Acute Renal Failure in the ICU : Prevention, Protection, Preservation and Recovery

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Division of Critical Care Medicine, Faculty of Medicine and Dentistry, University of Alberta

Kidney in Critical Illness

- Acute renal failure
- Predisposing causes
- Protection and prevention of ARF
  - Dopamine
  - Contrast nephropathy
  - Rhabdomyolysis
  - Insulin therapy
  - Sepsis
  - Targets for resuscitation
  - Vasopressors
  - Hepatic dysfunction
- Renal replacement therapy
- Recovery of renal function
- Economics of acute renal failure

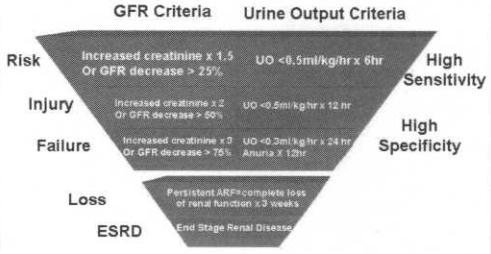
Problems of definitions of ARF

- Increase in SCr ≥ 0.5 mg/dl
- Increase in SCr ≥ 1.0 mg/dl
- Increase in SCr ≥ 25%
- Increase in SCr ≥ 50%
- Increase in SCr of ≥ 1 mg/dl/2d
- Increase in SCr of ≥ 25% to at least 2.0 mg/dl

Acute Dialysis Quality Initiative

ADQI

Rifle Criteria for Acute Renal Failure



B.E.S.T. Kidney

- Beginning and Ending Supportive Therapy for the Kidney
- Epidemiological study in response to issues raised by first Acute Dialysis Quality Initiative meeting (New York Aug. 2000)
- Major question: what is current worldwide practice with regard to RRT in ICU?

BEST Study Participating centers (preliminary results)

21 countries, 54 centres

Continent	Country	N of centers	Continent	Country	N of centers
	Japan	4		Italy	6
Asia	China	2		Germany	2
	Singapore	2		Holland	2
	Indonesia	1		Norway	2
				Portugal	2
Australia	Australia	6	Europe	Spain	2
				UK	2
North	USA	6		Greece	1
America	Canada	2		Israel	1
				Russia	1
South	Brazil	4		Sweden	1
America	Uruguay	1		Switzerland	1

BEST Study Definitions of ARF

- One of the following:
- Need for RRT
- Urea > 30 mmol/L
- BUN > 86 mg/dl
- Urine output < 200 ml/12 hours
- [K+] > 6.5 mmol/L

B.E.S.T. Study Incidence of ARF

- ICU admissions: 29,269
- ARF but no RRT: 498
- ARF with RRT: 1,260
- Total: 1,758
- Incidence of ARF: 6%
- Incidence of RRT: 4.2%

B.E.S.T. Study Demographics

- Number of patients: 1758
- Gender (M/F): 63.7 / 36.3%
- Age: 67 (53-75)
- SAPS-II score: 48 (38-61)
- CRF: 29.5%

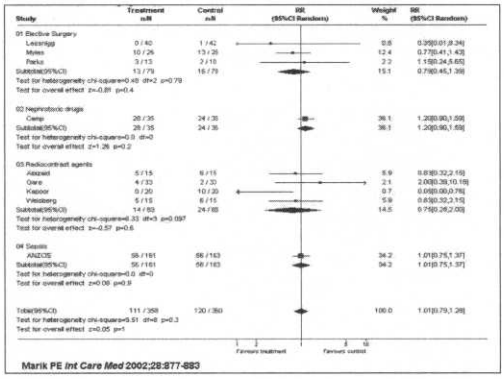
Contributing Factors

- Medical/Surgical: 58.8 vs. 41.2%
- Sepsis: 47.4%
- Major surgery: 34.4%
- Low cardiac output: 26.9%
- Hypovolemia: 25.5%
- Drugs: 19%
- Hepatorenal syndrome: 5.7%

Prevention and Protection

Low-dose dopamine?

"Hopeamine"



Marik PE *Int Care Med* 2002;28:877-883

Low-dose dopamine in patients with early renal dysfunction: a placebo-controlled randomised trial

Lancet 2000; **356**: 2139–43

*Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group**

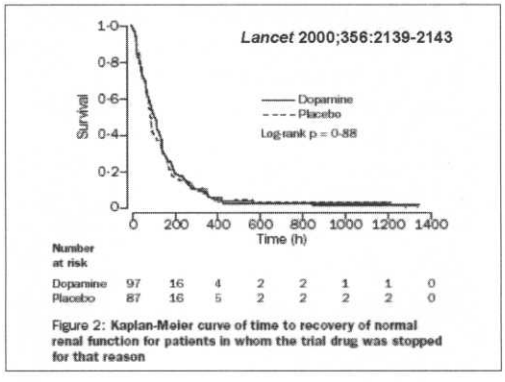
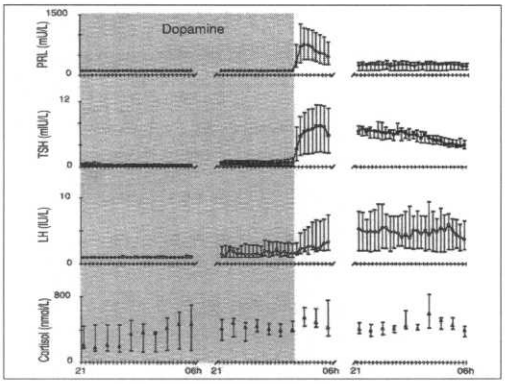


