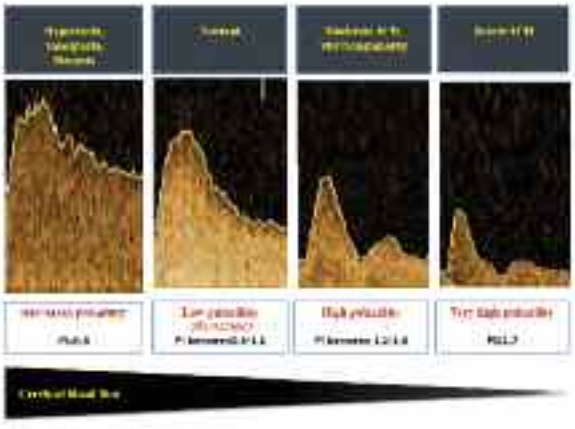
Trans-Cranial Doppler (TCD) ultrasonography is a bedside and non-invasive technique that allows repeated or continuous monitoring of blood flow velocity in the major intracranial arteries. Mean flow velocity cannot be directly interpreted as volume blood flow due to the unknown diameter of the insolated vessel, but it is possible to derive interesting additional information about cerebral haemodynamics from the TCD waveform analysis (Moppett and Mahajan 2004).

Since its introduction by Aaslid and colleagues (1982) TCD has rapidly evolved, and its application in critical care and research has expanded. The most widespread application of TCD is for the detection of vasospasm in patients with subarachnoid haemorrhage. TCD is also being studied as a noninvasive estimator of intracranial pressure (ICP) in patients with severe traumatic brain injury and in the setting of clinical brain death (Rasulo et al. 2008). In post-cardiac arrest syndrome TCD has been proposed to investigate CBF modifications during the first 72 hours in patients treated with therapeutic hypothermia, and their correlation with neurological outcome (Lemiale et al. 2008).

TCD is performed using a low-frequency probe (usually 2 MHz) to penetrate thin areas of the skull with an ultrasonic beam emitted in a range-gated, pulsed-wave manner. Three main ultrasonic windows are temporal, orbital and foramen magnum. The most popular window is the temporal window, which is located between the tragus and the ipsilateral eye. This window allows insonation of the anterior, middle, and posterior cerebral arteries, the terminal segment of the internal carotid artery, and the anterior and posterior communicating arteries. The patient should be in the supine position, and the probe faces perpendicular to the temporal bone to insonate. The middle cerebral artery is usually insonated at a depth of 35 to 55 mms. The anterior cerebral artery and posterior cerebral artery are insonated at 60 to 70 mms. The best quality signal can be obtained by making small adjustments in probe position and angle. It is possible to conduct the exam with a 'blind' probe to identify vessels from insonation depth and waveform, but it is also possible to use an echo colour-Doppler probe to visualise the main intracranial arteries and position the pulse wave Doppler-sample on the identified vessels. When flow velocity is displayed, the peak systolic velocity (PSV) and the end diastolic velocity (EDV) can be recorded and the mean velocity (MV) calculated. Dedicated TCD devices also calculate automatically derived parameters such as resistance index (RI) and pulsatility index (PI).

Different information can be obtained from TCD, depending on the clinical setting. Elevated flow velocities are associated with increased CBF, anaemia and cerebral vascular abnormalities (arterial stenosis, vasospasm or arterio-venous malformations), while low flow velocities may indicate a proximal flow-reducing lesion, a state of decreased cerebral metabolic rate (for example, during coma) or a low CBF such as in poor cardiac output conditions. The Gosling PI (peak systolic flow velocity - end diastolic flow velocity / mean flow velocity) is an index proposed to quantify waveform, and is not affected by the angle of insonation. Normal range is from 0.6 to 1.1 and PI variations reflect changes in resistance to flow in specific areas of the cerebral circulation (Czosnyka et al. 1996). A higher than expected PI might result from a distal occlusion, raised intracranial pressure (ICP) or hypocarbia. A PI below 0.5 suggests a proximal flow-reducing lesion, such as an extracranial stenotic lesion, or a low intracranial resistance (arterio-venous malformation) (see Figure 1). So PI was proposed for non-invasive monitoring of ICP in traumatic brain injury, but its accuracy and reliability remain controversial (Bellner et al. 2004; Behrens et al. 2010; Zweifel et al. 2012). Recent literature underlines that it is possible to describe PI as a complex mathematical function not dependent solely on CVR: it is a product of the interplay between CPP, pulse amplitude of arterial pressure, cerebrovascular resistance (carbon dioxide reactivity) and compliance of the cerebral arterial bed as well as the heart rate (De Riva et al. 2012). Particularly in post-cardiac arrest comatose patients, a better knowledge of cerebral haemodynamic changes during the post-resuscitation period is essential to treat patients correctly. As with other techniques routinely used in neuro intensive care monitoring, TCD could add complementary information, but more studies are warranted to define its role in clinical practice.

Figure 1. The value of Pulsatility Index According to the Severity of Intracranial Hypertension.



Key: PI (pulsatility index); ICH (intracranial hypertension)

Key Messages

- In adult patients after cardiac arrest, non-neurological organ failures affecting mortality are respiratory and cardiovascular failure.
- Protective ventilation by low tidal volume ventilation may decrease pulmonary dysfunction and improve the outcome. Low level of PEEP can be initiated and titrated with careful cardiac output monitoring.
- In paediatric patients after cardiac arrest, the optimal PaO2 level is between 60 -100 mmHg and pulse oximetry between 94-96 (98) %. Hypocapnia (PaCO2 < 35 mmHg) and hypercapnia (PaCO2 > 45 mmHg) are detrimental.
- In adults, hyperoxia and hypoxia are detrimental. We recommend titrating oxygen and keeping pulse oximetry between 94% and 98 % or PaO2 between 60-100 mmHg. We should avoid hypocapnia (PaCO2 < 35 mmHg).
- TCD is the visualised non-invasive tool that may play an important guided tool during ventilator setting. ■

Acknowledgements
We would like to thank Dr. Pezzato Stefano for providing figure material.

For full references, please send a request to **editorial@icu-management.org**

INFECTION CONTROL: A CONSTANT BATTLE

European hospitals are in a constant struggle with healthcare associated infections (HAI). While some infections, although not ideal, are easily treatable, others have serious effects on both patient health and the hospital budget. New programmes and initiatives for reducing infection in our hospitals appear every day, ranging from communication and awareness to new protocols and even new technologies. The European Centre for Disease Prevention and Control have been making strides in recent weeks with a comprehensive European survey on HAIs and new guidance on the prevention of surgical site infections.

Each Day, One in 18 Patients in European Hospitals has a Healthcare-Associated Infection: ECDC Estimates

ECDC has published the results of its first point prevalence survey (PPS) on healthcare-associated infections and antimicrobial use in European hospitals. Based on findings from this survey, ECDC estimates that on any given day, one in 18 patients in European hospitals has at least one healthcare-associated infection. The report also presents data on the most commonly reported infections, which microorganisms are most commonly reported as causing them, how often antimicrobial drugs are being used to treat these infections and data on infection control structure and processes in the hospitals. More than 1,000 hospitals in 30 European countries participated in this first Europe-wide PPS.

