Kidney Diseases beyond Nephrology

Kidney diseases beyond nephrology: intensive care

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Evidence-based and good sense-based critical care medicine

Critical care medicine has improved greatly, thanks to the implementation of guidelines and good clinical practice protocols. For this reason, the present clinical practice requires evidence-based medicine to answer unresolved debates and to further improve applied protocols. Randomized controlled trials are (even if not always [1]) essential in order to achieve a high level of scientific evidence good enough to support the application of new life-saving strategies or to change significantly current practice [2]. Such trials are now strongly needed because mortality has improved to such a level that large investments will be required to achieve relatively small improvements in clinical outcomes. Nevertheless, this approach has justified and encouraged changes in therapeutic strategies sometimes contradicted after only a few years. This not only demonstrates how difficult it is to reach a definitive consensus in the world of critical care medicine but it may also induce perplexity and diffidence among the operators of the field.

A good example of such a problem is represented by the issue of tight glycaemic control in critically ill patients. Hyperglycaemia associated with insulin resistance is common in critically ill patients, even in those who have not been previously diagnosed with diabetes [3]. It has been reported that pronounced hyperglycaemia may lead to significant complications. In diabetic patients with acute myocardial infarction, therapy to maintain the blood glucose at a level 7–215 mg/dL improves the long-term outcome [4]. In nondiabetic patients with protracted critical illnesses, high serum levels of insulin-like growth factor-binding pro-tein 1, which reflect an impaired response of hepatocytes to insulin, increase the risk of death [5]. Critical illness-related polyneuropathy and skeletal muscle wasting are associated with hyperglycaemia and the prolonged need for mechanical ventilation [6]. Moreover, in hyperglycaemic critically ill patients, increased susceptibility to severe infections and failure of vital organs, particularly the kidneys, occur and amplify the risk of an adverse outcome [3]. One landmark trial in 2001 showed significantly decreased mortality in a surgical intensive care unit (ICU) targeting blood glucose to 80–110 mg/dL with intensive intravenous insulin therapy [7]. A reduction in organ dysfunction and ICU length of stay (LOS) (from a median of 15 to 12 days) was also observed in the subset of patients with an ICU LOS >5 days. A second randomized trial of intensive insulin therapy, following the same protocol, enrolled medical ICU patients with an anticipated ICU LOS of >3 days [8]. Overall, mortality was not reduced but ICU and hospital LOS were reduced and associated with earlier weaning from mechanical ventilation and less acute kidney injury (AKI). In patients with a medical ICU LOS >3 days, hospital mortality was reduced with intensive insulin therapy. However, the investigators were unsuccessful in predicting ICU LOS and 433 patients (36%) had ICU LOS of <3 days. Furthermore, use of the intensive insulin strategy in the medical ICU resulted in a nearly 3-fold higher rate of hypoglycaemia than in the original experience (18% versus 6.2% of patients). Interestingly, a recent survey conducted in 29 Australian and New Zealand ICUs with 911 admissions showed that few of those ICUs had adopted intensive insulin therapy. That study could not separate insulin administration and highest daily blood glucose concentration in their association with hospital mortality [9]. Other clinical trials [10–13] performed over the last 7 years reported conflicting results about the impact on patient outcome of tight glycaemic control, and dangerous hypoglycaemia was frequently observed in tight glycaemic control regimes. The Surviving Sepsis Campaign now recommends glucose control in critically ill patients below a glucose level of 150 mg/dL. [14]. The data underlying this recommendation were critically evaluated from Wiener et al. who searched for studies in which adult intensive care patients were randomly assigned to a tight versus usual glucose control [15]. Of 1358 identified studies from all languages, 34 randomized trials (23 full publications,
9 abstracts, 2 unpublished studies) met the inclusion criteria. Twenty-nine randomized controlled trials (RCT) totalling 8432 patients contributed data for this meta-analysis. Hospital mortality did not differ between tight glucose control and overall usual care. There was also no significant difference in mortality when stratified by glucose goal (very tight: < 110 mg/dL or moderately tight: < 150 mg/dL) or intensive care unit setting (surgical, medical, medical–surgical). Tight glucose control was not associated with a significantly decreased risk for dialysis requirement, but was associated with a significantly decreased risk of sepsis and significantly increased risk of hypoglycaemia (glucose < 40 mg/dL). The authors conclude that in critically ill adult patients, tight glucose control is not associated with significantly reduced hospital mortality but with an increased risk of hypoglycaemia.