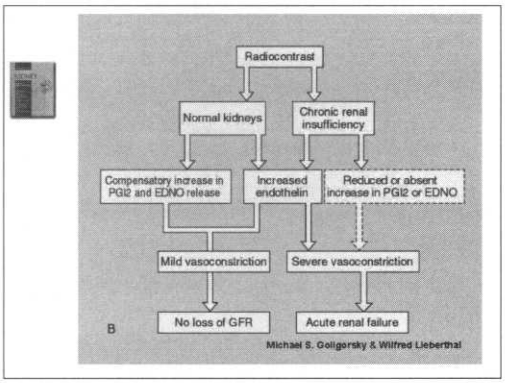
Figure 2: Kaplan-Meier curve of time to recovery of normal renal function for patients in whom the trial drug was stopped for that reason

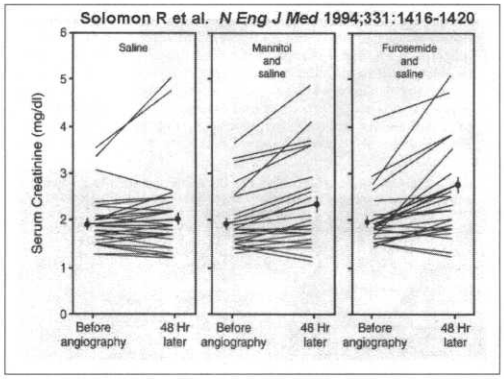
Van den Berghe G, de Zegher F. Anterior pituitary function during critical illness and dopamine treatment.

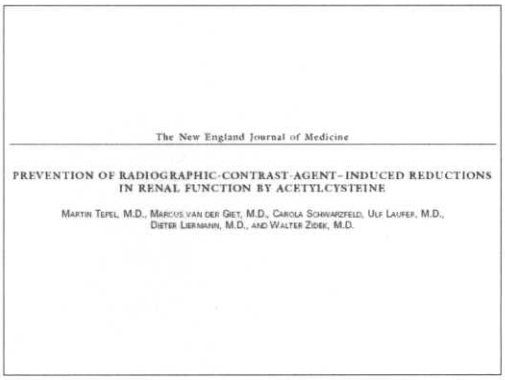
Crit Care Med 1996;24:1580-1590



Toxins and the kidney





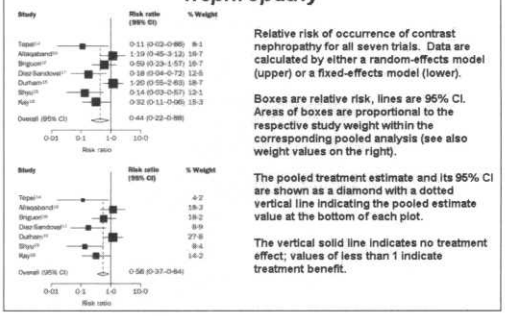


Acetylcysteine for prevention of contrast nephropathy: meta-analysis

Birck R , Krzossok S, Markowetz F et al

***Lancet* 2003; 362: 598–603**

Relative risk of occurrence of contrast nephropathy



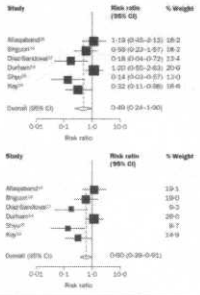
Relative risk of occurrence of contrast nephropathy for all seven trials. Data are calculated by either a random-effects model (upper) or a fixed-effects model (lower).

Boxes are relative risk, lines are 95% CI. Areas of boxes are proportional to the respective study weight within the corresponding pooled analysis (see also weight values on the right).

The pooled treatment estimate and its 95% CI are shown as a diamond with a dotted vertical line indicating the pooled estimate value at the bottom of each plot.

The vertical solid line indicates no treatment effect; values of less than 1 indicate treatment benefit.

Relative risk of occurrence of contrast nephropathy after exclusion of Tepel trial



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A Rapid Protocol for the Prevention of Contrast Induced Renal Dysfunction: The RAPPID Study.

Baker CS, Wragg A, Kumar S, De Palma R, Laurence Baker LRI, Knight CJ.

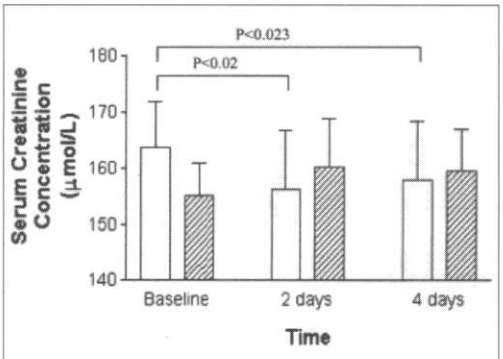
J Am Coll Cardiol 2003;41:2114–2118)

