The management of fluid overload in AKI: diuretics or starting replacement therapy?

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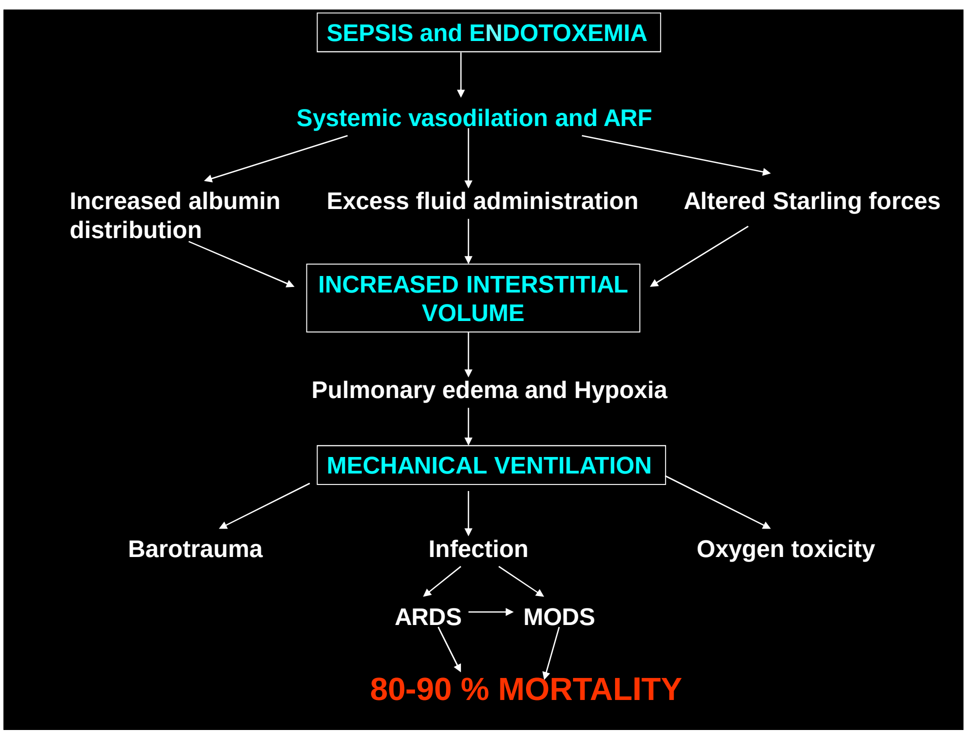
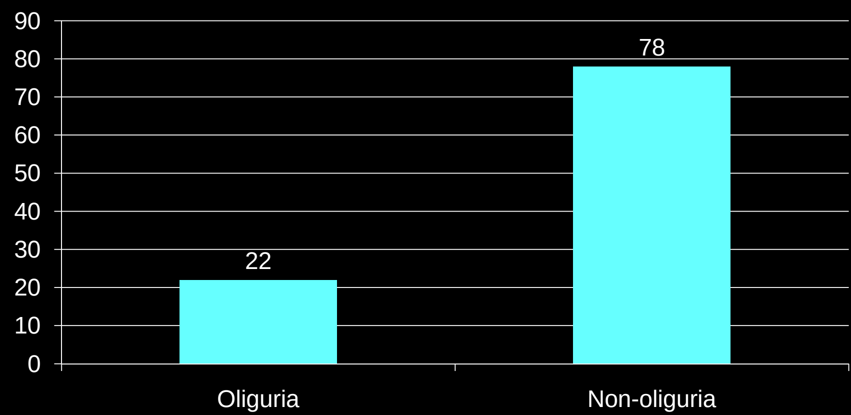


Estimating volume status in ICU

Fluid responsiveness

Prevalence of oliguria in the VA Trial (%)



Oliguria: <20 ml per hour for >24 hours

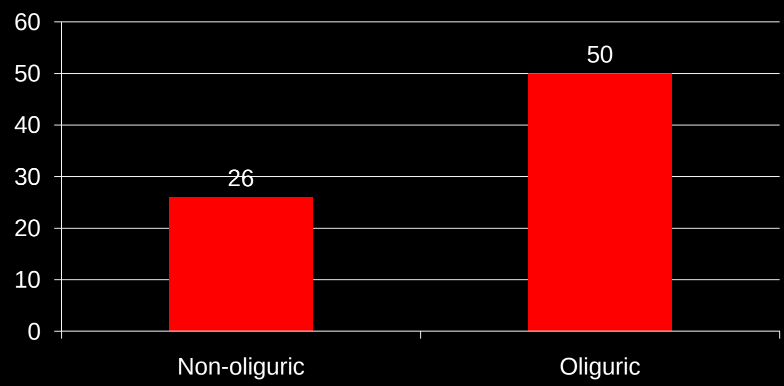
The VA/NIH Acute Renal Failure Trial Network, N Engl J Med 2008;359:7-20.