For this study, 30 countries used the same point prevalence survey standardised protocol. An estimated 2,800 healthcare workers from 1,200 hospitals across Europe were trained by national coordinating staff to implement the standardised methodology. Data from a total of 273,753 patients in 1,149 hospitals were submitted to ECDC. Of these, 231,459 patients from 947 hospitals were included in the final European sample for analysis.

"Many of these infections could be prevented by sustained, multifaceted infection prevention and control programmes, including surveillance of healthcare-associated infections"

Background

Healthcare-associated infections are those acquired by patients during their stay in a hospital or other healthcare setting. Although some of these infections can be treated easily, others may more seriously affect a patient's health, increasing their stay in the hospital, requiring further surgical intervention or prolonged treatment with antimicrobials and causing considerable distress to these patients.

A prevalence survey is a count of the number of patients with a particular condition/treatment (in this case either a healthcare-associated infection or an antimicrobial agent) at a particular time (in this case a day), as a proportion of the total number of patients who are hospitalised at that particular time. A point prevalence survey only counts the condition/treatment if present at the time (on the day) of the survey, but does not count it if present at other times during the patient stay in the hospital.

Increasing Surveillance and Raising Awareness

Through the ECDC PPS, a major step has been made towards increasing the skills for surveillance of healthcare-associated infections and antimicrobial use, and raising awareness of healthcare-associated infections among thousands of healthcare workers across Europe. The survey provides the most comprehensive database on healthcare-associated infections and antimicrobial use in European acute care hospitals to date, and based on these results ECDC has made recommendations that should be further developed and implemented across Europe.

19th International Symposium on Infections in the Critically Ill Patient

Barcelona
7-8 February
2014

The aim of this two days symposium is to review current concepts, technology and present advances in infections in the critically ill patients.

Sepsis, Pulmonary Infections, Basic Research, Pulmonary Infections Treatment and Prophylaxis Therapy of severe infections will be the topics of the main sessions presented by experts who will review and update the new advances on infections in the critically ill patient. At the end of each session a Clinical Controversy, Pannel Discussion or Case Report Discussion will be organized.

Organized by

Antonio Artigas, MD
Jean Carlet, MD
Michael Niederman, MD

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Marc Sprenger, ECDC Director, said: "The survey confirms that healthcare-associated infections pose a major public health problem and a threat to European patients: ECDC estimates that on any given day, about 80,000 patients, i.e. one in 18 patients, in European hospitals have at least one healthcare-associated infection". Overall, this amounts to an estimated total of 3.2 million patients (95% confidence interval: from 1.9 to 5.2 million) each year.

He added: "Many of these infections could be prevented by sustained, multifaceted infection prevention and control programmes, including surveillance of healthcare-associated infections. Such programmes, as well as prudent use of antibiotics, will help all actors involved to protect the patients of European hospitals".

Paola Testori Coggi, Director General of DG Health and Consumers, European Commission, said: "This survey represents an important milestone in monitoring healthcare-associated infections across Europe. Their prevalence is worrying and increased efforts are needed at local, national and European level to prevent such infections, for the safety of patients. Such efforts are also needed to fight against the development of antimicrobial resistance. The European Commission is actively monitoring the situation with the support of the European Centre for Disease Prevention and Control, and works in cooperation with the Member States to implement the 2009 Council Recommendation on Patient Safety."

Survey Findings

The prevalence of healthcare-associated infections was the highest among patients admitted to intensive care units (ICUs) in these hospitals, where 19.5% patients had at least one. The most common types of healthcare-associated infection in these ICUs were respiratory tract infections and bloodstream infections. Overall, of a total of 15,000 reported healthcare-associated infections, the most commonly reported types were respiratory tract infections (pneumonia, 19.4%; lower respiratory tract infections, 4.1%), surgical site infections (19.6%) and urinary tract infections (19.0%).

The survey also confirms that a large proportion of patients receive antimicrobial agents while being hospitalised. ECDC estimates that more than 400,000 patients, i.e. one in three patients, receive at least one antimicrobial agent on any given day in European hospitals. The following areas for improvement were identified:

- Limiting the use of broad-spectrum antimicrobials;
- Reducing the unnecessary prolongation of surgical prophylaxis;
- Promoting earlier change from parenteral to oral administration of antimicrobials; and
- Improving the documentation of the reason for the antimicrobial use in the patients' charts.

Individual results were disseminated to the participating hospitals through the national PPS coordinators allowing them to interpret the data, compare themselves with other hospitals on a national level and identify areas for improvement.

ECDC will organise a second Europe-wide point prevalence survey in all Member States in 2016–2017 and will continue supporting the organisation, data collection, validation and analysis of national surveys during the period 2013–2015.

Other Key Findings

About half (54.1%) of the healthcare-associated infections were reported with microbiological results on the day of the survey. Among these, the most commonly isolated microorganisms in HAIs were:

1. Escherichia coli (15.9%)
2. Staphylococcus aureus (12.3%)
3. Enterococcus species (9.6%)
4. Pseudomonas aeruginosa (8.9%)
5. Klebsiella species (8.7%)
6. Coagulase-negative staphylococci (7.5%)
7. Candida species (6.1%)
8. Clostridium difficile (5.4%)
9. Enterobacter species (4.2%)
10. Proteus species (3.8%)
11. Acinetobacter species (3.6%).

Among all Staphylococcus aureus isolates with known results from antimicrobial susceptibility testing, 41.2% were reported as resistant to meticillin (i.e. were MRSA). Among all isolates of Enterococcus species with known results, 10.2% were reported as resistant to vancomycin. Among all isolates of Enterobacteriaceae with known results, 33.4% and 7.6% were reported as resistant to third-generation cephalosporins and to carbapenems, respectively.

Preventing Surgical Site Infections

The European Centre for Disease Prevention and Control has released guidance for healthcare professionals on five key perioperative antibiotic prophylaxis modalities for preventing surgical site infections.

Perioperative antibiotic prophylaxis (PAP) is considered one of the most effective measures for the prevention of surgical site infections (SSIs). An ECDC commissioned 'Systematic review and evidence-based guidance on perioperative antibiotic prophylaxis' was performed to identify effective measures to improve compliance with PAP among healthcare professionals. The evidence-based conclusions of this systematic review were further evaluated and ranked by an expert group, thus producing five "key modalities". The ranking was performed taking into account the evidence with respect to effectiveness, implementability and EU-wide applicability.

The five key modalities presented in the guidance are the five most effective measures shown to improve the compliance of healthcare professionals with appropriate administration, timing, dosage and duration of PAP for the prevention of SSIs.

Indicators were also developed as part of the process, for the monitoring of the five key modalities. These include, among others, compliance with the indication, selection, timing, dosage and duration of PAP, the frequency of administration of PAP by an anesthesiologist or another designated professional when PAP is indicated and the presence and frequency of meetings of a multidisciplinary team.

These key modalities and indicators can be adopted or adapted by hospitals across Europe to supply a platform for healthcare professionals to use to increase compliance with the appropriate administration of PAP in European hospitals.■

For more information, please visit:
www.ecdc.europa.eu

PROS AND CONS OF PHYSICAL RESTRAINT

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This article discusses the pros and cons of physical restraint of ICU patients during critical illness.