In a recent article, Schetz et al. reported on the combined analysis of the two Belgian studies that investigated the renal effects of intensive insulin therapy in critically ill patients [16]. The analysis of the cumulative data showed that patients randomized to treatment with intensive insulin therapy were less likely to develop higher classes of a modified RIFLE (Risk, Injury, Failure, Loss and End-stage renal disease) criteria for AKI and were less likely to have oliguria or to develop the need for renal replacement therapy (RRT).

A large RCT is finally planned to compare glucose levels of 80–110 mg/dL versus 140–180 mg/dL and will recruit more than 6000 patients (Normoglycaemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation, or NICE-SUGAR). This RCT is scheduled to randomize its last patient before the end of the year 2008. The trial’s primary outcome is 90-day all-cause mortality, and information on renal function is among the secondary aims of the study. The maintenance of blood glucose levels within the conventional range (110–190 mg/dL) seems justified until the results on glucose control become available [17].

Interestingly, not only therapeutic approaches have been re-evaluated in the recent literature, but lack of evidence also exists for some monitoring systems and their utility in ICU patients. A recent analysis was aimed at determining which monitoring techniques might improve outcomes in ICU patients [18]. The authors retrieved about 4000 articles, of which 67 evaluated the impact of monitoring in acutely ill adult patients. There were 40 studies related to haemodynamic monitoring, 17 to respiratory monitoring and 10 to neurological monitoring. Positive non-mortality outcomes were observed in 17 of 40 haemodynamic studies, 11 of 17 respiratory and in all 10 neurological studies. Mortality was evaluated in 31 haemodynamic studies, but a beneficial impact was demonstrated in only 10. For respiratory monitoring, seven studies evaluated mortality, but only three of them showed an improved outcome. No neurological monitoring study assessed mortality. The authors conclude that there is no broad evidence that any form of monitoring improves outcomes in the ICU and that most commonly used devices have not been evaluated by RCTs. In particular, pulmonary artery catheters (PACS) have been considered for almost 40 years as a useful tool in the acutely ill patient to achieve information on intrathoracic intravascular pressures, cardiac output and mixed venous oxygen saturation (SvO2). Over the last 10 years, different trials were able to show that PACS do not improve outcome and can even be dangerous: in 1996, a multicentre observational study by Connors et al. suggested an increased mortality with PACS [19]. As a consequence, multiple randomized trials were performed [20–25] and a Cochrane Collaboration meta-analysis has recently shown that this technology has no impact on mortality in different critically ill patient populations [26]. Recently, a time trend analysis on national estimates of PAC utilization from 1993 to 2004 was performed. A primary analysis focused on admissions with a medical diagnosis and a secondary analysis on surgical admissions [27]. Between 1993 and 2004, PAC use decreased by 65% from 5.66 to 1.99 per 1000 medical admissions. Among the subgroup of patients who died during hospitalization, but whose disease severity was considered constant across time, the relative decline was similar, decreasing from 54.7 to 18.1 per 1000 deaths. A significant change in trend occurred following the 1996 trial. The decline in utilization was similar in surgical patients. The decline of PAC utilization was most prominent for myocardial infarction, which decreased by 81%, and least prominent for sepsis, which decreased by only 54%. Use of the PACS was previously a hallmark of critical care practice, and this significant trend towards decreased use in the United States in the last decade is possibly due to the evidence that this invasive monitoring does not reduce mortality. A group of experts in the field, however, met and wrote an interesting point of view article, strongly criticizing these conclusions [28]. They correctly stated that, ‘If we apply the argument that there is a lack of evidence showing a mortality reduction with PAC use, then practically every monitoring technique used in critical care should be abandoned’. Furthermore, if it is true that PACS are applied less often (especially in the United States), this might mean that they have been previously overused. If European trends were analysed, they would probably be less spectacular than those described above. Finally, evidence-based medicine can be interpreted in different ways: if it is true that several RCTs have indicated that using a PAC does not influence outcomes, they did not show that PACS are either inherently dangerous or beneficial (except for Connors’ study) and, so far, a PAC is still considered the gold standard of haemodynamic monitoring compared to alternative and less invasive systems. It is difficult, based on RCTs, to develop PAC-guided treatment protocols that are applicable across a heterogeneous population of acutely ill patients with complex comorbidities. Indeed, the way in which PAC findings are interpreted and used requires deep knowledge of the physiology and integration of the three PAC elements (pressures, cardiac output and SvO2): such interpretation may vary and often be inadequate among different operators. If a properly trained physician believes that invasive haemodynamic data are necessary for the management of a specific patient, then the use of the PAC is justified in that patient. The use of PACS, according to these authors, should still be considered a good medicine, and it should be utilized every time a pathophysiological rationale exists. Doctors should still be trained in PAC positioning and correct data interpretation.
Dialysis dose: a nihilistic approach?

