Pro: Renal replacement trauma or Paracelsus 2.0

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'Dosis sola facit venenum'—only dose determines the poison—is a famous phrase coined by the alchemist, physician and astrologer Paracelsus. Usually, this phrase applies to substances that can become toxic at a certain dose. It holds true for all known compounds even those generally associated with health and well-being like water or oxygen. Based on the landmark paper by Ronco, our idea as nephrologists and intensivists for the last decade was that an increase in renal replacement therapy (RRT) dose is beneficial in patients suffering from acute kidney injury (AKI) [1]. It was such an appealing hypothesis that even a discussion about it seemed utterly unnecessary. Non-adherence to this principle of cleaning things thoroughly has led to disastrous consequences, even if the subject is as trivial as a blue dress [2]. Despite the fact that recent prospective trials [3–5] could not confirm a benefit of higher RRT dose on patient survival, we still consider RRT dose escalation to be not beneficial at worst if it exceeds a certain range. Apart from hospital administrators hardly anyone would consider a high dose of RRT to be harmful. However, the Spanish physician Maynar-Moliner et al. [6] recently coined the term 'Dialytrauma' trying to integrate several complications of high-dose RRT in intensive care unit (ICU) patients. These consist of, but are not limited to, arterial hypotension (with need for vasopressors), metabolic (nutritional depletion, electrolyte disorders), haemorrhagic and infectious complications, hypothermia and maladapted drug doses—a mixture with potentially fatal consequences. This list (Table 1) of typical RRT-associated complications is probably true for any ICU population with AKI but seems to be of highest relevance for septic patients, i.e. the patient population that represents the highest percentage of AKI patients in the ICU today [7]. These patients might be highly susceptible to the 'Dialytrauma', especially if one looks at the aspect of drug dosing in those individuals who are critically dependent on appropriate serum levels of a given pharmaceutical compound. Indeed, one might find a rather simple but underappreciated explanation for the observed failure of increased RRT dose to improve survival in septic patients. Till today, the treatment of sepsis is mostly limited to supportive care, e.g. strategies like 'early goal directed therapy' [8]. The only true causative and therefore fundamental part of the treatment regimen of any septic individual is the anti-infectious medication. Most recommendations for dose adjustment of antibiotics in renal patients are derived from studies in CKD 5D patients on thrice-weekly maintenance dialysis. Less data are available in AKI.
patients treated with continuous renal replacement therapies (CRRT), particularly not from the era were modern high-flux membranes and high filtration volumes were routinely used [9]. Septic patients are critically dependent on the adequate dose of the appropriate antibiotic. It is conceivable that extensive clearance of those substances in the context of higher RRT doses (without adaptation of the administered drug doses) might actually harm the patients. In other words, the lack of survival differences between high and low dialysis dose in the newer trials might be explained by an artificially introduced bias, i.e. removal of necessary antibiotics (Figure 1). Besides catheter-associated bleedings and infections, the 'Renal Replacement Trauma' should not be understood as a direct procedure-related toxicity but rather as sort of a side effect of overlooked adjustments by us, the treating physicians. This bias probably has not been introduced in Ronco’s first study in 2000, as the percentage of septic participants was rather low (13%), so that intensive RRT did not interfere with key components of sepsis treatment, i.e. adequate dosing of antibiotics. In contrast, studies with a high percentage of septic patients in whom therapeutic drug levels of antibiotics are of vital importance tended sometimes even

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<th>Table 1: Potential contributors to the renal replacement trauma</th>
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<td>Copper</td>
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<td><strong>Vitamins (water-soluble)</strong></td>
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<td>Folic acid (B9)</td>
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<td>Pyridoxal phosphate (B6)</td>
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to have an even higher mortality with intensive renal support. Interestingly, in the Ronco study, the survival rate of septic patients was 25% (5/20) in the low-dose group (20 mL/kg/h) and 18% (3/17) in the group that received a dose of 35 mL/kg/h. Even though 7 out of 15 septic patients (48%) survived in the 45 mL/kg/h group, a proportional hazards model could not confirm that a high filtration rate improves survival in the subgroup of septic patients [1].

IS TOO MUCH OF A GOOD THING A BAD THING?

