

CITRATE DIALYSIS FLUID



CITRATE IN DIALYSIS

WHAT IS CITRATE?

Citrate is a natural metabolite, which is a source of cellular energy, providing buffering capacity to the patient. Citrate is an intermediate in the citric acid cycle and is widely used in the food and drug industry because of its buffering, anticoagulant and antioxidant capacities.

As a chelator, citrate is able to bind calcium and metals that catalyse the production of Reactive Oxygen Species.¹

Under physiologic circumstances, citrate is metabolised in the liver, skeletal muscle and renal cortex.²

Citrate clearance is not impaired in patients with chronic renal failure.³

WHY CITRATE IN DIALYSIS?

An acid is required in bicarbonate dialysis to avoid insoluble calcium and magnesium precipitation. Acetic acid is commonly used at a concentration up to one hundred times higher than normal plasma acetate levels.⁴ Body gain of acetate is particularly high in convective treatments.⁵ This results in a substantial increase in plasma acetate which may promote haemodynamic instability, inflammation and acidosis.⁴

Citric acid has been proposed as an alternative dialysis buffer due to its anticoagulant, anti-inflammatory and anti-oxidant properties.⁶

WHAT IS THE INTENDED PURPOSE?

The **SoftPac Citrate** product is intended to be used as a citrate-based acid concentrate together with a dry sodium bicarbonate cartridge for on-line preparation of haemodialysis, haemodiafiltration or haemofiltration fluids on compatible Vantive/Gambro dialysis systems.*

The **SelectBag Citrate** product is intended to be used as a citric acid-based concentrate together with the **BiCart** cartridge and the **SelectCart** cartridge for on-line preparation of haemodialysis, haemodiafiltration or haemofiltration fluids on compatible Vantive/Gambro dialysis systems.*

* Vantive **SoftPac Citrate** and **SelectBag Citrate** Instruction for Use.

The Vantive **SoftPac Citrate** and **SelectBag Citrate** concentrate allows for acetate-free dialysis fluids which may help to promote patient well-being with all the beneficial properties of Citrate.¹



SoftPac Citrate C165

REP 115755 3500 ml

K ⁺ 1.0 mmol/l	Ca ²⁺ 1.66 mmol/l	1+44	Glucose 1 g/l	Citrate 1 mmol/l
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- ① Check label and concentrate for defects. Make sure that the concentrate corresponds to physician's prescription and the dialysis machine settings. Do not use after medical expiration date. Do not use if the concentrate is older than 12 months from the date of manufacture.
- ② Check for leaks and damage to the bag. Do not use if the bag is damaged or if the bag is leaking. Do not use if the bag is damaged or if the bag is leaking.
- ③ Check for expiration date. Do not use if the bag is expired. Do not use if the bag is expired.
- ④ Check for lot number. Do not use if the bag is not the same lot number as the one on the label. Do not use if the bag is not the same lot number as the one on the label.
- ⑤ Check for the name of the manufacturer. Do not use if the bag is not the same manufacturer as the one on the label. Do not use if the bag is not the same manufacturer as the one on the label.
- ⑥ Check for the name of the product. Do not use if the bag is not the same product as the one on the label. Do not use if the bag is not the same product as the one on the label.
- ⑦ Check for the name of the concentrate. Do not use if the bag is not the same concentrate as the one on the label. Do not use if the bag is not the same concentrate as the one on the label.
- ⑧ Check for the name of the dialysis machine. Do not use if the bag is not the same dialysis machine as the one on the label. Do not use if the bag is not the same dialysis machine as the one on the label.
- ⑨ Check for the name of the patient. Do not use if the bag is not the same patient as the one on the label. Do not use if the bag is not the same patient as the one on the label.
- ⑩ Check for the name of the hospital. Do not use if the bag is not the same hospital as the one on the label. Do not use if the bag is not the same hospital as the one on the label.

