Extended daily on-line high-volume haemodiafiltration in septic multiple organ failure: a well-tolerated and feasible procedure

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Abstract

Background. The outcome of patients with septic multiple organ failure (MOF) remains poor. There are experimental and clinical data indicating a beneficial effect of high-volume haemofiltration. Delivering high-volume therapy is only cost effective using on-line devices because of high costs for additional solution bags in conventional continuous renal replacement therapy (CRRT). We investigated feasibility and effectiveness of extended daily on-line high-volume haemodiafiltration (HDF) with technically maximum convective volume in patients with septic MOF in a pilot study.

Methods. We included 21 consecutively ill patients with septic MOF having a mortality risk >50% (SAPS II >50, APACHE II >25). Renal replacement therapy (RRT) was applied with extended daily HDF for 6–23 h using the AK 200 Ultra S dialysis machine in the ultra-control pre-dilution mode. Dialysate and substitution fluid were prepared on-line. Patients underwent 289 treatments.

Results. The mean convective volume was 17.8 ± 3.7 L/h and 208 ± 66 mL/kg/h, respectively, median treatment time was 10:15 h/day. Seventeen of 21 patients survived 28 days (81%). The 90-day survival rate was 52% (11/21) versus 19% compared to the survival rate predicted by APACHE II (33.6 mean) and SAPS II (68.6 mean) scores. Haemodynamics improved significantly during the treatment procedures. Material costs per treatment amounted to 35 €.

Conclusions. Extended daily on-line HDF using maximum convective volume seems to improve the outcome of septic MOF, especially in the early phase. The investigated mode of treatment proved to be feasible, well tolerated and highly cost effective compared to conventional CRRT. At present, this procedure would be applicable at every ICU facility with nephrological support.

Keywords: extended daily haemodiafiltration; high-volume haemodiafiltration; pre-dilution; septic multiple organ failure

Introduction

Despite substantial medical progress, acute kidney injury (AKI) in patients with septic multiple organ failure (MOF) is associated with a high mortality rate. According to the largest prospective study on this topic (BEST Kidney), >70% of patients die [1].

The role of renal replacement therapy (RRT) techniques in the management of sepsis remains controversial [2]. There are clinical and experimental data suggesting additional beneficial effects of RRT in this setting by removing inflammatory mediators [3]. Grootendorst et al. [4] showed that the infusion of ultrafiltrate from endotoxic shock pigs into healthy pigs alters haemodynamic stability. Hence, this work produced evidence of inflammatory mediators being filtratable. Further research of this study group demonstrated that high-volume haemofiltration (HV-HF) improves haemodynamics of septic pigs [5].

Ronco et al. [6] investigated the effect of increasing doses of ultrafiltration on survival among patients with oliguric AKI in a randomized controlled study. Patients in the sepsis subgroup with the highest ultrafiltration dose of 45 mL/kg/h survived by 47 versus 18% with 35 mL/kg/h. Because of the small number of cases, this difference was not statistically significant. Further studies showed that application of so-called ‘very high-volume’ (VHV) HF [3] with >50 mL/kg/h in septic MOF was associated with a reduction in vasopressor requirements and mortality rates [7–11].

On the other hand, in a meta-analysis of eight trials, application of higher treatment doses up to 48 mL/kg/h did not prove to reduce mortality rates [12], nor did intensified extended daily dialysis in critically ill patients [13]. But in conventional RRT, clearance of middle-molecule inflammatory mediators remains insufficient [14]. In a recent experimental study [15] using continuous renal replacement therapy (CRRT) prescription of the ATN [16] and RENAL study [17], the clearance of middle-molecular-weight solutes (12 KD) was limited to 5–10 mL/min. Middle molecule clearance differed by <2 mL/min between the...
doses of 20 and 35 mL/kg/h. An adequate adjunctive sepsis therapy seems to require considerably higher doses. Data of a controlled prospective randomized trial in septic patients are lacking up until now. The IVOIRE study [18], comparing treatment doses of 35 and 70 mL/kg/h, was completed in October 2010, and included 139 patients instead of 460 as planned and thereby failed to be sufficiently powered. Because of increasing costs for additional solution bags, high-volume therapies have so far only been applied in the setting of experimental and small clinical studies [7–11, 18, 19]. Using the procedure in daily routine would cause an unacceptable financial burden for medical facilities given the increasing sepsis incidence.