The recent years in critical care medicine were filled with examples where too much of an intervention previously considered to be beneficial, was indeed harmful. This holds true for respirator settings such as positive end-expiratory pressure (PEEP) [10] as well tight glucose control [11]. The growth of higher delivered RRT doses as well as the improvement of RRT machines and filters has rendered old dosing guidelines for drugs, especially antibiotics, ineffectual and potentially dangerous [12]. Up-to-date pharmacokinetic studies conducted in patients receiving ‘Ronco dose’ CRRT or ED are rare. Dosing guidelines for these therapies to our knowledge have never been presented in a drug’s package insert. This problem, neglected for a long time, is increasingly recognized and has recently been addressed in a KDIGO statement on improving drug dosing in renal failure [13]. Most trials, developed to determine the optimal dose of CRRT/ED, have missed (or at least not reported) to increase antibiotic doses to account for the increased drug removal associated with the high-intensity approach [3, 5, 14]. A fact that as alluded above might have contributed to the result of those studies, i.e. that higher doses of RRT did not reduce mortality rates among patients with AKI [4]. This hypothesis is supported by the fact that the higher delivered clearance was associated with higher hypophosphatemia rates ranging from 18% [5] up to 66% [14] of patients in the intensive-therapy arm. The obvious failure to supplement phosphate, a parameter measured on a daily basis in most ICUs, suggests that the dosing of antibiotics, which in most instances cannot be routinely monitored, was at least as inefficiently adapted as phosphate, leading to under-dosing of these important drugs. Interestingly, hypophosphatemia alone has recently been shown to be associated with increased duration of mechanical ventilation (MV) [15], weaning failure from MV [16] and a higher all-cause in-hospital mortality as well as long-term mortality [17]. Our theory is further supported by a recent manuscript form Kron et al. which found an improved outcome of extended daily online HDF in septic individuals with AKI. In this study, the authors allude to the fact that antibiotics have either been monitored via blood levels whenever possible or have been given strictly after dialysis and in doses higher than those regularly used in stable non-AKI patients [18].

Taking these thoughts together, it is probably not the dialysis dose that makes the poison but rather the lack of dose adjustments of antibiotics (and micro-/nutritional support) that adversely affects the outcome of our patients. This hypothesis highlights the urgent need to adjust our old antibiotic dosing schemes to the high efficiency of modern RRTs in the ICU. Observed hypophosphatemia could be useful as a warning sign that should prompt re-evaluation of drug doses. Numerous pieces of a complex treatment puzzle require excellent synchronization in order to prove or to rebut if a thing such as a ‘renal replacement trauma’ really exists. Drug dosing recommendations from the vinyl age have no place in the iPhone era of RRT.

As in the treatment of diabetic patients, we have to understand that RRT needs to be a multimodal therapy that comprises much more than removing various toxins. To guide this multimodal therapy, we need new tools for tailoring anti-infective treatment and nutritional support in order to minimize the renal replacement trauma.

CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

ICU patients, however, is not without risk. Therefore, nephrologists familiar with the spectrum of effects and potential side-effects of dialysis in an ICU environment have introduced the terms dialy- and CRRT-trauma.

‘CRRT-trauma control’ basically intends to promote and optimise the safe use of CRRT in haemodynamically unstable critically ill patients at risk for or suffering AKI. The major aim is to protect the kidney from further injury, including any collateral damage caused by the renal epuration technique itself.

Preventing or limiting CRRT-trauma definitely requires better understanding of pathophysiology, definition of groups at risk, timely identification and finally adequate anticipation and/or correction of unwarranted effects. Examples of ‘CRRT trauma control’ are raising knowledge of antimicrobial PK/PD behaviour during CRRT resulting in more efficient antimicrobial therapy at less toxicity, a better understanding of mediator handling by CRRT in sepsis and its relation to survival and the potential benefit of using citrate as an anticoagulant.

The Paracelsus statement ‘dosis sola facit venenum’ (only the dose determines the poison) underscores that every substance may become poisonous when a certain dose is exceeded [1]. Volume overload represents such ‘poison’ in ICU patients [2] and intermittent haemodialysis (IHD) and CRRT have been introduced as ‘antidotes’ [3]. However, both techniques may cause unexpected harm, captured as ‘dialy-/ CRRT-trauma’ [4]. For instance, haemodynamically unstable patients with acute kidney injury (AKI) who underwent IHD had a 50% increased risk to remain dialysis dependent! [3]

Adequate antimicrobial therapy is largely determined by PK/PD variables [5,6]. Antimicrobial dosing is well standardized in AKI treated by IHD. Applying similar dose recommendations for CRRT, however, may expose patients to underdosing [5,6]. Here, the pioneering work of various PK/PD investigator teams [5,6] resulted in appropriate CRRT dosing guidelines at the bedside [5,6]. Kielstein et al. [2] consider hypophosphataemia as a warning sign, prompting re-evaluation of drug doses. However, hypophosphataemia during CRRT has a variable incidence [7], uncertain clinical effects [7] and is easily corrected [7]. Hypophosphataemia also never emerged as a surrogate marker of antimicrobial underdosing in CRRT but rather acts as an indicator of ICU care quality [8]. Kielstein et al. [2] argue that CRRT increases the risk for antimicrobial underdosing. On the contrary, CRRT allows safe administration of higher antimicrobial doses without increasing toxicity [6]. The loading dose of amikacin (up to 30–35 mg/kg) and the maintenance dose of polymyxin B were substantially increased [5]. Also, CRRT completely blunt the nephrotoxic effect caused by accumulation of the β-cyclodextrin solvent during voriconazole treatment [6]. Finally, the increasing role of ICU nephrologists in coordinating CRRT policy, including antimicrobial prescriptions, must be stressed. This challenges Dr Kielstein’s concerns of CRRT being performed without keeping pace with updated knowledge [2].

