ANTICOAGULAZIONE CON CITRATO

E COMPENSAZIONE AUTOMATICA DEL CALCIO

- ❑INDICAZIONI
- ❑VANTAGGI
- ❑MATERIALI E METODI

CITRATE ON 2003

- **Direct anticoagulation control difficult**
  - Need for complex protocol with meticulous calculation and many titration required
- **Complex metabolic consequences**
  - **Metabolic Alkalosis or acidosis**
  - **Hyper or hyponatremia**
  - **Calcium and magnesium loss**
- Citrate solution are either **customized or hospital pharmacy-formulated** and not applicable in all terapies .
- **Labor intensive** and close monitoring of electrolyte and acid-base required

Oliver et al, Semin Dial, Vol 14, pp 432-435, ***2001***
Little et al, AJKD, Vol 36, pp 1135-1139, ***2000***
Margetts et al, JASN, Vol 10, pp 211A, ***1999***

CITRATE ON 2013

1. **Review** Subscription Highly accessed
Bench-to-bedside review: Citrate for continuous renal replacement therapy, from science to practice
Heleen M Oudemans-van Straaten, Marlies Ostermann
Critical Care 2012, **16**:249 (7 December 2012)
Abstract | Full text | PDF | PubMed

2. **Commentary** Subscription
Good-bye CRRT, here comes SLED? ... not so fast!
Michael Joannidis
Critical Care 2012, **16**:167 (5 November 2012)
Abstract | Full text | PDF | PubMed

3. **Research** Open Access Highly accessed
Optimal Mode of clearance in critically ill patients with Acute Kidney Injury (OMAKI) - a pilot randomized controlled trial of hemofiltration versus hemodialysis: a Canadian Critical Care Trials Group project
Ron Wald, Jan O Friedrich, Sean M Bagshaw, Karen EA Burns, Amit X Garg, Michelle A Hladunewich, Andrew A House, Stephen Lapinsky, David Klein, Neesh I Pannu, Karen Pope, Robert M Richardson, Kevin Thorpe, Neill KJ Adhikari
Critical Care 2012, **16**:R205 (24 October 2012)
Abstract | Full text | PDF | PubMed | F1000 Biology

4. **Commentary** Subscription Highly accessed
Regional citrate anticoagulation in patients with liver failure - time for a rethink?
Sameer Patel, Julia Wendon
Critical Care 2012, **16**:153 (17 September 2012)
Abstract | Full text | PDF | PubMed

5. **Research** Open Access Highly accessed
Hemofiltration compared to hemodialysis for acute kidney injury: systematic review and meta-analysis
Jan O Friedrich, Ron Wald, Sean M Bagshaw, Karen EA Burns, Neill KJ Adhikari
Critical Care 2012, **16**:R146 (6 August 2012)
Abstract | Full text | PDF | PubMed | Cited on BioMed Central | F1000 Biology

6. **Research** Open Access Highly accessed
Sustained low efficiency dialysis using a single-pass batch system in acute kidney injury - a randomized interventional trial: the RElnal Replacement Therapy Study in Intensive Care Unit PatiEnts
Vedat Schwenger, Markus A Weigand, Oskar Hoffmann, Ralf Dikow, Lars P Kihm, Jörg Seckinger, Nexhat Miftari, Matthias Schaier, Stefan Hofer, Caroline Haar, Peter P Nawroth, Martin Zeier, Eike Martin, Christian Morath
Critical Care 2012, **16**:R140 (27 July 2012)
Abstract | Full text | PDF | PubMed | Cited on BioMed Central | F1000 Biology

7. **Research** Open Access Highly accessed
Regional citrate anticoagulation in cardiac surgery patients at high risk of bleeding: a continuous veno-venous hemofiltration protocol with a low concentration citrate solution
Santo Morabito, Valentina Pistolesi, Luigi Tritapepe, Laura Zeppilli, Francesca Polistena, Emanuela Strampelli, Alessandro Pierucci
Critical Care 2012, **16**:R111 (27 June 2012)
Abstract | Full text | PDF | PubMed | F1000 Biology

8. **Research** Open Access Highly accessed
Total-to-ionized calcium ratio predicts mortality in continuous renal replacement therapy with citrate anticoagulation in critically ill patients
Andreas Link, Matthias Klingele, Timo Speer, Ranja Rbah, Janine Pöss, Anne Lerner-Gräber, Danilo Fliser, Michael Böhm
Critical Care 2012, **16**:R97 (29 May 2012)
Abstract | Full text | PDF | PubMed | Cited on BioMed Central

9. **Poster presentation** Free
Regional citrate anticoagulation with a low-concentration solution in predilution-postdilution CVVH
V Pistolesi, S Morabito, L Tritapepe, L Cibelli, M Ambrosino, F Polistena, L Zeppilli, E Strampelli, MI Sacco, A Pierucci
Critical Care 2012, **16**(Suppl 1):P367 (20 March 2012)
Full text | PDF

10. **Poster presentation** Free
Regional citrate anticoagulation in CVVH: a new protocol combining citrate solution with a phosphate-containing replacement fluid
S Morabito, V Pistolesi, L Tritapepe, E Vitaliano, E Strampelli, F Polistena, L Zeppilli, A Pierucci
Critical Care 2012, **16**(Suppl 1):P366 (20 March 2012)
Full text | PDF

INDICAZIONI / VANTAGGI

I vantaggi di una metodica come l'anticoagulazione regionale sono evidenti così come le sue conseguenti indicazioni.

CLINICHE

- RISCHIO DI SANGUINAMENTO
- INTOLLERANZA ALL'EPARINA
- MANTENIMENTO DOSE DEPURATIVA

PRATICO/ORGANIZZATIVE

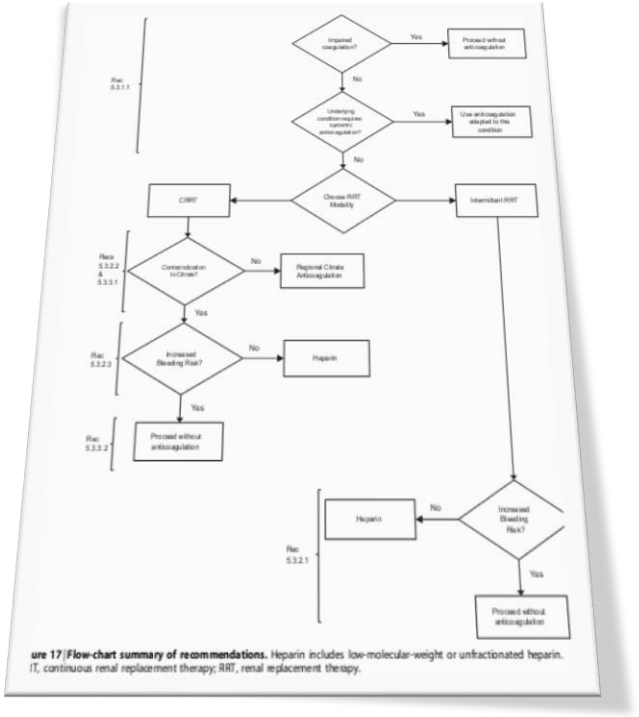
- OTTIMIZZAZIONE DELL'EMOFILTRO
- OTTIMIZZAZIONE DELLE RISORSE
- RIDUZIONE DEL WORKLOAD (?)

