

**FLUID MANAGEMENT IN AKI:
“FILL AND SPILL” OR
“SQUEEZE AND DIURESE?”**

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Edmonton April 16 2010

Disclosures

I have no actual or potential conflict of interest in relation to this program or presentation.



What is this debate about?

- Impending vs established AKI
- Oliguric vs non-oliguric AKI
- Urine Output or GFR
- Fluids or diuretics
- Prevention or treatment
- Fluid management with RRT



Fill and Spill!



AKI 2010
Acute Kidney Injury and Renal Support

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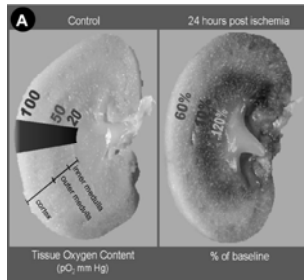
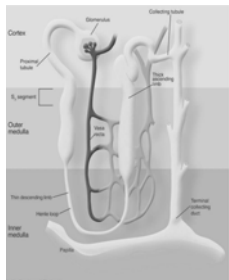
Considerations

- What makes you pee?

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AKI: Pathophysiology

Nephron structure determines susceptibility of various nephron segments to injury



Schrier et al: The Journal of Clinical Investigation 2004 :114:3
Molitoris BA et al: Crit Care Med 2002 Vol. 30, No. 5 S235-S240.

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Renal Compensatory Mechanisms

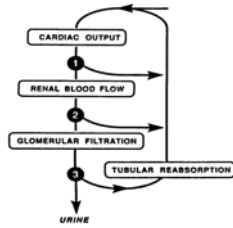


Figure 1. The Three Steps of Fractionation of Cardiac Output to Form Glomerular Filtrate in the Cardiovascular Loop. Note the three regulatory sites through which mechanisms intrinsic to the kidney are capable of modulating the glomerular filtration rate: fractional renal blood flow (renal blood flow/cardiac output), 1; filtration fraction (glomerular filtration rate/glomerular plasma flow rate), 2; fractional tubular fluid reabsorption (tubular reabsorption/glomerular filtration rate), 3.

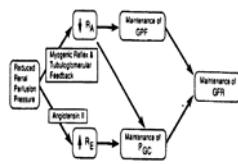


Figure 2. Mechanism of Autoregulation.

When an otherwise normal person faces a hypotensive episode, a highly efficient homeostatic mechanism (autoregulation) comes into play to maintain the glomerular filtration rate (GFR). This is accomplished by a marked reduction in afferent arteriole resistance (R_a), by virtue of both myogenic reflex and tubuloglomerular feedback mechanisms, and an increase in efferent arteriole resistance (R_e) in response to locally released angiotensin II. By maintaining the glomerular plasma flow rate (GFR) and glomerular capillary hydraulic pressure (P_{GC}), these arteriole adjustments successfully maintain the GFR.

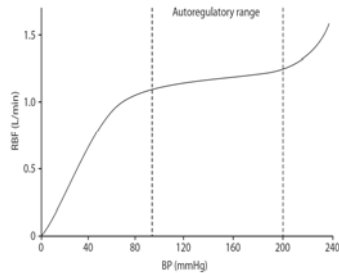
Badr and Ichikawa NEJM



Renal Autoregulation

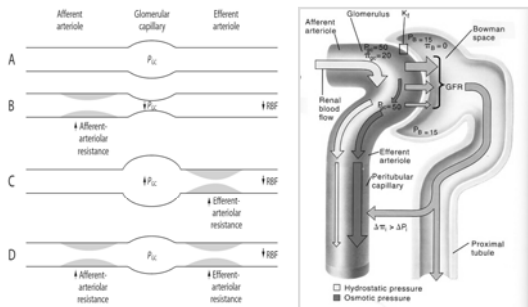
Mechanisms

- Myogenic response with afferent arteriolar vasoconstriction in response to alterations in systolic pressure
- Tubulo-glomerular feedback in response to chloride delivery to macula densa in DCT



