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Patients with Severe Lactic Acidosis in the Intensive Care Unit: A Retrospective Study of Contributing Factors and Impact of Renal Replacement Therapy

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Keywords

Severe lactic acidosis · Intensive care units · Contributing factors of renal replacement therapy · Outcome

Abstract

Introduction: Hyperlactatemia is a regular condition in the intensive care unit, which is often associated with adverse outcomes. Control of the triggering condition is the most effective treatment of hyperlactatemia, but since this is mostly not readily possible, extracorporeal renal replacement therapy (RRT) is often tried as a last resort. The present study aims to evaluate the factors that may contribute to the decision whether to start RRT or not and the potential impact of the start of RRT on the outcome in patients with severe lactic acidosis (SLA) (lactate ≥5 mmol/L). ***Materials and Methods:*** We conducted a retrospective single-center cohort analysis over a 3-year period including all patients with a lactate level ≥5 mmol/L. Patients were considered as treated with RRT because of SLA if RRT was started within 24 h after reaching a lactate level ≥5 mmol/L. ***Results:*** Overall, 90-day mortality in patients with SLA was 34.5%. Of the 1,203 patients who matched inclusion/exclusion criteria, 11% (*n* = 133) were dialyzed within 24 h. The propensity to receive RRT was related to the lactate level and to the SOFA renal and cardio score. The most frequently used modality was continuous RRT. Patients who were started on RRT versus those who did not have 2.3 higher odds of mortality, even after adjustment for the propensity to start RRT. ***Conclusions:*** Our analysis confirms the high mortality rate of patients with SLA. It adds that odds for mortality is even higher in patients who were started on RRT versus not. We suggest keeping an open mind to the factors that may influence the decision to start dialysis and bear in mind that without being a bridge to correction of the underlying condition, dialysis is unlikely to affect the outcome.

Introduction

Hyperlactatemia is a regular condition in the intensive care unit (ICU) which is associated with adverse outcomes [1–4]. It occurs when lactate production exceeds lactate clearance in the body and is defined as a serum lactate concentration >2 mmol/L [5]. Historically, based on the classification of Cohen and Woods, hyperlactatemia in critically ill patients was considered to represent

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tissue hypoxia, hypoperfusion, or both [6]. Yet, increasing evidence indicates that stress hyperlactatemia is actually due to increased aerobic lactate production, with or without decreased lactate clearance [7]. Although there is no doubt that increased lactate is a robust predictor of mortality in patients admitted to ICUs, the question remains whether it originates from a protective or a maladaptive response. It has been demonstrated that lactate provides necessary substrate for gluconeogenesis in severe illness and several cells, including skeletal muscle cells, cardiac myocytes, hepatocytes, and neurons, and rely on it in this setting [8]. Indeed, the brain and heart depend on lactate to fulfill energy needs in case of increased metabolic demand [9]. As a different clinical entity, hyperlactatemia can lead to lactic acidosis. This is a pathological process that increases the concentration of hydrogen ions and reduces HCO_3^- concentration in the body, which can lead to an acidemia, defined as a blood lactate level >5 mmol/L and pH <7.35. Severe acidemia has deleterious effects: it causes a decrease in myocardial contractility, can sensitize the myocardium to cardiac arrhythmias, and can attenuate the cardiovascular responsiveness to catecholamines [10]. However, when pyruvate is metabolized to lactate, as it typically occurs in the setting of sepsis, a hydrogen ion is consumed, retarding acidosis [11]. Additionally, bicarbonate infusion has not proven to be of any measurable benefit in correcting hemodynamic depression in patients with acidemia on vasoactive drugs. Moreover, it could cause potential harm by decreasing cardiac function, systemic vascular resistance, ionized calcium, oxygen tension, and intracellular pH [12–15]. In resting conditions, a considerable physiological reserve in lactate metabolization via the liver and kidney exists as daily lactate production is estimated to be 20 mmol/kg per day, while clearance of infused sodium L-lactate is between 800 and 1,800 mL/min [16, 17]. Human kidney tubules consume lactate to contribute to gluconeogenesis. Renal excretion accounts for <1–2% in resting conditions but increases in the setting of hyperlactatemia, especially in acidemia [18].

