The Use of Citrate as an Anticoagulant for Continuous Renal Replacement Therapy

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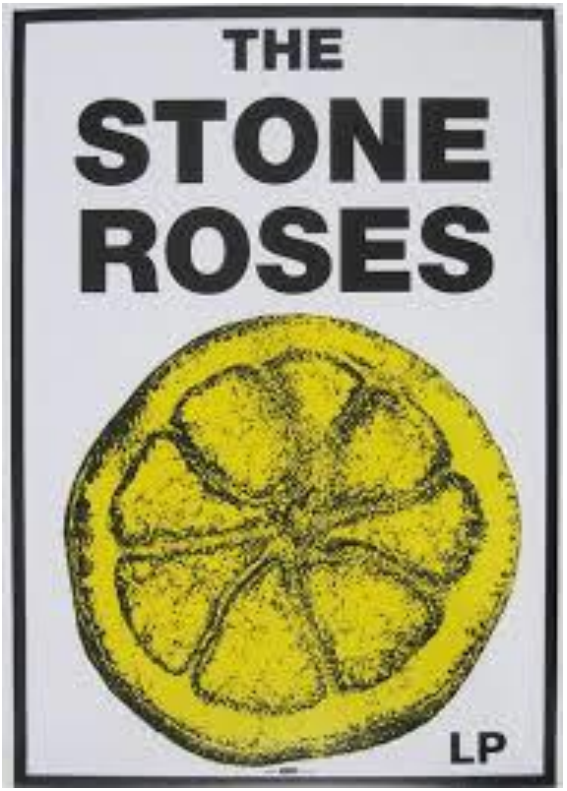
Tuesday 28th April 2015



Declaration

- Attended Gambro (now Baxter) user group meeting Feb 2015

- Free lunch & some nice biscuits

Introduction

- Why citrate?
- How citrate is used
- Our experience at RHH

Why Citrate at RHH?

- Needed new filters
- Wanted the option of using citrate

Ideal Anticoagulant

- During RRT, to prevent clotting in the extracorporeal circuit anticoagulation is needed

- Ideally this anticoagulant should be
  - Regional
  - Reversible/short half-life
  - Free from side effects
  - User friendly

Citrate vs Heparin

Citrate

- Regional coagulation
- No bleeding risk
- No extra-platelet effect
- Additional filter fluid; citrate
- Citrate toxicity

Heparin

- Systemic anticoagulation
- Bleeding risk
- Thromocytopenia, particularly Type 2 HIT
- Standard filter fluids

Why Citrate?

- Only the filter is anti-coagulated;
  - ideal for bleeding patient (trauma, intracerebral haemorrhage)
  - returning from Theatre etc.

- Invasive procedures (lines, tracheostomies, surgery etc.) can be done without stopping CRRT; increases effectiveness of therapy whilst saving laborious & expensive set changes, blood loss

- Less circuit downtime – higher dose of therapy delivered

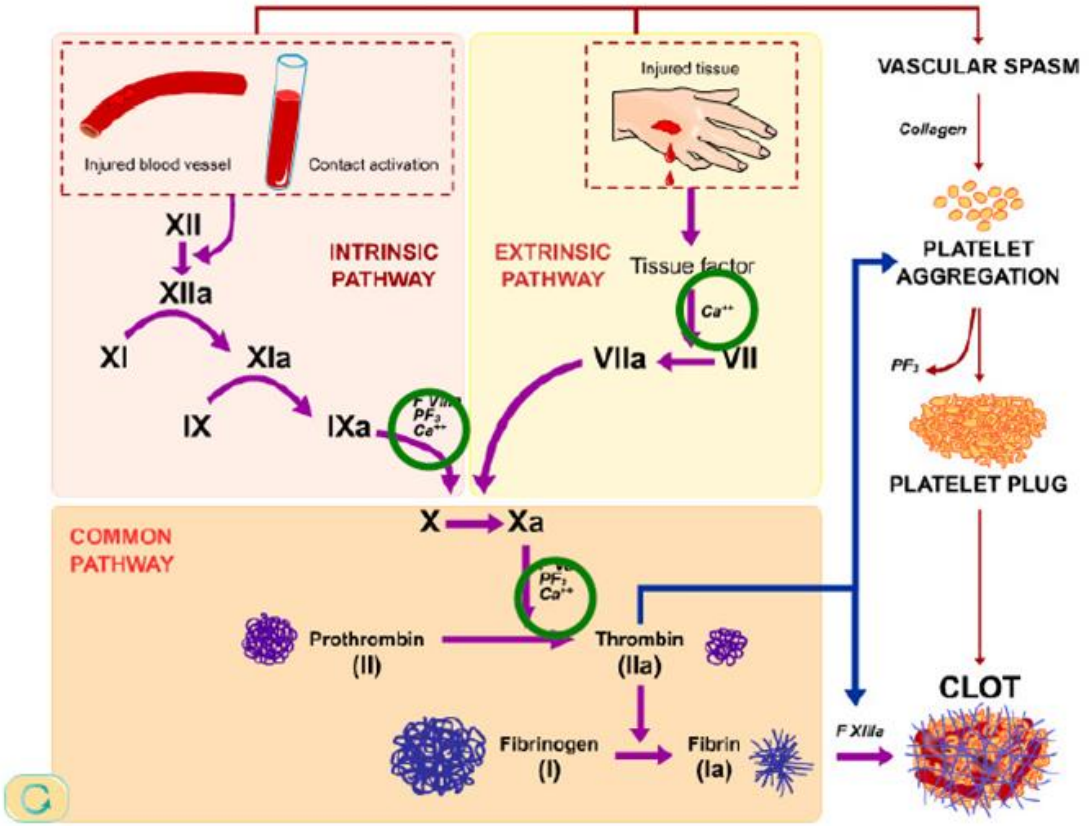
- Heparin needs monitoring & can be difficult to get right (NB patients prothrombotic despite apparent anticoagulation cf TEG)

Thrombocytopenia

- Patients requiring RRT are the most septic & so often their platelets are already low
- Thrombocytopenia; Type 1 (common, day 4-5 but usually mild, transient)
- Type 2; uncommon/rare immunological reaction, causes venous & arterial clots, not easy to diagnose (immunology to Bristol??) which takes time.
- Heparin then CId for that patient lifelong with many potential implications.