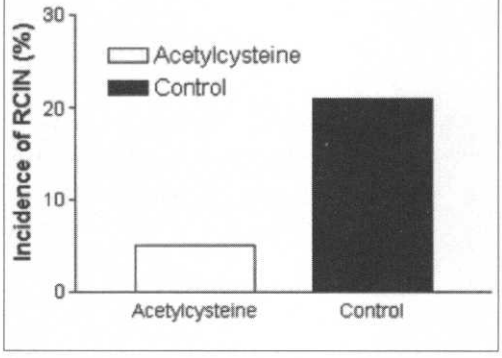
RAPPID Study

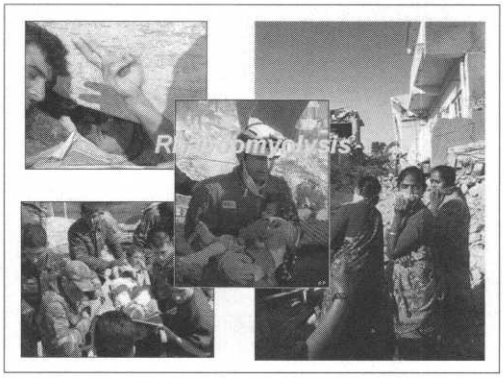
- NAC 150 mg/kg in 500 mls 0.9% saline over 30 mins prior to IV contrast
- NAC 50 mg/kg in 500 mls 0.9% saline over 4 hours post IV contrast

vs.

- IV Hydration 1 ml/kg/hr 0.9% saline over 12 hrs pre and 12 hrs post IV contrast







Rhabdomyolysis

- Destruction of skeletal muscle and release of myoglobin & K
  - Crush injury
  - Ischemia-reperfusion
  - Hyperthermia
  - Drugs
- Leads to acidosis, hyperkalemia, myoglobinuria, acute renal failure
  - Binding of NO by Mb → Renal vasoconstriction
  - Tubular toxicity
  - Tubular obstruction

Holt SG and Moore KP. *Int Care Med* 2001;27:803-811

Management of myoglobinuria

- Increase renal perfusion and GFR
  - **Aggressive** fluid loading
  - 3-4 litres in first hour
- Increase urinary pH
  - $NaHCO_3$
    - Reduce vasoconstriction
    - Reduce tubular cellular toxicity
    - Maintain tubular filtrate flow
- Osmotic diuretic - mannitol

Holt SG and Moore KP. *Int Care Med* 2001;27:803-811

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    - Reduce tubular cellular toxicity
    - Maintain tubular filtrate flow
- Osmotic diuretic – mannitol
- ? Sodium dantrolene – myocyte stabilization

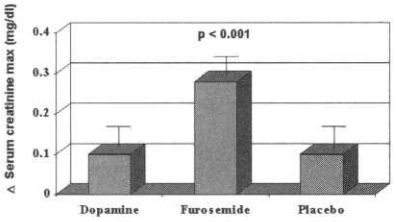
Holt SG and Moore KP. *Int Care Med* 2001;27:803-811

Myoglobinuria resuscitation

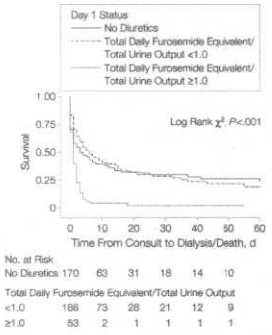
- Begin IV fluids before extrication - alternate
  - 1 L NS
  - 1 L D5W + 150 mmol $NaHCO_3$
- 3-4 litres in first hour
- 6-10 litres/day

What about diuretics?

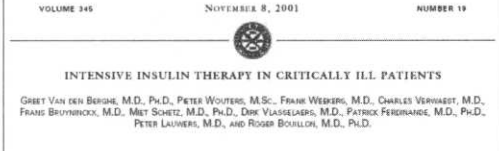
- Potential advantages
  - Conversion to non-oliguric renal failure
  - Removal of tubular debris
- Potential disadvantages
  - Hypovolemia
  - Increase in renal metabolic rate
  - Nephrotoxicity



Lassnig A et al. Lack of renoprotective effect of dopamine and furosemide during cardiac surgery. *J Am Soc Nephrol* 2000;11:97-104.



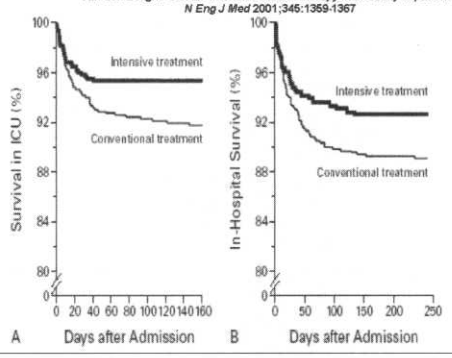
Mehta R et al. *JAMA.* 2002;288:2547-2553



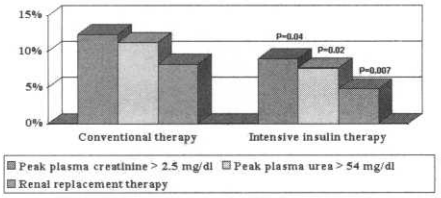
INTENSIVE INSULIN THERAPY IN CRITICALLY ILL PATIENTS

GREET VAN DEN BERGHE, M.D., PH.D., PIETER WOUTERS, M.SC., FRANK WEEKERS, M.D., CHARLES VERWAEST, M.D., FRANS BRUYNINCKX, M.D., MIET SCHETZ, M.D., PH.D., DIRK VLASSELAERS, M.D., PATRICK FERDINANDE, M.D., PH.D., PETER LAUWERS, M.D., AND ROGER BOUILLON, M.D., PH.D.