SoftPac Citrate C165	g/l	mmol/l	SoftPac Citrate C165 & BCart	mmol/l
NaCl	288.3	Na ⁺ 49.95	Na ⁺	143
KCl	3.565	K ⁺ 45.0	Ca ²⁺	1.66
CaCl ₂ · 2H ₂ O	10.932	Ca ²⁺ 38.28	Mg ²⁺	0.5
MgCl ₂ · 6H ₂ O	4.574	Mg ²⁺ 22.8	Cl ⁻	108.3
C ₆ H ₁₂ O ₆	1	48.888	C ₆ H ₅ O ₇ ³⁻	1
C ₆ H ₁₀ O ₅ · H ₂ O	7.565	C ₆ H ₁₀ O ₅ 45.0	C ₆ H ₅ O ₇ ³⁻	0.5
Na ₂ C ₆ H ₅ O ₇ · 2H ₂ O	2.647	45.0	Cl ⁻	1
C ₆ H ₅ O ₇ ³⁻	45.0	45.0	Cl ⁻	1
H ₂ O	100.0	100.0	Cl ⁻	1

In 100 ml water following: 0.2288 g in equivalent to 100 ml of NaCl solution.

CE 0123 Vantive Health GmbH Vantive S.p.A. Vantive S.r.l.

Vantive

LOT 114697

EXP 12/2025



SelectBag Citrate CX 275

K⁺ 2.0 mmol/l
Ca²⁺ 1.75 mmol/l

1000 ml

SoftPac Citrate CX 275	g/l	mmol/l	SoftPac Citrate CX 275 & BCart	mmol/l
NaCl	288.3	Na ⁺ 49.95	Na ⁺	143
KCl	3.565	K ⁺ 45.0	Ca ²⁺	1.75
CaCl ₂ · 2H ₂ O	10.932	Ca ²⁺ 38.28	Mg ²⁺	0.5
MgCl ₂ · 6H ₂ O	4.574	Mg ²⁺ 22.8	Cl ⁻	108.3
C ₆ H ₁₂ O ₆	1	48.888	C ₆ H ₅ O ₇ ³⁻	1
C ₆ H ₁₀ O ₅ · H ₂ O	7.565	C ₆ H ₁₀ O ₅ 45.0	C ₆ H ₅ O ₇ ³⁻	0.5
Na ₂ C ₆ H ₅ O ₇ · 2H ₂ O	2.647	45.0	Cl ⁻	1
C ₆ H ₅ O ₇ ³⁻	45.0	45.0	Cl ⁻	1
H ₂ O	100.0	100.0	Cl ⁻	1

In 100 ml water following: 0.2288 g in equivalent to 100 ml of NaCl solution.

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CITRATE IN DIALYSIS

ARE YOU AWARE OF THE BIOCOMPATIBLE PROPERTIES OF CITRATE?^{4,7}

In vitro data show that:

- > low concentration of citrate can reduce complement and granulocyte activation in human whole blood.⁷
- > the dispensation of citrate per se reduces endothelial death and inflammation in a hyperglycemic environment.¹
- > at concentration commonly used in clinical practice, acetate dialysate increases oxidative stress and may act as an adjunct to the other proinflammatory stimuli to which HD patients are exposed. Citrate dialysate does not produce such a cell activation.⁸
- > citrate dialysis reduces endothelial cell dysfunction and vascular smooth muscular cell osteoblastic differentiation.⁶
- > citrate dialysate favourably affects calcification propensity.⁹

Ex-Vivo data show that:

Citrate-acidified bicarbonate dialysis protects against calcium accumulation in rat aortic walls cultured ex vivo.¹⁰