KDIGO Guideline

Anticoagulation

Guideline 5.3.2.2: For anticoagulation in CRRT, we suggest using regional citrate anticoagulation rather than heparin in patients who do not have contraindications for citrate.

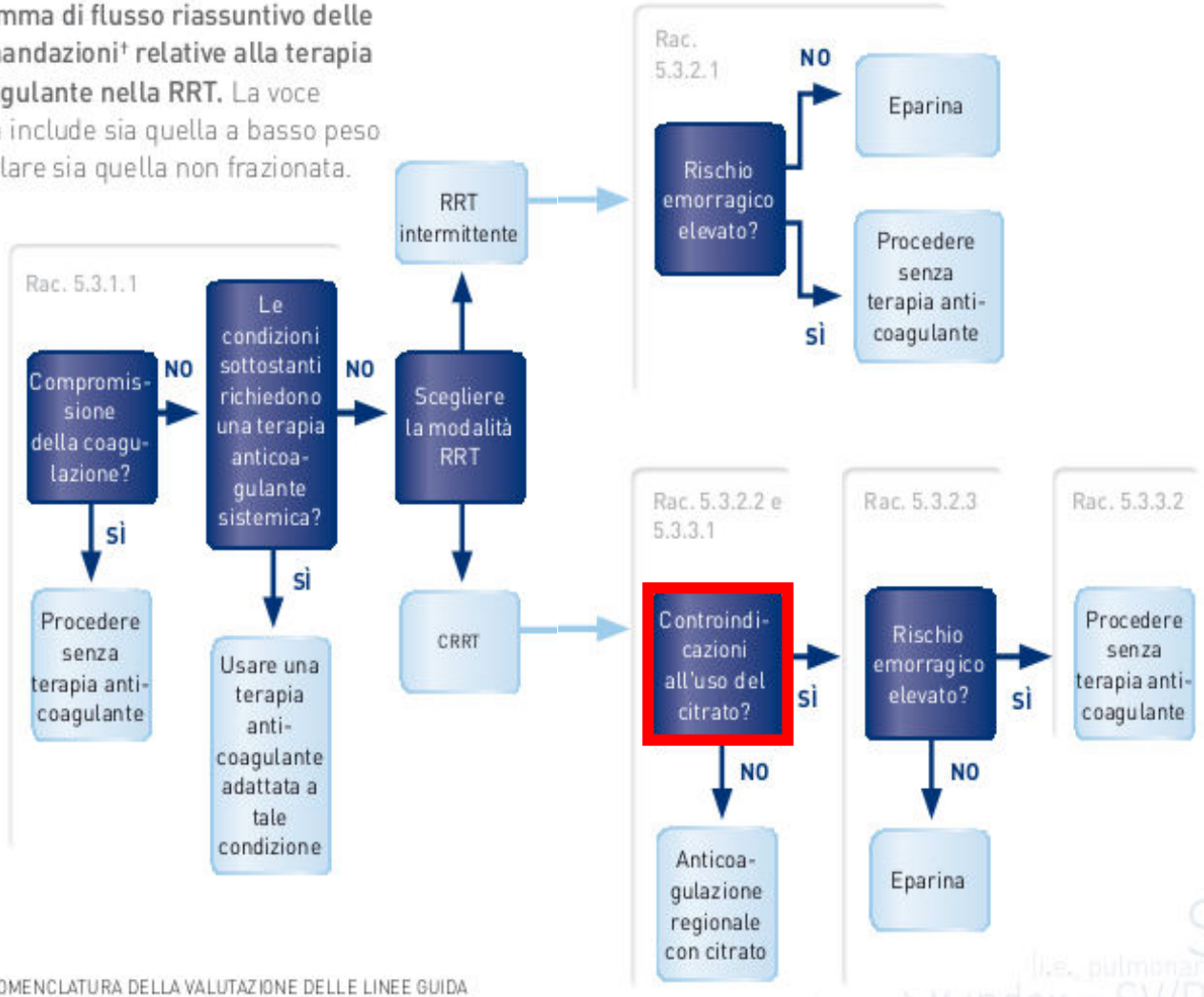
RATING 2B



ure 17 | Flow-chart summary of recommendations. Heparin includes low-molecular-weight or unfractionated heparin. IT, continuous renal replacement therapy; RRT, renal replacement therapy.