Van den Berghe G et al. Intensive insulin therapy in critically ill patients. *N Eng J Med* 2001;345:1359-1367



Effect of control of glucose on renal function

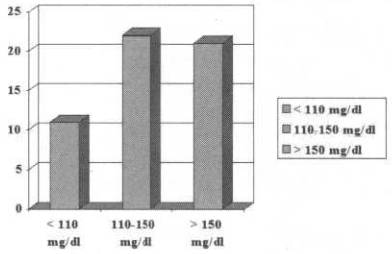


Van den Berghe G et al. Intensive insulin therapy in critically ill patients. *N Eng J Med* 2001;345:1359-1367

Outcome benefit of intensive insulin therapy in the critically ill: Insulin dose versus glycemic control*

Greet Van den Berghe, MD, PhD; Pieter J. Wouters, MSc; Roger Bouillon, MD, PhD; Frank Weekers, MD; Charles Verwaest, MD; Miet Schetz, MD, PhD; Dirk Vlasselaers, MD; Patrick Ferdinande, MD, PhD; Peter Lauwers, MD Crit Care Med 2003;31:359-366

% Risk of acute renal failure



Van den Berghe G. et al. Outcome benefit of intensive insulin therapy in the critically ill: Insulin dose vs benefit. *Crit Care Med* 2003;31:359-366

The New England Journal of Medicine

EARLY GOAL-DIRECTED THERAPY IN THE TREATMENT OF SEVERE SEPSIS AND SEPTIC SHOCK

Emanuel Rivers, M.D., M.P.H., Bryant Nguyen, M.D., Suzanne Havstad, M.A., Julie Ressler, B.S., Alexandria Muzzin, B.S., Bernhard Knoblich, M.D., Edward Peterson, Ph.D., and Michael Tomlanovich, M.D., for the Early Goal-Directed Therapy Collaborative Group*

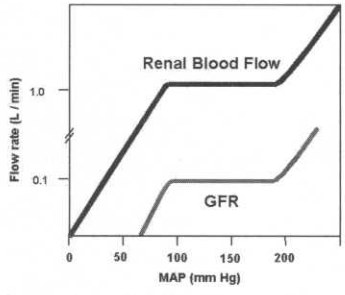
EGDT Outcomes

		Early Goal		
	Standard Therapy	Directed Therapy	Relative risk	
	(N=133)	(N=130)	(95% CI)	P Value
In-Hospital Mortality				
All patients	59 (46.5%)	38 (30.5%)	0.58 (0.38-0.87)	0.009
Pts with severe sepsis	19 (30.0%)	9 (14.9%)	0.46 (0.21-1.03)	0.06
Pts with septic shock	40 (56.8%)	29 (42.3%)	0.60 (0.36-0.95)	0.04
Pts with sepsis syndrome	44 (45.4%)	35 (35.1%)	0.66 (0.42-1.04)	0.07
28 Day mortality	61 (49.2%)	40 (33.3%)	0.58 (0.39-0.87)	0.01
60 Day Mortality	70 (56.9%)	50 (44.3%)	0.67 (0.46-0.96)	0.03
Causes of in-hosp mortality				
Sudden CVS collapse	25/119 (21.0%)	12/117 (10.3%)		0.02

NNT=16

Rivers E et al. *N Eng J Med* 2001;345:1368-77.

Normal Autoregulation



SIRS/Severe Sepsis

Peripheral vasodilatation
- Nitric oxide
- Prostacyclin
- Vascular K-ATP channels

Intrarenal vasoconstriction
- Endothelin
- Thromboxane A2
- Leukotrienes

Microvascular injury
- Inflammatory cytokines
- Activated leukocytes
- Intracapillary thrombosis

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Ischemic Renal Injury

SIRS/Severe Sepsis

Peripheral vasodilatation
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Microvascular injury
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- Intracapillary thrombosis

Potential concomitant Renal insults
- Nephrotoxic drugs
- Radiocontrast
- Rhabdomyolysis
- Hepatic dysfunction

Ischemic Renal Injury

Cytotoxic Renal Injury

SIRS/Severe Sepsis

Peripheral vasodilatation
- Nitric oxide
- Prostacyclin
- Vascular K-ATP channels

Potential concomitant Renal insults
- Nephrotoxic drugs
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- Endothelin
- Thromboxane A2
- Leukotrienes

Microvascular injury
- Inflammatory cytokines
- Activated leukocytes
- Intracapillary thrombosis

Ischemic Renal Injury — **Cytotoxic Renal Injury**

Acute Tubular Necrosis

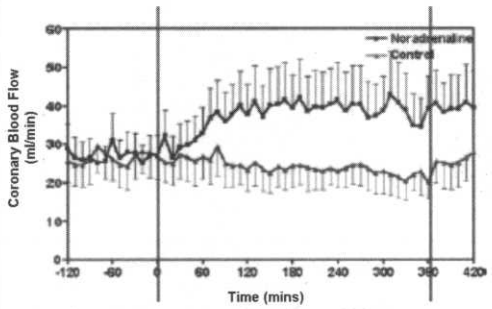
Levophed leaves 'em dead?