In clinical trials

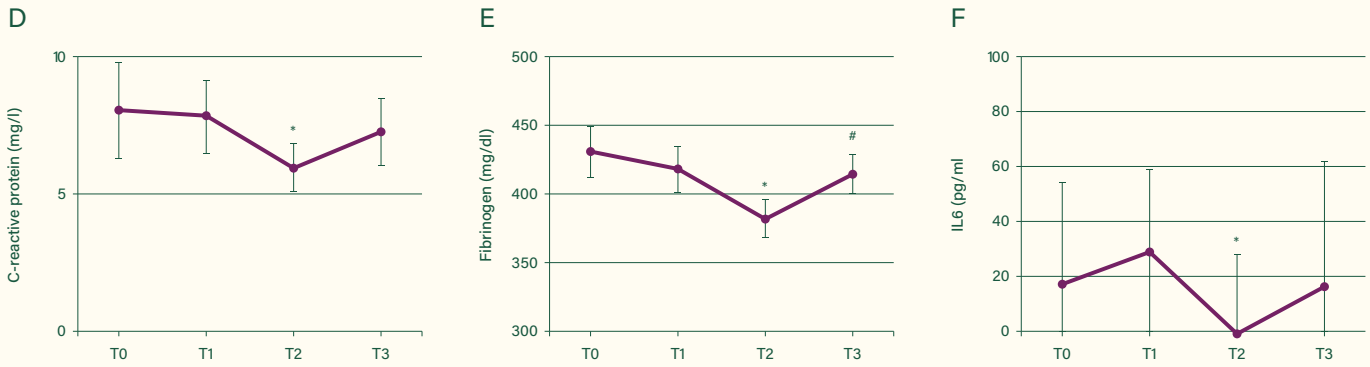
Vantive citrate concentrate fluid has been shown:

- > to reduce the intra-dialytic rise in pentraxin-3 (PTX3) compared to control in a short-term randomized controlled cross-over study. PTX3 is an inflammatory marker known to be induced by HD treatments.⁴
- > to lower pre-dialysis levels of the inflammatory marker C-reactive protein (CRP) in a controlled cross-over study in patients in on-line haemodiafiltration.¹¹
- > to significantly reduce chronic inflammation parameters such as CRP, fibrinogen, IL6, and adipokine chemerin, patients were treated in a sequence study with acetate, citrate and again acetate buffered dialysis solutions.⁶

Chronic HD patients suffer from high cardiovascular morbidity and mortality mainly due to a chronic systemic inflammation coupled with an aberrant metabolic state.⁶

In vitro studies show that citrate is a promising substitute for acetate for a more biocompatible dialysis, most likely resulting in less adverse effects for the patients.⁷

In this sequence study the duration was 9 months; in the first 3 months patients were treated with a standard dialysis solution containing 3 mmol/l acetate, the following 3 months an acetate-free solution containing 1 mmol/L citrate (**Select Bag Citrate**) and the last 3 months again the acetate solution were used.



Patients' clinical data at the different study time points, (D) pre-dialysis values of plasma C-Reactive Protein (CRP), (E) pre-dialysis plasma fibrinogen, (F) pre-dialysis serum IL6.

T0: study start; T1: end of 1st acetate period (3 months from study start);

T2 end of citrate (6 months); T3 end of 2nd acetate period (9 months).

*p < 0.05 when data were compared with T1; #p < 0.05 when data were compared with T2.

Adapted from Dellepiane6 N=45



IMPROVED HAEMODYNAMIC STABILITY

A recent randomized controlled study has shown that compared to acetate dialysates, citrate containing fluids may offer a greater haemodynamic stability with significantly fewer episodes of arterial hypotension.¹²

This is aligned with the results of previous studies:

- > reduction in the frequency of hypotensive episodes, especially in the most symptomatic and severe episodes of hypotension.¹³
- > the use of citrate rather than acetate as a dialysate decreases peripheral resistances and slightly reduces systolic and diastolic blood pressure. Nonetheless, both the analysis of maximum fluctuations in peripheral resistances during dialysis and data describing subjective tolerance suggest a trend towards improved haemodynamic stability for patients on the citrate schedule.¹⁴

WHY IS IT IMPORTANT TO REDUCE INTRADIALYTIC HYPOTENSION?