Some baseline data on 1238 ICU patients with severe AKI receiving RRT (BEST Kidney study)

RRT kidney function	
SCr, median (IQR), μmol/L	309 (202-442)
ΔSCr (μmol/L) [a]	163 (78-269)
Urea, median (IQR), mmol/L	24.2 (15.4-34.9)
ΔUrea (mmol/L) [b]	3.1 (0-13)
Urea >30 mmol/L (%)	36
RRT urine output	
6 h Pre-RRT, median (IQR), mL/h	17 (5-48)
24 h Pre-RRT, median (IQR), mL/h	24 (8-53)
Oliguria (%)	67.8
Loop diuretic therapy (%)	69.3
RRT modality	
CRRT	81.7
Other (including IHD, EDD, PD)	18.3

Bagshaw et al, Journal of Critical Care (2009) 24, 129–140

Mortality oliguric vs oliguric AKI



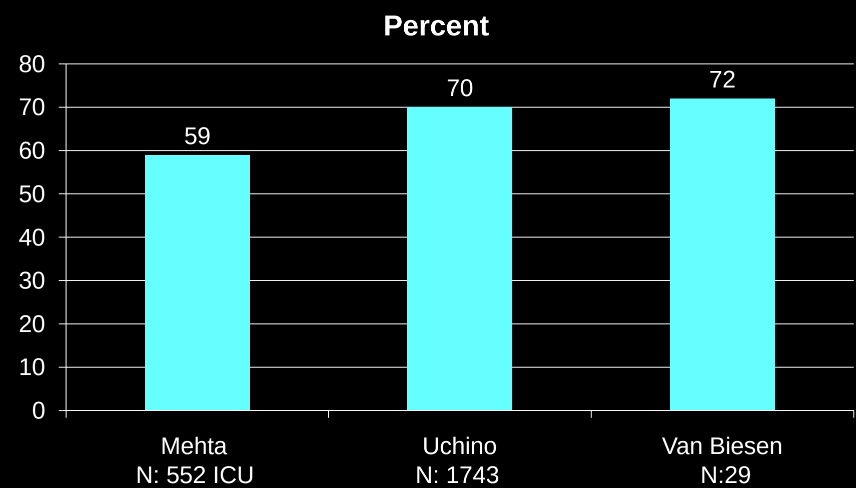
Non-oliguric : shorter hospital stay; less dialysis requirement, less complications

Anderson et al, New Engl J Med, 296: 1134, 1977

Advantages of non-oliguric ATN

- The prognosis of **spontaneous** non-oliguric ATN patients is better compared to oliguric patients, probably because of lesser renal damage
- The preservation of diuresis is advantageous for the fluid management of the patient (i.e. fluid administration, parenteral nutrition).
- Restoring the diuresis in a previously oliguric patient makes management easier but does it affect the prognosis of the patient?

Use of diuretics in AKI patients



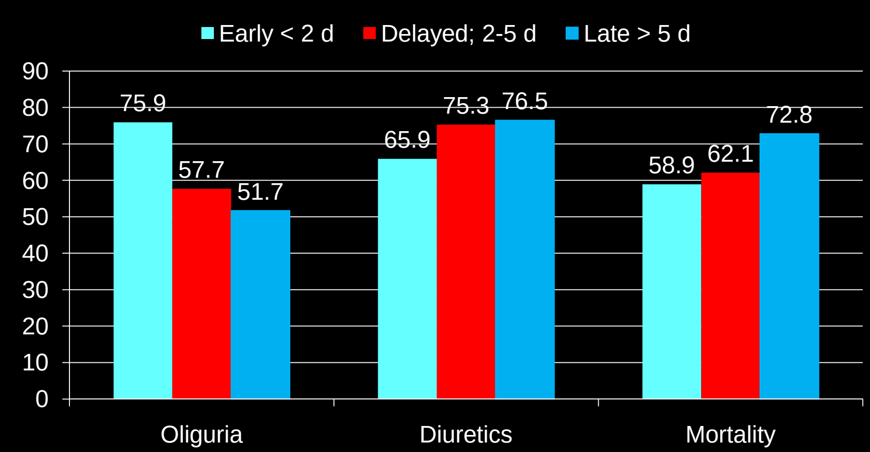
Beneficial effects of diuretics in prevention of ATN (1)

- Both mannitol and loop diuretics can induce a diuresis , potentially washing out obstructing cellular debris and casts
- Loop diuretics diminish active transport in the TAL, and the ensuing decrease in energy requirements protects the cell when there is a decrease in energy delivery

Beneficial effects of diuretics in the prevention of ATN (2)