At present, on-line substitution fluid preparation is a standard feature of modern dialysis devices for chronic treatments. It might as well offer a cost-effective option concerning high-volume CRRT. Moreover, on-line high-volume HDF has proved to remove middle-molecule solutes most effectively among currently available treatment modes. Under certain technical conditions, Pedrini et al. [20] reached beta-2-microglobulin clearances as high as 207 mL/min.

Applying conventional on-line haemodialysis devices in the ICU setting would favourably combine both maximum effectiveness concerning middle molecule elimination and minimum costs.

In our study, we therefore tested the feasibility of conventional on-line haemodialysis devices being used for RRT in patients with AKI and septic MOF. Treatments were delivered as a hybrid procedure of extended daily HDF.

**Materials and methods**

**Patients**

We conducted a prospective observational study between July 2007 and December 2009 in the interdisciplinary ICU of the DRK Kliniken Berlin-Köpenick, Germany, since 2007, all patients with severe septic MOF, with an AKI after out-of-hospital cardiac arrest and severe pancreatitis have been treated with extended daily on-line high-volume haemodiafiltration (HDF). We enrolled 21 consecutive patients with severe septic MOF, requiring RRT (Figure 1). Criteria for inclusion were results of the Acute Physiology and Chronic Health Evaluation (APACHE II) score and of the Simplified Acute Physiology Score (SAPS II) >25 and 50, respectively, thus comprising a mortality risk of >50%. Exclusion criteria were ICU treatment for >6 days until start of the RRT, end-stage renal or liver failure, dying patients without prognosis at time of admission on ICU.

Anuric or oliguric AKI was present in all patients, according to the RIFLE classification in the level of ‘failure’. All patients required mechanical ventilation, vasopressor support and showed a C-reactive protein value >24 mg/dL. Baseline characteristics are shown in Table 1.

All patients received a nutritional intake of 25–30 kcal/kg/day. The protein intake was 1.2–1.5 g/kg/day. vitamin B1 (100 mg) and 500 mg vitamin C were supplemented per day. Individual intravenous phosphate substitution based on daily serum phosphates measurements. Twelve patients received hydrocortisone (3 x 100 mg/d), 3 patients selenium (1000 µg/d) and 1 patient activated protein C.

**Renal replacement procedure**

RRT was performed as extended daily high-volume HDF with an operation time of a minimum of 6 h and maximum 23 h/day. The length of the treatment sessions was determined according to the patients’ clinical condition and procedural schedule i.e. diagnostic imaging and surgery. The dialysis system used in this study was the AK 200 ULTRA S (Gambro, Lund, Sweden) providing 700 mL/min on-line ultrapure dialysis fluid and sterile, non-pyrogenic substitution fluid. To improve haemodynamic stability, the temperature of dialysis and substitution fluid was adjusted to 35.5–36°C. The sodium concentration was 140 mmol/L, potassium, calcium and bicarbonate individually adjusted according to serum levels of the patients. Water was processed for dialysis on the principle of reverse osmosis with the water treatment system WRO 300 (Gambro) mounted onto the dialysis system. Vascular access was obtained with an 11 F dual lumen catheter inserted in the internal jugular or femoral vein. Blood flow rate was kept at 200 mL/min. HDF was performed with the high-flux membrane Polyflux 210 H dialyser (Gambro Dialysatoren, Hechingen, Germany) with a surface area of 2.1 m² and an ultrafiltration coefficient of 95 mL/h/mmHg.

Replacement fluid was delivered in a pre-dilution mode using the ultracontrol technique. The ultracontrol mode is an automated pressure control. Hereby, filtration volume is not prescribed as in conventional volume control in HF or HDF. The dose always meets the maximum, technically possible under the prevailing conditions in the patient’s blood and the filter. The volume is automatically adjusted according to the current transmembrane pressure (TMP). At the beginning of the treatment, the TMP is gradually increased with simultaneous measurements >30 s of the resulting increase in filtration rate every 25 mmHg. If ultrafiltration rate rises to 10 mL/min, TMP increases again by 25 mmHg.