In addition to a reduced sense of well-being caused by the symptoms of intradialytic hypotension (IDH), patients who experience IDH have been shown to be at higher risk of mortality.^{15,16}

In a prospective, multicentre, randomized and crossed study of 32 weeks duration, with 56 patients randomly assigned to receive 16 consecutive weeks of citrate concentrate followed or preceded by 16 weeks of acetate fluid, there were fewer episodes of hypotension during the sessions at the baseline visit with the citrate concentrate (1 versus 3, $p=0.04$). The 46 patients who completed the study performed 4416 HD sessions, 2208 with acetate and 2208 with citrate. **Hypotension occurred in 14.1% with acetate versus 10.8% with citrate ($p<0.01$).**¹²

IMPROVED CONTROL OF ACID-BASE BALANCE

Citrate is rapidly metabolised in the body into bicarbonate in a 1:3 molar ratio¹⁷
Patients with reduced kidney function are in positive acid balance. During each HD session, a large surge of HCO_3^- enters the circulation and typically overcorrects predialysis acidosis to alkalosis and alkalemia. The acid-base alterations may have an impact on cardiovascular system, central nervous system, pulmonary function, tissue oxygenation and metabolism, inflammation and defense against infection.¹⁸

Since 2000, KDOQI guidelines recommend maintaining predialysis serum bicarbonate at ≥ 22 mmol/L.¹⁹

As documented by the DOPPS, both high (>27 mEq/L) and low (≤ 17 mEq/L) serum bicarbonate levels are associated with increased risk for mortality and hospitalization.²¹
A more recent publication showed an increase in mortality with low serum bicarbonate, but did not show the same increase in mortality with higher serum bicarbonate levels.²⁰

ACIDOSIS & ALKALOSIS PREVENTION

CORRECTED BETWEEN-TREATMENT ACIDOSIS AND REDUCED POST-TREATMENT ALKALOSIS

	PRE-HAEMODIALYSIS		POST-HAEMODIALYSIS		SIGNIFICANCE	
	ADF	CDF	ADF	CDF	ADF-CDF	ADF-CDF
Bicarbonate, mmol/l	23.0 (1.87)	22.8 (2.20)	28.5 (3.0)	26.9 (1.5)	0.668	0.032

Adapted from de Sequera¹² N=56

In a prospective, multicentre, randomized and crossed study, of 32 weeks duration, in patients in three-week HD, 16 weeks with ADF (acetate dialysis fluid) and 16 weeks with CDF (citrate dialysis fluid) **SelectBag Citrate**.

Dialysis with citrate achieves a better control of post-dialysis acid-base balance by decreasing/avoiding post-dialysis alkalemia compared to acetate.¹²

Citrate dialysate helps to control acid base balance by correcting acidosis between sessions and avoiding/reducing post dialysis alkalosis. Acute alkalaemia induced by the addition of (missing) bicarbonate during dialysis is an issue which has considerable clinical significance. It has been related to important adverse effects, such as haemodynamic instability, cardiac arrhythmia, paraesthesia/cramps, reduced cerebral blood flow, respiratory distress, headache, and a procalcifying effect.²²

DECREASED THROMBOGENICITY

By chelating ionized calcium in plasma, citrate containing dialysate concentrates have anticoagulant properties in a concentration-dependent manner:

- > Citrate fluid induces a significant intradialytic increase in aPTT (activated partial thromboplastin time).⁴
- > Citrate has local anticoagulant effect inside the dialyser, allowing reduced heparin dosing while maintaining extracorporeal patency²³ and optimizing dialyser clearances.^{4,6,11}

