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New Developments in Renal Replacement Therapy (RRT)

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Renal replacement therapy (RRT) is now widely used within intensive care units (ICU) but despite its broad acceptance, there remains a general lack of consensus or recommendations regarding best practice. Despite these limitations, the interest in acute kidney injury (AKI) as well as blood purification techniques continues to grow with many small studies and a few precious large multicentre randomised controlled trials (RCT) although those that have been published so far have provided useful information. This review will address the 'hot topics' in RRT that involve the intensive care world and the latest developments and recommendations will be outlined.

First, the debate still remains ongoing as to the best technique for provision of RRT in our ICU patients including: Intermittent haemodialysis (IHD), continuous veno-venous haemodiafiltration (CVVHDF), continuous veno-venous haemofiltration (CVVH), Sustained low efficiency dialysis (SLED) and others. This debate continues to rage with two major questions: Continuous or intermittent techniques and diffusion or convection. A large RCT, the Haemodiafe study by Vinsonneau (Vinsonneau et al. 2006), compared IHD versus CVVHDF for ICU patients and showed that the techniques are comparable in term of patients' outcome and this was subsequently confirmed by another RCT. However many intensivists remain in favour of continuous methods especially where the patient is haemo dynamically unstable. Although some groups have reported no overt problems using IHD for unstable patients in the ICU (Fieghen et al. 2010; Schortgen et al. 2000), most of the expert opinion recommends continuous therapies, particularly during the acute phase of AKI and in particular for patients with haemodynamic impairment or the impact on drug removal (Bagshaw et al. 2008; Susla 2009). The choice between diffusion and convection also remains unclear. Diffusion permits efficient removal of small molecules with an excellent ionic equilibration whereas convection is more efficient for 'middle molecule removal, but when employing a high cut off membrane, the dialysis technique also has the capability to remove larger molecules (Messer et al. 2009; Ricci et al. 2006). However, no large RCT has demonstrated any clear superiority of one method over the other in terms of outcome improvement despite the superiority of large pore membrane reported in small studies (Morgera et al. 2006). A new generation of membranes has also emerged with specific properties as endotoxin adsorption (Toraymyxin® from Toray™ or Oxiris® from Gambro™) or specific immuno-adorsption (Prosorba® from Fresenius™) with promising results in recent studies (Cruz et al. 2009) and the promise of RCTs in the near future.

The dose of fluid exchange that we have to provide is now more clearly defined given the publication of the two large RCTs within the last few years. The study by Ronco et al in 2000, recommended a dose of haemofiltration for ICU patients of 35 ml/kg/h (Ronco et al. 2000). This new paradigm of beneficial effect in increasing RRT dose was further addressed by two large studies: One showed better outcomes for patients treated by daily haemodialysis rather than three times a week (Schiffl et al. 2002), the other that increasing dose and adding a dialysis treatment to haemofiltration also improved outcome (Saudan et al. 2006). However, the large multi-centre RCT conducted by Palevsky and collagues in 2008 showed that less intensive therapy (IHD three times a week, CVVHDF at 20 ml/kg/h or SLED) is comparable to intensive therapy (daily dialysis or CVVHDF at 40 ml/kg/h) (Palevsky et al. 2008). The definitive answer to this question came from the RENAL study that clearly demonstrated no beneficial effect of CVVHDF at 40 ml/kg/h in comparison with 25 ml/kg/h (Bellomo et al. 2009). Therefore, the consensus currently is that the dose of haemofiltration employed should be 25 ml/kg/h with no additional benefit from a dose increase. However, two points remain unanswered. First, most experts agree that patients should not be undertreated and to deliver at least 25 ml/kg/h of fluid exchange. In practice this recommendation implies prescribing 30-35 ml/kg/h to take into account the predictable (bags change, nursing...) or unpredictable breaks in treatment (surgery, clotting...) (Vesconi et al. 2009). Secondly, the debate about the dose remains open for septic patients as some small prospective or randomised studies have shown a beneficial effect of high dose haemofiltration (Honore et al. 2000; Joannes-Boyau et al. 2004; Boussekey et al. 2008). The multicentre RCT "IVOIRE study" compares haemofiltration at 35 ml/kg/h versus 70 ml/kg/h for patients with septic shock, AKI and multiple organ failure may bring some important information to this area in the near future (Joannes- Boyau; In progress).

When to commence RRT is also a major question. This was hampered in the past by a lack of a clear and consensual definition of acute kidney injury to enable stratification of the degree of renal impairment and to homogenise patients for study purpose and to help to define the best moment to start RRT. Fortunately, two new classifications have arrived within the last few years: the RIFLE criteria and AKIN (Cruz et al. 2009). These classifications alert aware clinicians about the presence of AKI and to allow early intervention. Some studies or meta-analysis published in the last few years have possibly fuelled interest for commencing RRT early but large RCT's to define the best moment to start are awaited (Shiao et al. 2009; Seabra et al. 2008). One RCT regarding timing to start haemofiltration was negative (Bouman et al. 2002), but this was insufficiently

powered and the patient population was too selective (post-cardiac surgery). Again, expert recommendations imply that commencing RRT earlier and in particular in the septic patient where we know that AKI is often progressive. However, a RCT from France has shown that it is probably not recommended to start RRT before AKI criteria have been fulfilled (Bouman et al. 2002) and some concerns have emerged from a Belgian study (but not randomised) about the possible harm of starting RRT too early (Elseviers et al. 2010). It seems acceptable to start RRT at the Injury level of RIFLE criteria (or stage 2 of AKIN) at least for septic AKI, especially when associated with shock but no consensus has emerged at present and large RCTs are needed. Early use of RRT may also be relevant in patients treated by Extra-corporeal membrane oxygenation (ECMO) for severe acute respiratory distress syndrome (ARDS) as shown in some very recent studies and in particular in children (Ricci et al. 2010; Santiago et al. 2009). Anticoagulation remains a field of continuous development and research, in particular since the description of citrate anticoagulation and new dedicated machines. Despite the fact that unfractionated heparin (UFH) remains the most commonly use anticoagulant around the world for RRT, citrate and other alternatives begin to assume more importance. The most recent important study was provided by Oudemans van Straaten and coll where they compared citrate anticoagulation to low molecular weight heparin (LMWH) but only in the surgical subgroup (Oudemans-van Straaten et al. 2009). Although no difference was found in terms of efficacy, they found an unexplained improved outcome for patients treated with citrate. In fact, the three-month mortality is probably abnormally high in the LMWH group (63%) when compared with the expected death rate in such patients with the citrate group being closer to the usual outcome (48% mortality). Thought must also be given to antithrombin levels when using UFH during RRT as it is a mandatory clotting co-factor (and sometime forgotten) although its activity level is often reduced, particularly in septic ICU patients and need to be supplemented (Lafargue et al. 2008). The last point is the one concerning the replacement fluids, where new products on the shelf are becoming closer to the plasma composition, in particular with phosphorus implementation directly in the fluid bag (Broman et al. 2010), which can avoid severe ionic disturbances shown in the past (Bellomo et al. 2010).

In conclusion, more and more developments are occurring in the field of RRT. Large RCTs on various key subjects are warranted to try to improve our knowledge and save more lives as patients suffering from AKI in ICU continue to have an unacceptably high mortality rate. In the meantime, the odyssey in the RRT universe will continue for the intensivists, enabling them to expand our knowledge in this exciting field.

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