

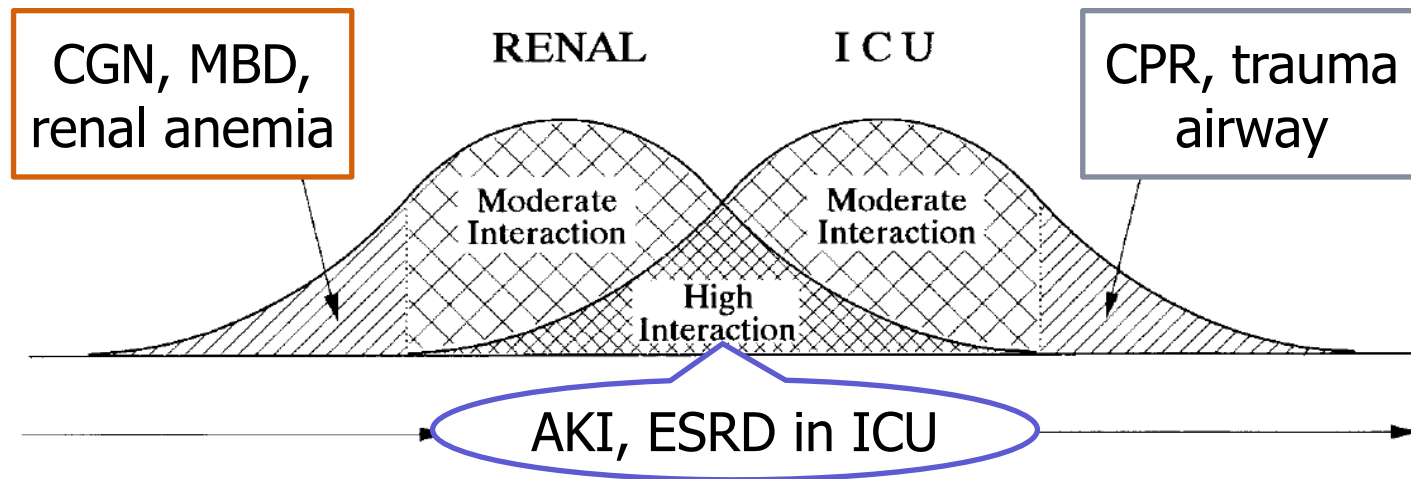


Critical Care Nephrology

Kent Doi, MD, PhD, FASN
Emergency and Critical Care Medicine
The University of Tokyo

Critical Care Nephrology

- What is Critical Care Nephrology?
 - Multidisciplinary approach in which nephrologists and intensivists work together.
 - Not specialty- but patient-oriented.





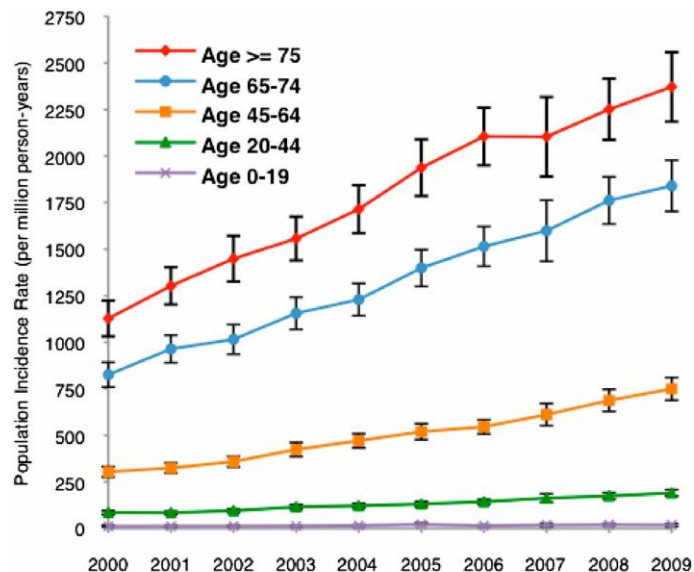
Critical Care Nephrology

- Who?
 - Intensivist
 - Nephrologist (blood purification, referral)
 - Cardiologist (surgery/medicine)
- Targets?
 1. Acute kidney injury (AKI)
 2. End-stage renal disease (ESRD)
 3. Multiple organ failure (MOF)