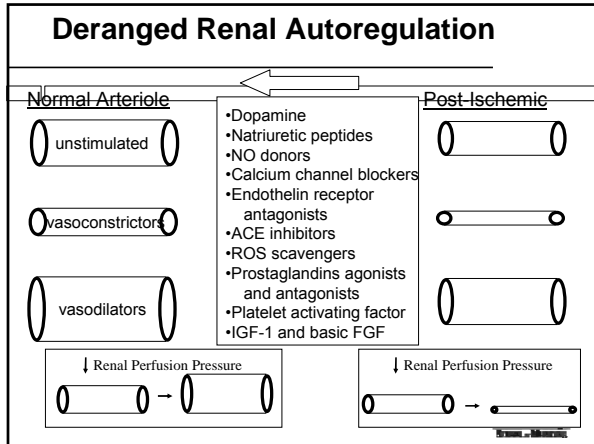
Pathophysiology of AKI

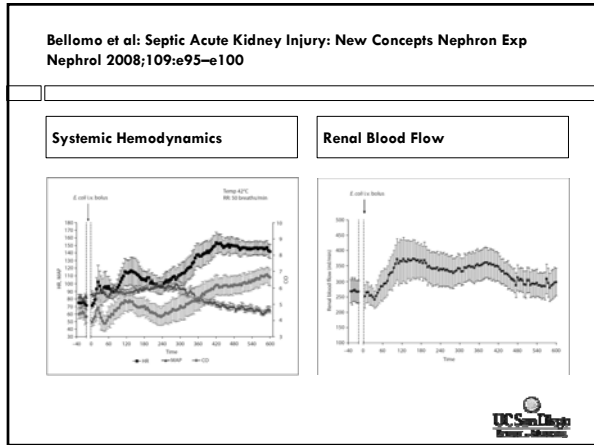
RENAL EFFECTS OF CRITICAL ILLNESS

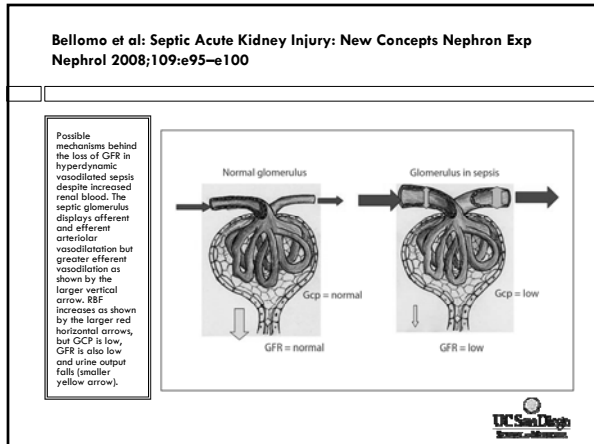


Murray P Eds: Intensive Care Nephrology





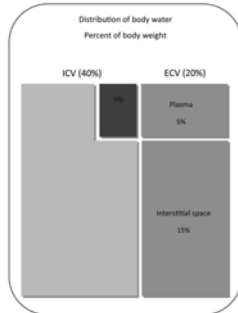




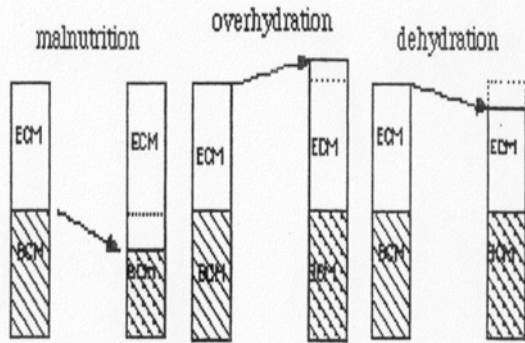
Composition of Body Compartments

The distribution of total body water divided into the intracellular (ICV) and extracellular (ECV) spaces. For an adult man weighing 70 kg, the body water is equivalent to 60% of total body weight.

This amounts to approximately 42 L, distributed as 40% intracellular volume (28 L) and 20% extracellular volume (14 L), of which 10.5 L is interstitial and 3.5 L is plasma volume (red cell volume is a component of intracellular volume).



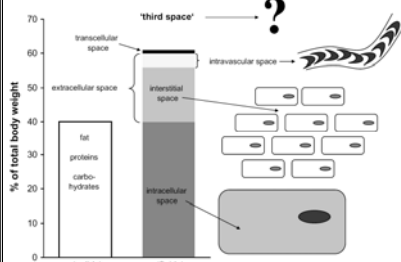
Body Compartment Alterations



Third Space: Fact or Fiction?

Intracellular fluid comprises two-thirds of the body water. The remaining one-third - about 15 l in the normal weighted adult - comprises the extra-cellular volume (ECV, namely 20% of the total body mass) consisting of the plasma (about 3 l), the interstitial space (about 12 l) and small amounts of the so-called trans-cellular fluids such as GI secretions, CSF and ocular fluid. The latter are considered to be anatomically separated and not in dynamic equilibrium with the interstitial space and the plasma, in which water and small solutes can easily be exchanged.

The 'third space', nothing more than a perception so far, has functionally been allocated to this trans-cellular compartment.

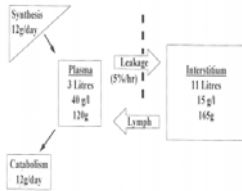


Jacob et al: Best Practice & Research Clinical Anaesthesiology 23 (2009) 145-157

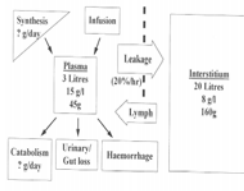


Albumin Pharmacokinetics

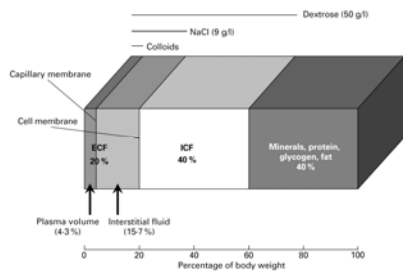
Normal



Critical Illness



Response to Fluid Administration



Distribution of infused fluids (dextrose (50 g/l), saline (9 g NaCl/l) and colloids) in the body water compartments. ECF, extracellular fluid; ICF, intracellular fluid.

Common Findings For Fluid Status In Critically ill Patients

- Overhydration with increased interstitial compartment fluid and decreased intravascular compartment
- Decreased albumin and intravascular colloid osmotic pressure
- Increased vascular permeability

Considerations

- What makes Pee?
- Fluid management and Pee
- Maintaining pee



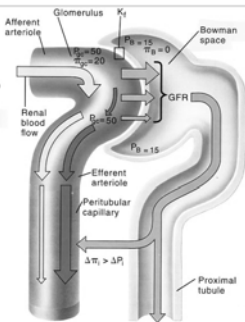
Preservation and optimization of renal function

- Goals:
 - Identify and correct any reversible factors such as volume depletion and obstruction
 - Restore effective renal perfusion and urine output



Preservation and optimization of renal function: Techniques

- Manipulate Renal Response
 - Physiologic Targets
 - Renal Perfusion
 - Renal auto-regulation
 - Medullary oxygenation
 - Reduce demand on kidney



Preservation and optimization of renal function: Maintain renal perfusion

□ Strategies:

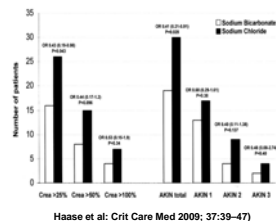
■ Optimize Systemic Hemodynamics

- Maintenance of mean blood pressure > 70 mmHg,
- Optimal circulating blood volume (central venous pressure > 5 mm Hg), Pulmonary capillary wedge pressure ~ 15 mmHg, Hematocrit ~ 30%.)
- Cardiac output > 4.5 l/min/m²,
- Systemic oxygen delivery > 550 ml/min,
- Adequate oxygenation at "best" PEEP