Terapia anticoagulante nella RRT

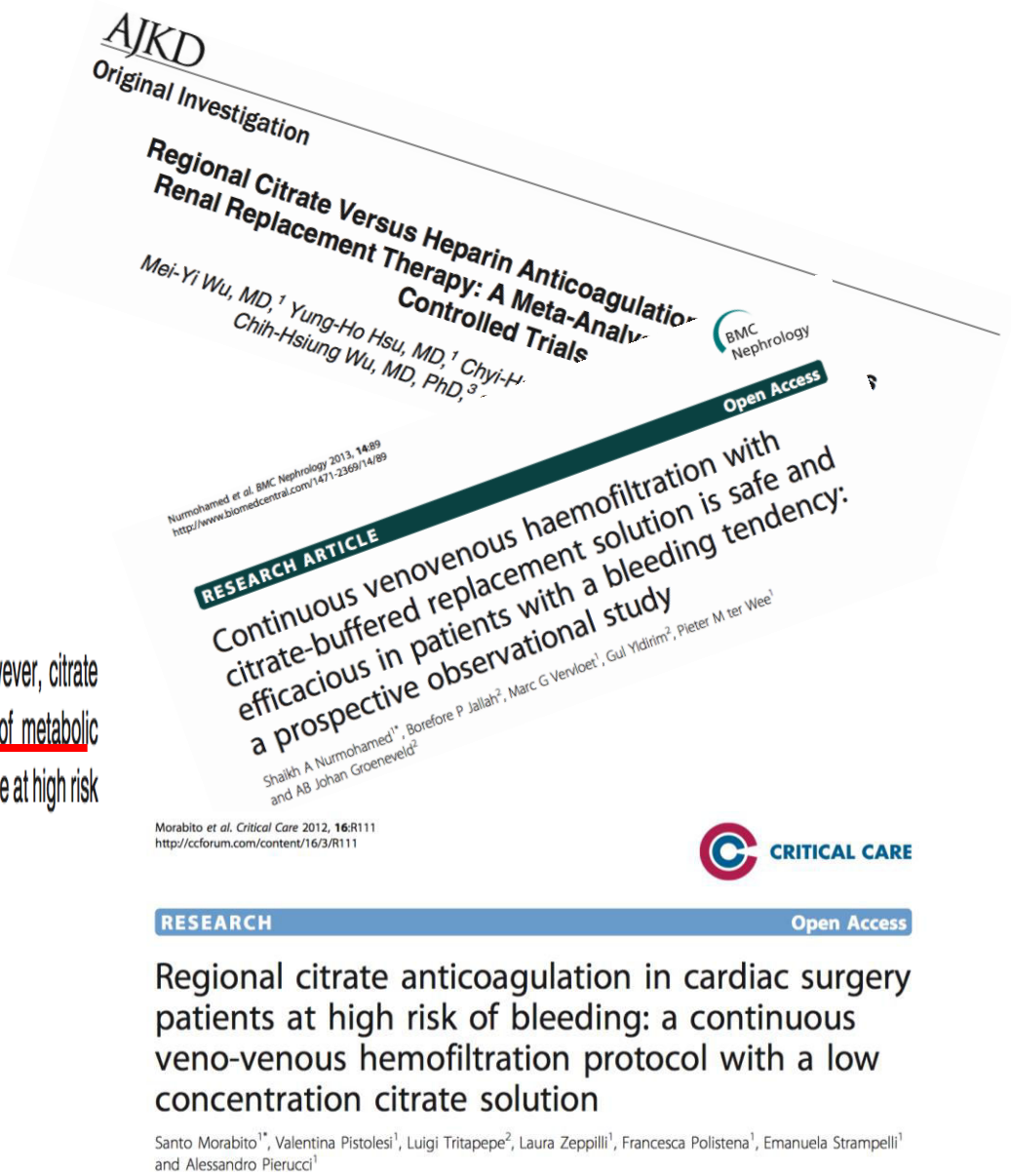
Diagramma di flusso riassuntivo delle raccomandazioni† relative alla terapia anticoagulante nella RRT. La voce eparina include sia quella a basso peso molecolare sia quella non frazionata.



† Vedere NOMENCLATURA DELLA VALUTAZIONE DELLE LINEE GUIDA

High Risk Bleeding

Conclusion: The efficacy of citrate and heparin anticoagulation for CRRT was similar. However, citrate anticoagulation decreased the risk of bleeding with no significant increase in the incidence of metabolic alkalosis. We recommend citrate as an anticoagulation agent in patients who require CRRT but are at high risk of bleeding.



Nelle Tecniche continue, ***l'anticoagulazione standard con eparina si associa a un elevato fabbisogno trasfusionale***.

Monchi et all Care Med 2004; 30: 260-5

Nei trattamenti con Sodio citrato
Il **fabbisogno trasfusionale si riduce a 0.98 vs 1.76 unità di EC/die**

Mariano F, Care Med 2010; 36: 1735-43

INTOLLERANZA ALL'EPARINA

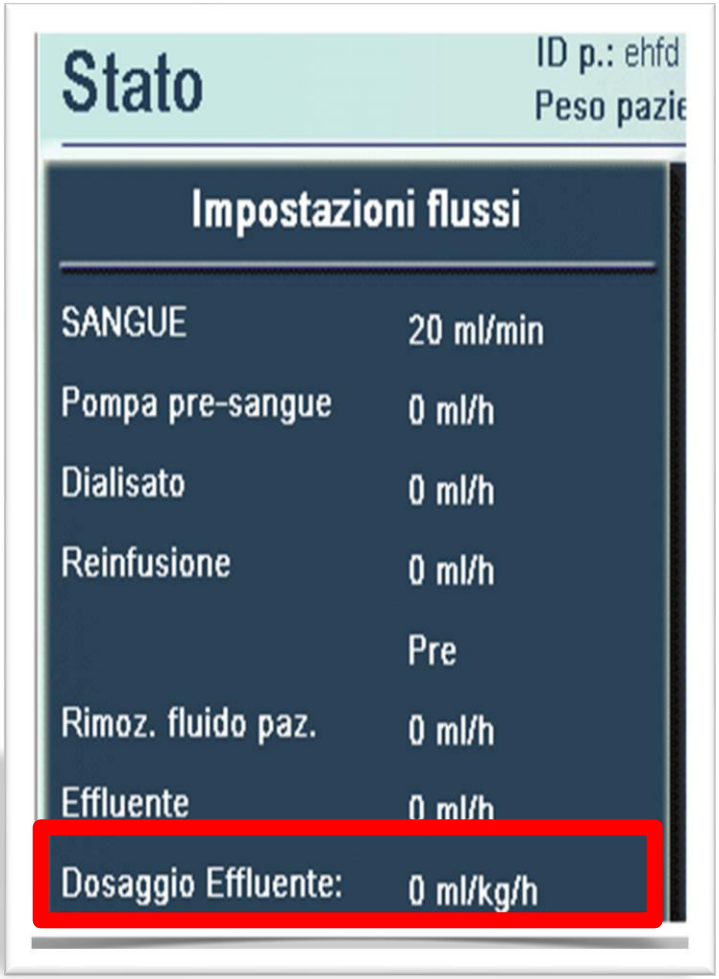
Nonostante l'incidenza di trombocitopenia indotta dall'eparina sia limitata (1-3%) l'utilizzo dell'eparina potrebbe essere impossibile in alcuni casi .