Intensive Care Med (2002) 28:1804–1809
DOI 10.1007/s00134-002-1444-x

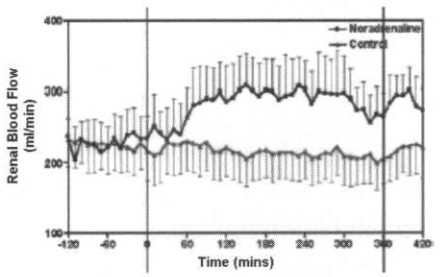
ORIGINAL

David Di Giantomasso
Clive N. May
Rinaldo Bellomo

Norepinephrine and vital organ blood flow

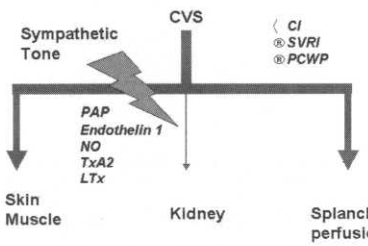


Bellomo R et al. Norepinephrine and vital organ flow.
Int Care Med 2002; 28:1804-1809



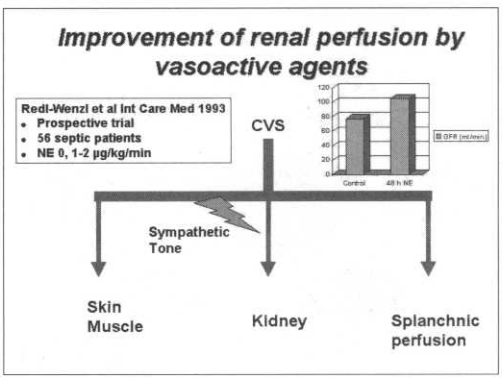
Bellomo R et al. Norepinephrine and vital organ flow.
Int Care Med 2002; 28:1804-1809

Hemodynamic changes in sepsis



Improvement of renal perfusion by vasoactive agents

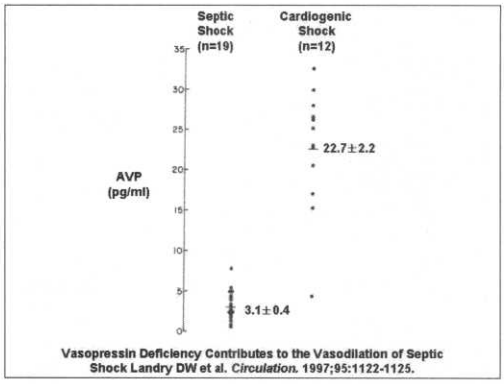
Redl-Wenzl et al Int Care Med 1993
- **Prospective trial**
- **56 septic patients**
- **NE 0, 1-2 μg/kg/min**



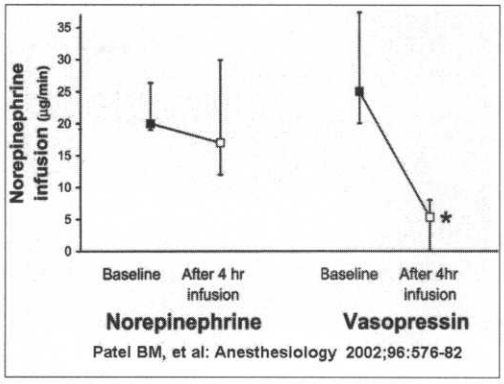
Vasopressin

- Secreted under osmotic control to modify permeability of renal collecting ducts to water (0.9-6.5 pmol/L) - V_2 receptors
- Secreted under baroreceptor control to modify BP (9-187 pmol/L) - V_1 receptors
- Rapid increase in vasopressin levels in early phase of hemorrhagic shock (>280 pmol/L)
- Subsequent decrease in levels (30 pmol/L) due to depletion of posterior pituitary stores

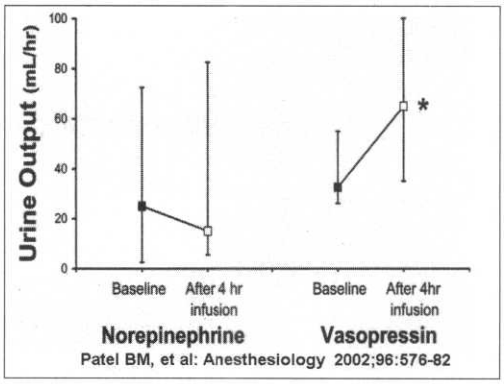
- Low levels of vasopressin in patients with septic shock
- Infusion of vasopressin to provide serum levels normally seen in shock provides significant improvement in BP even in patients refractory to NE and Epi



Vasopressin Deficiency Contributes to the Vasodilation of Septic Shock Landry DW et al. *Circulation.* 1997;95:1122-1125.



Patel BM, et al: Anesthesiology 2002;96:576-82



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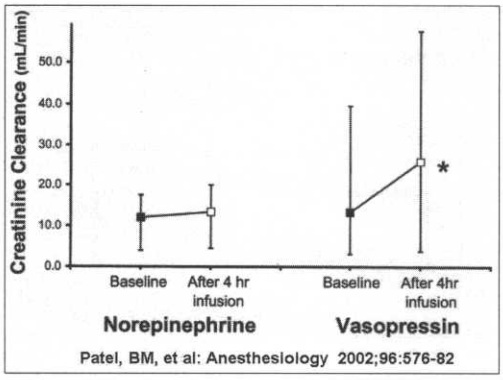