The only effective treatment of hyperlactatemia is to control the triggering condition, but in the literature and clinical practice, additionally renal replacement therapies are attempted to manage this condition. This idea is based on the knowledge that lactate has a molecular weight of 90 Da, only minimally larger than urea (60 Da) and, as such, is easily removed by renal replacement therapy (RRT) [19]. Second, it is thought that RRT corrects the acid-base disturbances and thus would support the patient during the time needed to overcome the underlying condition. However, the actual contribution of RRT to the outcome of these critically ill patients remains largely unknown. There are no randomized controlled trials and in observational case series, the effect of RRT on outcome may be confounded by numerous factors like indication bias.

The present study aims to evaluate the factors that may contribute to the decision to start RRT and the potential impact of RRT on outcome in ICU patients with severe lactic acidosis (SLA) defined as a lactate concentration of ≥5 mmol/L. Ultimately, this should contribute to answering 2 questions: whether we should measure lactate in ICU patients and subsequently, whether one should put efforts in using extracorporeal techniques to augment lactate clearance.

Materials and Methods

Data Collection

We performed a retrospective single-center cohort analysis over a 3-year period (from October 2012 to December 2015) in patients admitted to the ICU who had SLA. In this cohort, our main objective was to compare outcomes of patients who received RRT to patients who did not. We included all ICU patients, age 18 years and older who had or developed lactic acidosis with lactate levels ≥5 mmol/L during their hospitalization on the ICU. We excluded patients who received dialysis before reaching this lactate threshold and patients on maintenance dialysis. We also excluded patients with any "Do Not Resuscitate" level > 0, since this could have influenced the decision to start RRT irrespective of their lactic acidosis. Both hemofiltration (HF) and hemodialysis (HD) modalities were used, either as continuous or as intermittent modality according to the discretion of the treating physician. We categorized the modalities according to duration: intermittent HD (IHD), sustained low-efficiency daily diafiltration (SLEDD), and continuous RRT (CRRT), which includes continuous HD (CHD) and continuous veno-venous HF (CVVH). In our center, CHD (mean blood flow 200 mL/min, range 150–250 mL/min; mean dialysate flow 405 mL/min, range 350–500 mL/min) is the preferred modality in patients with SLA. We considered patients as treated with RRT if dialysis was started within 24 h after reaching lactate levels ≥5 mmol/L. If the patients received RRT >24 h after reaching this threshold, we assumed that SLA was not the primary indication to start RRT. Those patients were accordingly considered as nontreated with RRT. Demographic data, as well as data on comorbidities, were retrieved from the electronic hospital database, laboratory data from the laboratory database, and patient data from the electronic ICU and dialysis patient data management system (PDMS). Severity of illness was assessed on admission by the Acute Physiologic Assessment and Chronic Health Evaluation II (APACHE II) score (based on data recorded during the first 24 h of ICU admission) [20]. At thhe time of reaching the threshold level, severity of illness was assessed by parameters of organ dysfunction (SOFA score) [21]. Levels of lactate, bicarbonate, and pH were recorded at the timepoint of reaching the threshold.

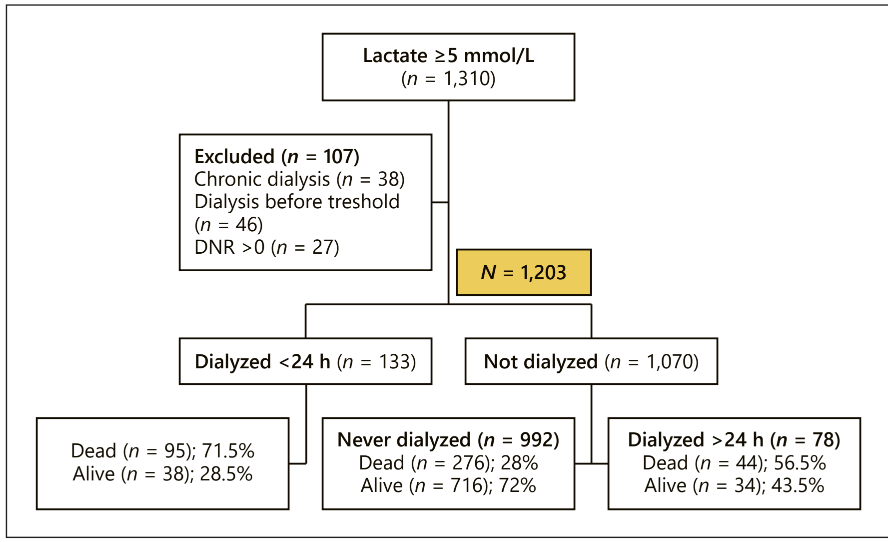

Fig. 1. Patient flowchart outcome.