Ballard JO Anticoagulant-induced thrombosis. JAMA : the journal of the American Medical Association 1999 Jul 28;282(4):310-2

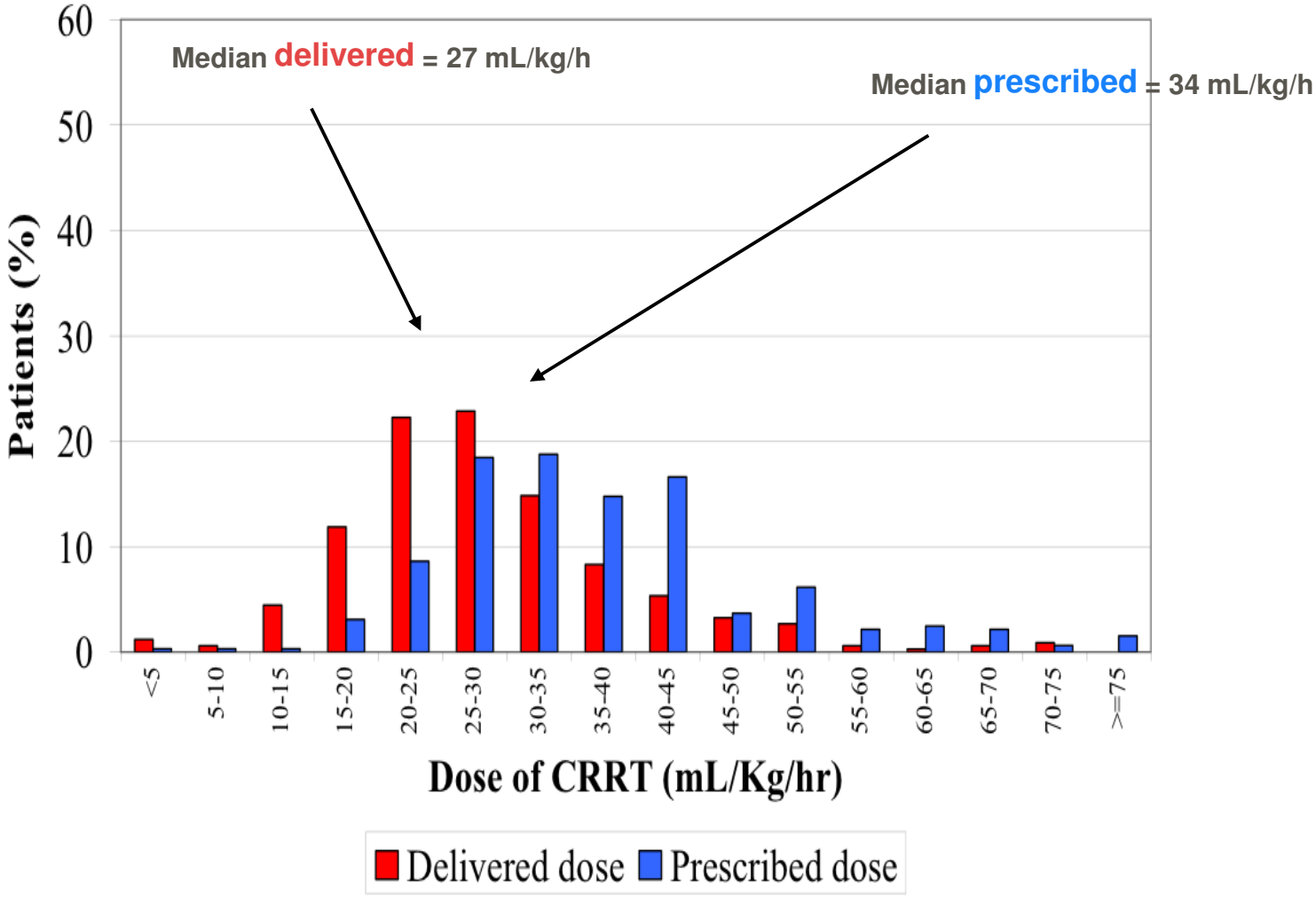
MANTENIMENTO DOSE DEPURATIVA

Guideline 5.8.4: We **recommend** delivering an ***effluent volume*** of ***at least*** **20-25 ml/kg/h** for CRRT in AKI

RATING 1A



Prescribed vs Delivered: DO-RE-MI Database (N=865)*



* Delivered dose of renal replacement therapy and mortality in critically ill patients with AKI, **Ronco et al,** Critical Care 2009

Cause di Downtime in CRRT

Table 3. Reasons for stopping CRRT

Reasons	Number of Filters	Percentage (%)	FUN/BUN Ratio
Factors affecting treatment time without affecting filter function			
D/C for surgical procedures	10	6.3	0.93 (0.92 to 0.99)
D/C for medical procedures	9	5.7	1.0 (0.95 to 1)
routine filter changes	16	10.1	0.95 (0.84 to 1.0)
machine problems	8	5.0	0.97 (0.85 to 1.0)
transition to IHD	17	10.7	0.96 (0.82 to 0.97)
venous access clot	6	3.8	0.97 (0.96 to 0.98)
physician decision	10	6.3	0.98 (0.94 to 1)
patient or family decision	11	6.9	0.96 (0.94 to 1)
patient recovery	6	3.8	0.95 (0.92 to 0.99)
death	3	1.9	0.98 (0.87 to 1.0)
access change	9	5.7	0.9 (0.87 to 0.95)
Factors affecting filter function			
filter clotted	41	25.8	0.89 (0.83 to 0.94)
filter leak	1	0.63	0.745
low-sieving concentration polarization	12	7.5	0.86 (0.79 to 1.0)

Factors that affect the estimated and delivered dose. These factors could reduce effective treatment time without affecting filter efficacy (*e.g.*, transition from CRRT to IHD), or they could reduce effective treatment time and affect filter efficacy (*e.g.*, filter clotting). Filter efficacy was estimated by FUN/BUN ratios and was measured every 12 hours. IHD, intermittent hemodialysis. D/C, discontinued.