When there is no further increase in filtration, the system works with this TMP at maximum effectiveness under the particular prevailing conditions at that particular time. The TMP thus ascertainment is maintained during further treatment. Every hour, an update of this scan is performed, providing a maximum fluid transfer according to the particular prevailing conditions. Filtration rate was limited at maximum 500 mL/min and TMP at maximum 450 mmHg, respectively.

The substitution fluid is taken from the dialysis fluid and thus reduced the dialysis fluid flow rate.

Anticoagulation was maintained by continuous infusion of unfractionated heparin at a patient-adjusted dose (mean 806 IU/h). Regional citrate anticoagulation was applied in 32 treatment sessions (11%) of patients at risk for bleeding complications. High-volume HDF was terminated in the case of clinical improvement and resolution of the septic state, as determined by the treating physicians. Further RRT was delivered with daily haemodialysis treatments for 4–6 h until renal function recovered.

**Statistics**

All statistical analyses were performed with SPSS statistics 18 (SPSS Inc., Chicago, IL). The data concerning norepinephrine dose, haemodynamic

![Fig. 1. Number of patients enrolled and included in the analysis. Inclusion criterion: Mortality risk of more than 50% (APACHE II > 25, SAPS II > 50).

<table>
<thead>
<tr>
<th>Patients with AKI and RRT</th>
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<tbody>
<tr>
<td>on-line high-volume HDF</td>
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</tr>
<tr>
<td>n = 19</td>
<td>dead (54 %)</td>
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<tr>
<td>conventional RRT</td>
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<tr>
<td>n = 55</td>
<td>dead (43 %)</td>
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<tr>
<td>severe septic MOF</td>
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<tr>
<td>n = 12</td>
<td>dead (48 %)</td>
</tr>
<tr>
<td>other indications</td>
<td>n = 10</td>
</tr>
<tr>
<td>n = 4</td>
<td>dead</td>
</tr>
<tr>
<td>AKI after out-of-hospital cardiac arrest</td>
<td></td>
</tr>
<tr>
<td>severe pancreatitis</td>
<td>n = 5</td>
</tr>
<tr>
<td>n = 4</td>
<td>dead</td>
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<table>
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</tr>
</thead>
<tbody>
<tr>
<td>n = 10</td>
<td>dead (48 %)</td>
</tr>
</tbody>
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<table>
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</thead>
<tbody>
<tr>
<td>n = 4</td>
<td>dead</td>
</tr>
<tr>
<td>1 dead after 30 min. HDF</td>
<td></td>
</tr>
<tr>
<td>3 treated with SAPS II &gt; 25 and RIFLE II &gt; 50</td>
<td></td>
</tr>
</tbody>
</table>

| 1 dead after 30 min. HDF   |
| 3 treated with SAPS II > 25 and RIFLE II > 50 |

**Table 1.** Baseline characteristics.
parameters, core temperature and ventilation were tested nonparametrically with the Wilcoxon-test for related samples. Data are presented as appropriate.

### Results

In 21 of the patients enrolled, 289 high-volume HDF treatments were performed daily. The median number of high-volume treatments was 10 (2–49) per patient. Median duration of treatment was 10.25 h. The median convective volume (filtrated and substituted volume) was 173 L/treatment with a mean exchange rate of 17.8 ± 3.7 L/h and 208 ± 66 mL/kg/h, respectively. Maximum convective volume amounted to 439 L/day and 26.6 L/h. Treatment characteristics are shown in Table 2.

In six patients, clotting was observed in 15 treatments. Seventeen of 21 patients (81%) survived through day 28 (Figure 2). The 90-day survival rate was 52% (11/21) compared to a survival rate of 19% predicted by APACHE II and SAPS II scores. Three patients died after the resolution of their septic state and after recovering their renal function. All survivors recovered renal function. The median serum creatinine at discharge was 97 μmol/L (53–299). A significant increase in the mean arterial pressure from 85.9 ± 8.3 to 90.9 ± 12.9 mmHg occurred during the treatment sessions (P < 0.001) even though the norepinephrine infusion could be reduced at the same time in 41% of all treatments. Profiles of blood pressure and norepinephrine doses are shown in Figure 3.

Heart rate, core temperature, PEEP, FiO₂ and ultrafiltration volume during the first four HV-HDF sessions are presented in Table 3.