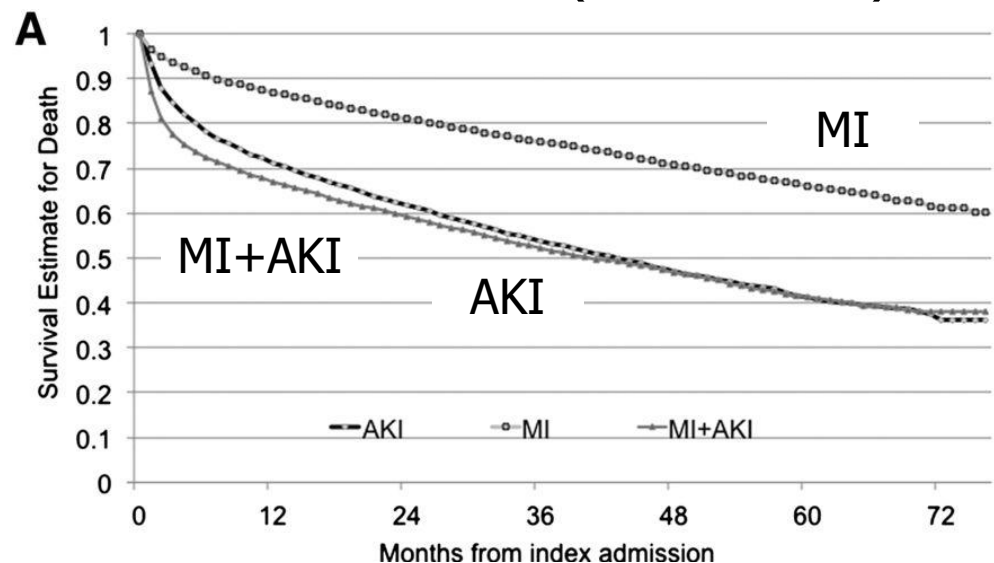
Critical Care Nephrology

1. Acute kidney injury (AKI)
 - Is increasing especially in the elderly.
 - Its mortality remains higher than AMI.

NIS database (JASN 2013)

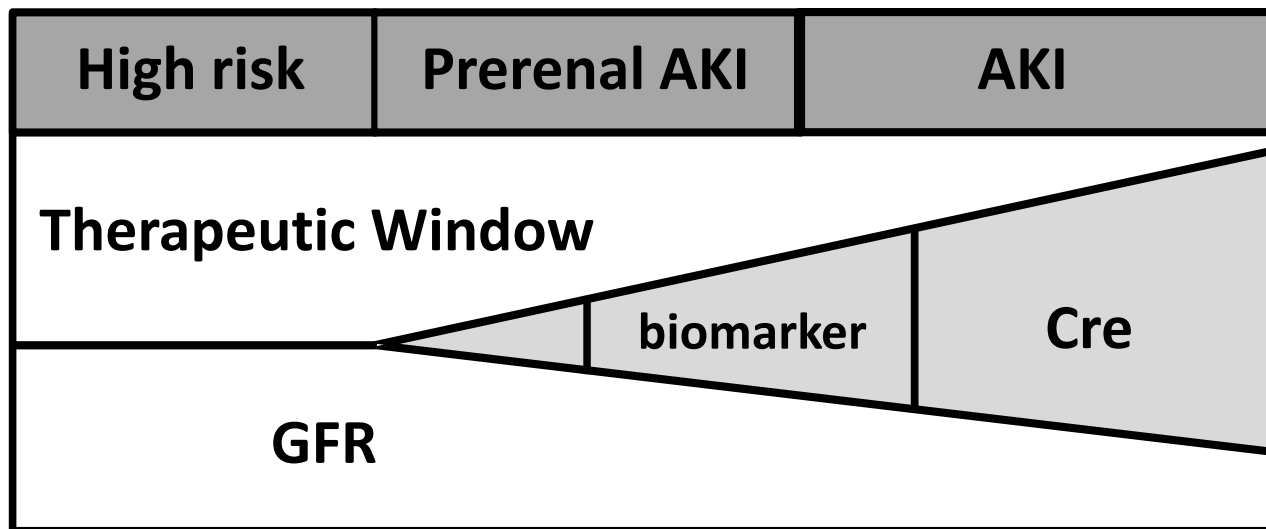


VA database (CJASN 2014)