Claure et al, Clin J Am Soc Nephrol 2011

Cause di Downtime in CRRT 2

	RCA (n = 152)	Heparin (n = 73)	No AC (n = 77)
CRRT STOPPING CAUSES			
CVC malfunction	34.9%	17.8%	15.6%
Alarm handling/technical issues	23.7%	12.3%	2.6%
Scheduled	19.7%	0%	1.3%
Medical procedures	13.8%	2.8%	3.9%
Clotting	0%	61.6%	68.8%
Unidentified	7.9%	5.5%	7.8%

Morabito et Al CCForum 2012

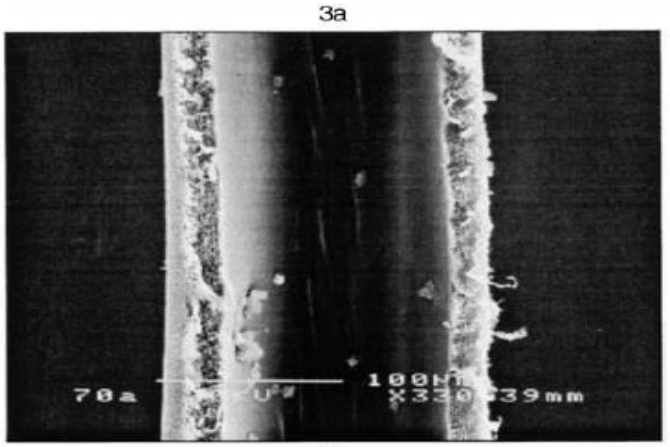
CRITICAL CARE

INDICAZIONI PRATICO/ORGANIZZATIVE

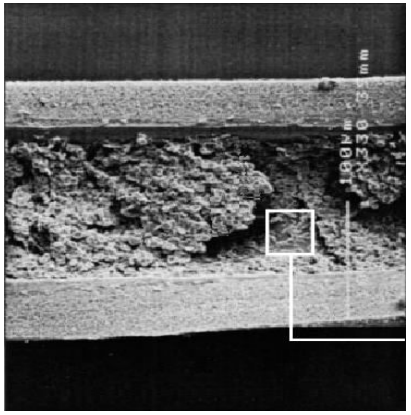
- Effetto sistemico
- Efficacia ritardata (sul circuito)
- Emivita medio-lunga
- Dipendenza da altri fattori
- Controllo dei TdC in Lab.

- Effetto regionale
- Efficacia immediata (sul circuito)
- Emivita breve
- Nessuna dipendenza
- Controllo diretto con EAB

OTTIMIZZAZIONE DEL FATTORE DEPURATIVO



2% OGNI 24h



20% OGNI 24h

Effect of Anticoagulation on Blood Membrane Interactions during Hemodialysis.

Hofbauer, R., Druml, W., et al., Kidney Int. Vol 56 (1999), pp. 1576-1583

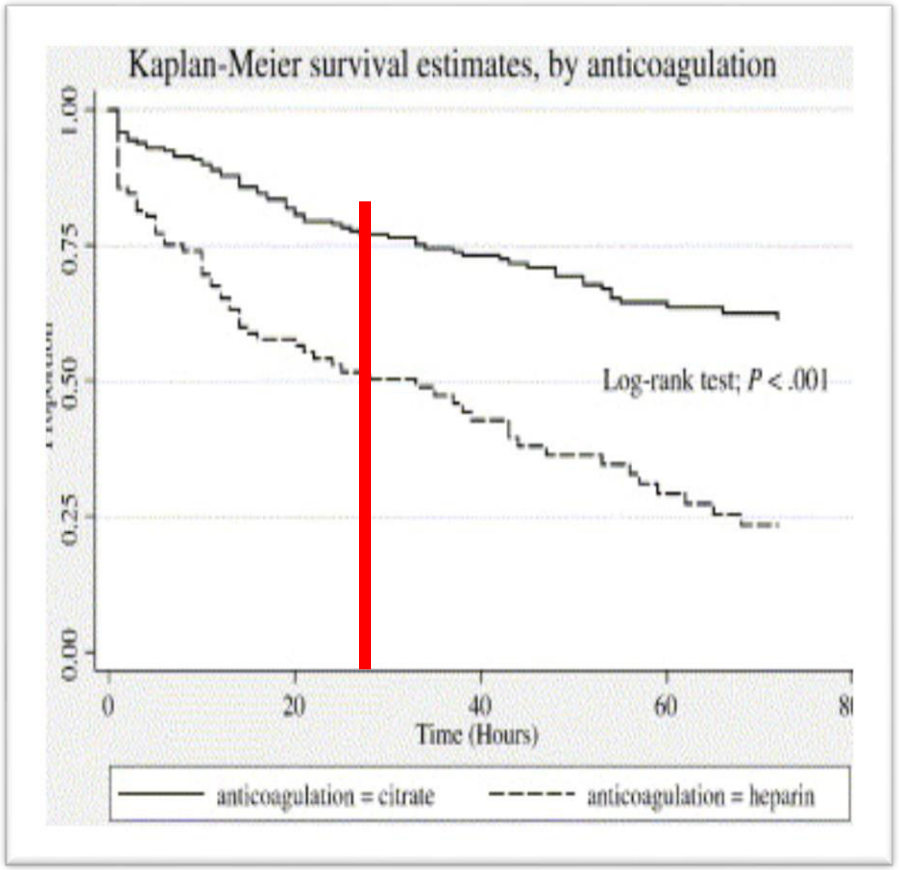
Hofbauer ha dimostrato minori effetti coagulativi con il citrato studiando l'interno delle fibre del filtro con il microscopio a scansione. Questo ci suggerisce che potremmo preservare più a lungo la capacità depurativa del filtro migliorando inoltre l'aderenza fra dose dialitica prescritta e quella realmente somministrata

AUMENTO DELLA DURATA DEI FILTRI

MEDIAN FILTER LIFETIME

Citrate 70 h VS Heparin 40 h

After 30 hrs >50% Heparin filter loss



Bagshaw SM, Laupland KB, Boite -au PJE, Godinez-Luna T. Is regional citrate superior to systemic heparin anticoagulation for continuous renal replacement therapy? A prospective observational study in an adult regio-nal critical care system. J Crit Care 2005; 20: 155-61.

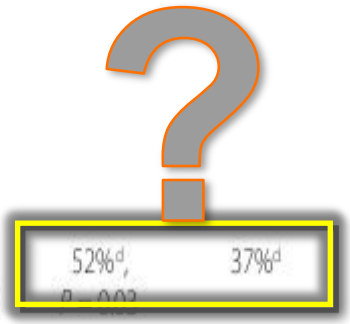
REVIEW

CRITICAL CARE

Bench-to-bedside review: Citrate for continuous renal replacement therapy, from science to practice

Heleen M Oudemans-van Straaten[1,*] and Marlies Ostermann[2]