Statistical Analysis

Data are presented as medians or percentages, as appropriate. Differences between patients with and without RRT were tested using the χ^2 statistic for discrete variables and the Wilcoxon rank-sum test for continuous variables, depending on the distribution. We used multiple logistic regression analysis to estimate the probability of receiving RRT and included this probability as a propensity score into a multiple logistic regression model with all-cause 90-day mortality as the outcome variable. All tests were 2-sided, and a p value <0.05 was considered significant.

Results

In the course of the 3-year study period, 1,310 patients reached a lactate level of ≥5 mmol/L during their stay in the ICU. We excluded 107 patients: 38 chronic dialysis patients, 46 patients who were already on RTT before reaching threshold, and 27 patients who had a do not resuscitate code > 0. The final study cohort therefore consisted of 1,203 patients. Of those, only 11% (n = 133) were dialyzed within the time window of 24 h. The most frequently used modality was CRRT (n = 100 of which CHD n = 98 and CVVH n = 2), followed by IHD (n = 22), and SLEDD (n = 11). Of the 1,070 patients considered as not receiving RRT, 992 were never dialyzed and 78 were dialyzed >24 h after reaching threshold (shown in Fig. 1).

Outcomes

The baseline characteristics according to outcome are presented in Table 1. We divided the patients according to outcome in 3 categories: death within 48 h (cat. 1), death between 48 h and 90 days (cat. 2), and 90 days survivors (cat. 3). The 90-day mortality of SLA (lactate ≥5 mmol/L) was 34.5%.

Patients who died were older and had a higher severity of illness as illustrated by the APACHE II score on ICU admission. In addition, patients who died versus those who survived in the first 48h had higher lactate levels, and total and individual component SOFA scores (except for SOFA CNS) and lower pH, and bicarbonate levels. The percentage of patients receiving dialysis was 29.2% in cat. 1, 18.4% in cat. 2, and 4.8% in cat. 3.

Predictors of Receiving Dialysis

In a multiple logistic regression model, factors that were independently associated with higher odds of receiving RRT were lactate levels, SOFA renal, and SOFA cardio but not age (shown in Table 2). We choose to include SOFA renal because this variable captures also other indications for dialysis than only increased lactate levels. SOFA cardio was included because it is assumed that acidosis contributes to an impaired response to vasopressors and therefore may favor the decision to start RRT.

Predictors of 90-Day Mortality

Variables associated with mortality at 90 days after reaching the lactate threshold were age, pH, and the total SOFA score. The lactate level itself at the moment of exceeding the threshold was also an independent predictor of mortality (shown in Table 3 Model A). In addition, patients who started RRT had 2.3 higher odds of mortality, even after including the predicted probability of receiving dialysis into the model (shown in Table 3 model B) to account for indication bias.

Table 1. Baseline characteristics of patients according to the outcome

Characteristic	Death <48 h (cat. 1) (*n* = 171; 14.2%)	Death ≥48 h (cat. 2) (*n* = 244; 20.3%)	Alive 90d (cat. 3) (*n* = 788; 65.5%)	*p* value
Demographic data				
Age, years	63.2	62.1	58.8	<0.001
Male, %	64.3	61.9	61.3	0.8
Diabetes, %	18.6	20.9	17.7	0.6
BMI, kg/m^2	26.2	26.0	26.1	0.8
Laboratory				
Lactate, mmol/L	7.6	6.8	6.0	<0.001
pH	7.27	7.31	7.35	<0.001
HCO_3^-, mmol/L	17.7	18.8	20.7	<0.001
Severity scores				
APACHE II	31	30	25	<0.001
SOFA total	12	10	8	<0.001
SOFA resp	3	3	2	<0.001
SOFA coag	1	1	0	<0.001
SOFA liver	1	1	0	<0.001
SOFA cardio	4	4	4	<0.001
SOFA CNS	4	4	4	0.38
SOFA renal	1	1	0	<0.001
Dialysis, % (*n*)	29.2 (50)	18.4 (45)	4.8 (38)	<0.001
Dialysis modality, % (*n*)				
CRRT*	84 (42)	73.3 (33)	66 (25)	0.14
SLEDD	0	13.3 (6)	13 (5)	
IHD	16 (8)	13.3 (6)	21 (8)	