Introduction

The debate about physical restraint of ICU patients during their critical care stay has been going on for many years. In some countries, such as the UK, it is considered an unacceptable practice (Bray et al. 2004). In other countries across Europe, such as France (De Jonghe et al. 2013), and in parts of the USA, it is a more common practice. In the USA practice guidelines to facilitate the safe application of physical restraint methods have been published (Maccioli et al. 2003). While the views of nurses and other healthcare staff on physical restraint have been examined, those of the patient and family on its use are sadly lacking. In addition, the long-term impact of physical restraint on the patients' recovery has not been really investigated.

Factors Influencing the Use of Physical Restraint

Physical restraint has been shown to be most often used with agitated, delirious patients, or where there has been an adverse event, such as self-extubation (Sneyers et al. 2013). A study comparing the use of physical restraint in two ICUs in different countries, ie the USA and Norway, found that the use of physical restraint was very different, with 40% of the U.S. patients receiving it at some point in their critical care stay and 0% in Norwegian patients (Martin and Mathisen 2005). The most common type of restraint used in this study was soft wrist restraints. Interestingly, there were seven incidents of unplanned removal of an invasive device during the study, and these were all in restrained U.S. patients. The study did show a distinct difference in nurse-patient ratios between the two countries, with a ratio of 1.05:1 for the Norwegian units and 0.65:1 for the USA ones. In Norway nurses tended to maintain direct visual observation of patients, fewer non-qualified staff were being used, and respiratory therapists were not present at all on the unit compared to the US. DeJonghe et al. (2013), in their survey of French ICUs, found that in 82% of ICUs physical restraint was used at least once in more than 50% of patients. Medical orders for starting or removing physical restraint were commonly lacking, and most of the decisions were made by nurses

Patient Autonomy

Martin and Mathisen (2005) point out in the discussion of their study examining the differences between U.S. and Norwegian practices that where physical restraint is an established practice there is a potential to violate the patient's dignity and the individual's autonomy ceases to be considered.

In a 1988 study of the perceptions of 20 elderly patients who had been physically restrained during a hospitalisation (not critical care), feelings such as anger, discomfort, fear and resistance were commonly expressed (Strumpf and Evans 1988). They concluded that the use of physical restraint was not a benign practice, and that there was a need to develop alternatives to ensure patient safety.

In a more recent study of elderly ICU patients only six patients (40%) could remember being restrained, but they did not report great distress at the memories (Minnick et al. 2001). The patients were much more bothered by memories of hallucinations and intubations. However, the research found it very difficult to recruit to the study because of ongoing health problems in this group of patients, which restricts the generalisability of the results.

> *"If we are to ensure that our patients recover with the minimum of physical and psychological sequelae then using the least traumatic method of keeping our patients safe is a necessity"*

In a multicentre European study of the precipitants of post-traumatic stress disorder (PTSD) in ICU patients one of the study units did interview restrained patients using the ICU Memory Tool (Jones et al 2007). This showed similar findings to Minnick et al. (2001), in that only one patient remembered being physically restrained. When the sedation score data was examined for those patients who had been restrained in this ICU all of them had been agitated prior to being restrained. Half of these restrained patients could remember delusional memories, such as hallucinations, nightmares and paranoid delusions from their time in ICU, rather

than the experience of being restrained. In contrast, a South African study of 98 ICU patients found that 24 (24%) participants could remember being physically restrained and were very distressed by it (Hatchett et al. 2010).

Physical and Psychological After Effects of Physical Restraint

Jones et al. (2007) found that being physically restrained was strongly associated with the development of PTSD, with a rate of 23% in the physically restrained patients. This was despite only one patient having any recall of being restrained. Other factors found to be related to the development of PTSD in this study of 238 patients were recall of delusional memories, heavy and prolonged sedation and a premorbid history of psychological problems (see Figure 1). Hackett et al. (2010) found the opposite, ie that those patients who had recall of being physically restrained in ICU were six times more likely to develop PTSD-related symptoms than those with no memory of restraint. One of the differences between the studies may be that 100% of the patients in the Jones (2007) study were mechanically ventilated but only 53% in the Hatchett (2010) study. The mean length of stay in the ICU was also significantly longer in the Jones' patient population compared to Hatchett so the Jones' study may more typically reflect the experience of the ICU patient, rather than those receiving high dependency unit (HDU) level care.

Figure 1. Structural Modelling of Factors Associated with the Development of PTSD

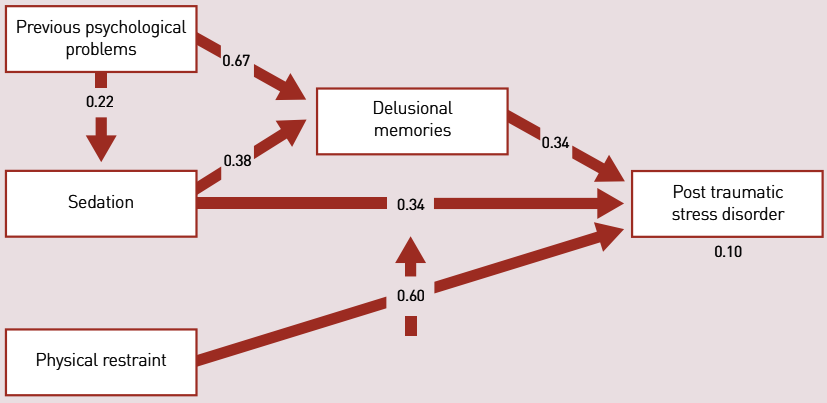

Table 1. Task Force Recommendations for Maintenance of Patient Physical Safety Using Restraining Therapies (Maccioli et al. 2003)

Number	Recommendations
1.	Institutions and practitioners should strive to create the least restrictive but safest environment for patients in regard to restraint use. This is in keeping with the goals of maintaining the dignity and comfort of our patients while providing excellence in medical care.
2.	Restraining therapies should be used only in clinically appropriate situations and not as a routine component of therapy. When restraints are used, the risk of untoward treatment interference events must outweigh the physical, psychological and ethical risks of their use.
3.	Patients must always be evaluated to determine whether treatment of an existing problem would obviate the need for restraint use. Alternatives to restraining therapies should be considered to minimise the need for and extent of their use.
4.	The choice of restraining therapy should be the least invasive option capable of optimising patients' safety, comfort and dignity.
5.	The rationale for restraint use must be documented in the medical record. Orders for restraining therapy should be limited in duration to a 24-hr period. New orders should be written after 24 hrs if restraining therapies are to be continued. The potential to discontinue or reduce restraining therapy should be considered at least every 8 hrs.
6.	Patients should be monitored for the development of complications from restraining therapies at least every 4 hrs, more frequently if agitated or otherwise clinically indicated. Each assessment for complications should be documented in the medical record.
7.	Patients and their significant others should receive ongoing education as to the need for and nature of restraining therapies.
8.	Analgesics, sedatives, and neuroleptics used for the treatment of pain, anxiety, or psychiatric disturbance of the ICU patient should be used as agents to mitigate the need for restraining therapies and not overused as a method of chemical restraint.
9.	Patients who receive neuromuscular blocking agents must be given adequate sedation, amnesia, and analgesia. The use of neuromuscular blocking agents necessitates frequent neuromuscular blockade assessment to minimise the serious sequelae associated with long-term paralysis. Neuromuscular blocking agents should not be used as chemical restraints when not otherwise indicated by the patient's condition.