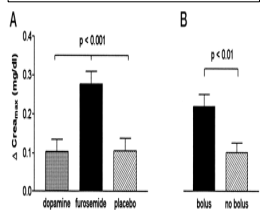
Maintaining Pee: Evidence Appraisal Primary Prevention: Cardiac Surgery

Fill and Spill



Haase et al: Crit Care Med 2009; 37:39-47

Squeeze and Diurese



Lassnig A et al: J Am Soc Nephrol 2000 Jan;11(1):97-104



Maintaining Pee: Evidence Appraisal Secondary Prevention: Hemodynamic Optimization

Outcome: POSTOPERATIVE & CLUTE KIDNEY INJURY

Study	Treatment Events	Treatment Total	Control Events	Control Total	Odds Ratio M-H, Random, 95% CI	Odds Ratio M-H, Random, 95% CI
Bonjour ¹⁰	0	51	0	53	Not estimable	
Berkau ¹⁰	1	68	1	21	0.30 [0.02, 4.99]	
Birkhøj ¹⁰	6	50	16	65	0.42 [0.15, 1.14]	
Bonazzi ¹⁰	0	50	0	50	Not estimable	
Boyd ¹⁰	3	53	7	54	0.40 [0.10, 1.65]	
Chryu ¹⁰	0	80	1	82	0.36 [0.01, 6.41]	
Donati ¹⁰	2	68	7	67	0.28 [0.06, 1.30]	
Gap ¹⁰	2	50	4	50	0.48 [0.08, 2.74]	
Lobo ¹⁰	2	19	1	18	2.00 [0.17, 24.19]	
Makrabra ¹⁰	1	13	1	14	1.08 [0.06, 19.31]	
Monrovia ¹⁰	1	89	3	85	0.29 [0.03, 3.05]	
Nakstad ¹⁰	0	51	2	52	0.25 [0.01, 4.19]	
Pearce ¹⁰	3	62	4	60	0.75 [0.15, 3.32]	
Falkner ¹⁰	1	196	3	197	0.53 [0.03, 3.22]	
Sandham ¹⁰	70	941	95	965	0.74 [0.53, 1.02]	
Shonkoff ¹⁰	0	28	14	60	0.06 [0.00, 0.98]	
Valentin ¹⁰	4	60	1	60	4.21 [0.46, 38.86]	
Vlaering ¹⁰	3	84	2	84	1.52 [0.25, 9.45]	
Wilson ¹⁰	16	92	13	46	0.53 [0.23, 1.24]	
Ziegler ¹⁰	0	32	0	40	Not estimable	
Total (95% CI)		2117		2163	0.64 (0.50, 0.83)	

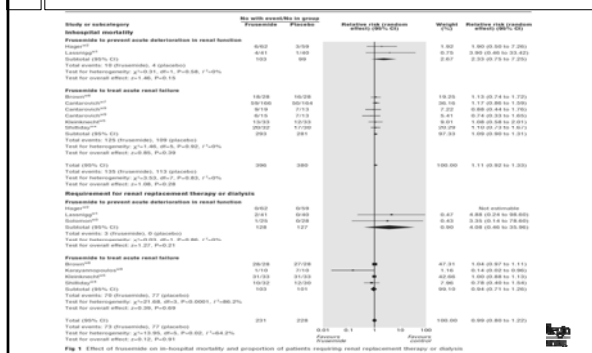
Total events: 115 (Treatment) / 175 (Control)
Heterogeneity: Tau² = 0.00; Chi² = 12.45, df = 16 (P = 0.71), I² = 0%
Test for overall effect: Z = 3.37 (P = 0.0007)

Favours treatment / Favours control



Brienza et al: (Crit Care Med 2009; 37:2079-2090)

Maintaining Pee: Evidence Appraisal Secondary Prevention: Diuretics



Mehta RL et al for the PICARD Study Group: Diuretics, Mortality, and Nonrecovery of Renal Function in Acute Renal Failure *JAMA*. 2002;288:2547-2553

Table 2. Effect of Diuretics on Mortality and Nonrecovery of Renal Function Compared With No Diuretic Use*

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 $\chi^2 P = .89$.

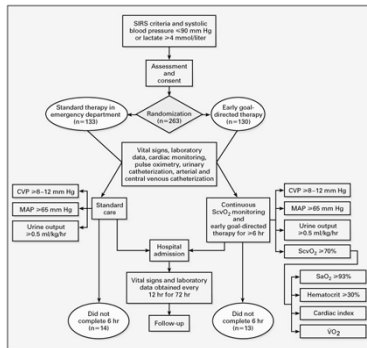
‡Area under ROC curve = 0.82; goodness-of-fit $\chi^2 P = .84$.

§Area under ROC curve = 0.81; goodness-of-fit $\chi^2 P = .58$.

Preservation and optimization of renal function: Maintain renal perfusion

- Strategies:
 - Goal Directed Hemodynamic management

Early goal-directed therapy in the treatment of severe sepsis and septic shock



Rivers et al: N Engl J Med 2001 Nov 8;345(19):1368-77

Murphy et al: The Importance of Fluid Management in Acute Lung Injury Secondary to Septic Shock. CHEST 2009; 136:102-109

Design: Single Center retrospective analysis of ICU patients

Patients: 212 pts with Acute lung injury (ALI) within 72 hrs of sepsis

Comparisons: Adequate initial fluid resuscitation (AIFR) administration of an initial fluid bolus of > 20 mL/kg prior to and achievement of a central venous pressure of > 8 mm Hg within 6 h after the onset of therapy with vasopressors. Conservative late fluid management (CLFM) was defined as even to negative fluid balance measured on at least 2 consecutive days during the first 7 days after septic shock onset.