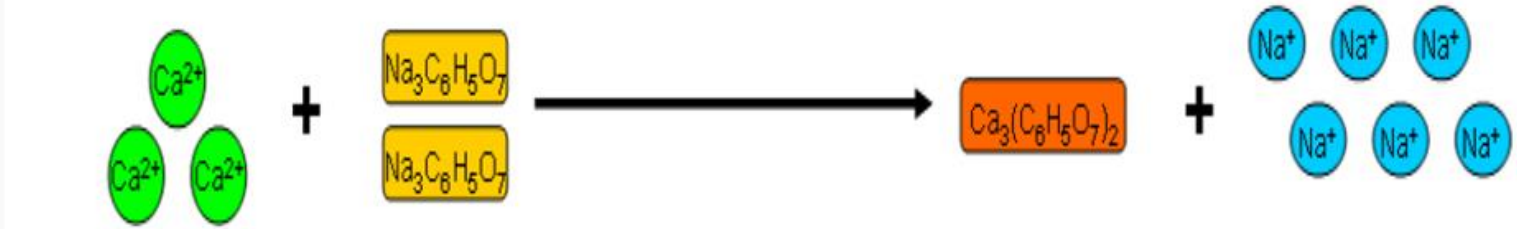
How Citrate Works

Coagulation cascade



Mode of Action I

- Citrate chelates ionised Calcium (and Magnesium)