Critical Care Nephrology

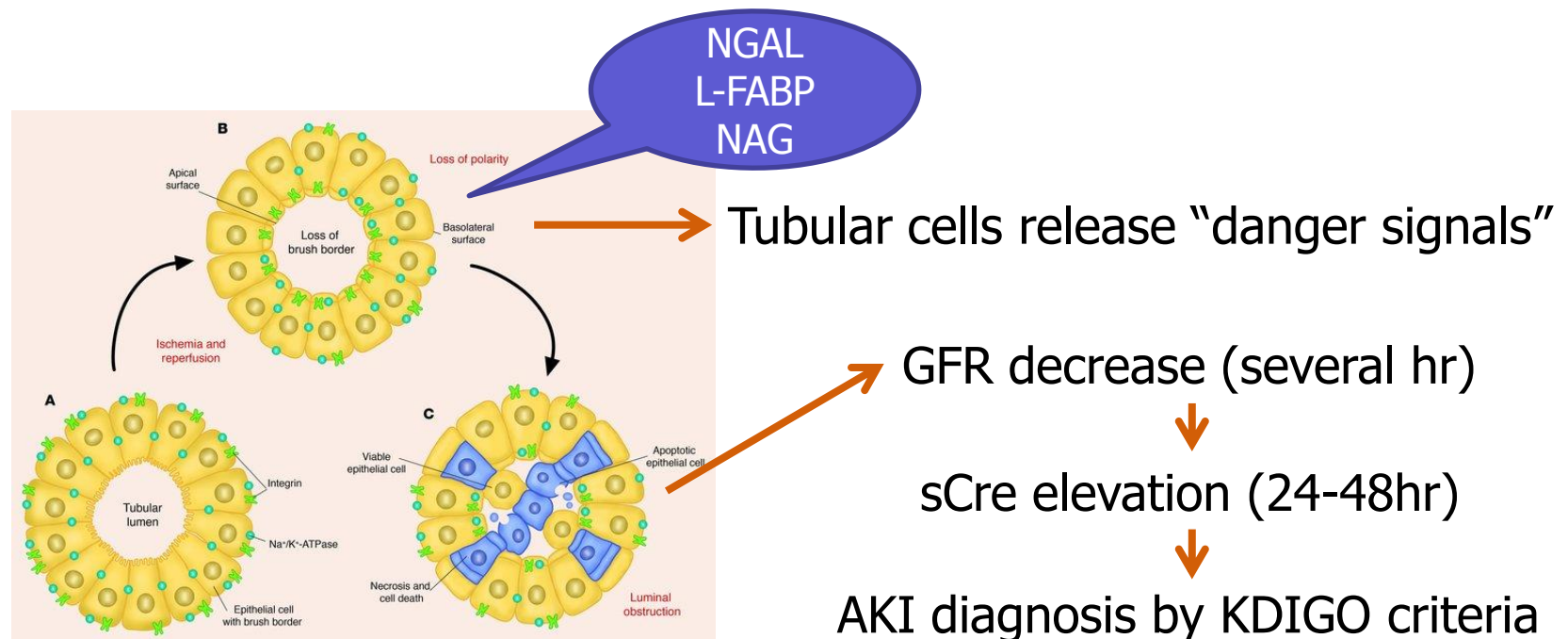
1. Acute kidney injury (AKI)
 - Early detection is important for successful intervention.




Critical Care Nephrology

1. Acute kidney injury (AKI)

- New AKI biomarkers will help to detect AKI earlier than serum Cre.