CRRT, continuous renal replacement therapy; IHD, intermittent hemodialysis; CVVH, continuous veno-venous hemofiltration; SLEDD, sustained low-efficiency daily diafiltration; APACHE II, Acute Physiologic Assessment and Chronic Health Evaluation II.

* Two patients were treated with CVVH at a dose of 25–30 mL/kg/h.

Table 2. Predictors of receiving dialysis

Variable	Beta coefficient	Exp(B) OR	95% CI for exp (B)	
			lower	upper
Lactate, mmol	0.097	1.102	1.043	1.165
SOFA cardio	0.789	2.193	1.643	2.929
SOFA renal	0.791	2.205	1.838	2.645

OR, odds ratio.

Discussion

We conducted a retrospective analysis of a cohort of patients on ICU with SLA. We found that mortality rates were high, despite all possibilities of modern intensive care medicine, with a 90-day mortality of 34.5%, of whom 41% died within 48 h of reaching the inclusion threshold. This is significantly higher than the average overall mortality on our ICU, which is around 7%. Our results are also compatible with the previous literature, where hyperlactatemia is an independent predictor of mortality [1–4]. Conventional indications for RRT in ICU are acute kidney injury with associated electrolyte disturbances or uremic symptoms or signs, fluid overload resistant to diuretic therapy, and poisoning with a dialyzable drug or toxin [22, 23]. Most of these conditions are associated with high ICU mortality rates [24–26]. In our unit, ICU mortality of patients with AKI who receive RRT is around 55% [27]. Although controversial, RRT has also been advocated as one of the therapeutic strategies to manage hyperlactatemia, and in most cases, the associated severe metabolic acidosis. Lactate is a small molecule (molecular weight 90 Da) that is easily removed both by HD and HF due to its high sieving coefficient [19]. Hence, the major determinant of removal in classic HD is blood flow, whereas in CVVH it is the dialysate or substitution flow. Furthermore, predilution volume substitution in CVVH may decrease the

Table 3. Predictors of 90-day mortality without (model A) and with adjustment (model B) for the propensity to receive RRT

Variable	Beta coefficient	Exp(B) OR	95% CI for exp (B)	
			lower	upper
Model A				
Lactate, mmol	0.109	1.115	1.064	1.170
pH	−3.069	0.046	0.014	0.159
SOFA total	0.109	1.116	1.077	1.156
Age	0.016	1.016	1.077	1.024
Dialysis	1.044	2.841	1.833	4.401
Model B				
Lactate, mmol	0.085	1.089	1.034	1.146
pH	−2.966	0.051	0.014	0.184
SOFA total	0.094	1.099	1.051	1.149
Age	0.013	1.013	1.004	1.022
Dialysis	0.830	2.294	1.447	3.636
Predicted propensity to receive dialysis	1.377	3.963	1.047	14.995

RRT, renal replacement therapy; OR, odds ratio.

efficiency by decreasing the prefilter lactate concentration. Therefore, in our center, CHD (mean blood flow 200 mL/min, range 150–250 mL/min; mean dialysate flow 405 mL/min, range 350–500 mL/min) is the preferred modality in patients with SLA. The dialysis blood flows were increased to what is maximally possible when metabolic control was not achieved. Therefore, lactate clearance was as maximal as can be achieved in clinical practice in our group of patients. However, there is a lack of controlled studies to support the use of RRT in these indications, and in the observational data, there is high-risk for indication bias. In the current study aiming to explore factors linked to the probability to start dialysis in this setting and factors impacting on outcome, we found that the lactate level, SOFA renal score, and SOFA cardio score were independently associated with higher odds to start dialysis. Our analysis also showed that patients in whom RRT was started had higher odds for 90-day mortality. Accordingly, patients who died within 48 h not only had higher SOFA cardio and renal scores and lactate levels but also in 1 of 3 patients in this group, dialysis was initiated. This suggests that propensity to receive dialysis increases with severity of underlying conditions but even after correction for the propensity to receive dialysis, the odds ratio of death remains 2.3-fold higher for patients who were versus were not dialyzed.