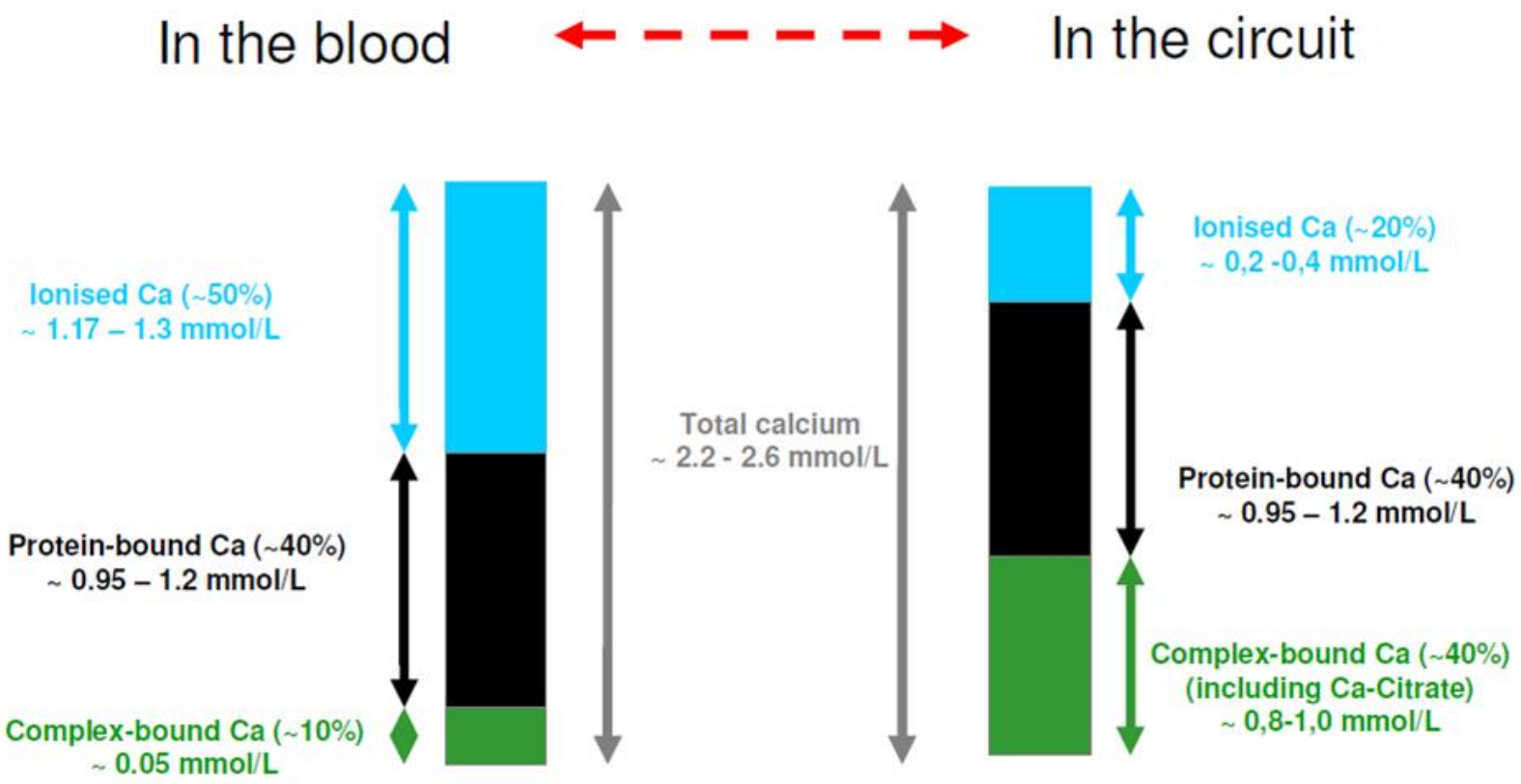


3 Calcium ions + 2 Sodium Citrate molecules = 1 Calcium Citrate molecule + 6 Sodium ions

Citrate Dose

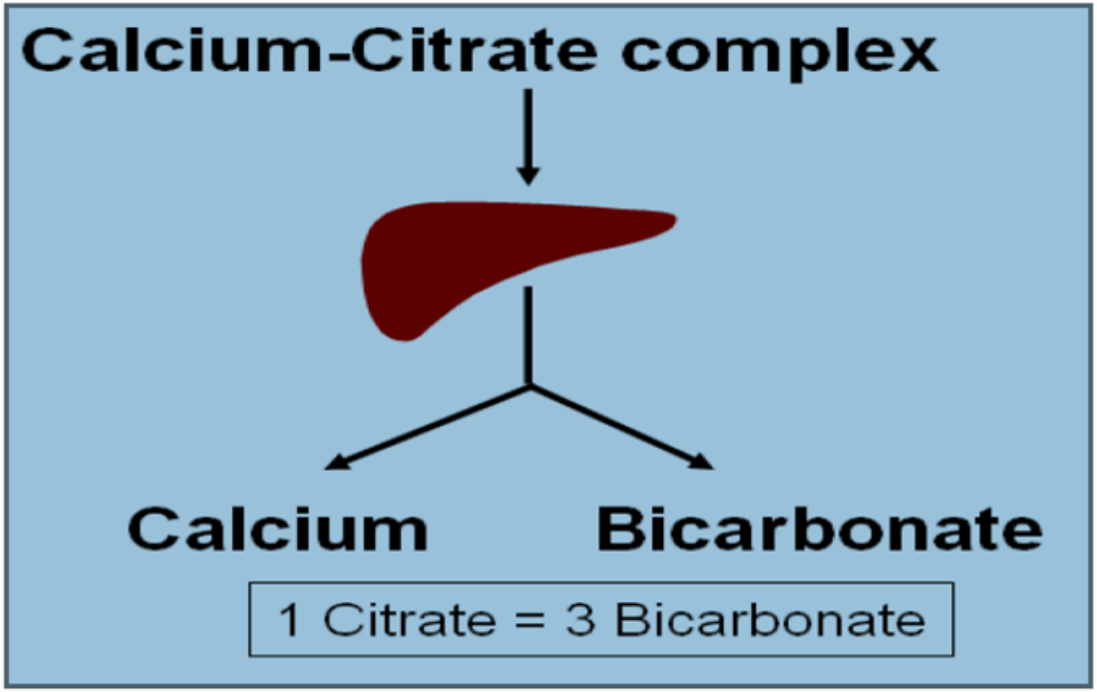
- Clotting does not occur with ionised calcium level in the extracorporeal circuit 0.25 - 0.35 mmol/L (in reality upper limit ~ 0.5mmol/L)
- Achieved by a concentration of citrate; 3 - 4 mmol/L blood