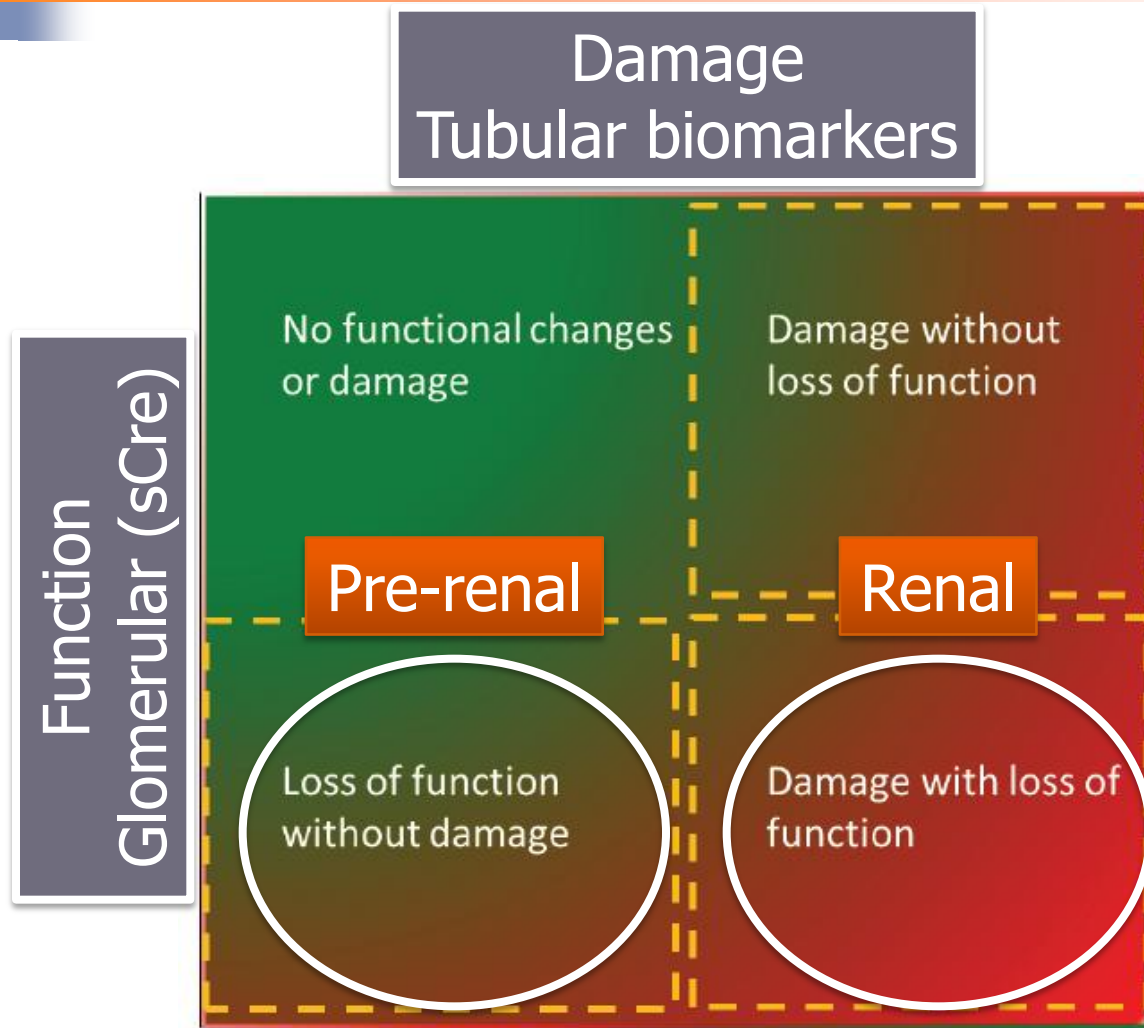
Pre-renal vs Renal AKI

–Differentiation by new biomarkers

	Pre-renal	Renal
Concept	Physiological reaction against hypoperfusion	Structural damage in renal tissue
Rapid recovery	Yes	No
Na reabsorption	Increased (low FENa)	Decreased (high FENa)
Location	Outpatient	Inpatient