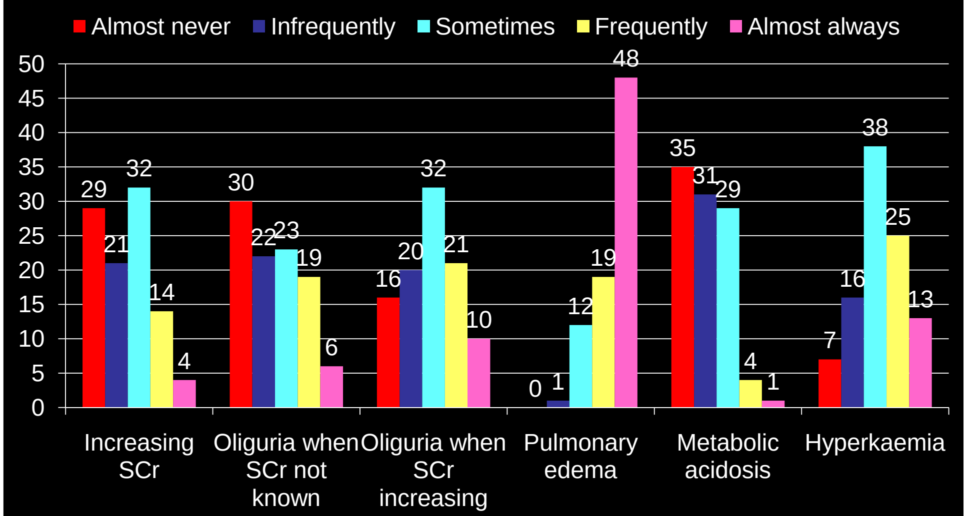
- Loop diuretics may act as renal vasodilators in particular circumstances
- Mannitol may preserve mitochondrial function by osmotically minimizing the degree of postischemic swelling , and by scavenging free radicals.

Prevalence of oliguria, treatment with diuretics and mortality related to timing of start RRT in days after ICU admission (BEST Kidney study)



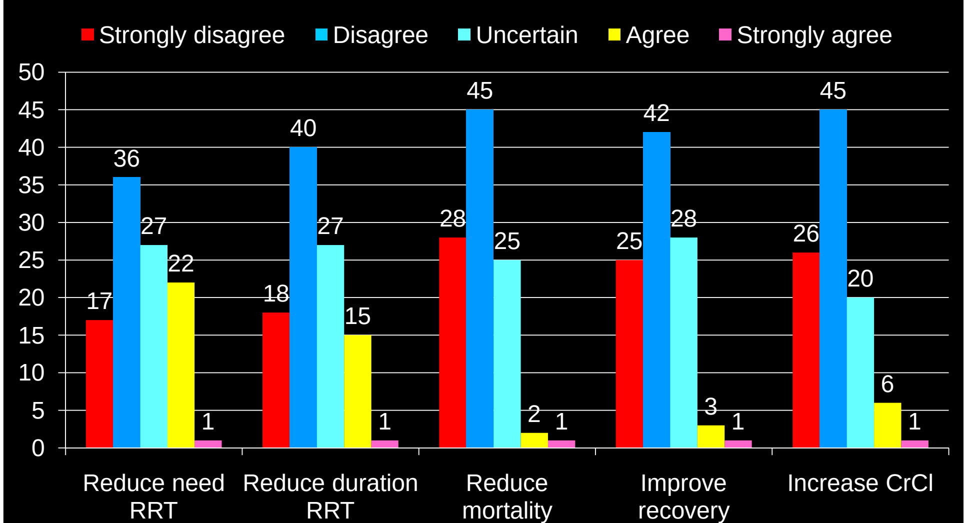
Bagshaw et al, Journal of Critical Care (2009) 24, 129–140

Responses to the questionnaire on physiologic indications for diuretics in AKI management



Bagshaw et al, Contr Nephrol , 156: 236-249, 2007

Responses regarding beliefs of impact diuretics on AKI outcome



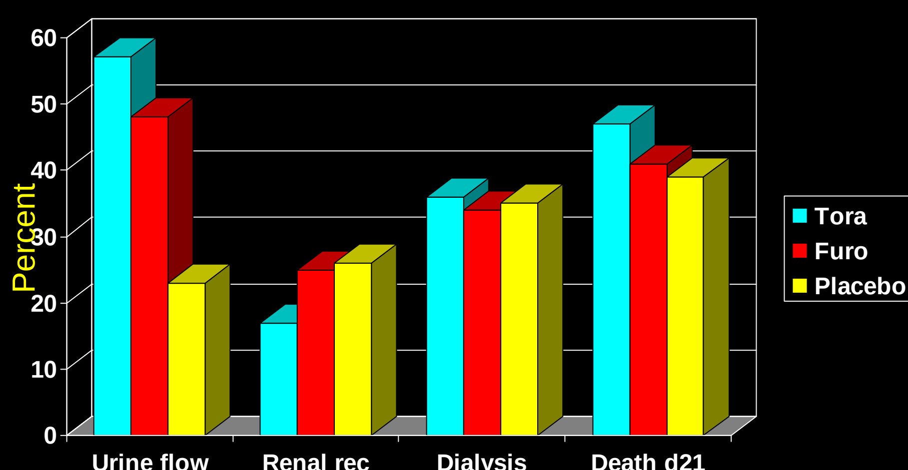
Bagshaw et al, Contr Nephrol , 156: 236-249, 2007

Loop diuretics in ARF: a double-blind randomized controlled trial

- Over 3 years, 278 oliguric patients were assessed as potential ARF. *Twenty five percent recovered with simple rehydration.*
- Ninety six patients were enrolled in the study. Study patients received i.v. dopamine 2 microgram/kg per min for 3 days ; mannitol i.v., 100 ml 6-hourly for 3 days, and randomized medication - i.v. torasemide 3 mg/kg, frusemide 3 mg/kg, or placebo- 6- hourly for 21 days or until renal recovery,dialysis, or death.
- Apache II scores were similar in the three groups.