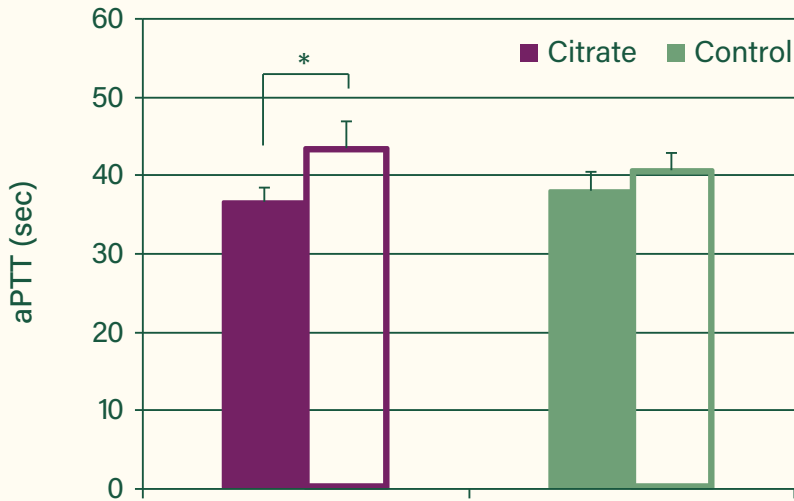
SoftPac Citrate and **SelectBag Citrate** products are not intended to obviate the need for anticoagulation in all patients.²⁴

ALTERNATIVE MODE OF LOW SYSTEMIC ANTICOAGULATION

The combination of citrate dialysate with the heparin-grafted membrane **Evodial** has been shown to be a valid alternative to regional citrate anticoagulation.^{23,25,26}

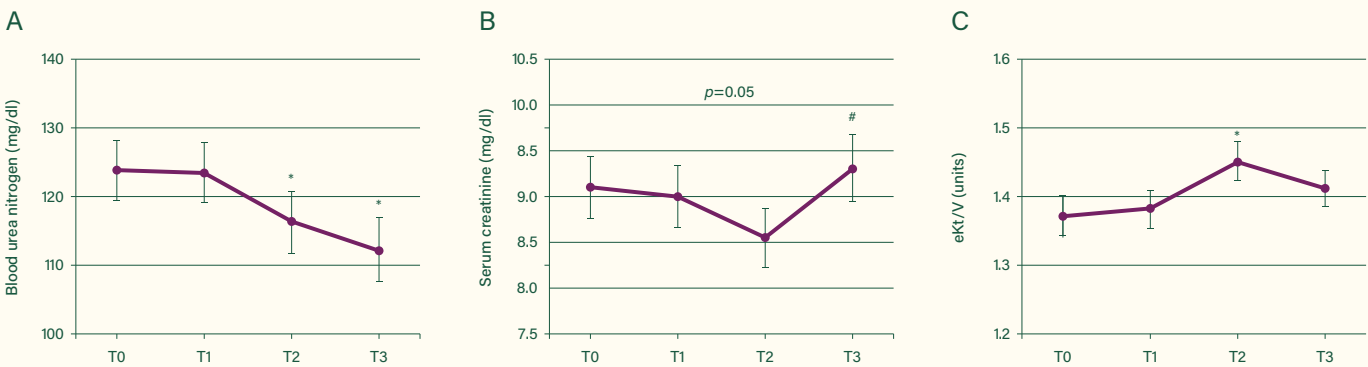


In an open-labeled cross-over trial (6+6) weeks with 8 treatments wash-out in between. Patients were randomly assigned to start with either citrate dialysis fluid rate or control acetate fluid.



Increased Activated Partial Thromboplastin Time (APTT) post dialysis when using **SelectBag Citrate** dialysis fluid. Solid bars represent pre-dialysis values and shadowed bars post-dialysis values. Data are shown as means \pm SEM, $p^*=0.003$. Adapted from Grundstrom.⁴ N=24

In this sequence study the duration was 9 months; in the first 3 months patients were treated with a standard dialysis solution containing 3 mmol/l acetate, the following 3 months an acetate-free solution containing 1 mmol/L citrate (**Select Bag Citrate**) and the last 3 months again the acetate solution were used.



Patients' clinical data at the different study time points, (A) Pre-dialysis blood urea nitrogen levels, (B) pre-dialysis serum creatinine values, (C) dialysis efficacy estimated with the eKt/V Daugirdas formula.