Following different reasoning, De Corte et al. [19] also reported that SLA is associated with higher mortality. They compared a cohort of patients who received RRT with or without SLA and found that compared with patients without SLA, those with SLA had higher ICU mortality and were more severely ill. In contrast to our study however, initial lactate concentration before initiation of RRT was not related to mortality in the group with SLA. This diverging result could be related to the much smaller group of patients with SLA (n = 116) than our study.

As expected, a higher SOFA renal score increases the propensity that RRT is initiated because it embeds the classical indications for dialysis. Nevertheless, even after accounting for SOFA renal, the lactate level independently enhances the propensity for initiation of RRT, which might indicate that in this patient cohort, dialysis is often started primarily to reduce elevated lactate levels. Whether SLA by itself is an appropriate indication for RRT remains controversial. In our outcome analysis, initiation of RRT was associated with a higher – not lower – mortality, which suggests that RRT has a very limited, if any, effect on the survival of these severely ill patients. A number of explanations can be put forward. First, several studies have pointed out that the contribution of extracorporeal clearance by RRT is at best minimal to modest as compared to the endogenous clearance of lactate. In many patients, the decrease in the lactate level and increase in pH are more due to the improving underlying condition than to the removal by RRT [18, 28–30]. One could assume that in patients with reduced endogenous clearance caused by, for example, liver dysfunction or AKI, the contribution of extracorporeal clearance may be more substantial and therefore potentially lifesaving when used as a bridge to allow recovery of the underlying condition. Second, RRT is still thought to be a rescue therapy when attempting every effort possible on the ICU. In those category of patients, continuation of care is often already considered as no longer beneficial prior to start of RRT, which could lead to an important selection bias.

Our study has several strengths. To the best of our knowledge, we are the first to evaluate the factors that may contribute to the decision to initiate RRT and adjust for these using a propensity score when assessing outcome in patients with SLA on the ICU. Furthermore, we were able to extract for a relatively large sample of patients, detailed and accurate information from the electronic hospital, dialysis and laboratory databases, including daily SOFA scores. The limitations of this study are primarily related to its retrospective nature. First, we included patients in whom dialysis was started

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within 24 h after reaching threshold, which could cause a certain degree of immortal time bias. Second, patients who were dialyzed after 24 h were analyzed as not being treated with RRT, similar to patients who never received dialysis. Because dialysis later during ICU admission may be associated with higher mortality, the mortality rate of patients who started RRT >24 h after reaching the lactate threshold can be overestimated. However, as this represents a small fraction of the group of patients who did not receive RRT (n = 78, 7%), we believe this effect is minimal. Furthermore, we did not account for the reason of admission nor underlying comorbidities except for diabetes.

In patients with SLA, the underlying condition is mostly very severe, and ethical and medicolegal considerations can be at play in the decision to escalate or downgrade therapeutic interventions. We acknowledge that since this study is retrospective, we could not capture whether or not patients were initiated on RRT for ethical or medicolegal reasons. To shed more light on those relevant factors, we selected some illustrative cases by purpose. First, in cat.1, 2 cases showed striking similarities regarding disease severity (cardiogenic shock) and age. Both died within 24 h after admission, one of them being dialyzed during that period. The biggest difference seemed to be that in the case wherein RRT was started, the patient underwent cardiac surgery before versus not in the other case. Several other cases were found where it was obvious that RRT was started despite an obviously very grim prognosis because of an iatrogenic complication after elective surgery. Finally, we also found some cases to illustrate that despite the higher mortality in patients receiving dialysis versus not, temporarily increasing lactate clearance by extracorporeal removal by RRT can be beneficial and lifesaving when applied in conditions of (temporarily) suppressed endogenous clearance as a bridge to further therapy strategies: 5 patients who underwent liver transplantation were dialyzed during the perioperative stage because of SLA and still showed >90-day survival. Severity of illness seems to be major determinant in outcome, as illustrated by the patients in this cohort who were admitted after unwitnessed cardiac arrest. Only 10% of these patients (4/37) survived, one of them being treated with RRT during ICU stay. Likewise, mortality was higher in patients needing urgent surgery (35%) versus elective surgery (12%), whereas in both groups approximately half of the nonsurvivors had been treated with RRT, the majority of them with CRRT treatment.