New spectrum of AKI

–Differentiation by new biomarkers

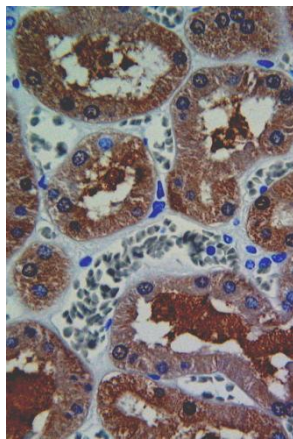


McCullough PA/Ronco C,
Contrib Nephrol 2013

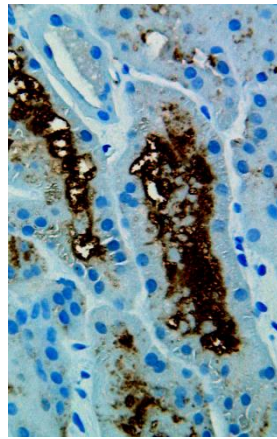
Potential renal hypoxia biomarker

Urinary L-FABP

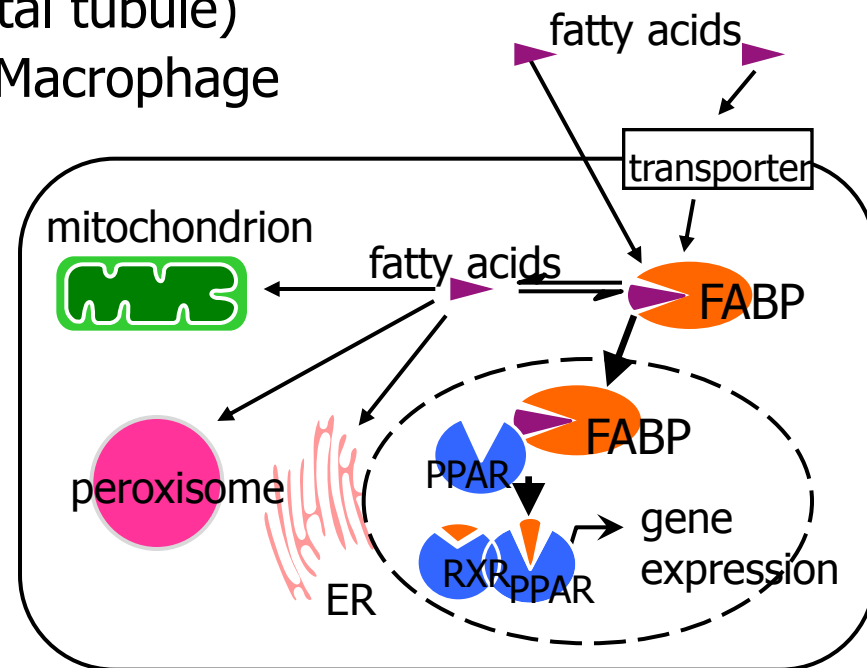
- FABPs (Fatty acid-binding proteins)
 1. L-FABP : Liver, Kidney (proximal tubule)
 2. H-FABP: Heart, Kidney (distal tubule)
 3. A-FABP (aP2) : Adipocyte, Macrophage
 4. I-FABP : Intestine, Liver



Normal

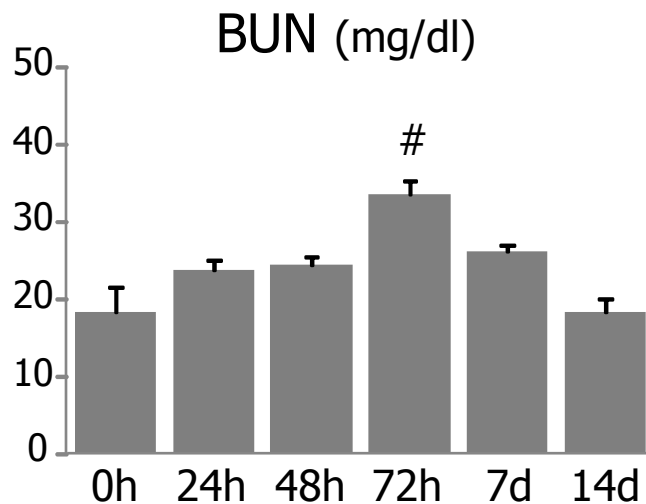


Ischemic (1h Bx)

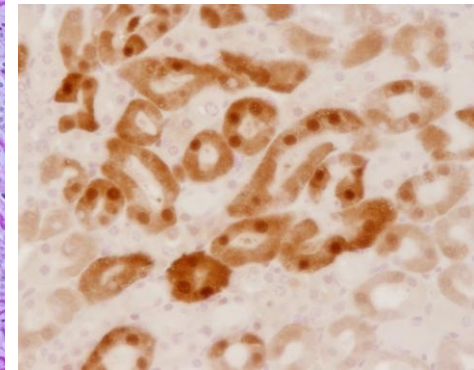
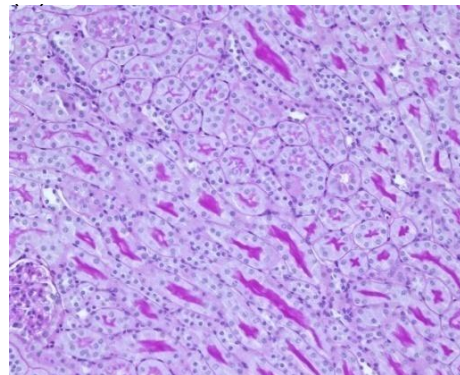


Urinary L-FABP in Pre-renal AKI – reflecting renal hypoxia?