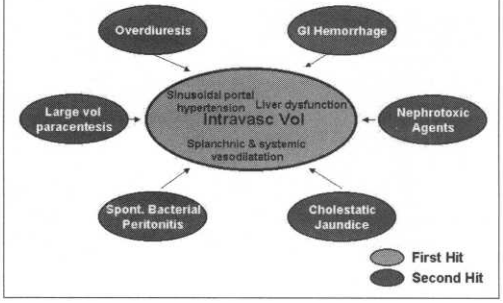
Patel, BM, et al: Anesthesiology 2002;96:576-82

The kidney in liver disease

Acute Renal Failure in Hepatic Failure

- Common – 45% of all cases
- Multifactorial
- More often ATN rather than HRS
- Role of intra-abdominal pressure
- Intolerant of intermittent hemodialysis
  - ➢ Hypotension
  - ➢ Cerebral edema

ARF in Liver Failure



Hepatorenal syndrome

Prevention: antibiotics + albumin
SBP with HRS 30% vs. 10%

1. Vasoconstriction ren. arteries
2. SVR
3. Effective blood volume

1. N-acetylcysteine
2. Terlipressin + albumin
   - Improved renal function 58-77%
   - 1 mo survival rates 40-60%
3. TIPS
   - No RCT, n=31- day 90 surv 81%
4. MARS
   - 1 RCT, n=13 - day 30 surv 25%
5. Liver transplant

Brensing et al. Lancet 1997;349:697-698
Solanki et al. J Gastroenterol Hepatol. 2003;18:152-157

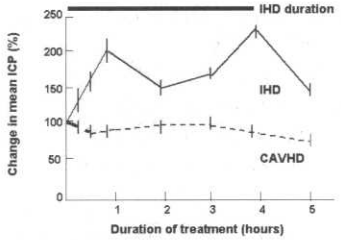
Hemodynamic management in Acute Liver Failure

- Volume first
- What end points?
  - MAP
  - CVP
  - ?PCWP
  - Elimination of pulse pressure variation
  - ?PiCCO
- Norepinephrine
- Vasopressin (or Terlipressin)
- Hydrocortisone
- ?Methylene blue

Hemodynamic management in Acute Liver Failure

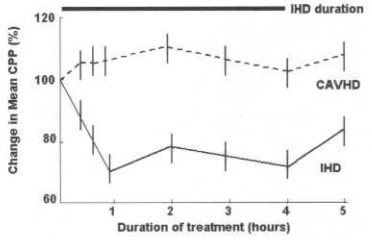
- Volume first -yes
- What end points?
  - MAP 75-85mmHg
  - CVP mid-teens
  - ?PCWP No
  - Elimination of pulse pressure variation Yes
  - ?PiCCO Maybe
- Norepinephrine Yes
- Vasopressin (or Terlipressin) 0.03u/min
- Hydrocortisone 50 mg q 6H
- ?Methylene blue No

ICP during Renal Replacement Therapy in Acute Liver Failure



Davenport A et al. Kidney Int 1993; 43 Suppl 41: S245-S251.

CPP during Renal Replacement Therapy in Acute Liver Failure



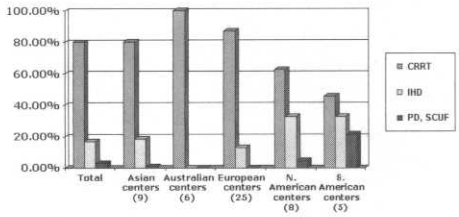
Davenport A et al. Kidney Int 1993; 43 Suppl 41: S245-S251.

Indications for renal replacement therapy

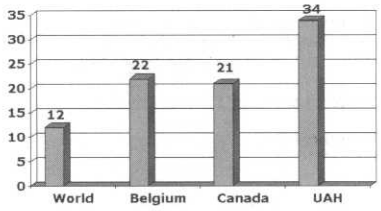
- Uncontrollable hyperkalemia
- Severe fluid overload unresponsive to diuretics
- Symptomatic uremia
- Acidosis
- Intoxication
  - Methanol/ethylene glycol
  - Lithium, ASA

- Anuria in setting of shock, acidosis

B.E.S.T Study RRT Practice



% Patients receiving IHD in ICU

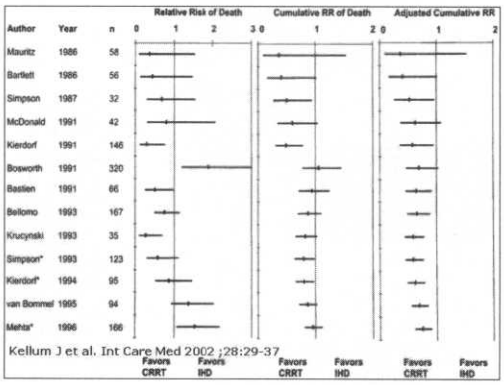


Bellomo R BEST Study - Preliminary Data

IHD or CRRT?