- Prismaflex administers citrate solution into the circuit at a dose to maintain circuit ionised calcium levels between 0.25 and 0.35 mmol/L post filter – default starting dose 3.00 mmol/L blood

Calcium Distribution



Mode of action II

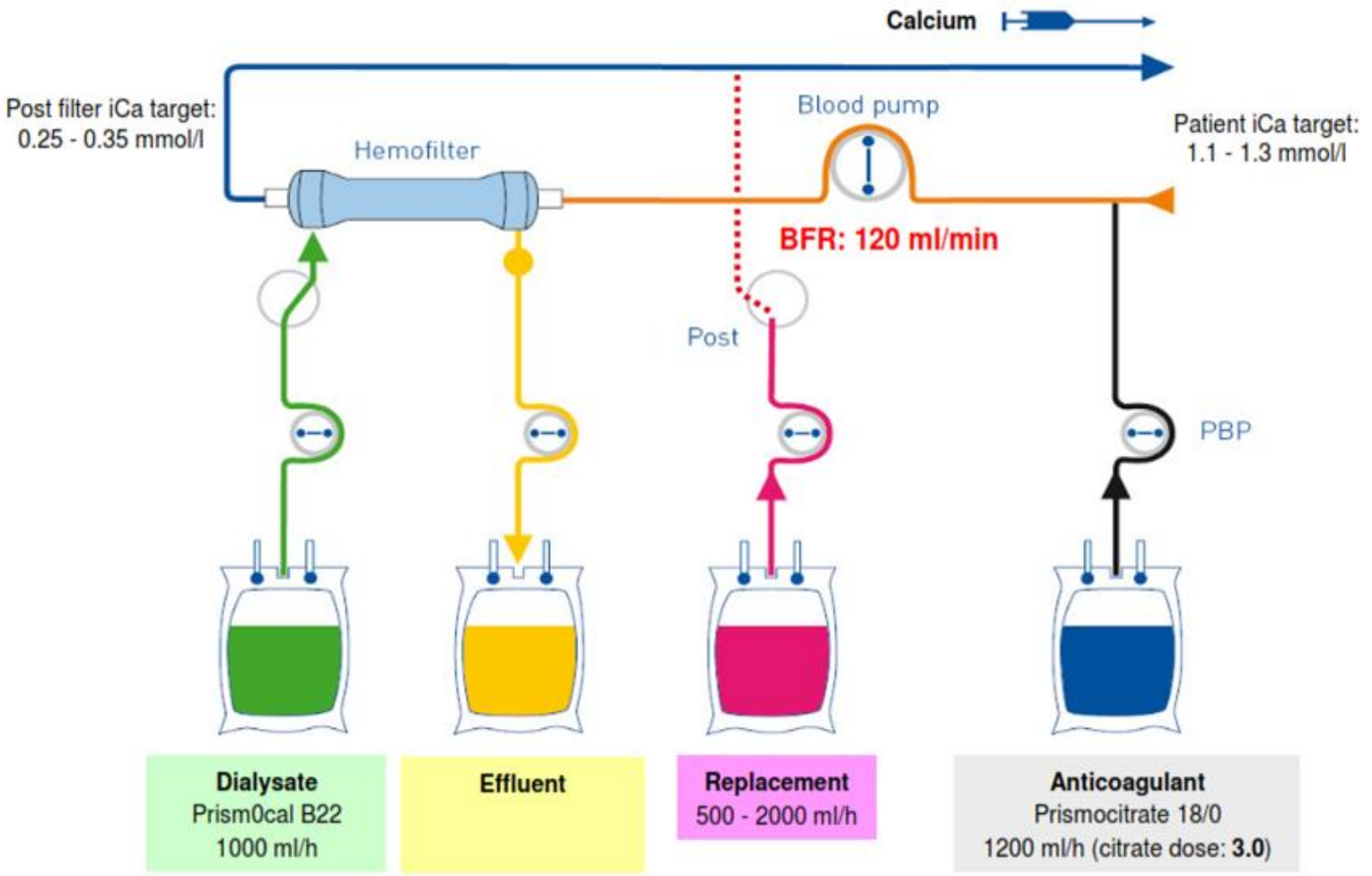
- Citrate is metabolised in liver, skeletal muscle and kidney into bicarbonate releasing the chelated calcium