		Circuit life (hours)[a]		Bleeding		Transfusion (RBC/day[b])		Survival	
Reference	Design	Citrate	Heparin	Citrate	Heparin	Citrate	Heparin	Citrate	Heparin
Monchi and colleagues [63]	RCOT, $n = 20$	70 (44 to 140), $P < 0.001$	40 (17 to 48)	$n = 0$	$n = 1$	0.2 (0 to 0.4), $P < 0.001$	1.0 (0 to 2.0)		
Kutsogiannis and colleagues [64]	RCT, $n = 30$	125 (95 to 157), $P < 0.001$	38 (25 to 62)	RR 0.17 (0.03 to 1.04), $P = 0.06$		0.53 (0.24 to 1.20), $P = 0.13$			
Betjes and colleagues [65]	RCT, $n = 48$			0%, $P < 0.01$	33%	0.43, $P = 0.01$	0.88		
Oudemans-Van Straaten and colleagues [35]	RCT[c], $n = 200$	27 (13 to 47), NS	26 (15 to 43)	6%, $P = 0.08$	16%	0.27 (0 to 0.63), $P = 0.31$	0.36 (0 to 0.83)	52%[d],	37%[d]
Hetzel and colleagues [66]	RCT, $n = 170$	37.5 ± 23, $P < 0.001$	26.1 ± 19.2	14.5%, $P = 0.06$	5.7%			±30%[e], NS	±43%[e]



CONTROINDICAZIONI AL CITRATO

The main limitation of citrate anticoagulation is accumulation as a result of reduced mitochondrial citrate metabolism. Reduced metabolism is seen in patients with liver failure due to decompensated chronic liver disease and also in those with ischemic hepatitis and poor muscle perfusion as seen in prolonged cardiogenic shock.

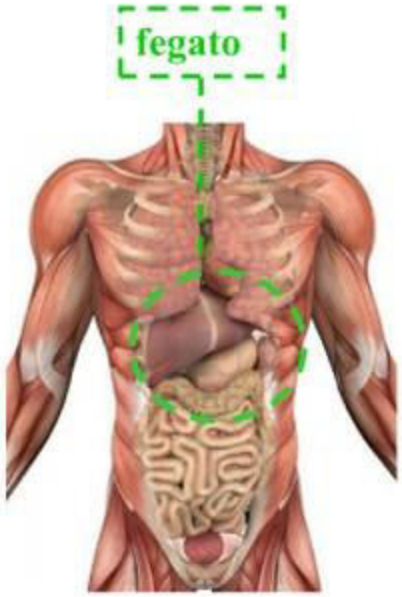
Oudemans-van Straaten and Ostermann Critical Care 2012, 16:249

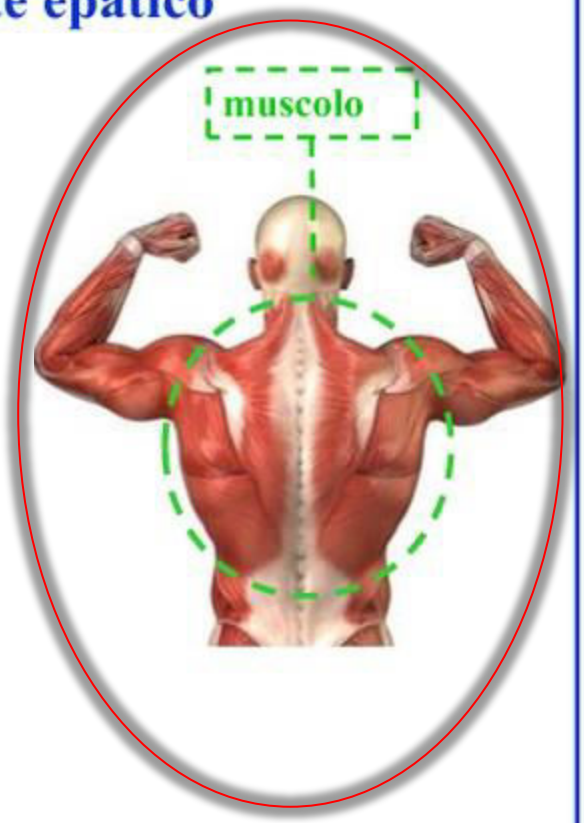
Regional citrate anticoagulation in patients with liver failure - time for a rethink?

Sameer Patel[1] and Julia Wendon[2,*]

See related research by Schultheiss et al., http://ccforum.com/content/16/4/R162

Metabolismo prevalentemente epatico





Aumentato apporto
e scarso metabolismo epatico e muscolare

AUMENTO DEL GAP ANIONICO
ACIDOSI METABOLICA
= insufficiente degradazione epatica del citrato a bicarbonato

A) accumulo di citrato per ridotto metabolismo

il citrato si accumula come anione

gap anionico = $Na^+ - (HCO^{3-} + Cl^-)$ *(range normale 12±2 mmol/l)*

B) la prescrizione dialitica

Elevato Qd con basso contenuto di bicarbonato (20 mmol/L)

+

Basso Qb

perdita di basi (bicarbonato, citrato) > somministrazione

Valutazione indiretta dell'accumulo di citrato nel paziente

Ca ionizzato (~50%)

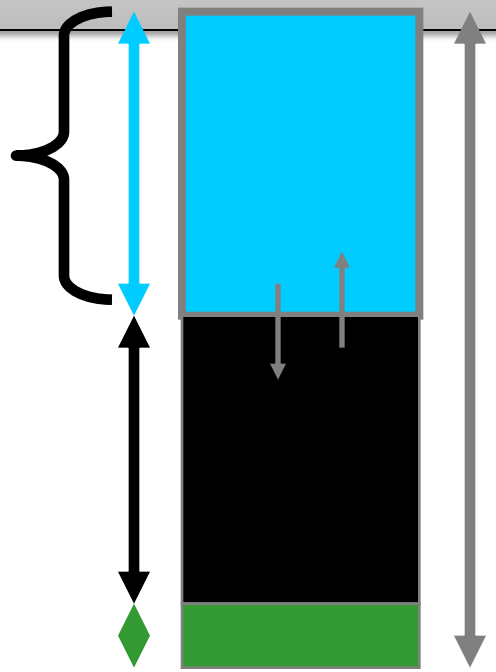
~ 1.17 – 1.3 mmol/L

Ca legato proteine (~40%)

~ 0.95 – 1.2 mmol/L

Ca complessato (~10%)