Using those individual cases, we wanted to highlight that a decision whether or not to start dialysis in ICU patients with SLA is not entirely captured by laboratory and PDMS alone. Finally, we want to point out that RRT may also cause harm since it is associated with an increased risk of bleeding, thrombocytopenia, hemodynamic instability, and catheter-related complications, and may result in increased costs [31, 32].

Conclusion

In ICU patients, SLA is associated with a high 90-day mortality of 34.5%. The propensity of receiving RRT is related to the degree of hyperlactatemia and SOFA renal and SOFA cardio scores. Even after adjustment for age, severity of illness, and factors that may influence the indication for dialysis, RRT remains associated with a >2-fold higher mortality and thus does not seem to improve survival for the majority of patients. The results confirm the value of lactate as a prognostic marker but question the sense of starting RRT just in order to increase lactate clearance. If there is no bridge to further therapy that may reverse the underlying cause of lactic acidosis, intensifying the supportive treatment with dialysis is unlikely to affect the outcome. We suggest awareness and an open mind to subjective factors that may influence our decision to start dialysis.

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Statement of Ethics

The study was approved by the Ethics Committee of the Ghent University Hospital RRT (Ghent University Ethical Committee, study B670201731687, date: 3 March 2017) and conducted in accordance with the Declaration of Helsinki. Informed consent was waived for this study.

Conflict of Interest Statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Author Contributions

All authors have made material contributions to this manuscript according to the rules of authorship. L.V.D.G., F.V., and W.V.B. helped to design the study, participated in data collection and analysis, and wrote the first draft of the manuscript and revised it. J.M.K. and F.V.O. had the original idea for the study, helped set up the design, and read the first manuscript. All authors read and approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