In 14 patients, a hypophosphataemia (<0.8 mmol/L) occurred despite phosphate supplementation.

Material costs per treatment amounted to 35 € being comparable to the costs for a haemodialysis session in a chronic patient except for a slightly higher consumption of dialysis concentrates.

### Discussion

The third international consensus conference of the Acute Dialysis Quality Initiative (ADQI) agreed that there is currently a clear biological rationale for extracorporeal blood purification treatment (EBT) in sepsis. Patients with AKI and sepsis should be treated differently from those with AKI alone. Patients with refractory septic shock may benefit from high-volume plasma water exchange. According to the ADQI workgroup, future research should aim to develop safer, technically simpler, more efficient and more efficacious techniques of EBT that might increase the ease of clinical operation, ensure wider applicability and offer a greater chance of achieving clinical effectiveness [21]. Our study meets all these approaches. We used dialysis devices and equipment already existing in daily routine of dialysis facilities and having proved to be easy and safe to handle.

Hence, at present, a routine application of the on-line HDF procedure is restricted to medical facilities working with a trained nephrological team. But, on the other hand, this fact might offer the chance of more intense and active nephrological participation in interdisciplinary care of critically ill patients.

We decided to apply intermittent extended daily procedures, which turned out to be highly flexible and well adapted to patients’ requirements. Especially during the first days of treatment, we performed extended sessions meeting the standard of continuous treatments [22].

On the other hand, we were free to reduce treatment time if necessary for diagnostic and therapeutic procedures. As demonstrated in other HV-applications, haemodynamics improved during the treatment and vasopressor demand decreased. Our data show that the extended intermittent daily procedures was as suitable as CRRT at maintaining
haemodynamic stability. The low temperature of the dialysis and substitution fluid contributed to stability as well (Maggiore effect) [23]. High-volume therapy allows an excellent control of the blood and body temperature (Table 3).

A comparable 28-day survival rate to the one here described has not previously been reported.

In the BEST Kidney study [1], with conventional RRT, two-third of septic patients died within 28 days.

Compared to previously published studies, applying a very high-exchange volume of >50 mL/kg/h, we had much better survival rates (Table 4).

At present, there are four studies dealing with VHV HF in severe septic MOF [7, 9–11], suggesting a favourable outcome, as does a further study by Oudemans-van Straaten, although their patients only partly met the criteria of septic shock [19].

In previous studies, RRT was delivered as haemofiltration only. In contrast, we applied HV therapy as HDF using a very high mean dialysate flow of 400 mL/min. Moreover, we used a convective dose well above the one being applied in previous studies. A plasma water exchange volume of 208 mL/kg/h has not been described up until now. Laurant et al. [24] achieved the highest ultrafiltration rates of 12.5 L/h (up to 200 mL/kg/h in patients weighing up to 60 kg) for a duration of 8 h in patients following out-of-hospital cardiac arrest. In their randomized controlled trial, they found an increased 6-month survival in the HF group compared to conventionally treated patients. They used the same dialysis system and dialysers as we did in our study.

We included solely patients with a mortality risk of >50%, thus comprising the highest patient mortality risk among all previous studies and creating a cohort of absolutely ‘poor chance’. Hence, as a result of the severity of

Fig. 2. Survival rates (Kaplan–Meier) after initiation of on-line high-volume HDF.

Fig. 3. Mean arterial pressure (MAP) and norepinephrine (NE) doses during the first 4 on-line high-volume HDF sessions.
their organ failure, even surviving patients required RRT for nearly 4 weeks and ICU treatment for >9 weeks.

In contrast to previous studies, there was no time limitation concerning duration of HV therapy with our approach. HV-HDF was continued until full control of septic state or death occurred. This issue represents a substantial difference from other studies owing to either time limitations of HV therapy or restricting HV-HF to the very early phase of sepsis [7, 9–11, 19], up to 4 days maximum. In a randomized study, Morgera et al. [25] investigated the effectiveness of continuous venovenous haemofiltration (CVVHF) in septic MOF using a high cut-off membrane but with that membrane being employed for only 48 h. Despite an increased clearance of IL-6 and IL-1α and a reduced vasopressor demand during treatment sessions, they found no difference in the 28-day mortality between the high cut-off group and a group treated with conventional membranes (60 versus 61%). In the study of Joannes-Boyau [9], HV-HF was limited to 96 h as is the treatment duration in the currently ongoing multicentre randomized IVOIRE study conducted by the same author [18]. Controlling the septic state within 4 days was an outstanding exception in our study and occurred in only one patient, where the septic focus (infected port system) could be immediately removed surgically. Our surviving patients required HV-HDF for the duration of 9-day median and 21-day maximum, respectively.