Outcomes:

- Survival
- Return of renal function

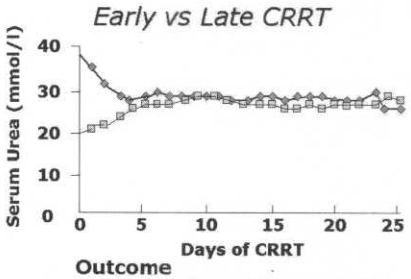


Kellum J et al. Int Care Med 2002;28:29-37

Early vs late CRRT

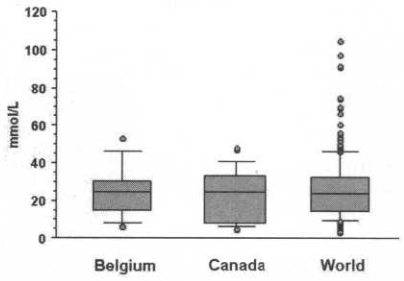
- Retrospective
- 100 adult trauma patients with ARF on CRRT
- Similar APACHE II scores
- Mean BUN / Start day
  - 38 mmol/l - start day 19.4
  - 20 mmol/l - start day 10.5

Gettings LG et al. Intensive Care Med 1999;25:805-813



Gettings LG et al. Intensive Care Med 1999;25:805-813

Serum Urea Level at Start of RRT



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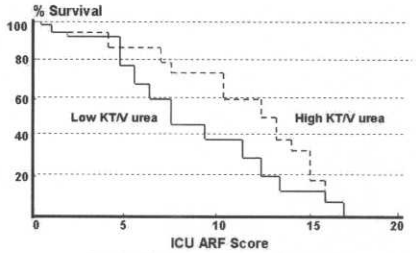
Dialysis Dose vs Outcome



Topolayi M et al. J Am Soc Nephrol 1994,5:530

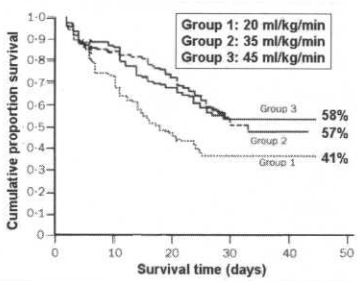
ARTICLES

Effects of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure: a prospective randomised trial

Lancet 2000;356:26-30

Claudio Ronco, Rinaldo Bellomo, Peter Homel, Alessandra Brendolan, Maurizio Dan, Pasquale Piccinni, Giuseppe La Greca

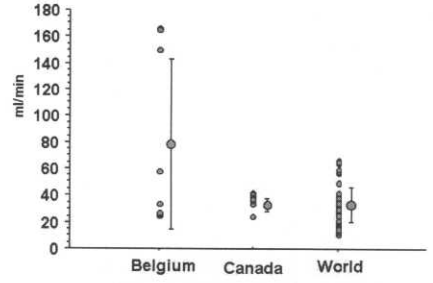
Kaplan Meier estimation of survival rates



Ronco C et al. *Lancet* 2000;356:26-30

CRRT Dose

(Ultrafiltrate+Dialysate Flow Rate)



Bellomo R BEST Study - Preliminary Data

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VOLUME 346 JANUARY 31, 2002 NUMBER 5

DAILY HEMODIALYSIS AND THE OUTCOME OF ACUTE RENAL FAILURE

HELMUT SCHIFFL, M.D., SUSANNE M. LANG, M.D., AND REINALD FISCHER, M.D.

Outcomes according to treatment group

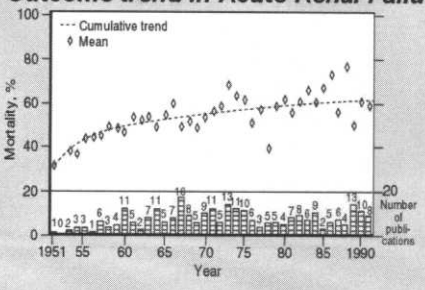
	Alternate day hemodialysis (N=80)	Daily hemodialysis (N=80)	P Value
Mortality	37 (46%)	22 (28%)	0.01
Days to resolution of ARF	16±6 (mean±SD)	9±2 (mean±SD)	0.001

Schiffl H et al. *N Eng J Med* 2002;346:305-310

Return of renal function

- Mehta et al Kidney Int 2001;60:1154-1163
  - IHD 59.4%
  - CRRT 92.3%
- BEST Study (submitted for publication)
  - Aust (100% CRRT) 96%
  - N. America (63% CRRT) 70%
- Jacka MJ & Gibney RTN (submitted for publication)
  - IHD (34%) 50%
  - CRRT (66%) 88%

Outcome trend in Acute Renal Failure



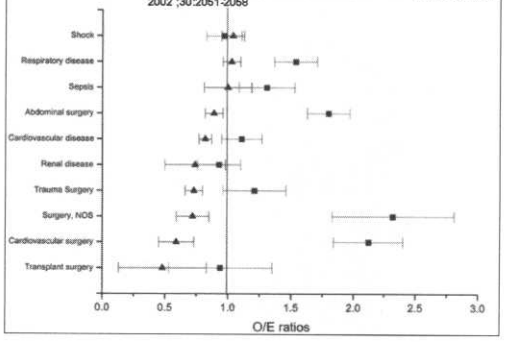
Kierdorf H, Sieberth HG: Continuous treatment modalities in acute renal failure. *Nephrol Dial Transplant* 1995; 10:2001–2008.