Critical care nephrology seems also to be affected by conflicting results coming from RCTs, in particular when dialysis dose is concerned. In an interesting ‘practice point’, Kellum commented, after an analysis of the most important studies on dialysis dose, that the best evidence supported the use of at least 35 mL/kg/h for continuous renal replacement therapy (CRRT), or daily intermittent haemodialysis (IHD). Lower doses of RRT should be limited to research protocols that actively test this hypothesis [29]. New high-level evidence finally came from two very recent trials. A (small) RCT in 200 critically ill AKI patients concluded that neither survival nor renal recovery was different between patients receiving either a high dosage (35 mL/kg/h) or standard dosage (20 mL/kg/h) of continuous venovenous haemodiafiltration (CVVHDF) [30]. A second trial, under the sponsorship of The Veterans Affairs/National Institutes of Health (VA/NIH) Acute Renal Failure Trial Network, randomly assigned 1124 critically ill patients with AKI and failure of at least one non-renal organ or sepsis to receive intensive or less intensive RRT [31]. The study was a multicentre, prospective, randomized, parallel-group trial conducted between November 2003 and July 2007 at 27 VA and university-affiliated medical centres. In both groups, only haemodynamically stable patients underwent IHD, whereas haemodynamically unstable patients underwent CVVHDF or sustained low-efficiency dialysis (SLED). Patients receiving the intensive treatment strategy underwent IHD (Kt/V 1.2) and SLED six times per week and CVVHDF at 35 mL/kg/h of body weight; for patients receiving the less-intensive treatment strategy, the corresponding treatments were provided three times weekly and at 20 mL/kg/h, respectively. Sixty-day mortality was 53.6% with intensive therapy and 51.5% with less-intensive therapy. There was no significant difference between the two groups in the duration of RRT or in the rate of renal recovery or non-renal organ failure. So far, this is the first multicentre clinical trial with adequate statistical power on different RRT strategies. The findings of this study contrast with other single-centre trials [32,33] and are similar to smaller studies by Tolwani et al. and Bouman et al. [18,34]. However, these results add to the debate on dialysis dose and they will be discussed for a long time. After this trial, operators might reasonably change their standard RRT dose prescriptions to a lower level than previously recommended. Nonetheless, many concerns about the external validity of the study have risen [35]. First of all, patients were allowed to transition from one dialysis modality to another; in this condition, the dialysis dose is impossible to be compared and unlikely to be equivalent. Furthermore, a physiologically logical approach to comparing the two modalities is the standardized urea Kt/V parameter, as described by Gotch [36]. This parameter provides a continuous equivalent estimate of weekly urea removal for disparate therapies. In the ATN Study, the weekly standardized urea Kt/V value for intensive IHD can be estimated as being ~4.0 while for the less-intensive CRRT ~5.0. On a time-averaged basis, therefore, greater urea removal occurred in patients receiving less-intensive CRRT on a given day than in those receiving intensive IHD. This uncertain separation of the dose during periods of unknown duration makes failure to observe a treatment effect not surprising. Finally, it is not known if the study findings can be generalized to health care systems different from the United States and to different RRT approaches [for example, the sole use of continuous venovenous haemofiltration (CVVH) in many European centres]. Of note, the relatively high rate of severe hypotensive events in patients treated with IHD, despite being judged clinically ‘haemodynamically stable’, may cast doubt on the ATN approach to the modality assignment and suggests that, from a haemodynamic point of view, a greater number of patients may have benefited from a more liberal CRRT use than that chosen for the study. In any case, it is possible that other strategies besides only increasing RRT dose might help AKI patients. Current approaches to dialysis are probably not adequate to fully replace critical functions such as regulation of fluid balance, electrolyte and acid–base homeostasis and efficient down-regulation of the inflammatory response, which all might play a major role in the pathophysiology of AKI [37].