Period (3 months from study start);

T2 end of citrate (6 months);

T3 end of 2nd acetate period (9 months).

* $p < 0.05$ when data were compared with T1;

$p < 0.05$ when data were compared with T2.

Adapted from Dellepiane⁶ N=45

THE EFFECT OF CITRATE ON CALCIUM BALANCE

CALCIUM MASS BALANCE IS EASILY MAINTAINED DURING TREATMENT

Citrate binds ionized calcium and causes a change in the total calcium mass transfer compared to dialysis fluids without citrate, unless compensated for. A kinetic model developed by Vantive Research shows that with one mmol/l of citrate in the dialysis fluid an additional 0.15 mmol/l of calcium is required to achieve a mass balance within the dialyser that is equivalent to dialysis fluid without any citrate.²⁷ Clinical data support these theoretical results.^{4,28,29}

Vantive citrate concentrates offer augmented calcium concentration, making it easy to maintain the proper calcium mass balance.

Some patients may not benefit from the use of citrate dialysate and need to be closely monitored: patients with hypocalcemia, hypomagnesemia and uncontrolled secondary hyperparathyroidism.¹²

CITRATE DIALYSIS

SUITABLE FOR EVERY PATIENT

Citrate is a well-known antioxidant and anticoagulant buffer that is a well-tolerated and biocompatible alternative to regular acetate.

Citrate-containing acetate free dialysis is suitable for every patient.

Citrate clinical advantages:

- > Improved haemodynamic stability
- > Improved control of acid-base balance
- > Decreased thrombogenicity
- > Reduction of inflammatory indicators