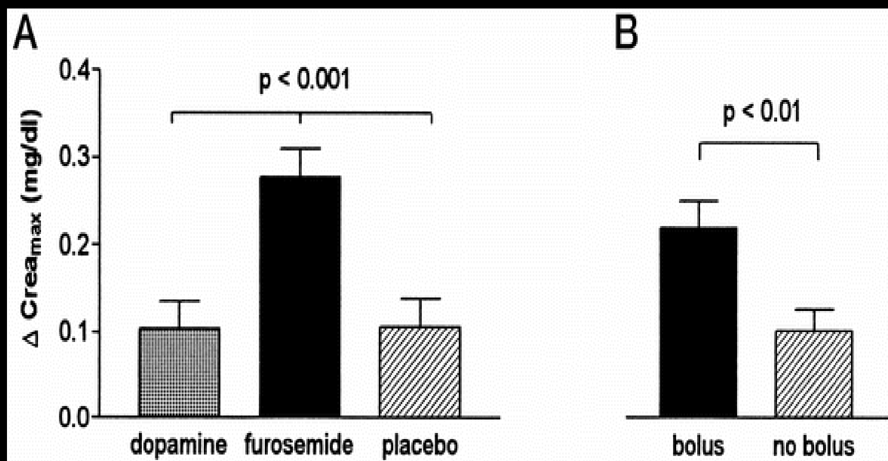
Shilliday IR et al. Nephrol Dial Transplant 11: 1684, 1996.

Loop diuretics in ARF: a double-blind randomized controlled trial



Shilliday et al. Nephrol Dial Transplant 11,1684,1996.

Effect of furosemide, dopamine, or placebo in patients undergoing cardiac surgery-
maximal increase in creatinine 48 hrs after surgery



Lassnigg et al. J Am Soc Nephrol 11, 2000

Prevention studies with furosemide- effect on need for RRT

Study or sub-category	Furosemide n/N	Control n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI	Year
01 Prevention						
Solomon[7]	1/25	0/28		0.16	3.35 (0.14, 78.60)	1994
Hager[6]	0/62	0/59			Not estimable	1996
Lassnigg[5]	2/41	0/40		0.18	4.88 (0.24, 98.60)	2000
Mahesh[15]	1/21	0/21		0.16	3.00 (0.13, 69.70)	2008
Subtotal (95% CI)	149	148		0.49	3.69 (0.62, 22.12)	
Total events: 4 (furosemide), 0 (control)						

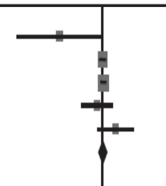
Prevention studies with furosemide – effect on all cause mortality

Hager[6]	6/62	3/59		1.84	1.90 (0.50, 7.26)	1996
Lassnigg[5]	4/41	1/40		0.71	3.90 (0.46, 33.42)	2000
Mahesh[15]	1/21	2/21		0.61	0.50 (0.05, 5.10)	2008
Subtotal (95% CI)	124	120		3.16	1.73 (0.62, 4.80)	
Total events: 11 (furosemide), 6 (control)						

Ho and Power, Anaesthesiology, 2010, 65: 283-293.

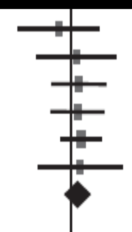
Treatment studies studies with furosemide- effect on need for RRT

Study or sub-category	Furosemide n/N	Control n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI	Year
02 Treatment						
Karayannopoulos[12]	1/10	7/10		0.44	0.14 (0.02, 0.96)	1974
Kleinknecht[13]	31/33	31/33		42.93	1.00 (0.88, 1.13)	1976
Brown[9]	28/28	27/28		50.39	1.04 (0.94, 1.14)	1981
Shilliday[8]	10/32	12/30		3.32	0.78 (0.40, 1.54)	1997
van der Voort[14]	13/36	7/35		2.44	1.81 (0.82, 3.99)	2009
Subtotal (95% CI)	139	136		99.51	1.01 (0.86, 1.19)	
Total events: 83 (furosemide), 84 (control)						