Physical Restraint and Delirium

Physical restraint used prior to the onset of delirium significantly increases the risk of ICU patients developing delirium (OR 33.84) (Van Rompaey et al. 2009). Restraint also impedes early rehabilitation on the ICU, which has been shown to reduce the risk of the patient developing delirium (Schweickert et al. 2010).

In hospitalised older patients (non-ICU) the use of a multi-component intervention designed to tackle the risk factors for delirium, including activities such as repeated reorientation, the provision of cognitively stimulating activities, a nonpharmacologic sleep protocol, early mobilisation, removal of catheters and physical restraints, use of eyeglasses, magnifying lenses and hearing aids has been shown to significantly reduce the incidence of delirium in the intervention group (OR 0.6) (Inouye et al. 1999).

Reducing the Use of Physical Restraint

Mion et al. (2001) implemented a physical restraint reduction programme with four core components: administrative, educational, consultative and feedback. However, only a small number of units achieved a > 20% reduction in physical restraint use.

The American College of Critical Care Medicine Task Force developed clinical practice guidelines for the use of restraining therapies (Maccioli 2003). The task force developed nine

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recommendations to maintain patient safety in the ICU (see Table 1). The whole thrust of the guidelines is to try to reduce the use of physical restraint, unless it is felt clinically to be the only way to keep the patient safe. The impact of these guidelines has not been assessed.

The learning programme Knot-so-fast (Hurlock-Chorostecki and Kielb 2006) was implemented following new legislation in Ontario, Canada, introduced in 2001, called the Patient Restraint Minimization Act. All Canadian hospitals were mandated to develop a policy to minimise the use of restraints. In the study ICU a survey of ICU nursing staff was undertaken to establish learning needs and develop the learning plan Knot-So-Fast, in addition to a decision tool titled the Restraint Decision Wheel. They were created to support staff in making restraint decisions quickly and appropriately. The key points of Knot-So-Fast are that alternatives to restraints should be tried first. If felt to be absolutely necessary then restraint can only be used on doctors' orders, and frequent monitoring has to be documented in the medical notes. Staff were resurveyed one year after the introduction of these measures, and a statistically significant decrease in restraint use was found in the study ICU. A particular effect noted by the research team was that patients returning from theatre were not automatically restrained. Other ICUs have implemented the programme and decision wheel and found an equal reduction in restraint use (Hurlock-Chorostecki and Kielb 2006).

De Jonghe et al. (2013), when they surveyed French physical restraint practice, found that restraint was often used without written medical orders and on awake, calm and cooperative patients. They felt the results of the survey showed that physical restraint was an essential component of the management of mechanically ventilated patients in French ICUs. The authors suggest that a restraint protocol may reduce the use of restraint, and point out the effectiveness of the education programme Knot-so-fast and the decision making wheel. The lack of written medical orders in the study put the onus on the nursing staff to decide when to stop restraint, and they may therefore be reluctant to take that decision.

Conclusion

As the way we nurse our ICU patients changes, with less sedation and more emphasis on early physical rehabilitation and the prevention of delirium, then the use of therapies such as physical restraint also has to be revised. If we are to ensure that our patients recover with the minimum of physical and psychological sequelae then using the least traumatic method of keeping our patients safe is a necessity. Thinking before automatically turning to physical restraint can only be of benefit to our patients in the long run. ■

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Cover Story: The Kidney

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and non-septic patients with AKI. Practically, 30-35 ml/kg/h needs to be prescribed to deliver a dose of 25 ml/kg/h. High-volume haemofiltration in septic AKI is no longer recommended outside a clinical trial. An early start of CRRT (at RIFLE Injury level?) in septic AKI could be anticipated but further evaluation is needed. CRRT is the preferred first-line therapy in haemodynamically unstable patients with AKI. Whether haemodynamically stable AKI patients might also benefit remains to be established. Newly designed membranes with higher porosity or increased adsorption capacity may tackle the sepsis cascade by eliminating inflammatory mediators. Large trials confirming the benefit of PMX B therapy are eagerly awaited. Cartridges containing a filtration surface as high as 10,000 m² (e.g. CytoSorb) placed within a CRRT circuit may represent an exciting next step in treating septic AKI patients. Extended daily IHD has still some room in ICU but mostly as second line therapy. ■

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in 90-day risk of death, but also with more RRT-free days at day 90. These associations persisted after adjustment for numerous potential confounders using different statistical models.

Notably, continuous RRT was used in more than 90% of patients in the RENAL study. The superiority of continuous over intermittent RRT in achieving net fluid removal in critically ill AKI patients has been clearly demonstrated (Bouchard et al. 2009). The incapability of managing fluid balance with intermittent haemodialysis in critically ill patients is one likely explanation for the negative impact of this modality on renal recovery seen in previous studies (Bell et al. 2007).

Conclusions

AKI is associated with high mortality and long term outcomes like chronic kidney disease and end-stage renal disease. The outcomes are affected by intrinsic factors, such as age and comorbities, but the ICU management of these patients does play a role. Modality, dose and timing of RRT with a focus on early prevention of harmful fluid accumulation, and not only for clearance of waste products, may be important factors. For certain patients, a nephrology referral could lessen the risk of the transition from AKI via CKD to ESRD. ■

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CRITICAL CARE: THE VIEW FROM CANADA

AN INTERVIEW WITH PROFESSOR GORDON RUBENFELD

Professor Gordon Rubenfeld is Chief of the Trauma, Emergency & Critical Care Program at Sunnybrook Health Sciences Centre and Professor of Medicine at the University of Toronto, Canada. His research focuses on the clinical epidemiology and outcomes of critical illness syndromes, the transfer of evidence into clinical practice, and end-of-life care issues in the intensive care unit. He has served on numerous advisory panels and consensus groups in critical care, including the American European Consensus Conference on Acute Lung Injury, the working group that developed the Berlin ARDS (acute respiratory distress syndrome) definition and the surviving sepsis guideline committee.

Integration of trauma, emergency and critical care at Sunnybrook is a relatively new model for Canada. Can you tell us more about the programme and how critical care fits into that?

Clinicians and researchers understand integration between these areas, but it is relatively novel as a hospital organisational approach. Hospitals are generally organised along departmental structures with surgery, critical care and emergency medicine in different places. Obviously that doesn't make much sense. Real novelty comes at the hospital and administrative level, with several advantages. It aligns the multidisciplinary team, not just the physicians, along the continuum of care, with base hospital and pre-hospital management and oversight through to hospital discharge. We are now thinking about how to integrate post hospital follow-up and rehabilitation. This structure lets us integrate, share knowledge and training, and provide continuity of care, handovers and quality improvement projects in an easier way. It gives accountability to the executive for the whole area. From a budgeting and operational standpoint it's really quite innovative and aligned with the hospital structure the way clinicians think, work academically and operate.

You co-authored a paper in The Lancet about the global burden of critical illness in adults (Adhikari NK et al. 2010). What do you see as the biggest challenge?

The biggest barrier to understanding the global epidemiology of critical illness is a shocking lack of data, not just from developing nations, but also from Europe.