Outcomes: Hospital Mortality

Variables	Sepsis (n = 120)	Nonsepsis (n = 92)	p Value
Initial IV fluid resuscitation			
Volume within 6 h of septic shock onset			
mL	3,260 (1,825-6,000)	3,000 (1,000-6,200)	0.078
mL/kg	45.8 (20.5-90.5)	42.9 (13.4-94.6)	0.132
CVP increased	113 (93.0)	61 (70.1)	< 0.001
AIFR	98 (79.2)	47 (54.0)	< 0.001
ScvO ₂ > 70%	37 (45.0)	34 (39.1)	0.345
Urine output > 0.5 mL/kg/hr	30 (32.0)	30 (34.8)	0.785
Cardiac index increased	50 (47.0)	53 (60.0)	0.049
PEEP > 8 cmH ₂ O	67 (68.0)	71 (81.6)	0.061
Vasopressor and inotropic usage			
Norepinephrine	117 (98.0)	66 (69.0)	0.002
Dopamine	20 (18.0)	15 (20.7)	0.487
Phenylephrine	17 (13.0)	5 (5.7)	0.071
Vasopressin	36 (30.0)	22 (25.3)	0.442
Epinephrine	1 (0.8)	1 (1.1)	0.506
Dobutamine	6 (5.0)	11 (12.0)	0.144
Inotropic support at day 7 after septic shock onset	11 (9.2)	20 (22.7)	< 0.001
Late fluid management			
Consecutive 7-day fluid balance, mL	6,962 (2,411-13,523)	13,404 (7,113-20,140)	< 0.001
L:F:M	61 (72.0)	36 (39.5)	< 0.001
ICV fluid balance, mL	6,602 (2,467-13,570)	19,335 (9,705-27,274)	< 0.001
Septic fluid balance, mL	6,602 (2,467-13,570)	22,211 (11,643-30,692)	< 0.001
Septic and nonseptic deaths in patients with positive cultures	43 (35.0)	34 (35.5)	0.301
Cardiovascular	30 (26.0)	30 (37.5)	0.532
Drostatically untreated	9 (7.5)	7 (8.0)	0.799

Values are reported as the median (IQR) or No. (%). Values otherwise indicated. CVP = central venous pressure; PEEP = peeped EBC.

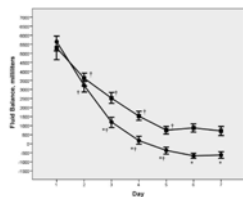


Figure 1. Factors Influencing Fluid Management in Acute Lung Injury.

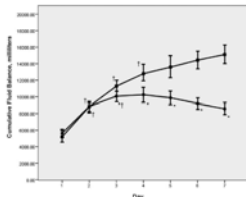


Murphy et al: The Importance of Fluid Management in Acute Lung Injury Secondary to Septic Shock. CHEST 2009; 136:102-109

Daily Fluid Balance



Cumulative Fluid Balance



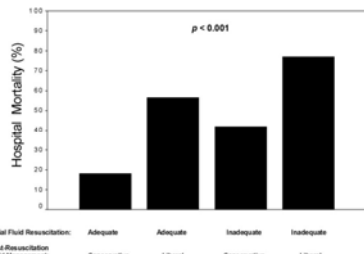
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Outcomes: Hospital Mortality



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Outcomes: Hospital Mortality

Variables	Adjusted		p Value
	OR	95% CI	
APACHE II score, 1-point increments	1.07	1.01-1.14	0.030
Charlson comorbidity score, 1-point increments	1.11	1.01-1.23	0.040
Renal replacement therapy	3.15	1.51-4.70	0.020
CRRT administration	2.94	1.41-4.47	0.011
AIFR not achieved	4.94	2.07-11.70	< 0.001
Duration of vasopressors, 1-day increments	1.24	1.04-1.47	0.017
CLFM not achieved	6.13	2.77-13.57	< 0.001

Other covariates not in the table had a p value < 0.5, including BMI ≥ 40 kg/m², patient location prior to ICU admission, medical ICU patients, and transfusion of packed RBCs (p = 0.558 [Hosmer-Lemeshow goodness-of-fit test]). CI = confidence interval; OR = odds ratio.

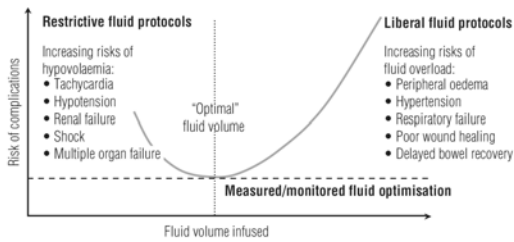


Considerations

- Optimizing Fluid management
 - Assess patient need and establish goals of therapy (short and long term)
 - Desired fluid balance
 - Fluid management strategy (removal, even, positive balance)
 - Adjustments: Frequency
 - Develop strategy to match fluid goals



Hypothetical curve of the risk of fluid therapy-related complications versus volume of fluid infused



Hilton et al: MJA 2008; 189: 509

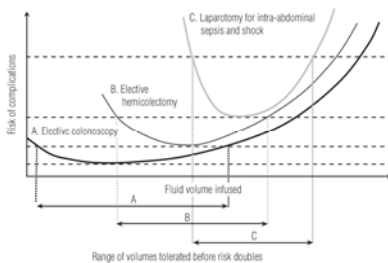


Hypothetical risk versus volume replacement curves for an individual patient in different clinical scenarios

Curve A: Low-risk clinical context, such as elective colonoscopy, where optimal fluid requirements are minimal, and the patient can tolerate significant variations in volume replacement.

Curve B: The same patient in a slightly higher-risk context, such as elective colectomy. The volume for optimal fluid replacement is likely to be higher than in Scenario A, and the tolerance for error slightly lower, given the larger volume and pathophysiological changes associated with surgery.

Curve C: The same patient in a high-risk clinical context, such as urgent laparotomy for intra-abdominal sepsis and hypotension. Fluid requirements are likely to be high, and the patient is unlikely to tolerate significant deviations from this amount.



Hilton et al: MJA 2008; 189: 509



Fluid Management in AKI: Fill and Spill or Squeeze and Diurese?