REFERENCES

1. Bryland A, Wieslander A, Carlsson O et al. *Citrate treatment reduces endothelial death and inflammation under hyperglycaemic conditions.* *Diab Vasc Dis Res* 2012; 9(1): 42-51.
2. Zheng Y, Xu Z et al. *Citrate Pharmacokinetics in Critically Ill Patients with Acute Kidney Injury.* *PLoS ONE* 2013; 8(6): e65992.
3. Bauer E., Derfler K. Et al. *Citrate Kinetics in Patients Receiving Long-Term Hemodialysis Therapy.* *Am J Kidney Dis* 2005; 46:903-907.
4. Grundstrom G, Christensson A, Alquist M et al. *Replacement of acetate with citrate in dialysis fluid: a randomized clinical trial of short term safety and fluid biocompatibility.* *BMC Nephrol* 2013, 14:216.
5. Pizzarelli F, Cerrai T et al. *On-line haemodiafiltration with and without acetate.* *Nephrol Dial Transplant* 2006; 21: 1648-1651.
6. Dellepiane S, Medica D., Guarena C et al. *Citrate anion improves chronic dialysis efficacy, reduces systemic in-flammation and prevents Chemerin-mediated microvascular injury.* *Sci Rep* 2019; 9: 10622.
7. Huang S, Sandholm K, Jonsson N et al. *Low concentrations of citrate reduce complement and granulocyte activation in vitro in human blood.* *Clin Kidney J* 2015; 8: 31-37.
8. Perez-Garcia R, Rafael Ramirez Chamond RR, De Sequera Ortiza P et al. *Citrate dialysate does not induce oxidative stress or inflammation in vitro as compared to acetate dialysate.* *Nefrologia* 2017; 37(6): 630-637.
9. Lorenz G, Mayer C et al. *Acetate-free, Citrate-acidified bicarbonate dialysis improves serum calcification propensity- a preliminary study.* *Nephrol Dial Transplant* 2018; 33(11): 2043-2051.
10. Villa-Bellosta R. et al. *Impact of acetate- or citrate-acidified bicarbonate dialysate on ex vivo aorta wall calcification.* *Sci Rep* 2019; 9: 11374.
11. Molina Nunez M, de Alarcon R et al. *Citrate versus Acetate-Based Dialysate in On-Line Haemodiafiltration. A Pro-spective Cross-Over Study.* *Blood Purif* 2015; 39:181-187.
12. de Sequera P, Garcia R P, Molina M et al. *Prospective randomized multicenter study to demonstrate the benefits of haemodialysis without acetate (with citrate): ABC-treat Study. Acute effect of citrate.* *Nefrologia* 2019; 39(4): 424-433.
13. Daimon S, Dan K, Kawano M. *Comparison of acetate-free citrate hemodialysis and bicarbonate hemodialysis re-garding the effect of intra-dialysis hypotension and post-dialysis malaise.* *Ther Apher Dial* 2011; 15(5): 460-5.
14. Gabutti L, Lucchini B et al. *Citrate- vs. acetate-based dialysate in bicarbonate haemodialysis: consequences on haemodynamics, coagulation, acid-base status, and electrolytes.* *BMC Nephrol* 2009, 10: 7.
15. Stefansson B, Brunelli S et al. *Intradialytic Hypotension and Risk of Cardiovascular Disease.* *Clin J Am Soc Nephrol* 2014; 9: 2124-2132.
16. Chou J, Streja E. *Intradialytic hypotension, blood pressure changes and mortality risk in incident hemodialysis patients.* *Nephrol Dial Transplant* 2018; 33: 149-159.
17. Monchi M. *Citrate pathophysiology and metabolism.* *Transfus Apher Sci* 2017; 56(1): 28-30.
18. Qian Q. *Acid-base alterations in ESRD and effects of hemodialysis.* *Semin Dial.* 2018; 31: 226-235.
19. K/DOQI. *Clinical practice guidelines for nutrition in chronic renal failure.* *Am J Kidney Dis* 2000; 35[Suppl 2]: S1-S140.
20. Tentori F, Karaboyas A et al. *Association of Dialysate Bicarbonate Concentration with Mortality in the Dialysis Outcomes and Practice Patterns Study (DOPPS).* *Am J Kidney Dis.* 2013; 62(4).
21. Bommer J, Francesco Locatelli F et al. *Association of Predialysis Serum Bicarbonate Levels With Risk of Mortality and Hospitalization in the Dialysis Outcomes and Practice Patterns Study (DOPPS).* *Am J Kidney Dis* 2004; 44(4): 661-671.
22. De Sequera Ortiz P, Albalade Ramon M et al. *Acute effect of citrate bath on postdialysis alkalaemia.* *Nefrologia* 2015; 35:164-71.
23. Meijers B., Christoph Metalidis C. et al. *A noninferiority trial comparing a heparin-grafted membrane plus citrate-containing dialysate versus regional citrate anticoagulation: results of the CITED study.* *Nephrol Dial Transplant* 2017; 32: 707-714.
24. Dolley-Hitze T. *Is Anticoagulation Discontinuation Achievable with Citrate Dialysate during HDF Sessions?* *Int J Nephrol.* 2016; 7: 1-8.
25. Karlien F et al. *Avoidance of systemic anticoagulation during intermittent haemodialysis with heparin-grafted pol-yacrilonitrile membrane and citrate-enriched dialysate: a retrospective cohort study.* *BMC Nephrol* 2014; 15:104.
26. Skagerlind M, Stegmayr B. *An evaluation of four modes of low-dose anticoagulation during intermit-tent haemodialysis.* *Eur J Clin Pharmacol* 2018; 74:267-274.
27. Nilsson A, Sternby J, Grundstrom G, Alquist M. *Citrate dialysis fluid and calcium mass balance.* *Nephrol Dial Transplant* 2013;28 (suppl1): i207.
28. Steckiph D, Bertucci A, Petrarulo M et al. *Calcium mass balances in on-line HDF using citrate-containing acetate-free and regular dialysis concentrates.* *Nephrol Dial Transplant* 2013;28 (suppl1).
29. Teatini U. et al. *Calcium mass balance of an acetate free citrate containing dialysis fluids: Ad interim analysis of citrus study.* *Nephrol Dial Transplant.* 2017; 32 (Supplement 3): iii78-iii79.