Effect of acute renal failure requiring renal replacement therapy on outcome in critically ill patients*

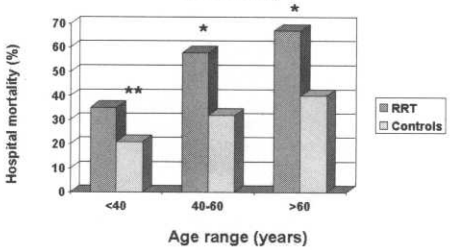
Philipp G. H. Metnitz, MD, PhD, DEAA; Claus G. Krenn, MD; Heinz Steltzer, MD; Thomas Lang, PhD; Jürgen Ploder, MS; Kurt Lenz, MD; Jean-Roger Le Gall, MD; Wilfred Druml, MD

Crit Care Med 2002;30:2051-2058

Metnitz PG et al. Effect of acute renal failure requiring renal replacement therapy on outcome in critically ill patients. Crit Care Med 2002 ;30:2051-2058



Effect of ARF requiring RRT on mortality

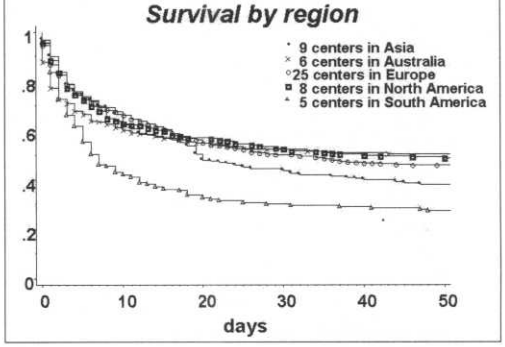


Metnitz PG et al. Effect of acute renal failure requiring renal replacement therapy on outcome in critically ill patients. *Crit Care Med* 2002;30:2051-2058

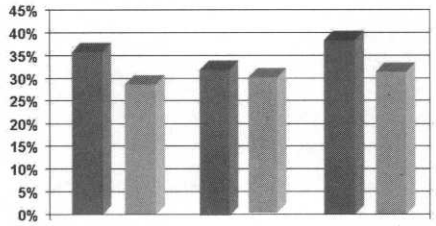
BEST Study-Overall Outcomes

- ICU stay: 9 days (4-21)
- Hospital stay: 22 (11-44)
- ICU mortality: 51.7%
- Hospital mortality: 60.2%
- Hospital discharge with RRT: 5.4%

Survival by region

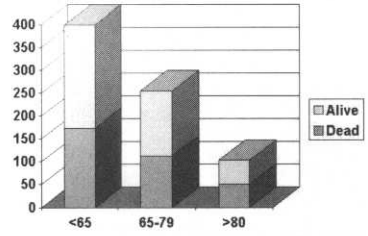


Hospital Survival Rate



Bellomo R BEST Study - Preliminary Data

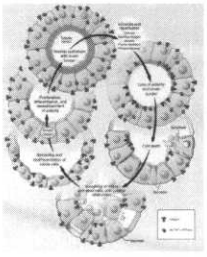
ARF Outcome by age



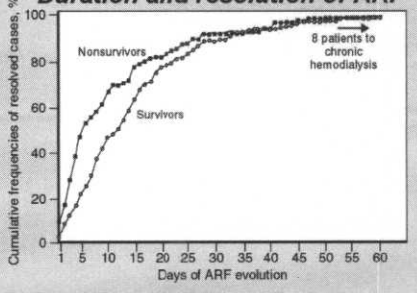
Liaño F, Pascual J the Madrid ARF Study Group: Epidemiology of acute renal failure: A prospective, multicenter, community-based study. *Kidney Int* 1996, 50:811–818.

Resolution of Acute Tubular Necrosis

- Depends on ability of tubular cells to regenerate
- Needs participation of growth factors
  - Epidermal growth factor (EGF)
  - Insulin-like growth factor (IGF-1)
  - Growth hormone (GH)
- Rat ARF resolution improved by EGF and IGF-1
- Human studies
  - IGF-1 no improvement
  - GH higher mortality



Duration and resolution of ARF



Liaño F, Pascual J the Madrid ARF Study Group: Epidemiology of acute renal failure: A prospective, multicenter, community-based study. *Kidney Int* 1996, 50:811–818.

Long Term Outcome

- 979 patients with ARF treated with CRRT
- 678 (69%) died in hospital
- 301 (31%) survived to discharge
  - 155 (52%) alive
    - 41% impaired renal function
    - 10% required chronic dialysis
  - 112 (37%) dead
  - 34 (11%) no outcome available
- 77% felt current health status was good or excellent
- 5 year probability of survival - 50%

Morgera S et al. *Am J Kidney Dis* 2002;40:275-279

"The doctors never gave up."

Cost per survivor

- US $80,000 per 6 month survivor - Finland
- Almost complete functional recovery
- Survivors had earlier RRT
- Non-survivors had more organ failures at start of RRT

Korkeila M et al. *Int Care Med* 2000; 26:1824-31

- Dependent on 6 month survival
- 0-10% chance of survival $274,000 per QUALY
- 41-60% chance of survival $61,900 per QUALY
- Rule of thumb for 2003:
  - Cost effective above 20% chance of survival
  - 20-60% 6 month survival $107, 500 per QUALY

Angus D 2003 CRRT Meeting San Diego

Conclusions

- Prevention of ARF is preferable to renal replacement therapy
- We need to re-evaluate our target end-points for resuscitation
- There are new views and approaches to CV support in sepsis and hepatic dysfunction
- Tighter glycemic control may improve outcomes and reduce incidence of ARF
- Probably no difference in mortality between IHD and CRRT but seems to be improved return of renal function with CRRT
- Support of patients with ARF is expensive but worth it if they survive, as quality of life is often excellent