References

1 Nichol AD, Egi M, Pettila V, Bellomo R, French C, Hart G, et al. Relative hyperlactatemia and hospital mortality in critically ill patients: a Retrospective Multi-Centre Study. Crit Care. 2010;14(1):R25.
2 Ferreruela M, Raurich JM, Ayestarán I, Llompart-Pou JA. Hyperlactatemia in ICU patients: incidence, causes and associated mortality. J Crit Care. 2017 Dec;42:200–5.
3 Haas SA, Lange T, Saugel B, Petzoldt M, Fuhrmann V, Metschke M, et al. Severe hyperlactatemia, lactate clearance and mortality in unselected critically ill patients. Intensive Care Med. 2016 Feb;42(2):202–10.
4 Villar J, Short JH, Lighthall G. Lactate predicts both short- and long-term mortality in patients with and without sepsis. Infect Dis. 2019 Aug 6;12:1178633719862776.
5 Kraut J, Madias N. Lactic Acidosis. N Eng J Med. 2014 Dec 11;371(24):2309–19.
6 Scrutton MC. Clinical and biochemical aspects of lactic acidosis. FEBS Lett. 1976;70(1–2):294–5.
7 Garcia-Alvarez M, Marik P, Bellomo R. Stress hyperlactataemia: present understanding and controversy. Lancet Diabetes Endocrinol. 2014 Apr;2(4):339–47.
8 Brooks GA. The Science and translation of lactate shuttle theory. Cell Metab. 2018 Apr 3;27(4):757–85.
9 Brooks GA. The tortuous path of lactate shuttle discovery: from cinders and boards to the lab and ICU. J Sport Health Sci. 2020;9(5):446–60.
10 Kraut JA, Madias NE. Treatment of acute metabolic acidosis: a pathophysiologic approach. Nat Rev Nephrol. 2012 Oct;8(10):589–601.
11 Gevers W. Generation of protons by metabolic processes in heart cells. J Mol Cell Cardiol. 1977 Nov;9(11):867–74.
12 Cooper DJ, Walley KR, Wiggs BR, Russell JA. Bicarbonate does not improve hemodynamics in critically ill patients who have lactic acidosis. a Prospective, Controlled Clinical Study. Ann Intern Med. 1990;112(7):492.
13 Rudnick MR, Blair GJ, Kuschner WG, Barr J. Lactic acidosis and the role of sodium bicarbonate: a narrative opinion. Shock. 2020 May;53(5):528–36.
14 Forsythe SM, Schmidt GA. Sodium bicarbonate for the treatment of lactic acidosis. Chest. 2000 Jan;117(1):260–7.
15 Jaber S, Paugam C, Futier E, Lefrant JY, Lasocki S, Lescot T, et al. Sodium bicarbonate therapy for patients with severe metabolic acidaemia in the intensive care unit (BICAR-ICU): a multicentre, open-label, randomised controlled, phase 3 trial. Lancet. 2018 Jul 7;392(10141):31–40.
16 Connor H, Woods HF. Quantitative aspects of L(+)-lactate metabolism in human beings. Ciba Found Symp. 1982;87:214–34.
17 Gómez H, Mizock BA. Hyperlactatemia and lactic acidosis. Critical Care Nephrology. 3rd ed. 2019.
18 Bellomo R. Bench-to-bedside review: lactate and the kidney. Critical Care. 2002 Aug;6(4):322–6.
19 De Corte W, Vuylsteke S, De Waele JJ, Dhondt AW, Decruyenaere J, Vanholder R, et al. Severe lactic acidosis in critically ill patients with acute kidney injury treated with renal replacement therapy. J Crit Care. 2014 Aug;29(4):650–5.
20 Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: A severity of disease classification system. Crit Care Med. 1985 Oct;13(10):818–29.
21 Vincent JL, de Mendonça A, Cantraine F, Moreno R, Takala J, Suter PM, et al. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a Multicenter, Prospective Study. Crit Care Med. 1998 Nov;26(11):1793–800.
22 Ahmed AR, Obilana A, Lappin D. Renal replacement therapy in the critical care setting. Crit Care Res Pract. 2019;2019:6948710.
23 Mehta RL. Challenges and pitfalls when implementing renal replacement therapy in the ICU. Criti Care. 2015;19(Suppl 3):S9.
24 Claure-Del Granado R, Mehta RL. Fluid overload in the ICU: evaluation and management. BMC Nephrol. 2016 Aug 2;17(1):109.
25 Folkestad T, Brurberg KG, Nordhuus KM, Tveiten CK, Guttormsen AB, Os I, et al. Acute kidney injury in burn patients admitted to the intensive care unit: a systematic review and meta-analysis. Crit Care. 2020;24(1):2.
26 Brueske B, Sidhu MS, Schulman-Marcus J, Kashani KB, Barsness GW, Jentzer JC. Hyperkalemia is associated with increased mortality among unselected cardiac intensive care unit patients. J Am Heart Assoc. 2019 Apr 2;8(7):e011814.
27 De Corte W, Dhondt A, Vanholder R, De Waele J, Decruyenaere J, Sergoyne V, et al. Long-term outcome in ICU patients with acute kidney injury treated with renal replacement therapy: a Prospective Cohort Study. Crit Care. 2016 Aug 12;20(1):256.
28 Hilton PJ, Taylor J, Forni LG, Treacher DF. Bicarbonate-based haemofiltration in the management of acute renal failure with lactic acidosis. QJM. 1998 Apr;91(4):279–83.
29 Briglia AE. The current state of nonuremic applications for extracorporeal blood purification. Semi Dial. 2005;18(5):380–90.
30 Levraut J, Ciebiera JP, Jambou P, Ichai C, Labib Y, Grimaud D. Effect of continuous venovenous hemofiltration with dialysis on lactate clearance in critically ill patients. Crit Care Med. 1997 Jan;25(1):58–62.
31 Fayad AII, Buamscha DG, Ciapponi A. Timing of renal replacement therapy initiation for acute kidney injury. Cochrane Database Syst Rev. 2018 Dec 18;12(12):CD010612.
32 Chaudhuri D, Herritt B, Heyland D, Gagnon LP, Thavorn K, Kobewka D, et al. Early renal replacement therapy versus standard care in the ICU: a systematic review, meta-analysis, and cost analysis. J Intensive Care Med. 2019 Apr;34(4):323–9.