Summary

- Development of AKI reflects the interplay of baseline kidney capacity, adaptive mechanisms, nature and severity of injury and time
- Fluid management in AKI needs to recognize underlying kidney autoregulatory mechanisms and be targeted to achieve and maintain an adequate filtration pressure gradient of 10-15 mm Hg based on the clinical situation
- Volume status should be assessed frequently and fluid management adjusted to achieve optimal fluid balance and prevent fluid accumulation and overload

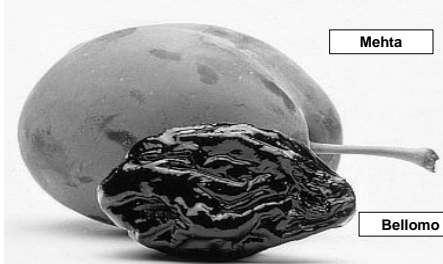


Fluid Management in AKI: Fill and Spill or Squeeze and Diurese?

Need to Fill before you can Squeeze and Diurese!

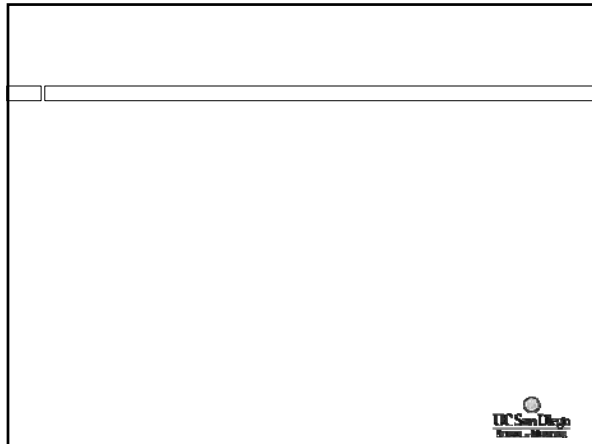


Squeeze and Diurese!

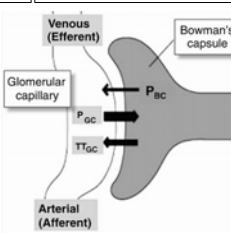


AKI 2010
Acute Kidney Injury and Renal Support





Impact of ↑CVP on glomerular hemodynamics



	Normal		↑ RA pressure	
	Afferent end of glomerular capillary (mmHg)	Efferent end of glomerular capillary (mmHg)	Afferent end of glomerular capillary (mmHg)	Efferent end of glomerular capillary (mmHg)
1. Favoring Filtration Glomerular-capsule hydrostatic pressure, P _{ac}	60	58	55	63
2. Opposing Filtration a. Hydrostatic pressure in Bowman's capsule, P _{ac}	15	15	15	15
b. Oncotic pressure in glomerular capillaries, π _{GC}	21	33	21	33
Net filtration pressure (1-2)	24	10	19	15
<i>Filtration pressure:</i>	<i>14 mmHg</i>		<i>4 mmHg</i>	

EDITORIAL COMMENT
The Cardiorenal Syndrome
 Do We Need a Change of Strategy or a Change of Tactics?
 Marif Jousq, MD, FACC¹
 Maria Rosa Costanzo, MD, FACC²
 Philadelphia, Pennsylvania, and Lombard, Illinois
 J Am Coll Cardiol 2003;41:1000-1006

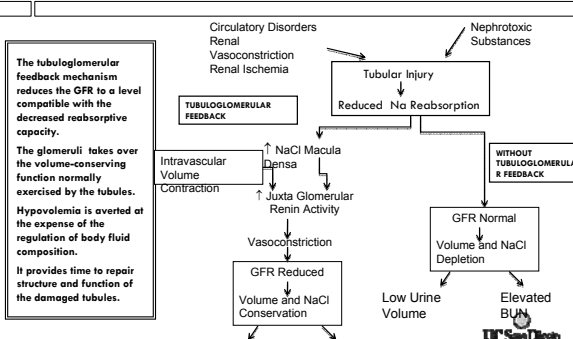
Tubuloglomerular Feedback

The tubuloglomerular feedback mechanism reduces the GFR to a level compatible with the decreased reabsorptive capacity.

The glomeruli takes over the volume-conserving function normally exercised by the tubules.

Hypovolemia is averted at the expense of the regulation of body fluid composition.

It provides time to repair structure and function of the damaged tubules.



Deruddre et al: Renal arterial resistance in septic shock: effects of increasing mean arterial pressure with norepinephrine on the renal resistive index assessed with Doppler ultrasonography Intensive Care Med (2007) 33:1557–1562

- **Patients and participants:** 11 patients with septic shock who required fluid resuscitation and norepinephrine to increase and maintain MAP at or above 65 mmHg.
- **Interventions:** Norepinephrine was titrated in 11 patients in septic shock during three consecutive not randomized periods of 2 h to achieve a MAP at successively 65, 75, and 85 mmHg.
- **Measurements and results:** At the end of each period hemodynamic parameters and renal function variables (urinary output, creatinine, clearance) were measured, and Doppler ultrasonography was performed on interlobar arteries to assess the renal resistive index. When increasing MAP from 65 to 75 mmHg, urinary output increased significantly from 76 ± 64 to 93 ± 68 ml/h and the resistive index significantly decreased from 0.75 ± 0.07 to 0.71 ± 0.06. No difference was found between 75 and 85 mmHg.

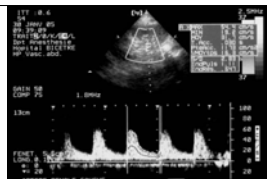


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	65 mmHg	75 mmHg	85 mmHg	p ^b
Heart rate (bpm)	103 ± 23	103 ± 27	102 ± 29	NS
Cardiac index (l min ⁻¹ m ⁻²)	3.4 ± 0.8	3.6 ± 0.9*	3.7 ± 0.9	0.002
Norepinephrine (µg kg ⁻¹ min ⁻¹)	0.3 ± 0.2	0.5 ± 0.3*	0.7 ± 0.5	<0.0001
Blood Lactate (mg dl ⁻¹)	2.8 ± 1.9	2.9 ± 2.1	2.9 ± 2.4	NS
Urinary output (ml h ⁻¹)	76 ± 64	93 ± 68*	96 ± 73	0.02
Serum creatinine (µmol l ⁻¹)	232 ± 123	234 ± 136	234 ± 141	NS
Creatinine clearance (ml min ⁻¹)	42 ± 31	42 ± 31	43 ± 32	NS
Resistance index	0.75 ± 0.07	0.71 ± 0.06*	0.71 ± 0.05	0.003

* p < 0.05 65 vs. 75 mmHg (Wilcoxon post-hoc test); ^b Friedman test



Deruddre et al: Renal arterial resistance in septic shock: effects of increasing mean arterial pressure with norepinephrine on the renal resistive index assessed with Doppler ultrasonography Intensive Care Med (2007) 33:1557–1562

Patients and participants: 11 patients with septic shock who required fluid resuscitation and norepinephrine to increase and maintain MAP at or above 65 mmHg.