Key Point

- Citrate anti-coagulation is in effect like giving Bicarbonate

Circuit Set-Up



Flow Settings

Actual Body Weight (Kg)	Blood flow, ml/min.	Dialysate, ml/hr.	Replacement, ml/hr.	Resulting Treatment Dose
60	110	1100	400	37mls/Kg/hr
70	120	1200	500	35mls/kg/hr
80	130	1300	500	33mls/kg/hr
90	140	1400	500	31mls/kg/hr
100	150	1500	600	31mls/kg/hr
110	160	1600	700	30mls/kg/hr
120	170	1700	800	30mls/kg/hr
130	180	1800	1000	30mls/kg/hr

Cautions with Citrate

- Not metabolised in
  - fulminant hepatic failure
  - cirrhosis
  - liver blood flow very poor
  - conditions associated with severely reduced muscle perfusion

- Citrate accumulation results in rising measured blood total calcium
  - watch total:ionised calcium ratio approaching 2.5
  - Rising calcium compensation

Citrate Accumulation

- Due to large amounts of citrate being infused more rapidly than they can be cleared by either dialysis or metabolic pathways
- Citrate circulates in plasma mainly bound to calcium.
- Accumulation of citrate causes progressive ionised hypocalcemia (<0.95 mmol/L) and may be associated with metabolic acidosis or metabolic alkalosis, depending on citrate metabolism and infusion rate
- Clinical manifestations include tetany, seizures, hypotension and cardiac dysrhythmias

Characteristics of citrate accumulation

- Decreasing iCa++
- Increasing calcium replacement requirement
- Increasing TotCa / iCa++ ratio (>2.5) and TotCa - iCa++ gap
- Hypercalcemia

Citrate Disadvantages

- Initial educational work
- Requires close monitoring of calcium, pH and electrolytes
- Metabolic complications
- Citrate toxicity if citrate not adequately metabolised
- Fluid costs

Monitoring Regime

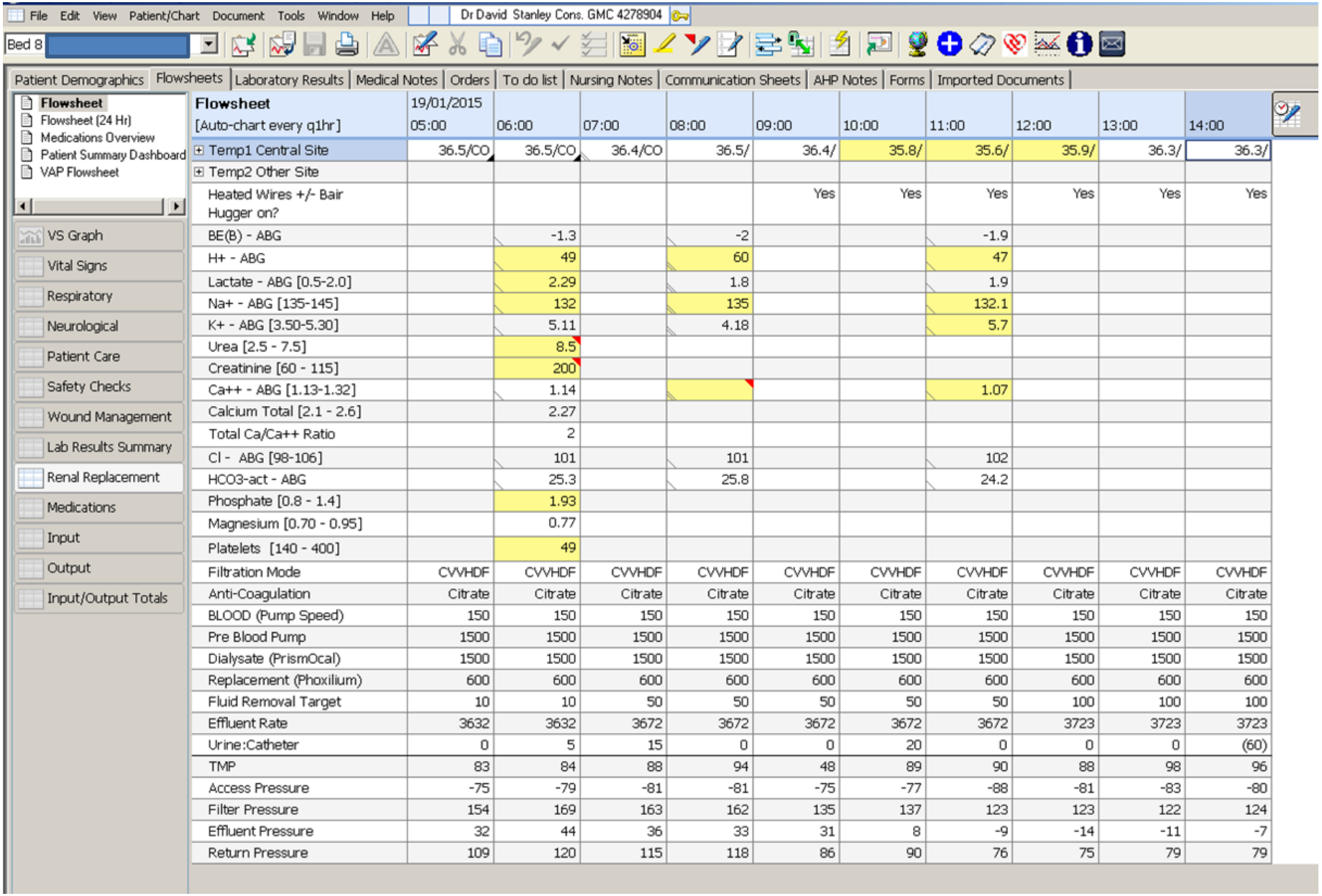
1.2.13 Calcium Monitoring & Adjusting Citrate (Prismocitrate)