~ 0.05 mmol/L



Ca totale

~ 2.2 - 2.6 mmol/L

~ 2

Ca ionizzato

~ 0.9 - 1.2

DA ESEGUIRE ALMENO UNA VOLTA AL GIORNO

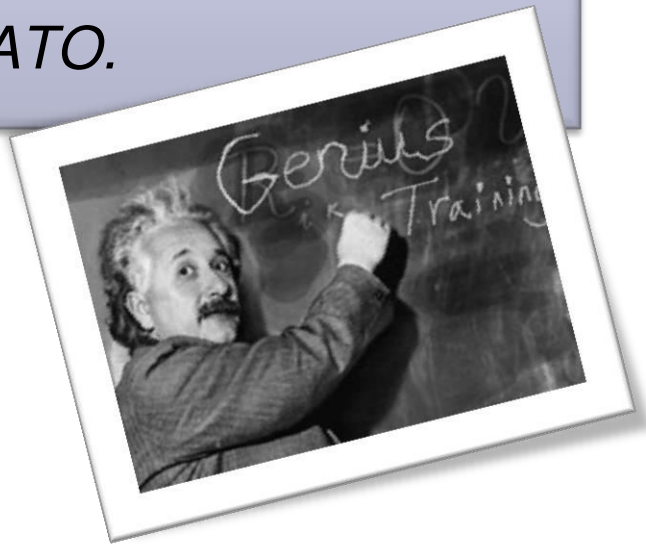
VALORI NORMALI < 2,5

Cubattoli et al. IJAO, 2007

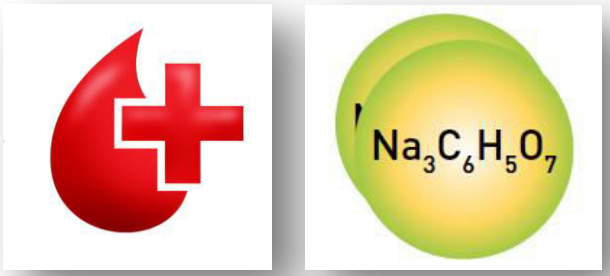
MATERIALI E METODI

CONCETTO DI BASE

NELLA CASCATA COAGULATIVA ALCUNI PASSAGGI SONO ***CALCIO DIPENDENTI****. SE IN QUALCHE MODO SI RIESCE A RIDURRE LA DISPONIBILITA' (LIVELLI PLASMATICI) DEL CALCIO INOIZZATO (Ca++) IL PROCESSO SI INTERROMPE MANTENENEDO IL SANGUE ANTICOAGULATO.*



Concentrazione ed effetto



= ANTICOAGULAZIONE

RAPPORTO COSTANTE $\frac{\text{SANGUE}}{\text{CITRATO}} = \frac{\text{1 lt}}{\text{3 mmol/l}}$

Effetti del Citrato

Action and adverse actions

Citrato Sacca

Calcio Paziente

FILTRO

Calcio-citrato

RIMOZIONE PER DEPURAZIONE

PAZIENTE

Buffer overload → Alcalosi metabolica

Ridotto metabolismo → Acidosi metabolica
- Incremento Anion Gap
- Ridotto iCa^{++}
- $totCa^{++}/iCa^{++}$ >2.5

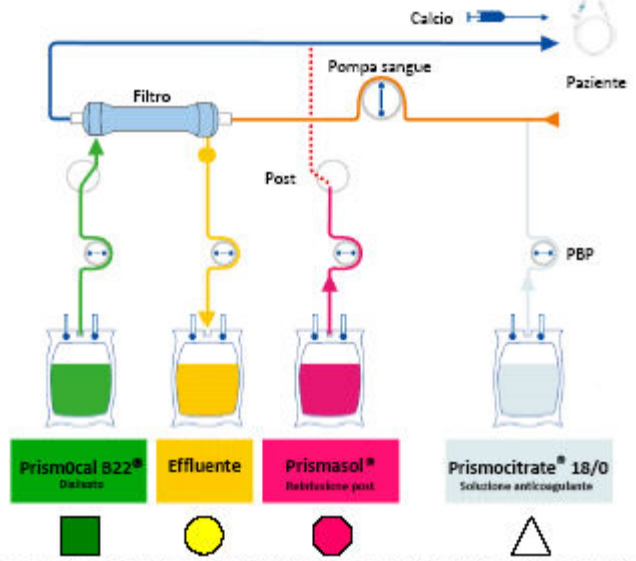
CVVHDF CITRATO

CVVHDF con Citrato con Prismaflex

(Prismocitrate® 18/0 e Prismasol®)

IMPOSTAZIONE FLUSSI	Peso paziente fino a 80 Kg	Peso paziente superiore a 81 Kg
FLUSSO SANGUE	120 ml/min	140 ml/min
Infusione PBP Prismocitrate® 18/0	Dose = 3 mmol/L sangue Flusso = 1200 ml/h	Dose = 3 mmol/L sangue Flusso = 1400 ml/h
DIALISATO Prism0cal® B22	1200 ml/h	1500 ml/h
REINFUSIONE post Prismasol®	300 ml/h	500 ml/h
SIRINGA PRISMAFLEX *	Compensazione = 100 % Impostazione di default	Compensazione = 100 % Impostazione di default

* Utilizzare esclusivamente una siringa da 50 cc contenente fiale non diluite di CALCIO CLORURO al 10% collegata al CVC paziente tramite linea dedicata CA250. Assicurarsi che la soluzione di calcio utilizzata sia la stessa impostata sull'apparecchiatura Prismaflex.



Le informazioni contenute in questo documento sono da considerarsi puramente indicative. A fini prescrittivi seguire i protocolli locali del proprio centro e rivolgersi al medico referente.

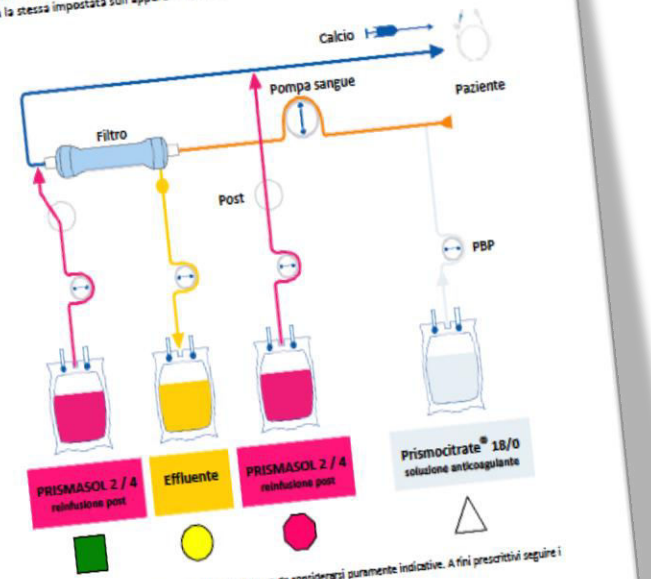
IMPOSTAZIONE FLUSSI E CONDUZIONE TRATTAMENTO