Interventions: Norepinephrine was titrated in 11 patients in septic shock during three consecutive not randomized periods of 2 h to achieve a MAP at successively 65, 75, and 85 mmHg.

Results: When increasing MAP from 65 to 75 mmHg, urinary output increased significantly from 76 ± 64 to 93 ± 68 ml/h and the resistive index significantly decreased from 0.75 ± 0.07 to 0.71 ± 0.06. No difference was found between 75 and 85 mmHg.

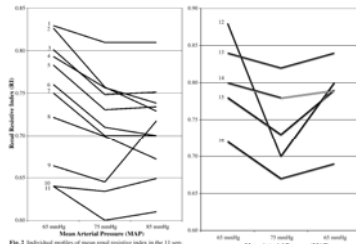


Fig. 2 Individual profiles of renal resistive index in the 11 septic patients included when mean arterial pressure is increased from 65 to 75 mmHg with norepinephrine. An identification number is given to each patient from 1 to 11

Fig. 3 Individual profiles of renal resistive index in the septic patients when mean arterial pressure is increased from 65 to 75 mmHg with norepinephrine and decreased back to 65 mmHg. An identification number is given to each patient from 12 to 16



Summary of clinical studies showing an association between fluid balance and clinical outcome

Study, ref.	Year	Number of patients	Design	Population	Intervention	Outcome
Simmons [50]	1987	113	P, C	ARDS	N/A	mortality associated with positive daily/ cumulative fluid balance and weight gain
Schuller [45]	1991	89	R, C	ALI/ARDS	N/A	mortality associated with higher positive fluid balance >1 l over 36 h (50 vs. 20%, p = 0.03) along with longer duration of MV and ICU/hospital stay
Goldstein [48]	2001	21	R, C	pediatric AKI	N/A	mortality associated with higher %FO at RRT initiation (24 vs. 18.4%, p = 0.03)
Brandstrup [52]	2003	172	RCT	elective colorectal surgery	restrictive vs. standard peri-operative fluid strategy	restrictive strategy reduced post-operative weight gain and complications (33 vs. 51%, p = 0.003)
Edlund [44]	2004	113	R, C	pediatric AKI	N/A	mortality associated with higher %FO at RRT initiation (15.5 vs. 9.2%, p = 0.01)
Gillespie [47]	2004	77	R, C	pediatric AKI	N/A	mortality associated with higher %FO at RRT initiation (>10%, RR 3.02, p = 0.002)
Goldstein [49]	2005	116	R, C	pediatric AKI	N/A	mortality associated with higher %FO at RRT initiation (22.4 vs. 14.2%, p = 0.03)
Sakr [34]	2005	393	P, C	ALI/ARDS	N/A	mortality associated with positive cumulative fluid balance (+4.4 vs. -3.0 L, OR 1.5, p = 0.003)
Uchino [51]	2006	331	P, NR	critically ill	N/A	mortality associated with positive fluid balance (OR 1.0002 per each ml/day, p = 0.01)
Wiedemann [15]	2006	1,000	RCT	ALI/ARDS	conservative vs. liberal fluid strategy	conservative strategy had lower cumulative 7-day fluid balance (0.13 vs. 6.9 L, <0.0001), improved gas exchange, shorter time on ventilator and ICU days, no difference in rate of RRT or mortality

P = Prospective; R = retrospective; C = cohort; RCT = randomized clinical trial; NR = nonrandomized; ALI = acute lung injury; ARDS = acute respiratory distress syndrome; N/A = not applicable; %FO = percentage fluid overload; RR = risk ratio; MV = mechanical ventilation

Foland J et al Fluid overload before continuous hemofiltration and survival in critically ill children: a retrospective analysis. Crit Care Med. 2004 Aug;32(8):1771-6.

%FO was defined as total fluid input minus output (up to 7 days before CVVH for both hospital stay and ICU stay) divided by body weight.

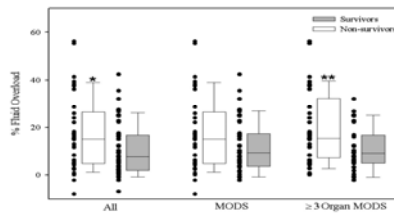
Table 1. Diagnostic categories

Category	Patients	Survivors (%)	% Fluid Overload, n
All categories	113	69 (61)	10.9 (2.8, 22.1), 94
Primary renal disease	29	26 (90)	3.9 (1.8, 12.9), 17
Secondary renal failure	84	43 (51)	12.0 (4.1, 24.4), 77
Heart transplant	18	9 (50)	7.9 (4.4, 15.0), 18
Bone marrow transplant	16	3 (19)	15.2 (3.7, 31.4), 16
Oncologic disorders	14	7 (50)	4.3 (2.2, 22.3), 8
Metabolic/other	13	8 (62)	3.5 (0.2, 29.2), 7
Congenital heart disease	9	5 (56)	16.7 (7.2, 24.9), 9
Respiratory failure	7	7 (100)	22.8 (9.4, 25.2), 7
Liver transplant	7	4 (57)	27.6 (22.5, 34.4), 6

Pediatric Patients: Higher percentages of fluid overload (FO) at dialysis initiation linked with increased mortality

- Goldstein, Pediatrics 2001
- Foland, Crit Care Med 2004
- Gillespie, Pediatr Nephrol 2004
- Goldstein, KI 2005

%FO was defined as total fluid input minus output (up to 7 days before CVVH for both hospital stay and ICU stay)



Pediatric Patients: Higher percentages of fluid overload (FO) at dialysis initiation linked with increased mortality

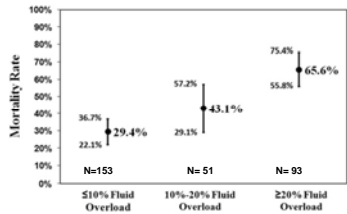
Setting & Participants: 297 children from 13 centers across the United States participating in the Prospective Pediatric CRRT Registry.