Treatment studies with furosemide – effect on all cause mortality

Study	Furosemide n/N	Control n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI	Year
Cantarovich[11]	15/34	7/13		8.30	0.82 (0.44, 1.54)	1971
Kleinknecht[13]	13/33	12/33		8.60	1.08 (0.58, 2.01)	1976
Brown[9]	18/28	16/28		18.38	1.13 (0.74, 1.72)	1981
Shilliday[8]	20/32	17/30		19.37	1.10 (0.73, 1.67)	1997
Cantarovich[10]	59/166	50/164		34.51	1.17 (0.86, 1.59)	2004
van der Voort[14]	13/36	11/35		7.69	1.15 (0.60, 2.21)	2009
Subtotal (95% CI)	329	303		96.84	1.10 (0.92, 1.33)	
Total events: 138 (furosemide), 113 (control)						



Ho and Power, Anaesthesiology, 2010, 65: 283-293

Effect of diuretics on mortality and nonrecovery of renal function

Variable	OR (95% CI) Unadjusted	Covariate Adjusted	Covariate and Propensity Score Adjusted
In-hospital mortality	1.37 (0.97-1.92)	1.65 (1.05-2.58)	1.68 (1.06-2.64)
Nonrecovery of renal function	1.53 (1.08-2.15)	1.70 (1.14-2.53)†	1.79 (1.19-2.68)§
Death or nonrecovery	1.48 (1.02-2.12)	1.74 (1.12-2.68)‡	1.77 (1.14-2.76)‖

*Covariate adjusted for age; sex; log urine output; serum creatinine level; blood urea nitrogen level; respiratory, hepatic, and hematologic failure; and heart rate. The referent group was no diuretics; time was first day of intensive care unit consultation. OR indicates odds ratio; CI, confidence interval.
†Area under receiver operating characteristic (ROC) curve = 0.76; goodness-of-fit χ^2 $P = .89$.
‡Area under ROC curve = 0.82; goodness-of-fit χ^2 $P = .39$.
§Area under ROC curve = 0.85; goodness-of-fit χ^2 $P = .84$.
‖Area under ROC curve = 0.81; goodness-of-fit χ^2 $P = .58$.

Database analysis of the effect of diuretics on mortality in patients with ARF

	Total	No Diuretics	Diuretics
Length of ICU stay, days	10 (5–22)	9 (4–20)	11 (5–22)
Length of hospital stay, days	22 (11–44)	21 (9–44)	23 (12–45)
ICU mortality, %	51.6	48.2	53.4
Hospital mortality, %	60.5	57.1	62.4
Hospital discharge without RRT, %	34.7	38.2	32.7
Hospital discharge with RRT, %	4.8	4.6	4.9
Number of patients	**1743**	**626**	**1117**

Data are presented as median (interquartile range) or percentage.

Uchimo et al Crit Care Med 2004, 32 (8):1669-1677.

When to initiate acute dialysis ?
Generally accepted indications

- Acute (life-threatening) hyperkalemia
- Severe volume overload (pulmonary edema)
- Severe metabolic acidosis
- Uremic organ complications (e.g. pericarditis)

- ‚“Prophylactic‘ dialysis:
  - **- RIFLE criteria ?**
  - **- Serum urea concentrations, e.g. 150, 200, ... mg/dl ?**
  - **- Manipulation of cytokine „storm“ in sepsis, pancreatitis?**