There are two important reasons for what makes critical illness difficult to study from an epidemiological standpoint. Firstly, critical illness is an acute disease. People get it; they either die or get better. There are sequelae, but we don't think of patients having chronic critical illness. It is much harder to study acute diseases from an epidemiological standpoint, as you have a shorter window in which to capture these data. Secondly, critical illness is inextricably linked to critical care. If you don't have ventilators, for example, you're not going to have respiratory failure: people will simply die. That makes critical illness different from other diseases. When people die from pneumonia without being on a ventilator, it's hard to study their critical illness. Another factor is the difference in ICU beds per population in different countries. If there is a 10-fold difference in ICU beds, comparing for example the US and Germany to the UK, there's no way the ICU epidemiology of sepsis is going to be the same in those countries, as you simply don't have the beds to have the disease in.

The real reason we wanted to write the Lancet paper, despite the limitations of the data, was to get a dialogue going about what the epidemiology might look like.

How can critical care develop interventions that can be used in both developed and developing countries?

For a long time we've thought that all we need to do is simplify the interventions we have in developed countries, then apply them to developing country diseases. The FEAST trial by Professor Kathryn Maitland in children with sepsis challenges this assumption (Maitland 2011). That hypothesis may not be true; we may need to do some specific evaluation. I still think it's a reasonable hypothesis that we start with the idea of taking some of our interventions from developed countries, making simpler versions of them and engaging with our colleagues in developing countries to test and implement them. A number of researchers are working on this. The challenge intensivists have with engaging with this research is, for example, issues such as if it really makes sense to think about catheter-related bacteremia and infections in a country that doesn't have clean water. I think that's a fair discussion to have, and probably as a field we need to do a better job of economic evaluations of interventions. One of the areas that has engaged developing countries, where many of the pandemic infec-

tions gain a hold, is screening for pandemic respiratory infections. This is an area of intense interest, understanding how these develop, how they spread and how we might be able to limit that. In developing countries critical care means things such as crystalloid resuscitation, antibiotics and oxygen, what we think of as basic care. Those are what constitutes intensive care in developing countries, and it's a matter of getting good at that. If you think of critical care in a broader sense that probably has huge advantages for mortality reduction.

You presented at ISICEM this year on the limitations of ICU research, particularly outcomes data on quality of life. Could you explain more about these limitations?

People are increasingly frustrated with 28-day and 90-day mortality as the endpoint for critical care trials. Many studies were negative, then some were positive and now they are negative again. There's demand for some endpoint other than mortality, but we haven't demonstrated a valid surrogate. We've certainly shown that things like reversal of organ dysfunction, making oxygenation look like it's doing better, making blood pressure go up a little bit more, none of those things seems to correlate very well at all with mortality. We're intensely focused on organ function, which doesn't appear to be the holy grail for endpoint. The challenge with long term outcomes is that much recent research has suggested that the morbidity we are seeing after critical illness in many of our patients is probably there beforehand, so obviously we're not going to make that better. We need to be cognisant of those sorts of limitations on the outcomes, both quality of life and organ reversal.

Many of our patients come into the ICU with poor quality of life beforehand, so some of the poor quality of life we are studying afterwards is probably pre-existing, and a lot appears to be reversible on its own. Another problem is what we epidemiologists call informative censoring. What that means is, if you do for example an RCT, you are looking at long term outcomes only studying those in people who are alive, and it's very possible that if the intervention improves survival, even by a little bit, what they're doing is shifting people who otherwise would have died, now they are surviving, with a reduced quality of life, but are alive. It's quite possible that studies that improve mortality in critical care may have absolutely no effect or maybe even worsen quality of life, and we have to be aware of that limitation of using quality of life as an outcome.

None of these outcome issues in critical care is insurmountable. They are probably going to be fixed not by devising a new outcome measure, but by doing larger studies, being aware of the issues and analysing the data correctly.

> *"There's demand for some endpoint other than mortality, but we haven't demonstrated a valid surrogate"*

Do you see a role for telemedicine in intensive care medicine given that many countries have a shortage of intensivists?

Almost certainly yes, if you look at it from a broad definition of telemedicine. We need to focus on what telemedicine means and what it can substitute for.

With regard to the projected deficit of intensivists, that's largely been argued in the U.S. There's a projected doctor shortage, driven by the explosive rate in which the U.S. uses healthcare and the ageing of the patient population. It's a demand problem as much as supply. Something is going to have to be done around the demand issue. Telemedicine is a way to address quality issues potentially, and what may be a shortage in intensivists now, but we need to understand the right way of delivering it. This predicted shortfall is part of a bigger problem.

Why do you think the definition of ARDS might need changing and why does it matter?

The definition needed some updating, as there was a lot of new data related to a number of smallish issues, such as excluding the diagnosis of heart failure, issues around x-ray and simplification in terminology. For example, you see frequently in the literature the term ALI/ ARDS. That does not mean anything, because anyone with ALI by the old definition also has ARDS. It was very confusing. What population are you talking about when you say ALI/ ARDS? The terminology needed to be clarified, and new data needed to be incorporated into the definition.

One of the challenges with consensus conference definitions is that they are not always evidence-based, tested or evaluated. The group came up with a fairly complicated physiologic definition for severe ARDS. Sitting round the table it sounded pretty good; it incorporated respiratory system compliance, FiO_2 and some other features that all made good physiologic sense. The problem is that when going to large databases applying these more complicated definitions, it identified a very small group of patients, probably not so clinically important. The mortality really wasn't that much different than a group of patients we could identify with our criteria.

Does the definition need to be radically revised? There are lots of challenges with radical revisions of these kinds of syndromic definitions, in terms of applying it to previous literature and understanding who the patient population is. For example, one of the things people really wanted to be part of the definition, which makes a lot of sense, and a lot of clinical studies are incorporating this now, was to have a run-in period on standard ventilator settings, have the diagnosed severity, you don't really have that diagnosis until the patient has been on very specific settings for 24 hours then we look at oxygenation for example. It's a great idea; lots of studies are doing that. Nothing about the Berlin definition prevents people from doing that. The problem with making that as the definition is that it eliminates all epidemiology, because epidemiology relies on what doctors are just doing. If a doctor doesn't or can't put patients on these specified ventilator settings, then in a way the patient doesn't have the syndrome, so we can't study that in observational research, and that's a real limitation. There were some challenges in incorporating some things people really wanted, so I would call it an incremental improvement.

What do you see as the priorities for intensive care medicine research?

There are a tremendous number of lives that can be saved from dissemination of fairly sim-

ple strategies to implement basic measures, such as around sepsis, mechanical ventilation, potentially checklists, medical drug error avoidance, and improving handover and communication. Systems approaches to making those sorts of changes should be really high priority for our field. They are things that most intensivists are already doing and should be easy to do. In terms of lives to be saved, those are extremely important.

> *"There are a tremendous number of lives that can be saved from dissemination of fairly simple strategies"*

Canada is a multicultural country. Are there cultural differences the intensivist needs to be aware of, for example regarding end-of-life care?

The multicultural nature of Canada makes end-of-life care discussions extremely challenging, important and rewarding. It requires a whole different skill to deal with patients from many different kinds of cultures. For example, we have this kind of 'Western' modern bioethics that places a powerful role on patient autonomy, the idea that the individual directs their own life and their own care. What happens if you have a medical culture that's completely focused on that way of communicating, and it encounters a patient culture that doesn't think that way at all, that embraces the idea of the authoritarian or patriarchal physician? You have an incredible clash of culture and values, and you are speaking different languages. There are ways to address that with education. We need to have a lot more tools in our toolkit working in a multicultural environment to engage with families. That's the challenge and that's the reward too. We all go into this field because we love working with and helping people and it's a real opportunity to learn about different cultures and how they communicate.