Monitoring of Anticoagulation	**After Onset or Any Change in Flow Rates**	**If Flow Rates Unchanged**	
Post Filter Ionised Calcium (Blood gas from circuit) Target; 0.25 - 0.50 mmol/L	1 hour	4 Hours	6 Hours Then every 6 hours
Patient Ionised Calcium (ABG from patient) Target: 0.99 - 1.20 mmol/L	1 hour	4 Hours	6 Hours Then every 6 hours
Patient Total Calcium (Laboratory Biochemistry)	Once a day from laboratory Biochemistry result		
Calcium Ratio (Patient Total Calcium : Ionised Calcium ratio) Target: < 2.5mmol/L	Ratio checked daily & calculated. Displayed on ICCA in 'Renal Replacement' Flowsheet. If ratio > 2.5; **inform medical staff immediately**		

RHH Data 01/04/14-31/03/15

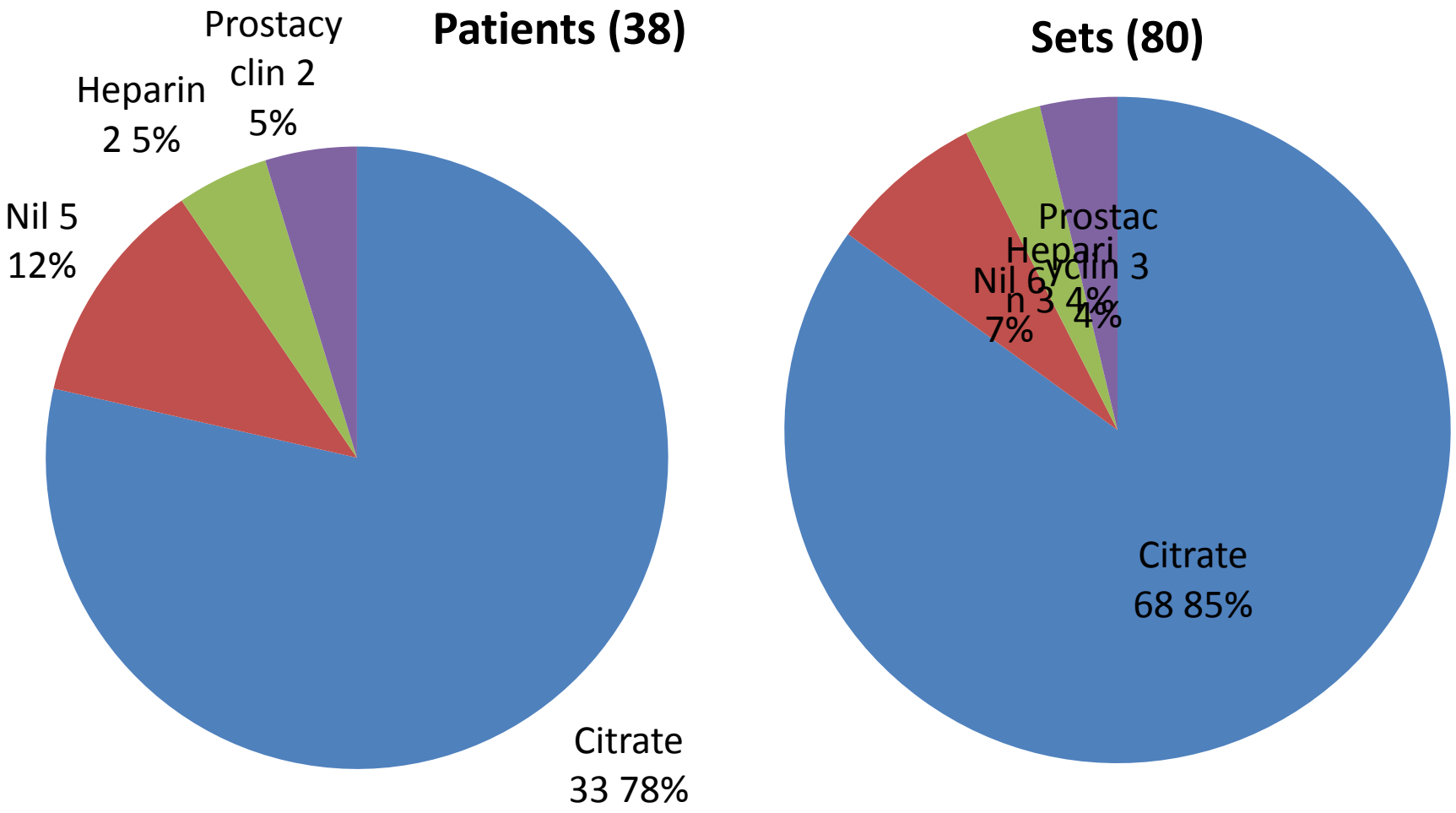
RHH Data

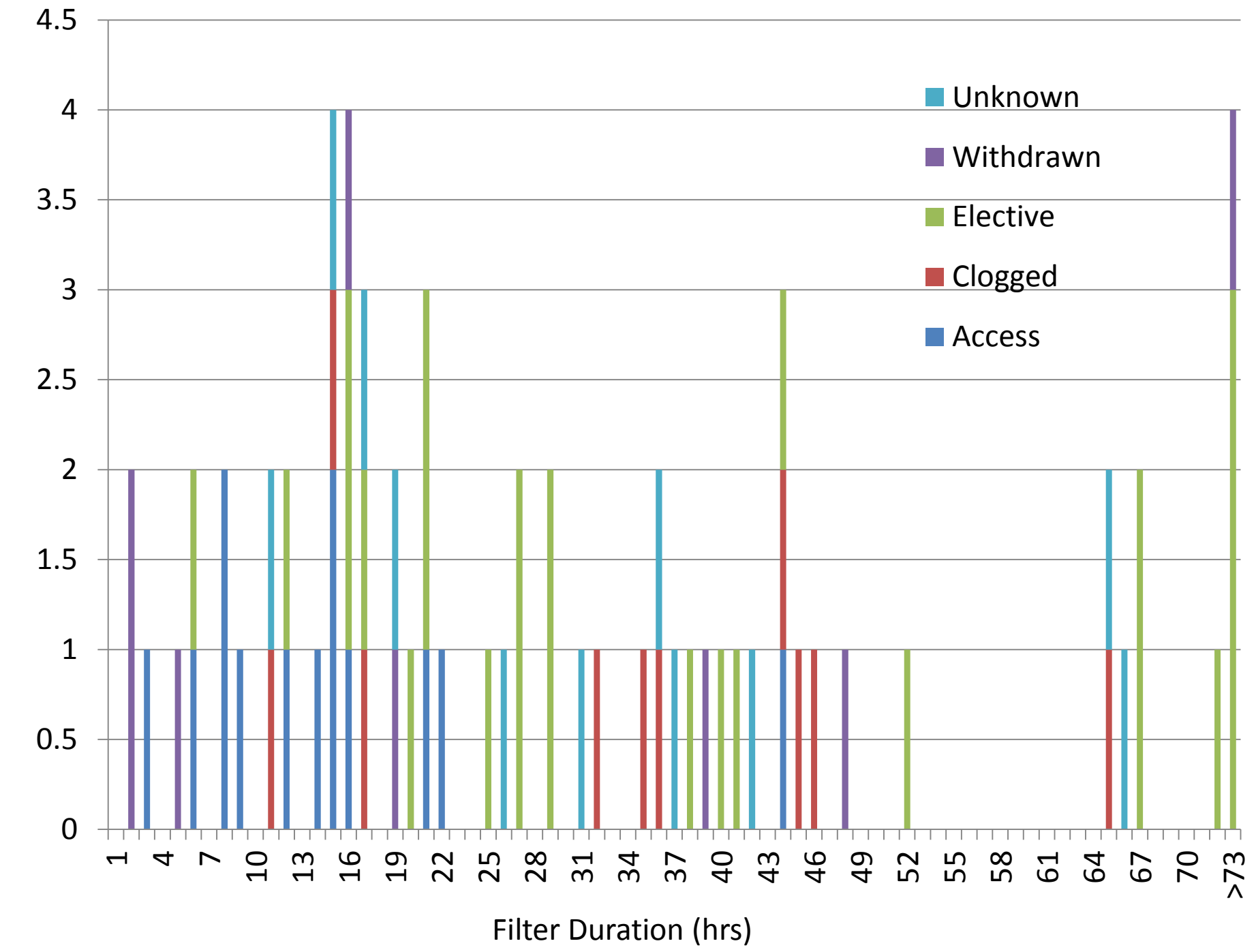
- Retrospective analysis of ICU EPR
- 41/326 (8%) patients received RRT
- 2 IHD
- 1 patient data missing
- 39 patients analysed
- Probably underestimated number of filters used, if no gap in the hourly flowsheet
- Reason for filter stopping very subjective



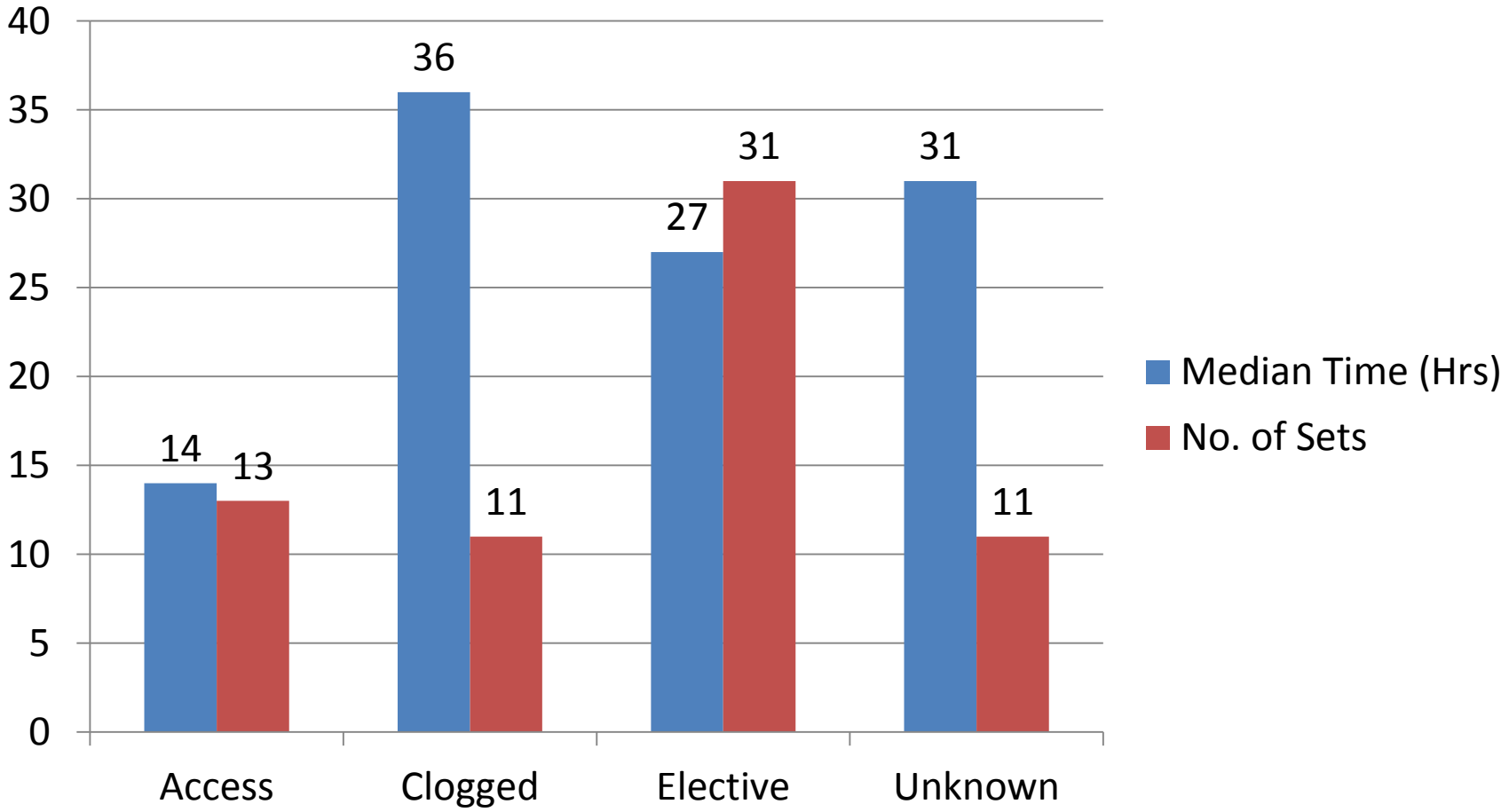
Flowsheet [Auto-chart every q1hr]	19/01/2015 05:00	06:00	07:00	08:00	09:00	10:00	11:00	12:00	13:00	14:00
⊞ Temp1 Central Site	36.5/CO	36.5/CO	36.4/CO	36.5/	36.4/	35.8/	35.6/	35.9/	36.3/	36.3/
⊞ Temp2 Other Site										
Heated Wires +/- Bair Hugger on?					Yes	Yes	Yes	Yes	Yes	Yes