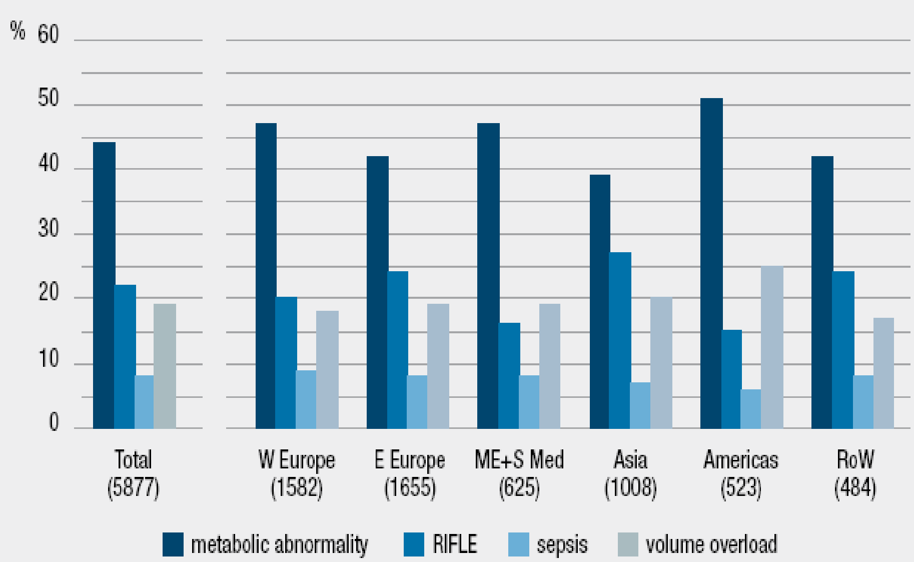
Indications for RRT in ICU patiens

Clinical characteristics of ICU patients receiving RRT

	All	CRRT	IRRT	Mixed RRT	*P CRRT vs IRRT*	*P (three groups)*
Indication for RRT initiation						
Azotaemia	72.1	67.9	86.2	76.1	0.001	0.003
RIFLE class	64.4	64.9	60.9	67.4	0.495	0.715
Fluid overload	58.6	61.6	51.7	50.0	0.096	0.116
Oliguria	43.6	48.1	28.7	39.1	0.001	0.004
Outcome						
ICU mortality (%)	47.6	54.1	22.1	44.7	<0.001	<0.001
Mechanical ventilation (days)	10 (3 to 19)	10 (4 to 19)	8 (1 to 17)	16 (11 to 38)	0.037	0.002
ICU length of stay (days)	14 (7 to 27)	13 (6.5 to 26)	14 (6 to 23)	25 (15 to 42)	0.769	<0.001

Vesconi et al, *Critical Care 2009*, ***13:R57***

Criteria for dialysis therapy initiation **Gambro survey**



RIFLE as parameters for initiation of RRT

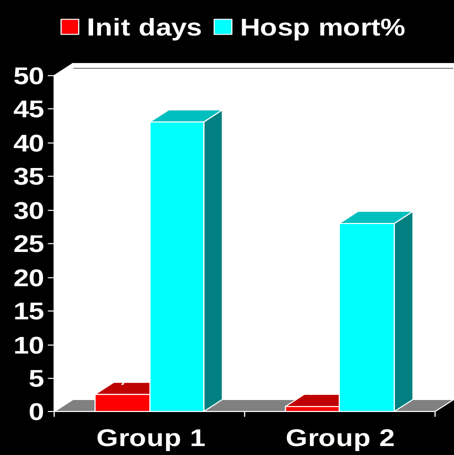
Group 1: (n-28)

CVVH was started when urea levels were >30 mmol/l, creatinine levels were >250 mmol/l or potassium levels exceeded 6.0 meq./l

Group-II (n:36

CVVH was started when UO was

< 100 ml within 8 h consecutively after surgery despite furosemide infusion.



Elahi et al, Eur J Cardiothor Surg 2004, 26:1027-1031

Impact of start RRT and of definition on prognosis of ARF post cardiac surgery

Intraoperative and Postoperative Variables

	Group 1 (n = 27)	Group 2 (n = 34)	P Value
Mean CPB time (min)	72.1 ± 16.6	79.8 ± 9.1	0.055"
Mean cross-clamp time (min)	44.7 ± 11	51 ± 7.9	0.010"
Inotropy requirement	18	22	0.873*
IAB	8	13	0.482*
Mechanical ventilation time (day)	3 ± 2.1	1 ± 0.6	0.014"
CVVHDF initiation after surgery (day)	2.56 ± 1.67	0.88 ± 0.33	0.0001"
CVVHDF time (day)	4.56 ± 1.31	4.32 ± 1.45	0.512"
ICU stay (day)	12.41 ± 3.44	7.85 ± 1.26	0.0001"
Hospital stay (day)	20.9 ± 7.0	15.4 ± 4.0	0.016"
ICU mortality (%)	48.1 (13/27)	17.6 (6/34)	0.014*
Hospital mortality (%)	55.5(15/27)	23.5 (8/34)	0.016*

Group 1: CVVHDF was initiated when Screat > 5mg/dl or K: > 5.5 mmol/L
Group 2: CVVHDF was initiated when Urine output was < 100 ml within 8 hours after surgery, despite 50 mg of furosemide

Demirkiliç et al, J Card Surg 2004, 19:17-20

CVVH for septic patients with septic shock

- Retrospective study (two-times 40 patients)
- Before vs. after introduction of early isovolaemic haemofiltration using bicarbonate based fluids (45 ml/kg/h)
- Septic shock defined by
  - Focus of infection
  - Clinical signs of SIRS
  - Acute renal injury with oliguria
    - Creatinine 2-fold increased, GFR < 50% normal value
      (but not ARF: creatinine 3-fold increased, GFR < 25% normal value)
    - No classical CRRT-Indication
      (fluid overload, severe electrolyte derangement etc.)
  - Acute lung injury (ALI)

	EIHF group (n=40)	Control group (n=40)	p
Age (mean±SD)	55.1±15	56.3±17	NS
APACHE II (mean±SD)	27.2±2.8	27.8±3.1	NS
Leukocyte (×10^9l mean±SD)	13.7±8.1	11.5±7	NS
Organ failure score	3(2–3)	3(2–3)	NS
SOFA score	3(2–3)	3(2–3)	NS
Patients with positive blood cultures (%)	19(47)	21(52)	NS
Number of patients with ARDS (%)	40(100)	40(100)	0.65
PaO_2/FiO_2 ratio (mean±SD)	117.5±59	125±55	0.001
Cause of septic shock			
Surgical 28	12(3D)	16(8D)	n.s.
Post-traumatic 10	7	3	n.s.
Combined 2	1	1	n.s
Medical 40	20(9D)	20(16D)	n.s