- Volume depletion model shows
 1. transient BUN elevation
 2. no pathological finding in PAS
 3. Hypoxia = pimonidazole incorporation.



Hypoxia induced by dehydration

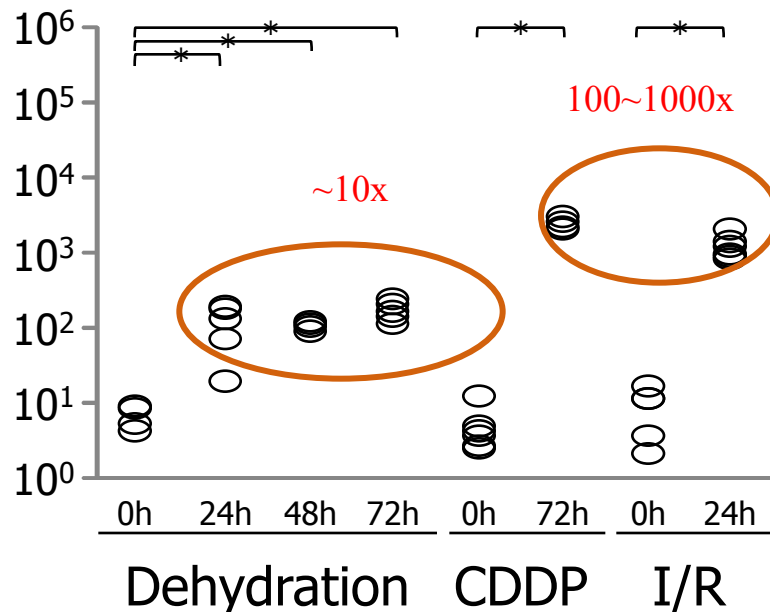


Pimonidazole

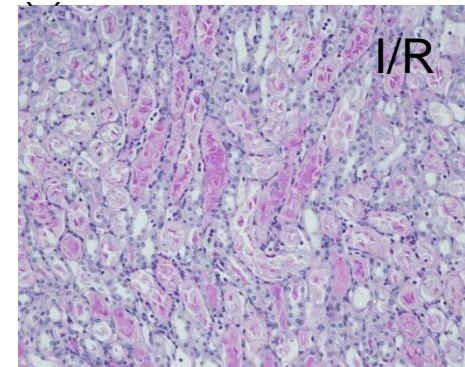
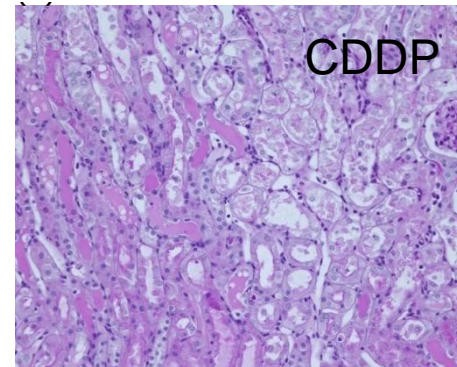
Urinary L-FABP in Pre-renal AKI – reflecting renal hypoxia?

- Urinary L-FABP detects renal hypoxia with no structural damage, discriminates pre-renal from renal AKI.