The definitive answer to the never-ending debate of dialysis dose will hopefully come from Australia and New Zealand [38]. The Randomized Evaluation of Normal versus Augmented Level Replacement Therapy Trial will test the hypothesis that a higher dose of CVVHDF, at an effluent rate of 40 mL/kg/h, will increase survival compared to CVV HDF at 25 mL/kg/h of effluent dose. This trial is currently randomizing critically ill patients in 35 intensive care units in Australia and New Zealand with a planned sample size of 1500 patients. This trial will be the largest trial ever conducted on acute blood purification in critically ill patients. It is scheduled to be concluded by the end of 2008. The aim of this trial is to provide high-quality evidence on the comparative effects of different levels of CRRT dose in patients with AKI treated in the ICU. This evidence will have direct relevance for decisions about the care of critically ill patients worldwide. If this study shows a benefit similar to the Ronco study [32], given the current incidence of severe AKI, it may save an estimated 15 000 lives/year worldwide.

The issue of fluid balance

Before the results from the RENAL trial are available, we have to consider some new interesting results that are coming from the population of AKI patients treated with RRT.

Payen and co-authors, utilizing the data coming from the Sepsis Occurrence in Acutely Ill Patients (SOAP) study, analysed the influence of patient characteristics and fluid balance on the outcome of AKI in ICU patients [39]. The SOAP study is a multicentre observational cohort study to which 198 ICUs from 24 European countries contributed. For this analysis, patients were divided into two groups according to the presence or absence of AKI. Of the 3147 patients included in the SOAP study, 1120 (36%) had AKI at some point during their ICU stay. Sixty-day mortality rates were 36% in patients with AKI and 16% in patients without. Oliguric patients and patients treated with RRT had higher 60-day mortality rates than patients without oliguria or the need for RRT. Independent risk factors for 60-day mortality included being septic, having hypotension, and receiving renal replacement therapy.
mortality in the patients with AKI were age, simplified acute physiology score II (SAPS II), heart failure, liver cirrhosis, medical admission, mean fluid balance and need for mechanical ventilation. Among patients treated with RRT, the length of stay and mortality were lower when RRT was started early (< 48 h from ICU admission). According to these authors, a positive fluid balance was an important factor associated with increased 60-day mortality. Several studies have previously shown a statistical difference in the percentage of fluid overload among children with severe renal dysfunction requiring RRT. At the time of dialysis initiation, surviving children tended to have less fluid overload than non-survivors, especially in the setting of multiple organ dysfunction syndrome (MODS) [40,41]. For this reason, in children, the priority nowadays is given to the correction of fluid water overload. If this concept is so important in critically ill small children, where capillary leak syndrome is a dramatic manifestation of MODS, this problem is probably underestimated in critically ill adults where huge amounts of volume are infused for either correcting hypovolaemia, for drug infusion and/or parenteral/enteral nutrition, and eventually as blood derivatives. It is possible that more severely ill patients are those who receive relatively higher amount of fluids, and this could thus explain the more positive fluid balance of non-surviving patients. A prospective trial should now clarify whether this group would really benefit from a goal-oriented aggressive ultrafiltration therapy.