Predictor: Fluid overload from intensive care unit (ICU) admission to CRRT initiation.

Outcome & Measurements: The primary outcome was survival to pediatric ICU discharge.

Results: The association between degree of fluid overload and mortality remained after adjusting for intergroup differences and severity of illness. The adjusted mortality OR was 1.03 (95% CI, 1.01-1.05), suggesting a 3% increase in mortality for each 1% increase in severity of fluid overload. **When fluid overload was dichotomized to 20% and 20% of patients with 20% fluid overload had an adjusted mortality OR of 3.5 (95% CI, 2.8-25.7).**

%FO was defined as a percentage equal to (fluid in [L] fluid out [L]) / (ICU admit weight [kg]) 100%.



Sutherland et al. AJKD 2010, 55: 316

In septic patients with AKI, fluid overload was associated with decreased survival at 60 days

- In this large multicenter European observational study in critically ill patients, 60-day mortality rate among patients with acute renal failure (ARF) was more than twice as high as among other patients (26.7% versus 16.4%; $P < 0.01$).
- In patients with ARF, mean daily fluid balance was significantly more positive among nonsurvivors than among survivors (0.88 ± 1.5 versus 0.15 ± 1.08 L/24 hours; $P < 0.001$).

Hazard ratios: results of multivariate Cox regression analysis for 60-day mortality in critically ill patients with acute renal failure

Characteristic	Hazard ratio	95% CI	P value
Age	1.02	1.01-1.03	<0.001
SAPS II (per point)	1.03	1.02-1.04	<0.001
Heart failure	1.36	1.05-1.81	0.02
Medical admission	1.68	1.35-2.08	<0.001
Mean fluid balance, L/24 hours	1.21	1.13-1.29	<0.001
Mechanical ventilation	1.55	1.14-2.11	<0.001
Liver cirrhosis	3.73	1.68-8.65	<0.001

CI, confidence interval; SAPS II, Simplified Acute Physiology Score II.

- Among oliguric patients and patients treated with renal replacement therapy (RRT), mean daily fluid balance was significantly more positive (0.42 ± 1.20 versus 0.17 ± 1.31 L/24 hours; $P < 0.02$), and 60-day mortality rates were significantly higher (28.8% versus 22.1%; $P < 0.02$) and 48.9% versus 31.2%; $P < 0.01$).
- Among patients in whom treatment with RRT was started early in the course of ICU admission, median length of ICU stay was significantly shorter (8.1 versus 12.2 days; $P < 0.001$) and 60-day mortality rate was significantly lower (44.8% versus 54.8%; $P < 0.01$).

Mean daily fluid balances and outcome among patients with acute renal failure, stratified by urine output and treatment

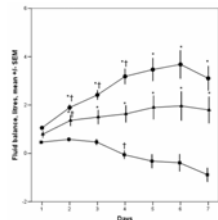
Characteristic	Non-oliguric n = 572	Oliguric n = 548	P value	No RRT n = 842	RRT n = 278	P value
Mean fluid balance, L/24 hours	0.27 ± 1.23	0.62 ± 1.33	<0.01	0.39 ± 1.21	0.80 ± 1.50	<0.01
ICU mortality	197 (27.4)	181 (33.0)	0.04	214 (25.4)	124 (44.6)	<0.01
60-day mortality	181 (32.1)	214 (39.4)	0.01	208 (24.7)	136 (49.0)	<0.01
ICU stay	$4.5 (3.0-11.1)$	$3.1 (4-8.6)$	<0.01	$3.9 (1.8-8.3)$	$8.4 (3.0-19.4)$	<0.01
Hospital stay	$12.7 (5.5-21.0)$	$10.3 (3.3-22.2)$	<0.01	$10.8 (3.8-24.1)$	$16 (6.8-34.8)$	<0.01

Data are expressed as mean \pm standard deviation, median (interquartile range), or number (percentage). ICU, intensive care unit; RRT, renal replacement therapy.

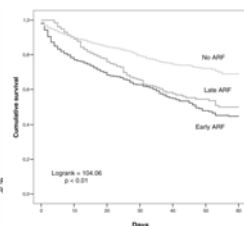
Payen et al. Critical Care 2008, 12:R74

In septic patients with AKI, fluid overload was associated with decreased survival at 60 days

Of the 1,120 patients with ARF, 642 (57%) had early-onset ARF (occurring within 2 days of ICU admission) and 278 (25%) had late-onset ARF (occurring more than 2 days after ICU admission).

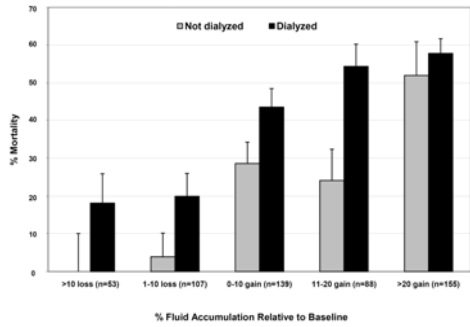


Kaplan-Meier survival curves



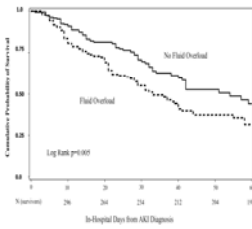
Payen et al. Critical Care 2008, 12:R74

Influence of Fluid Accumulation on Mortality

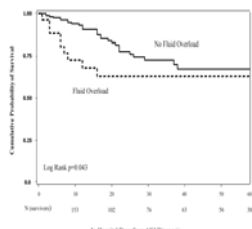


Kaplan-Meier survival estimates by fluid overload status at dialysis initiation (dialyzed) and AKI diagnosis (non-dialyzed).