BE(B) - ABG		-1.3		-2			-1.9			
H+ - ABG		49		60			47			
Lactate - ABG [0.5-2.0]		2.29		1.8			1.9			
Na+ - ABG [135-145]		132		135			132.1			
K+ - ABG [3.50-5.30]		5.11		4.18			5.7			
Urea [2.5 - 7.5]		8.5								
Creatinine [60 - 115]		200								
Ca++ - ABG [1.13-1.32]		1.14					1.07			
Calcium Total [2.1 - 2.6]		2.27								
Total Ca/Ca++ Ratio		2								
Cl - ABG [98-106]		101		101			102			
HCO3-act - ABG		25.3		25.8			24.2			
Phosphate [0.8 - 1.4]		1.93								
Magnesium [0.70 - 0.95]		0.77								
Platelets [140 - 400]		49								
Filtration Mode	CVVHDF	CVVHDF	CVVHDF	CVVHDF	CVVHDF	CVVHDF	CVVHDF	CVVHDF	CVVHDF	CVVHDF
Anti-Coagulation	Citrate	Citrate	Citrate	Citrate	Citrate	Citrate	Citrate	Citrate	Citrate	Citrate
BLOOD (Pump Speed)	150	150	150	150	150	150	150	150	150	150
Pre Blood Pump	1500	1500	1500	1500	1500	1500	1500	1500	1500	1500
Dialysate (PrismOcal)	1500	1500	1500	1500	1500	1500	1500	1500	1500	1500
Replacement (Phoxilium)	600	600	600	600	600	600	600	600	600	600
Fluid Removal Target	10	10	50	50	50	50	50	100	100	100
Effluent Rate	3632	3632	3672	3672	3672	3672	3672	3723	3723	3723
Urine:Catheter	0	5	15	0	0	20	0	0	0	(60)
TMP	83	84	88	94	48	89	90	88	98	96
Access Pressure	-75	-79	-81	-81	-75	-77	-88	-81	-83	-80
Filter Pressure	154	169	163	162	135	137	123	123	122	124
Effluent Pressure	32	44	36	33	31	8	-9	-14	-11	-7
Return Pressure	109	120	115	118	86	90	76	75	79	79