Kielstein et al. [2] suggest that the lack of survival difference between high and low CRRT dose might be explained by the inclusion of more septic patients. We respectfully disagree. Regardless of the presence of sepsis, more small-sized molecules, including antibiotics, are removed by higher dosed CRRT [9]. Higher CRRT doses are associated with better outcome [10]. More rapid protein precipitation and concomitant decrease in cytokine removal may then cause a more pronounced decline in biological and eventually survival benefit. Meta-analyses comparing high and low doses show that doubling the dose does not simply result in a similar mathematical increase in mediator removal, in particular with heparin anticoagulation [9]. By significantly reducing membrane clogging during high-dose CRRT, citrate has emerged as an attractive alternative to heparin for the removal of middle- and large-sized molecules [10]. Different haemodynamic and outcome results are conceivable when previous large trials [3] would be repeated using citrate [10].

In conclusion, the concept of dialytrauma honours the principle ‘nil nocere’ and provides clinicians with adequate tools for bedside identification, prevention and treatment [4]. CRRT protocols within ICUs, including technical and therapeutic (e.g. antimicrobial dose adaptation) aspects, are increasingly controlled by dedicated nephrologists. The inverse relationship between CRRT dose and survival probably does not result from a higher incidence of sepsis but from insufficient clearance of inflammatory mediators [9]. Citrate may reverse this dose/survival relationship [10]. Finally, CRRT is no hindrance for achieving adequate levels of antimicrobials [6].

Undoubtedly, Paracelsus would be very pleased to see his paradigm revisited and translated into a dedicated quality program guaranteeing both safety and a better outcome.

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REFERENCES

In this issue of NDT’s Polar Views section, the concept of ‘dialy-trauma’ is discussed by two groups of experts in the field. Let me first briefly summarize the subject of the discussion. Acute kidney injury (AKI) in critically ill patients, who are often admitted to the intensive care unit, is a challenging condition for the nephrologist and intensivist. Especially in the presence of sepsis, the incidence of AKI is high, even up to 50%. When renal replacement therapy is necessary, basically two options exist, i.e. continuous (CRRT) and intermittent (IRRT) renal replacement therapies. Neither of the two options is clearly superior to the other, except, perhaps, for the haemodynamically unstable patients, for whom CRRT is generally recommended. The second most frequently debated issue is the dosing of CRRT. A wide range of doses have been proposed ranging from alternate day dialysis to (semi-)continuous high-volume haemofiltration. However, also on this issue controversy still reigns.

After the initial introduction of the concept of dialytrauma or CRRT trauma by Maymar Moliner et al. [1], it was further defined elsewhere [2]. The main characteristic of this condition is that by applying CRRT, the non-selective transport of fluid and substances not only removes toxins from the patients, but also induces loss of heat, electrolytes, nutrients, vitamins, trace elements, useful inflammatory mediators and medications, especially antibiotics. It is likely that these losses occur particularly in high-volume treatment regimens. It is difficult to establish the precise individual relevance of these unwanted removals in determining the outcome, but this again underlines that haemofiltration techniques offer only a poor copy of normal human kidney function. Indeed, Honore et al. produced a list of suggestions to reduce the risk of ‘adverse events’ of CRRT [2]. In line with this, is their call for studies on the effects of these preventive measures. However, most colleagues will likely feel that it will be difficult to prove, in patients in whom the outcome is determined by a complex of many different things, that implementing such a systematic programme of preventive measures will affect the outcome.

Kielstein and David also present a list of potential contributors to the CRRT trauma, but they put much emphasis on the risk of inadequate dosing of antibiotics as a result of increased removal during CRRT. They correctly stress that very little is known about how to dose antibiotics when using modern high-flux membranes and high filtration volumes [3]. As with the suggestions of Honore et al., we have to realize that it is most likely difficult to prove that clinical outcome is superior in CRRT patients receiving ‘adequately’ dosed antibiotics versus patients inadequately dosed. Further, they propose that hypophosphataemia could be used as an overall indicator of insufficient attention for the need of supplementation of certain compounds.

Putting this whole discussion together, one may conclude the following. The overall aim of RRT in AKI is to gain time for the spontaneous return of (enough) kidney function so that RRT can be stopped again. The fact that it is so difficult to prove superiority of one therapy over the other may be interpreted not only as a lack of difference between the

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