CVVH con Citrato con Prismaflex

(Prismocitrate® 18/0 e PRISMASOL 2 / 4)

IMPOSTAZIONE FLUSSI	Peso paziente fino a 80 Kg	Peso paziente superiore a 81 Kg
FLUSSO SANGUE	130 ml/min	150 ml/min
Infusione PBP	Dose = 3 mmol/L sangue	Dose = 3 mmol/L sangue
Prismocitrate® 18/0	Flusso = 1300 ml/h	Flusso = 1500 ml/h
REINFUSIONE	1200 ml/h	1500 ml/h
PRISMASOL 2 / 4		
SIRINGA PRISMAFLEX *	Compensazione = 100 % Impostazione di default	Compensazione = 100 % Impostazione di default

* Utilizzare esclusivamente una siringa da 50 cc contenente fiale non diluite di CALCIO CLORURO al 10% o CALCIO GLUCONATO al 10% collegata al paziente tramite linea dedicata CA 250. Assicurarsi che la soluzione di calcio utilizzata sia la stessa impostata sull'apparecchiatura Prismaflex.



Le informazioni contenute in questo documento sono da considerarsi puramente indicative. A fini prescrittivi seguire i protocolli locali del proprio centro e rivolgersi al medico referente.

CONDUZIONE DEL TRATTAMENTO

Monitoraggio consigliato durante la fase iniziale del trattamento

Ca ionizzato post filtro 0,25-0,50 mmol/L o 1,0 - 2,0 mg/dL	30'			Almeno ogni 12 ore
Ca ionizzato sistemico 1,00-1,20 mmol/L o 4,0-4,8 mg/dL	30'	1 ora	2 ore (DALLA PARTENZA)	Almeno ogni 8 ore

AGGIUSTAMENTO DEL CALCIO IONIZZATO POST FILTRO

mg/dl	<1.00	1.00 - 2.00	>2.00	mg/dl
mmol/l	<0.25	0.25 - 0.50	>0.50	mmol/l
	EGA 6 ORE	EGA 12 ORE	EGA 6 ORE	
OSE CITRATO	- 0.3 mmol	NESSUNA MODIFICA	+ 0.3 mmol*	

*Da eseguire solo se HCO3- <27

AGGIUSTAMENTO DELLA CALCEMIA PAZIENTE TRAMITE SIRINGA PRISMAFLEX

mg/dl	<3.2	3.6	4.0	4.4	4.8	5.4	mg/dl
mmol/l	<0.80	0.90	1.0	1.1	1.2	1.35	mmol/l
	EGA 1 ora	EGA 2 ore	EGA 4 ore	EGA 6 ore	EGA 4 ore	EGA 2 ore	
	+30 %	+20 %	+10 %	Compensazione adeguata Nessuna modifica	-10 %	-20 %	

Le variazioni si intendono rispetto al valore attualmente impostato

AGGIUSTAMENTO BICARBONATO (applicare entrambe le modifiche suggerite)

mmol/l	20	22	27	28	
	EGA 6 ORE	EGA 6 ORE	EGA 12 ORE	EGA 6 ORE	EGA 6 ORE
EINFUSIONE			NESSUNA MODIFICA		+600 ml/h
OSE CITRATO	+ 0,6	+ 0,3	NESSUNA MODIFICA	- 0,3	- 0,6

Le variazioni si intendono rispetto alla prescrizione iniziale

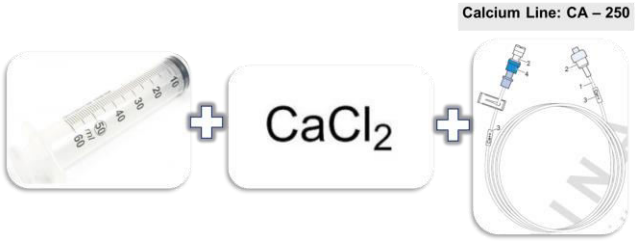
Si consiglia di eseguire almeno una volta al giorno il rapporto CA Tot. / CA++

CONDUZIONE DEL TRATTAMENTO

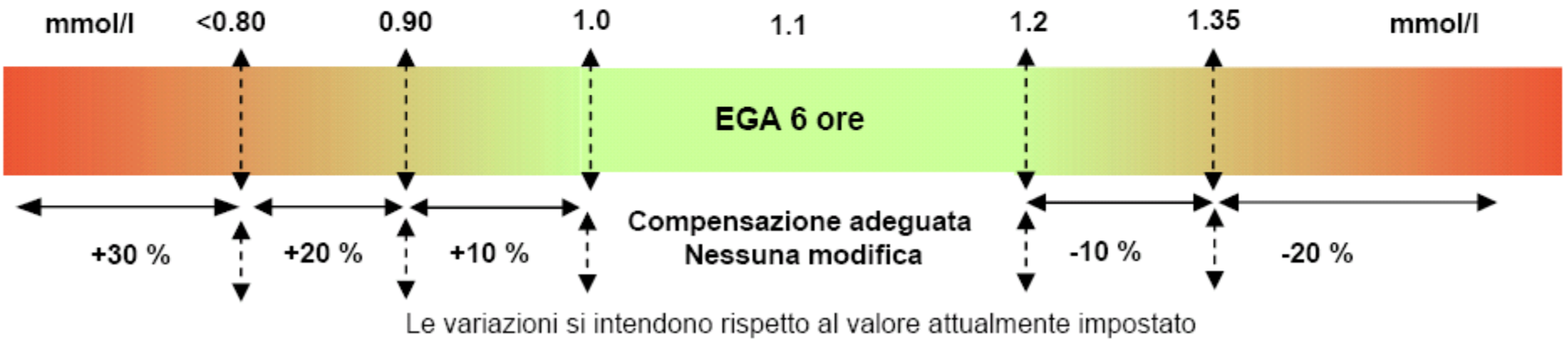
Monitoraggio consigliato durante la fase iniziale del trattamento

Ca ionizzato post filtro **0,25-0,50 mmol/L o 1,0- 2,0 mg/dL**	**30'**			Almeno ogni 12 ore
Ca ionizzato sistemico **1,00-1,20 mmol/L o 4,0-4,8 mg/dL**	**30'**	**1 ora**	**2 ore**	Almeno ogni 6 ore
	DALLA PARTENZA			

PRIORITA’ 1



COMPENSAZIONE % CALCIO IONIZZATOPAZIENTE TRAMITE SIRINGA PRISMAFLEX



Le variazioni si intendono rispetto al valore attualmente impostato

GRAZIE