In a recent article on fluid management with continuous venous haemofiltration (CVVH) in paediatric patients receiving extracorporeal membrane oxygenation (ECMO) [42], Hoover et al. showed that the use of CVVH in ECMO was associated with improved fluid balance, increased caloric intake and less diuretic administration compared with case-matched ECMO controls. These authors concluded that routine application of CVVH to ECMO circuits should be considered, and they supported a randomized trial to evaluate such strategy. An important study of Shaheen et al. [43], however, showed that patients who required ECMO and CVVH suffered from 1.5-fold increased mortality with respect to the group of patients who required CVVH alone. Hence, the potentially detrimental effects of RRT added to ECMO should not be underestimated. First, CVVH balance errors occur, especially when the treatment is delivered in parallel with ECMO circuits [44]. These errors can be harmful, and it is still uncertain exactly when clinical and engineering investigators will develop an alternative device to improve the accuracy of CVVH on ECMO. Furthermore, the need for machine troubleshooting and constant staff monitoring for alarms cause a significant increase in workload. In addition, CVVH dose prescription is another controversial issue, where the evidence of beneficial or unfavourable clinical effects is still unclear. If it is true that the use of CVVH could enhance removal and absorption of undesirable inflammatory mediators, the removal of beneficial solutes, such as natriuretic factors, might on the other hand be correlated to side effects, such as decreased urine output after the start of haemofiltration [45]. Finally, it is not clear how patients with the diagnosis of fluid overload and renal insufficiency can be compared to patients without renal failure in terms of fluid balance.

We think that strong evidence (i.e. coming from a prospective trial) about the impact of fluid balance on outcome in paediatric patients undergoing ECMO is still lacking. After such verification, dedicated CVVH machines should be developed and validated to the specific setting of ECMO children. Only after these achievements, a randomized trial comparing paediatric patients with ECMO versus patients with ECMO plus CVVH can be attempted: at this point, it should be considered whether to enrol or to exclude patients with fluid overload and/or renal failure in both study arms. In any case, it is possible that such a study might turn out to be very difficult to perform due to ethical reasons or an inadequate inclusion rate.

Conclusions

We would like to conclude from where we started, by quoting the British Medical Journal [46]: ‘What should clinicians do when faced with conflicting recommendations? …Disagreements occur for both valid and non-valid reasons. Valid reasons include honest differences in the many judgments that go into a recommendation—judgments about which research is relevant; the risk of bias in that research; the applicability of the research findings to the question at hand, and the relative importance of the anticipated benefits, adverse effects, and costs. Non-valid reasons include conflicts of interest, lack of awareness of relevant evidence or ignoring such evidence, failure to appraise the relevant research critically, failure to consider outcomes that are important to patients, and inappropriate valuations of outcomes… The bottom line is that clinicians need guidelines and use them all the time, but they should not accept recommendations passively or without discrimination. To serve their patients well, clinicians must be able to make informed judgments about which guidelines are appropriate, and what to do when recommendations conflict with one another’.

Furthermore, they must be aware that targets are sometimes difficult to achieve and the best attempts possible should perhaps be made to approach the desired targets without jeopardizing the holistic management of critically ill patients.

Conflicts of interest statement. None declared.

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