Your team has recently completed a clinical trial on post-hospital case management to improve clinical outcomes in patients requiring mechanical ventilation? Are there any data or observations you are able to share from that trial (University of Washington)?

I can't comment specifically as the manuscript is in preparation. There's a growing body of literature that suggests that most ICU interventions don't work. The possible reasons are that we have been enrolling the wrong patients, that most of the patients have a morbidity that is fixed and pre-existing to the ICU, and a post- ICU intervention probably will not fix it because it's going to have its own trajectory of illness, and lastly, that we are just delivering the wrong post-ICU intervention. That is unlikely, because there have been enough trials with enough different kinds of interventions. Future research is probably going to focus on collecting the right sub-population, and spend less time on the post-ICU period. One of the challenges in long-term outcomes after critical illness is that there are a whole bunch of patients who have had a life-changing event that put them into the ICU. For example, if you're 25 and in a car crash and a paraplegic now, it may or may not matter at all what happens to you in the ICU as you have had a life-changing event that will alter your quality of life and functional status thereafter. There are many patients who come to the ICU because of diseases that themselves alter their quality of life trajectory, for whom the ICU is a bit of a blip. It is hard to imagine that a post-ICU intervention will alter their trajectory. More importantly, in most countries these are people who are going to get specific rehabilitation for brain injury, trauma etc., and receive very targeted rehabilitation targeted at multiple domains including psychiatric.

Can you tell us more about the Lung Injury Knowledge Network (LINK) study?

It's targeted at multidisciplinary teams in large community hospitals in the United States. Resources include videos and an interactive web-based teaching environment targeted at low tidal volume ventilation for ARDS. This is very simple and inexpensive, and one of the few therapies we know that are effective in critical illness, probably still under-performed.

What's your greatest leadership challenge?

Without sounding trite, effective communication is still really hard. I draw the analogy with communication with different cultures. Particularly in a programme, which integrates nurses, respiratory therapists, physiotherapists, pharmacists, neurosurgeons, burns surgeons, intensivists, anaesthetists, emergency medicine doctors, effective horizontal communication across all those different cultures may be just as different as for patient cultures. Vertical communication problems arise from translating academic and clinical speak into administrative operational language.

What do you see as the biggest challenge in intensive care generally?

I get worried when we have these pendulum swings in critical care. People see studies that are positive then negative, and get intensely tired and frustrated about the value of research. There's a potential in our field to figure that we can't really study what we do very rigorously because what we do is complicated and so hard, so different from what everybody else does that we should just do what makes sense to an individual smart doctor or nurse. We have to fight against this kind of creeping fatigue, frustration and depression. I think it's an exciting time in critical care, I think we have learnt an incredible amount in the last 20 years, both simple and complex. ■

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STATE OF CRITICAL CARE IN FRANCE

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Access to Critical Care

• The French Healthcare System

The French social security system was formalised by the Ordinance of October 4th 1945 and has the particularity of being funded both by employers and employees (Chevreul et al. 2010). It is divided into five branches: health, retirement, family allowances, work-related illness and elderly. The main advantages of the statutory health insurance are universal coverage, access without waiting lists and patient choice. Total expenditure on healthcare represents 11.6% of GDP, of which 77% is publicly funded. The average government expenditure on health per capita is US$4,952 (World Health Organization). An increasing number of French people apply to complementary private assurances in order to obtain reimbursements for copayments and coverage for medical goods and services. This system suffers from geographical disparities (a medical heliotropism is observed), and is facing chronic increasing deficits.

• Acute Care in France

Acute care includes pre-hospital care, organisation of emergency departments and availability of appropriate hospital beds. The European emergency number 112 is linked to call centres, either from medical emergency centres (SAMU: Service d'Aide Médicale d'Urgence), or from fire brigades (depending on the department) (SAMU de PARIS 2013). If the patient request requires intensive care, a mobile Intensive Care Unit (ICU) will be sent, which includes at least an intensivist or emergency physician and a nurse anaesthetist, and the patient will be transferred to the closest ICU. In some areas there is also a mobile paediatric ICU. There are 630 emergency departments in France, of which 97% are public (Mouton 2009). Patients in the emergency departments, who require invasive mechanical ventilation or vasopressors, are directly transferred to an intermediate or intensive care unit. Since 2004 acute care is paid following a diagnosis-related group payment model (Tarification à l'activité (T2A)).

Acute Care in France

Acute medical care is mainly provided by public hospitals. Some treatments, such as auto- or allografts, are only conducted in public or non-profit hospitals. Two-thirds of surgical procedures are conducted in private hospitals, but most complex procedures such as transplants are only performed in public or non-profit hospitals.

• Critical Care Organisation

The geographical distribution of ICUs is regulated by the Agence Régionale de Santé through the Schémas Régionaux d'Organisation des Soins. The density of critical care beds in France is 11.6/100,000 inhabitants (in comparison to 29.2/100,000 in Germany and 6.4/100,000 in the Netherlands) (Rhodes et al. 2012). A national census conducted in 2009 reported 409 ICUs (204 mixed, 79 surgical, 49 medical and 77 undefined) with a total of 4,769 beds, of which 85% are in public hospitals (Mouton 2009). Large academic hospitals are more likely to have larger and specialised ICUs whereas smaller hospitals are more likely to have a mixed ICU. In 2009, 624 hospitals reported at least one intermediate care unit, with a total of 5,311 beds (of which 51% are in public hospitals). The presence of intermediate care beds within the ICU is common. There are 8,433 post-anaesthesia care unit (PACU) beds, of which 46% have the possibility to ventilate. There are 45 paediatric ICUs with a total of 329 beds and 460 PACU pediatric beds.

According to French law, an ICU should have at least eight beds, a minimum of two nurses to five patients and a minimum of one helper to four patients (Décret n°2002-465). An on-site medical presence 24/7 is mandatory. Each ICU has a head of ICU who often has a lifetime position and at least one head of nurses. In a recent survey of 215 medical French ICUs, the average number of beds was around 12 per unit. 32%, 58% and 9% of ICUs respectively reported a patient to nurse ratio of 2-2.5, 2.5-3 and >3 (Annane et al. 2013). 3%, 46%, 43% and 8% of ICUs respectively reported a patient to helper ratio of <3, 3-4, 4-5, >5. The presence of a physiotherapist within the ICU was inconstant (7% of ICUs did not have one). The presence of a social worker or psychologist within the unit was uncommon. In this survey, conducted 4 years ago, information technology was scarce. Fewer than half of respondent ICUs had an electronic medical record system. There is no medical emergency team within French hospitals. Usually, each day, one senior intensivist is in charge of emergency calls from the floor and calls from the emergency medical call centres.

There is a regionalised system for perinatal and trauma care. There are regionalised systems with telemedicine use in some regions (e.g. acute neuro-vascular care).