When the septic focus was not removable, HV-HDF seemed to stabilize the patients’ condition for quite a long time. In our study, most patients died within the 5th to 7th week of treatment (Figure 3). They suffered from septic peritonitis which failed to improve sufficiently with surgical treatment. In settings like these, the adjunctive therapeutic effect of HV-HDF appears to be limited. On the other hand, the treatment procedure seems perfectly capable of providing a window for surgical therapy in the early phase of sepsis.

Applying regimens for the most effective blood purification may contain risks as well, that should be taken into consideration such as removing anti-inflammatory mediators, electrolytes, nutrients and especially antibiotics. Despite substitution, about two-thirds of our patients developed hypophosphataemia at some time, mostly after the first session. In both arms of the RENAL trial, 65 and 54 % of the patients developed a hypophosphataemia [17]. In the ATN study, this was observed in 17.6 and 10.9 %, respectively [16], as well. With a daily high-dose RRT, phosphate substitution is absolutely necessary. Especially in septic MOF, there is a substantial and life-threatening risk of under-dosing antibiotics [26]. In former studies of extended daily treatments with high-flux membranes, antibiotics had to be given up to twice the recommended dose [26–29]. In the ATN study, septic patients in the high-intensity group tended to have a higher mortality [16]. In a randomized French study, patients with sepsis but without AKI being additionally treated with CVVHF for 96 h showed a more severe courses of disease [30]. The dilemma of under-dosing antibiotics, eliminated by RRT, could explain why especially septic patients in whom therapeutic levels of antibiotics are of vital importance tended to have an even higher mortality with intensive renal

| Table 3. Heart rate, core temperature, PEEP and FiO2 start (pre) and end (post) ultrafiltration of the first four HV-HDF sessions |
|-------------|-------------|-------------|-------------|-------------|-------------|
| Heart rate (min⁻¹) | Temperature (°C) | PEEP (mmHg) | FiO2 | Net ultrafiltration |
| Mean (95% CI) | P | Mean (95% CI) | P | Mean (95% CI) | P |
| Without net UF | With net UF | Without net UF | With net UF |
| Session no.1 | Pre | 111.7 (100.6–122.8) | 0.004 | 37.2 (35.1–39.3) | 0.001 | 37.7 (36.2–39.2) | 0.001 | 0.34 |
| Post | 100.4 (90.7–110.1) | 36.7 (36.3–37.1) | 11.9 (10.7–12.9) | 0.58 (0.49–0.66) |
| Session no.2 | Pre | 91.5 (83.6–99.4) | 0.334 | 36.5 (35.6–37.4) | 0.015 | 12.2 (11.1–13.3) | 1.0 |
| Post | 91.3 (80.2–102.4) | 36.9 (36.5–37.4) | 12.1 (11.1–13.3) | 0.53 (0.44–0.64) |
| Session no.3 | Pre | 92.1 (82.5–101.8) | 0.003 | 37.4 (36.5–38.2) | 0.005 | 12.3 (11.2–13.3) | 1.0 |
| Post | 91.5 (79.2–101.8) | 36.8 (36.4–37.2) | 12.3 (11.2–13.3) | 0.52 (0.44–0.60) |
| Session no.4 | Pre | 86.3 (75.1–97.4) | 0.587 | 37.1 (36.9–37.7) | 0.116 | 7 (6–8.5) | 1.0 |
| Post | 89.9 (77.2–102.7) | 37.1 (36.7–37.5) | 8.5 (7.5–9.5) | 1.0 |

For net ultrafiltration (net UF) percentage of sessions without net UF is shown. For the remaining sessions with net UF medium (range), net UF is given. *P for comparison of sessions 1–4 pre versus session no. 1 pre.
support [28]. Therefore, optimizing antibiotic therapy should be a priority in the management of critically septic patients [31]. Therefore, we intended to avoid inadequate antibiotic therapy. Generally, antibiotics were administered after treatment sessions as a rule. During HV-HDF treatments, antibiotic doses were increased to a level above the one prescribed for normal renal function. Antibiotic dosing according to blood levels obtained during the treatment did work in individual cases only. Pharmacokinetic research is necessary in this setting.