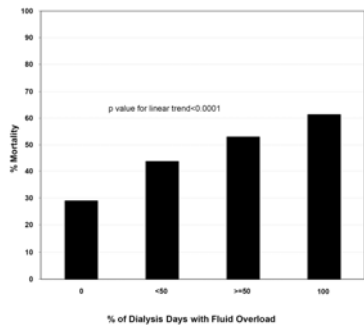
Dialyzed Patients



Non-Dialyzed Patients



Duration of Fluid Overload



Effect of Correction of Fluid Overload

- Effect of fluid overload correction on survival when %FO >10% at dialysis initiation :

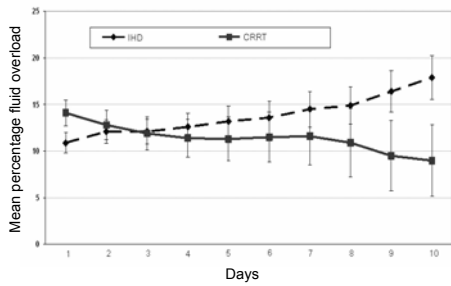
	%FO ≤ 10% at dialysis end	%FO > 10% at dialysis end	p
Survival rate	65%	44%	0.004
	Survivors	Non-survivors	P
Mean % FO at dialysis cessation	13.0%	22.1%	0.004

Adjusted OR for death with %FO >10% at dialysis cessation:
2.52 (95% CI 1.55-4.08)

PICARD Data Boucharde et al 2009



Influence of Modality on Fluid Overload



Summary of results

- %FO >10% at dialysis initiation:
2 fold increase in mortality
- Duration and correction of fluid overload
influences mortality rates
- %FO >10% at dialysis cessation:
2.5 fold increase in mortality
- Modality choice influences fluid management

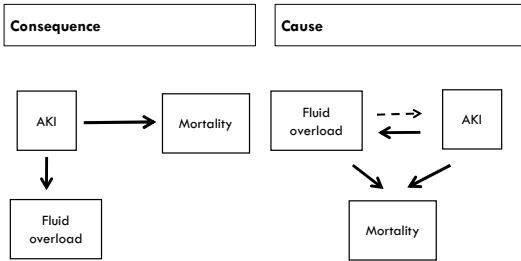


Issues

- What is the relationship of fluid accumulation and mortality
 - Marker for severity of illness and AKI dysfunction
 - Risk factor for mortality
 - Direct mediator of adverse outcomes



Fluid accumulation and AKI



Fluid Balance and AKI

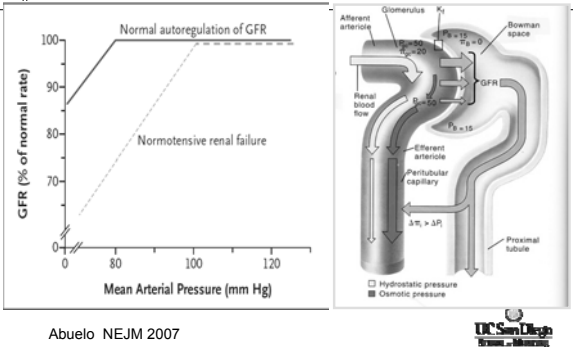
Table 2 | Publications describing two groups of critically ill patients with differing fluid balances where a renal outcome was reported*

Reference	Study type	Population	n	Average fluid balance in less-positive group	Average fluid balance in more-positive group	Renal function measure	Renal outcome with more-restrictive fluid balance strategy	Principal outcome with more-restrictive fluid balance strategy
AROS Clinical Trials Network (2006) ¹	Multi-center RCT	ARDS	1,000	-136 ml on day 7	+6,992 ml on day 7	Need for RRT; change in creatinine	No difference	Shorter duration of ventilation and ICU stay
Martin et al. (2005) ²	Single-center RCT	Mixed AUI	40	-5,480 ml on day 5	-1,490 ml on day 5	Change in creatinine	No difference	Improved oxygenation
Martin et al. (2002) ³	Single-center RCT	AUI after trauma	37	-3,300 ml on day 5	+500 ml on day 5	Change in creatinine	No difference	Improved oxygenation
Mitchell et al. (1992) ⁴	Single-center RCT	Mixed ICU needing PAC	102	+142 ml	+2,298 ml	Change in creatinine	Small rise in creatinine	Shorter duration of ventilation and ICU stay
Blanchard et al. (2003) ⁵	Retrospective observational	Mixed ICU with AKI	542	+10% rise	+10% rise	Dialysis independence	Improved	Decrease in mortality
Papan et al. (2006) ⁶	Retrospective observational	Mixed ICU with or without AKI	3,147	-1,000 ml	+3,000 ml	Renal SOFA score	Improved	Decrease in mortality in patients with AKI
Vidal et al. (2006) ⁷	Prospective observational	Mixed ICU with elevated or normal BP	83	+9,000 ml	+9,000 ml	Renal SOFA score	Improved	Renal IQR associated with less organ failure and shorter ICU stay
Adisanya et al. (2006) ⁸	Retrospective observational	Surgical ICU	41	+5 kg	+8.3 kg	Change in creatinine	No difference	Shorter duration of ventilation and ICU stay
McAville et al. (2007) ⁹	Retrospective observational	Surgical ICU	100	+7,500 ml	+10,000 ml	Change in creatinine	No difference	Decrease in postoperative complications
Adani et al. (2007) ¹⁰	Prospective observational	Burns ICU	24	+7,500 ml	+12,000 ml	Urine output	No difference	Decrease in organ dysfunction score

Prowle, J. R. et al. *Nat. Rev. Nephrol.* 6, 107–115 (2010)



Pathophysiology of AKI



Abuelo NEJM 2007