• Heterogeneity of Care

Several French studies suggest that selected patients cared for at ICUs with a larger number of annual admissions are more likely to survive than those hospitalised in ICUs with a smaller volume of annual admissions (Darmon et al. 2011; Lecuyer et al. 2008; Zuber et al. 2012; Dres et al. 2013). This positive volume-outcome relationship has been observed not only for patients requiring invasive or non-

Statistics	
Total population	63,937,000
Gross national income per capita (PPP international $)	35910 (2011)
Per capita government expenditure on health at average exchange rate (US$)	3800.2
Per capita total expenditure on health at average exchange rate (US$)	4952 (2011)
Physicians per 10,000 population	34.47 (2010)
Population % over 60	23.82
Population % under 15	18.26
Population living in urban areas (%)	86 (2011)
Population growth rate	-0.6
Private prepaid plans as a percentage of private expenditure on health	59.7 (2011)

Figures are for 2012 unless indicated. Source: World Health Organization Global Health Observatory http://apps.who.int/gho/data/node.country

invasive mechanical ventilation, but also for haemato-oncologic patients with acute respiratory failure or severe sepsis. On the other hand, some data do not suggest any survival benefit for critically ill patients requiring renal replacement therapy (Nguyen et al. 2011).

Healthcare Providers

• Intensivists

According to a recent survey of 1795 intensivists working in 290 ICUs, more than three-quarters of French intensivists are male, and are on average 42 years old (Annane 2013). Nearly half of them are trained in anaesthesiology and critical care medicine. The others have usually an internal medicine background (mostly cardiology) and a sub-specialty of critical care. The prescription of mechanical ventilation, renal replacement therapy or antibiotics is performed by the intensivists. An increasing number of intensivists are trained in echocardiography. Shift lengths longer than 16 hours remain common in French ICUs.

• Nurses

Despite the technical complexity of critical care nursing, there is currently no critical care nurse specialty in France. Critical care nurses' training is done within the ICU. Beyond the 'regular' tasks of other nurses, critical care nurses take care of the establishment and surveillance of renal replacement therapy and non-invasive ventilation. They are allowed to measure blood gases, but cannot insert arterial lines. Depending on the unit, they may have the responsibility for protocols such as glycaemic control, sedation analgaesia or vasopressors management. They are not allowed to prescribe drugs. Very few critical care nurses have the possibility to do research. They work 35 hours per week either in 8 hour or 12 hour shifts. There are no nurse-practitioners or physician assistants in France.

Statistics	
No. of emergency departments	630
Total PACU beds	8,433
Total intermediate care beds	5,311
No. of ICUs	409
No. of paediatric ICUs	45
Total ICU beds	4,769
Critical care beds per 100,000 population	11.6

Sources: Mouton 2009; Rhodes 2012.

• Other Allied Healthcare Professionals

Helpers (or nurse-assistants) work in collaboration with nurses, and take care of nursing, feeding and room hygiene. There is no clinician pharmacist in France. The majority of ICUs have a physiotherapist, but most of them have to share it with other wards. Physiotherapists take care of general rehabilitation, not only respiratory, and also manage non-invasive mechanical ventilation. If the ICU has dieticians and psychologists, they are often shared with other wards within the hospital. The concept of infectious consultant or renal consultant does not exist in France. Surgeons work in close partnership with intensivists but they are not trained in critical care.

Academics in Critical Care

After high school, all students may apply to the first year of PACES (a course for those applying for medicine, dentistry and midwifery). At the end of this year, an examination test (with a numerus clausus) controls access to the second year of medical schools. At the end of the sixth year, a national competitive examination allows medical students to choose their specialty and the location of their residency, according to their national ranking. Anaesthesiology and critical care medicine residencies last for five years. In academic centres, after their residency, young physicians have the possibility to do a two year contract of 'Chef de Clinique' (often traduced by fellows), during which their schedule is shared between resident and medical student supervision at the bedside, teaching and research projects. Becoming a Professor in a French medical school requires at least a PhD degree and one year experience outside the unit to which you are applying (not necessarily abroad). The main characteristics of this position are lifetime employment and no obligation to obtain research grants or a minimum annual number of publications. Consequently, academic positions are scarce and such a system may turn away young ambitious physicians from an academic career.

French Touch

• Clinical Research

French intensivists are very active in clinical research. Due to the lack of clinical research nurses, interns or fellows usually take care of inclusions, consent and data collection. On the other hand, the patients to resident ratio is usually very high - between 3 to 6 patients per resident. Similarly to other countries, the current economic crisis has led to a significant reduction in the amount of academic research grants.

• Decision-Making Patterns

The traditional paternalistic approach remains common in France. It is only since 2002, and the promulgation of the Kouchner law, that the consent (oral consent is sufficient) of patients is requested before conducting any invasive treatment or procedure (Loi n°2002-303 du 4 mars 2002). Concerning end-of-life care, the Leonetti law, voted in 2005, clarified the decision-making process (with the notion of surrogate designation and advance directives) when the patient is incapacitated or not (Loi n° 2005-370 du 22 avril 2005). Similarly to other Northern European countries, around half of deaths in French ICUs are preceded by

decisions to forgo life-sustaining therapies (Ferrand et al. 2001; Azoulay et al. 2009). These decisions to withdraw or withhold therapies are preceded by multidisciplinary meetings, including nursing staff and sometimes a consultant from another ward, during which the detailed modalities are discussed and written in the medical report.

• Quality and Safety of Care

The Haute Autorité de Santé, an independent public authority that contributes to the regulation of health system quality, has conducted since 1996 a periodic certification in all healthcare institutions, which includes an external evaluation of quality and safety of the infrastructure and processes of care (Haute Autorité de Santé). However, this institution does not evaluate outcomes or provide benchmarking. There are currently only part-time dedicated medical staff for quality and safety of care in French hospitals. The organisation of morbidity-mortality conferences is mandatory in critical care, but there is currently no regular evaluation of their impact on quality and safety within the unit (Pelieu et al. 2013).

• Health Economics

The chronic increasing deficits of the French healthcare system have led to reduced budgets and reduction in numbers of healthcare providers. The use of expensive therapies prescriptions (e.g. anti-fungal agents) is controlled on the level of evidence-based medicine but never restricted or benchmarked. To our knowledge, there is no cost-effectiveness study in our area in France.

• Burnout

The level of burnout among critical care healthcare providers is very high in France. Nearly one-half of intensivists suffers from a high level of burnout. The identified risk factors of burnout for physicians are workload and impaired relationships (Embriaco et al. 2007). One-third of nursing staff suffers from a high level of burnout. The risk factors for nurses are age, the relationship with head nurses and physicians, ICU organisation and end-of-life care policy) Poncet et al. 2007). ■

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HOT TOPICS IN CRITICAL CARE IN FRANCE

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This article briefly reviews selected recent French critical care medicine studies that currently impact medical practices.

Introduction

Clinical research activity in the field of intensive care and perioperative medicine in France has been very productive in the last two years. In this review article, we provide a state-of-the-art update on the recent main French published randomised controlled trials (RCTs) as well as reviewing some promising completed trials for which the results should be published in the next few weeks.

ARDS Clinical Trials

Despite its high incidence and devastating outcomes, acute respiratory distress syndrome (ARDS) has no specific treatment, with effective therapy currently limited to minimising potentially harmful ventilation. Until 2012, lung protective mechanical ventilation strategies were the only supportive therapy that clearly improved survival in patients with ARDS. Lung protective ventilation combines limited low tidal volume (5-6 ml/kg of ideal body weight) and positive end-expiratory pressure (PEEP from 5 to 20 cm H_2O) with respect to limited plateau pressure lower than 30cm H_2O. Two recent major French multicentre RCTs gave new insights, which permit improved ARDS mortality (Papazian et al. 2010; Guerin et al. 2013).