Anticoagulation




4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
Unknown
Withdrawn
Elective
Clogged
Access
1
4
7
10
13
16
19
22
25
28
31
34
37
40
43
46
49
52
55
58
61
64
67
70
>73
Filter Duration (hrs)

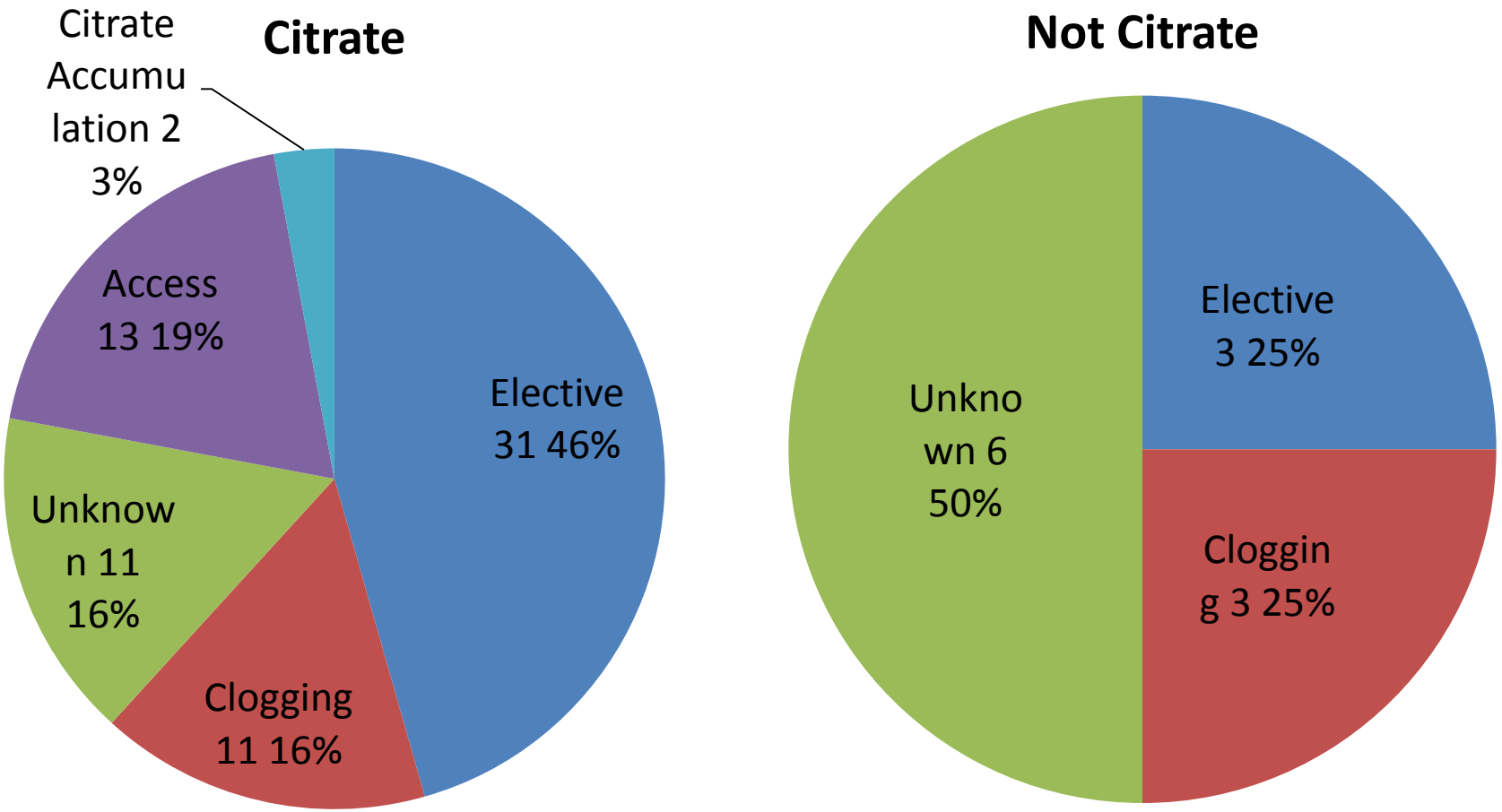
Duration using Citrate



Filter Duration without Citrate (hrs)

- Elective (treatment withdrawn); 8, 17, 84
- Clogged; 14, 15, 41
- Unknown; 16, 26, 29, 53, 55, 90

Reason for stopping



Citrate Accumulation

- After 46 & then 64 hours in the same patient with liver failure
- Detected by Total:Ionised Ca 2.5
- No adverse features
- Self-resolved with time

Costs

- Fluid costs for a 90kg patient on a standard regime £210/day
- Calcium gluconate £37
- £28,431 in 2014-15 on renal fluids

Pros

- Removed all the worries of the bleeding patient
- Reassurance that thromocytopenia is not due to anticoagulant
- Citrate toxicity not a problem (advisory built in to the EPR)
- Anecdotally sets lasting longer; retrospective data actually hard to interpret (real reason filter stopped?)

Cons

- Big mindshift out of our comfort zone
- Staff training;
  - Internally
  - Gambro
  - Consultant M&M
- Junior medical staff no knowledge
- As with all new treatment modalities a big learning curve
- Patients under/overtreated/reluctance to change prescription
- Very shutdown / poorly perfused acidotic patients are challenging

Acknowledgements

- Baxter for slides 10,11,13,14

- Dr Borgstom, Kalmar Hospital, Sweden for the schematic on slide used for 16

References

- Monchi M. Citrate vs. heparin for anticoagulation in continuous venovenous hemofiltration: a prospective randomized study. *Intensive Care Med.* 2004 Feb;30(2):260-5.
- Longer circuit life; 70 vs 41

- Oudemans-van Straaten HM et al. Citrate anticoagulation for continuous venovenous hemofiltration. *Crit Care Med.* 2009 Feb;37(2):545-52.
- Vs nadoraparin; Less bleeding, lower mortality, less metabolic alkalosis. Circuit lives similar.

- Oudemans-van Straaten HM et al. Citrate for continuous renal replacement therapy: safer, better and cheaper. *Critical Care* 2014, 18:143 (19 May 2014)

- Ronco C et al. Renal replacement therapy in acute kidney injury: controversy and consensus. *Critical Care* 2015 19:146

- Gattas D et al. A randomized controlled trial of regional citrate versus regional heparin anticoagulation for continuous renal replacement therapy in critically ill adults. *Critical Care Medicine* 2015 (accessed 26/4/15; not in print yet)
- Median duration 39 vs 23 hrs, reduced complications, no difference in outcomes; mortality, LoS, RBC transfusion

“In this citrus soaking sunshine I don’t care”

- Brown I, Squire J. *Bye, Bye Badman, Track 5, The Stone Roses, The Stone Roses*. Silvertone Records 1989

ICU Renal Replacement Therapy (RRT) Chart for Citrate

The Dudley Group NHS
NHS Foundation Trust

To be completed by prescriber	To be completed by operator

Date ____ / ____ / 20___

Patient name ____________________

Unit number ____________________

NHS no ____________________

DoB ___/___/___

VALID FOR 24 hours only

Indication: ______________ Treatment Mode: CVVHDF

Total Fluid Balance Target for Next 24hrs: ______L

Hourly Fluid Removal: _____ml/hr

Na^+	_____mmol/l	Platelets	_____ $\times 10^9/l$
K^+	_____mmol/l	Total Calcium	_____ mmol/l
Urea	_____mmol/l	Creatinine	_____ mcmol/l

Ca Ratio = Total Ca / Patient ionised Ca _____

If Ratio > 2.5 Stop Prismocitrate & seek medical advice

RRT Fluids Flowrate Instructions

Refer to Guidelines

Patient Total Body Weight	_____	kg	
Dialysate Rate	_____	ml/hr	(0 - 4000 ml/hr)
Replacement Rate	_____	ml/hr	(Minimum 500ml/hr)
Blood Pump Speed	_____	ml/hr	

Anticoagulation Prescription

0.9% NaCl priming	1- 2L	Sign______________
Calcium Gluconate;		Print Name______________
	start@15ml/hr	GMC No:______________

RRT Fluids Prescription

Prismocitrate 18/0	5000ml	Sign______________
Phoxilium	5000ml	Print Name______________
PrismOcal	5000ml	GMC No:______________

Sodium Bicarbonate 8.4% add systemically if required

No / Yes

Calcium Gluconate Infusion (Neat)

Time	Dose / mls	1st Sig	2nd Sig

Fluids - Citrate, Phoxilium or PrismOcal

	1st Sig	2ndSig		1st Sig	2nd Sig
Cit / P4 /Ocal/Bic			Cit / P4 /Ocal/Bic		
Cit / P4 /Ocal/Bic			Cit / P4 /Ocal/Bic		
Cit / P4 /Ocal/Bic			Cit / P4 /Ocal/Bic		
Cit / P4 /Ocal/Bic			Cit / P4 /Ocal/Bic		
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Cit / P4 /Ocal/Bic			Cit / P4 /Ocal/Bic		

Anticoagulant Documentation

Time	Filter Calcium (aim 0.25 - 0.5)	Citrate Dose mmol/L	Prt. Calcium (aim 0.99 - 1.20)	Calcium dose ml/hr / mmol	Citrate Load ml/hr mmol