**Limitations of the study**

The usual limitations of single-centre studies are definitely present in our survey like an enthusiastic and sometimes over-motivated working team. Other treatments the patients were on may have been under an outstanding supervision.

The surgery team of our facility did tend to offer far more active therapeutic strategies, performing an increased number of second look operations and i.e. daily abdominal lavage procedures.

Secondly, in our study there was no control group. Mortality rates were only compared to predicted mortality rates.

Thirdly, the number of patients included was considerably small.

Fourthly, in random investigations we obtained a reduction rate of beta-2-microglobulin over 40% during the first hour of treatment. But we did not perform a systematic analysis concerning changes in cytokines and other middle molecules.

And fifthly, the exclusion criteria might have influenced the high survival rates.

In our study, HV-HDF was initiated early in the course of disease, 75% of patients were treated on the first day on the ICU, 86% within the first 2 days.

We excluded patients having been treated on the ICU for >6 days. According to the BEST kidney data, late initiation of RRT almost doubled the risk of mortality compared to starting RRT within the first 2 days [32]. We consider adjunctive sepsis therapy being most useful in the early phase of MOF.

But all these limitations certainly apply to every other VHV study as well.

**Costs**

Although showing favourable outcome data in all studies, VHV procedures in septic MOF have not been established in routine sepsis therapy, mostly due to high costs. Joannes-Boyau [8] calculated them to be a total of 400 €/day (excluding nurse, medical doctors and the haemofiltration machine). Using material and equipment already available in dialysis facilities could solve this problem. Performing an HV-HDF with an exchange volume of 400 L daily would still be more cost effective than performing a conventional CRRT at a substitution dose of 1 L/h with solution bags.

The on-line solute preparation offers favourable possibilities of conducting cost-effective randomized controlled multicentre trials to answer the important question of optimal dosage of RRT in septic MOF [33].

In conclusion, using HV-HDF with maximum doses and the longest duration of therapy reported to date, we achieved the best survival rates in the early phase of septic MOF. The intermittent application of the procedure was well tolerated and maintained haemodynamic stability. It seems that on-line HV-HDF is more effective in the treatment of septic patients with MOF compared to other CRRT techniques. On-line HV-HDF combining maximum convective and diffusive volumes offers new promising perspectives on sepsis therapy. Because of its low costs, the procedure would be easily applicable at every ICU facility with nephrological support at present already.

**Conflict of interest statement.** T.S. has received speaker fees and grant support from Gambro, Germany. All other authors have nothing to declare.

**References**


**Table 4.** Comparison of on-line HDF with published VHV-HF studies (UF > 50 mL/kg/h)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Number of patients</th>
<th>UF rate (mL/kg/h)</th>
<th>Duration</th>
<th>SOFA</th>
<th>SAPS</th>
<th>APACHE II</th>
<th>28-day mortality (%)</th>
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<td>Joannes-Boyau et al.</td>
<td>9</td>
<td>60</td>
<td>96 h</td>
<td>10.2</td>
<td>-</td>
<td>-</td>
<td>46</td>
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<tr>
<td>Honore et al. [7]</td>
<td>7</td>
<td>116</td>
<td>1 × 4 h</td>
<td>67.5</td>
<td>31</td>
<td>55</td>
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<tr>
<td>Ratanarat et al. [10]</td>
<td>15</td>
<td>85</td>
<td>6 h × 3.4 days (+18 h CVVH/day)</td>
<td>55</td>
<td>31.2</td>
<td>47</td>
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<tr>
<td>Cornejo et al. [11]</td>
<td>20</td>
<td>100</td>
<td>1 × 12 h (9 Pat. 2–3 days12 h)</td>
<td>13.3</td>
<td>-</td>
<td>26.1</td>
<td>40</td>
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<tr>
<td>This study</td>
<td>21</td>
<td>208</td>
<td>10.25 h × 10 days</td>
<td>15.1</td>
<td>68.4</td>
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