• Neuromuscular Blockade and ARDS: The ACURASYS Study

Lung protective ventilation can be achieved in the majority of patients without using neuromuscular blocking agents (NMBA). However, in the severely hypoxaemic ARDS patient (PaO_2/FiO_2 < 150 mmHg), NMBA may permit lower pressure, lower tidal volume ventilation with a consequent reduction in ventilator-induced lung injury. These beneficial effects led to the ACURASYS multicentre, randomised, placebo-controlled trial to assess the effect of NMBA upon mortality (Papazian et al 2013). This trial was the first to report decreased mortality by using a pharmacological agent in ARDS. The ACURASYS study included 340 hypoxaemic ARDS patients (PaO_2/FiO_2 <150 mmHg with PEEP >5cm H_2O). A control group without NMBA was compared to an intervention group who received early infusion with cisatracurium besylate within 48 hours of mechanical ventilation. The conclusion of the study was that in patients with severe ARDS early use of NMBA for a short period (<48h) significantly improved mortality at 28-day (23.7% vs 33.3% (P=0.05)) and also improved 90-day survival (31.6% vs 40.7% (p= 0.08)).

• Prone Position and ARDS: the PROSEVA Study

Prone position (PP) in ARDS patients has proved to improve oxygenation and lung recruited volume. Until 2013, previous RCTs involving patients with ARDS failed to show a beneficial effect of PP during mechanical ventilatory support on outcomes, although there were significant improvements in oxygenation.

The PROSEVA study evaluated the effect of early application of PP on outcomes in patients with severe ARDS (PaO_2/FiO_2 <150 mmHg with PEEP >5 cm H_2O) (Guerin et al. 2013). In this multicentre, prospective, randomised, controlled trial, 466 patients were randomly assigned to undergo PP sessions of at least 16 hours (n=237) or to be left in the supine position (n=229). The conclusion of the study was that, in patients with severe ARDS, early application of prolonged PP sessions significantly decreased 28-day (16% vs 33%; p<0.001) and 90-day mortality (24% vs 41%; p<0.001).

Other Published Clinical Trials

• Lung Protective Ventilation in Operating Room In Patients with Healthy Lungs: the IMPROVE Study

In our opinion, preventive strategies should also include protective ventilation with low tidal volume in patients at risk, such as from elective abdominal surgery. Although one physiological study supports this approach, until 2013 no RCT has evaluated the effect of a lung protective strategy on postoperative complications in patients with uninjured lungs in the operating room for abdominal surgery. The IMPROVE trial was a multicentre, double-blind, parallel group trial, which randomly assigned 400 adults at intermediate to high risk of pulmonary complications after major abdominal surgery to either nonprotective mechanical ventilation (tidal volume 10-12 ml/kg ideal body weight and no PEEP) or a strategy of lung protective ventilation (tidal volume 6-8 ml/kg ideal body weight and PEEP 6-8 cm H2O with recruitment manoeuvres) (Futier et al 2013). The primary outcome was a composite of major pulmonary and extrapulmonary complications occurring within the first seven days after surgery.

The study conclusion was that, compared with a practice of nonprotective mechanical ventilation, the use of a lung protective ventilation strategy in intermediate-risk and high-risk patients undergoing major abdominal surgery was associated with improved clinical outcomes and reduced health care utilisation.

• Stress-Dose Hydrocortisone in Trauma Patients: the HYPOLYTE Study

The HYPOLYTE trial was a multicentre, randomised, double-blind, placebo-controlled study, which evaluated the efficacy of hydrocortisone therapy in trauma patients (Roquilly et al. 2011). The study included 150 patients with severe trauma. Patients were randomly assigned to a continuous intravenous infusion of either hydrocortisone (200 mg/d for five days, followed by 100 mg on day six and 50 mg on day seven) or placebo. The treatment was stopped if patients had an appropriate adrenal response. The primary endpoint was hospital-acquired pneumonia within 28 days. Secondary outcomes included the duration of mechanical ventilation, hyponatraemia, and death. The conclusion of the study was that, in intubated trauma patients, the use of an intravenous stress-dose of hydrocortisone, compared with placebo, resulted in a decreased risk of hospital-acquired pneumonia (36 vs 54%; P=0.01).

• Cardiopulmonary Resuscitation and Patients' Family

The effect of family presence during cardiopulmonary resuscitation (CPR) on the family members themselves and the medical team remains controversial. A multicentre RCT enrolled 570 relatives of patients who were in cardiac arrest and were given CPR by 15 pre-hospital emergency medical service units (Jabre 2013). The units were randomly assigned either to systematically offer the family member the opportunity to observe CPR (intervention group), or to follow standard practice regarding family presence (control group). The primary endpoint was the proportion of relatives with post-traumatic stress disorder (PTSD)-related symptoms on day 90. The frequency of PTSD-related symptoms was significantly higher in the control group than in the intervention group, and the conclusion of the study was that family presence during CPR was associated with positive effects on psychological variables and did not interfere with medical efforts, increase stress in the healthcare team, or result in medicolegal conflicts.

Promising Completed Trials

Besides this recent literature, several promising French multicentre studies have been completed, and these trials may provide us with interesting results for practice. Asehnoune and coworkers have studied traumatic brain injured patients, who frequently suffered from glucocorticoid insufficiency associated with an increase in the rate of pneumonia, responsible for significant burden. Corti-TC study is a double-blinded RCT supported by the French Anaesthesia and Critical Care Society (SFAR), designed to assess the treatment of glucocorticoid insufficiency (hydrocortisone associated with fludrocortisone) for prevention of post-trauma pneumonia in a population of severe traumatic brain injury patients (Nantes University Hospital).

To come also are the results of the STATIN VAP study by Papazian et al. on the effect of the association of a statin to antibiotics on hospital mortality of patients presenting with a suspicion of ventilator-associated pneumonia (Assistance Publique Hopitaux De Marseille). Another study to come is focused on fluid resuscitation. The CRISTAL study by Annane et al. is a large multinational open randomised trial designed to compare the effects on hospital mortality of crystalloids and colloids when given for fluid resuscitation in critically ill patients (University of Versailles). There is no doubt that this study will probably boost the debate about fluids in ICU.

The last study is dedicated to the evaluation of the streamlining of antimicrobial therapy after the identification of the pathogen responsible for infection. Even if it is a classical guideline, few randomised clinical trials have tested this strategy prospectively. In the DEA (Désescalade) study, Leone et al. are conducting a randomised clinical trial comparing a strategy based on de-escalation (streamlining of the empirical antimicrobial therapy) and a conservative strategy (continuation of the empirical antimicrobial therapy) (Assistance Publique Hopitaux De Marseille). They aim to show that a strategy based on de-escalation is not inferior to a conservative strategy in terms of intensive care unit length of stay.

Conclusion

Clinical research in intensive care and perioperative medicine in France is very productive. Recently it has addressed relevant questions, providing us with interventions associated with a positive impact on the outcomes of critically ill patients. Results of further studies are awaited in the hope of continued improvement of our daily clinical practice. ■

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Rio de Janeiro, Brazil
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19-21 11th Doppler-Echocardiography in Intensive Care Medicine
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29-30 3rd International Fluid Academy Day
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