Piccinni P et al
Intensive Care Med 32:80-86, 2006

CVVH for Patients With Septic Shock: Early Start

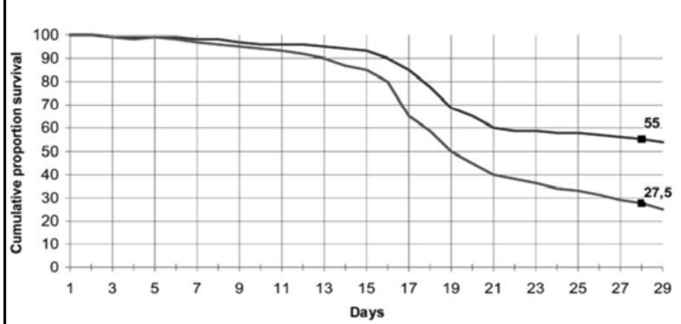
	Baseline values (group A)	Baseline values (group B)	After 48 h of standard care (group A)	After 48 h of EIHF (group B)
Heart rate (bpm)	135±9	140±10	130±10	120±12*
Mean arterial pressure (mmHg)	60±12	50±10	65±10	95±10*
Central venous pressure (mmHg)	7±2	5±3	14±2	10±2
Pulmonary artery pressure (mmHg)				
Systolic	25±2	27±3	24±3	22±2
Diastolic	10±2	12±2	18±2	12±3
Mean	16±2	17±2	22±2	18±2
Pulmonary artery wedge pressure (mmHg)	8±2	9±3	12±2	13±2
Cardiac index (l/min m^2)	3.0±0.8	3.0±0.7	3.3±0.9	4±0.5
Systemic vascular resistances (dynes s/cm^{-5})	600±260	800±200	900±350	1,100±200*
Pulmonary vascular resistance(dynes s/cm^{-5})	270±30	402±38	390±40	310±31
Urine output (ml/day)	550±170	600±200	650±180	1,200±250*
BUN (mg/dl)	110±38	120±30	98±48	88±40
Creatinine (mg/dl)	1.7±2	1.8±2	1.9±2	1.6±2
PaO_2/FiO_2 ratio	125±55	117±59	160±50	240±50*
Noradrenaline dose (μg/kg/min)	0.20±2	0.20±2	0.20±0.2	0.02±0.2*

*p<0.05 compared with baseline and between groups. The reported values are means ± SD

Piccinni P et al
Intensive Care Med 32:80-86, 2006

CVVH for Patients With Septic Shock: Early Start

	EIHF (n=40)	Control (n=40)	p
Successful weaning	28 (70%)	15 (37%)	<0.001
Duration of MV(days)	11±3	20±5	<0.001
Independence from vasopressor support	30 (75%)	10 (25%)	<0.001
ICU stay (days)	12±5	16±4	0.002
Hospital stay (days)	19±5	34±4	<0.001
ICU survival	28 (70%)	16 (40%)	0.003
(predicted survival based on individual risk of death)	(41±12)	(40± 10)	n.s.
28-day survival	22 (55%)	11 (27.5%)	0.005
(predicted survival based on individual risk of death)	(41±12)	(40± 10)	n.s.

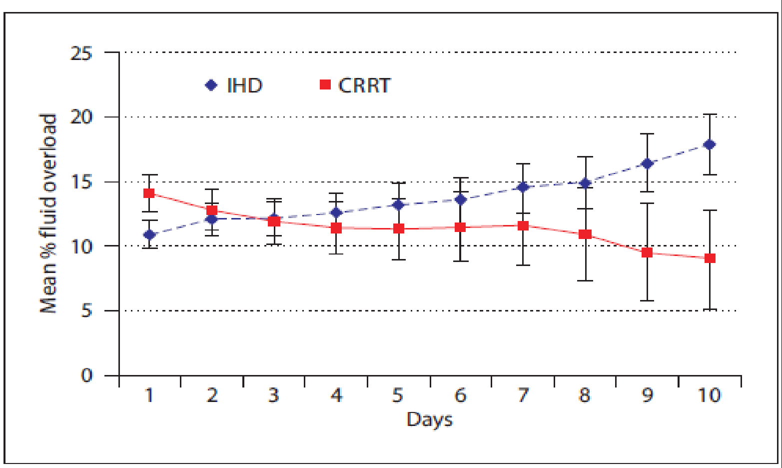


Early isovolemic haemofiltration

Control group

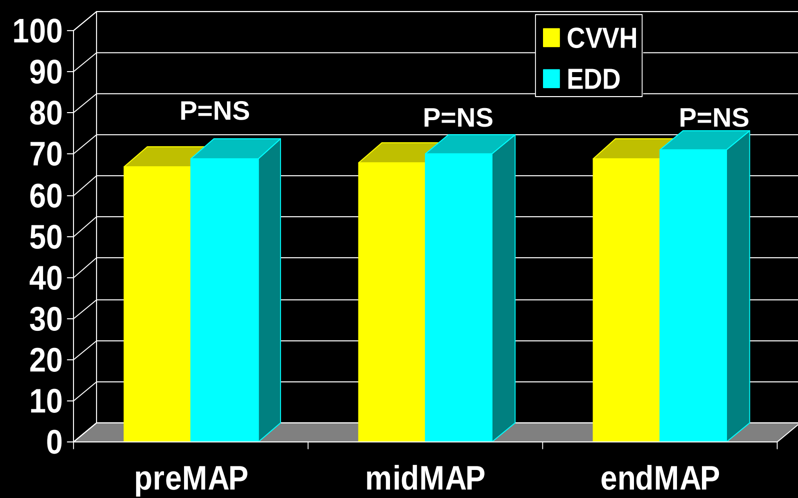
Piccinni P et al
ntensive Care Med 32:80-86, 2006

Correction of fluid overload in AKI by IHD and CRRT



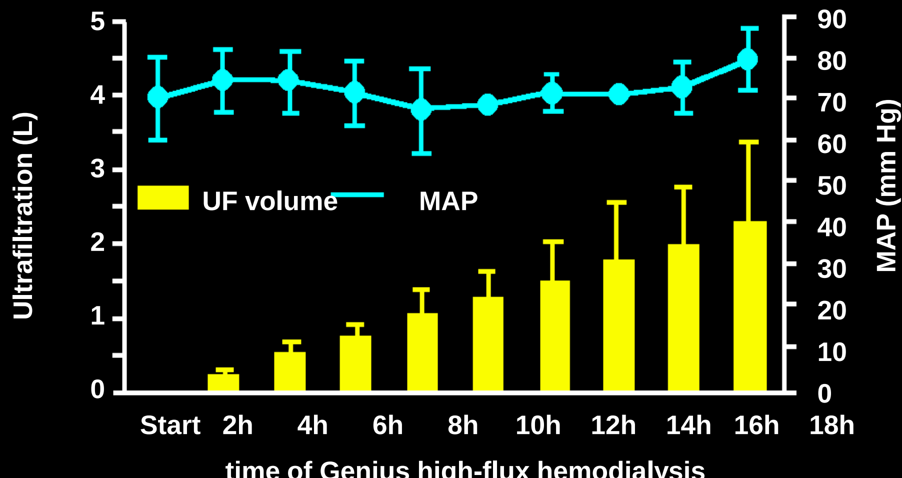
Bouchard et al, Kidney Int 76: 422–427, 2009

Comparison of MAP during EDD vs. CVVH.



Kumar et al, AJKD, 36, 294-300, 2(

Cumulative ultrafiltration volume and mean arterial pressure during 18h of extended high-flux HD using the Genius System.



Lonnemann et al, NDT, 15, 1189-1193, 20(

Analysis for successful discontinuation of CRRT-role of diuretics

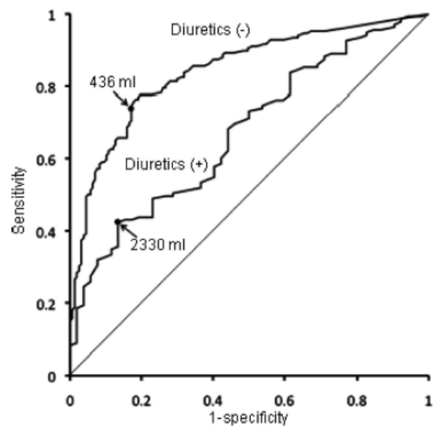


Figure 3. Impact of diuretics use on predictive ability of urine output. The area under the receiver operating characteristics curve of urine output for successful discontinuation of continuous renal replacement therapy was 0.671 (0.585–0.750) with diuretics and 0.845 (0.799–0.883) without diuretics. Urine output of 436 mL/day for patients without diuretics and of 2330 mL for those with diuretics had the highest accuracy.

Uchino et al, Crit Care Med 2009; 37:2576 –2582

Analysis for successful discontinuation of CRRT

	Odds Ratio (95% CI)	*p*
Urine output, 100 mL/day	1.078 (1.049–1.108)	<.0001
Urine output increased	3.097 (1.873–5.121)	<.0001
Creatinine, µmol/L	0.996 (0.994–0.998)	.0005
Chronic kidney disease	0.534 (0.338–0.844)	.0072
First CRRT period, days	0.969 (0.947–0.993)	.010

Uchino et al, Crit Care Med 2009; 37:2576 –2582

Reasons to stop CRRT-BEST Kidney study

Reasons to stop CRRT, %			
Urine output increased	63.2	19.9	<.0001
Metabolic state improved	49.2	39.8	.039
Fluid overload improved	36.2	31.3	.26
Urea/creatinine decreased	59.0	47.4	.012
Hemodynamically stable	42.7	51.7	.049

Uchino et al, Crit Care Med 2009; 37:2576 –2582

Good advice is something a man gives when he is too old to set a bad example.

Francois de La Rochefoucauld
French author & moralist (1613 - 1680)