Urinary L-FABP (ng/ml)



Acute tubular necrosis





Critical Care Nephrology

- Who?
 - Intensivist
 - Nephrologist (blood purification, referral)
 - Cardiologist (surgery/medicine)
- Targets?
 1. Acute kidney injury (AKI)
 2. End-stage renal disease (ESRD)
 3. Multiple organ failure (MOF)



Critical Care Nephrology

2. End-stage renal disease (ESRD)
 - Is more frequently treated in ICU/CCU
 - Remarkable technical progress (CRRT)

British Journal of Anaesthesia **110** (1): 13–20 (2013)
Advance Access publication 20 November 2012 · doi:10.1093/bja/aes401

BJA



Patients with end-stage renal disease admitted to the intensive care unit: systematic review

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² Division of Medicine, University College London, Rayne Building, University Street, London WC1E 6JF, UK

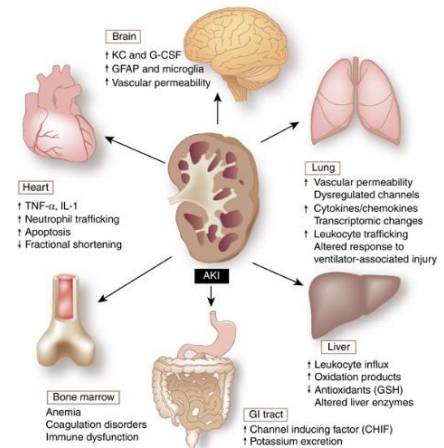
* Corresponding author. E-mail: nish_arul@yahoo.com

- Better ICU/hospital survival than dialysis-AKI
Odds ratios AKI vs ESRD; 3.9 (3.5-4.4) and 1.5 (1.4-1.6)
 - ESRD pts will have more benefit from ICU admission

Critical Care Nephrology

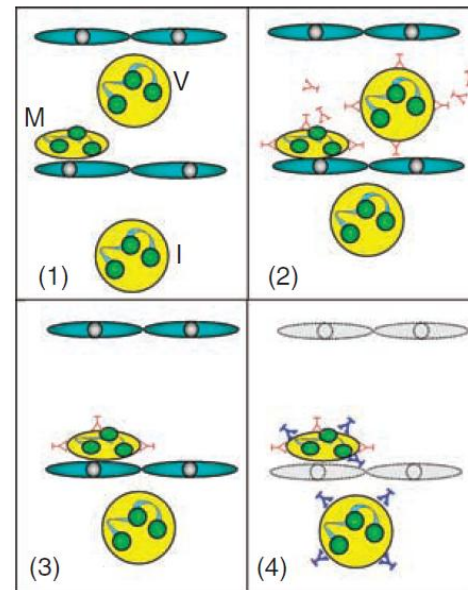
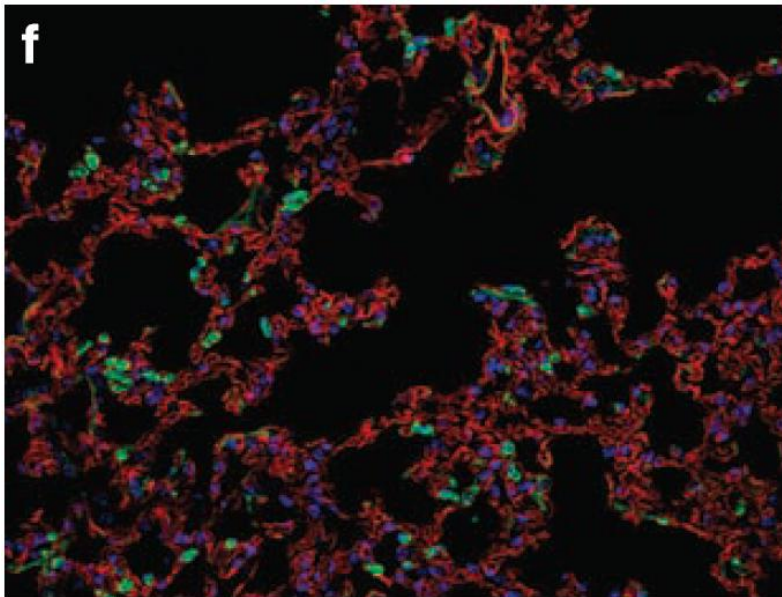
3. Multiple organ failure (MOF)

- Pts will die not by “uremia/renal failure” but MOF.
- Nephrologists should know standard management in critical care.
 - ABx, Mechanical ventilation, Sedation, Nutrition, etc
- Organ cross-talk in AKI has been investigated.
 - Heart-kidney (cardiorenal)
 - Lung-kidney
 - Liver-kidney (hepatorenal)



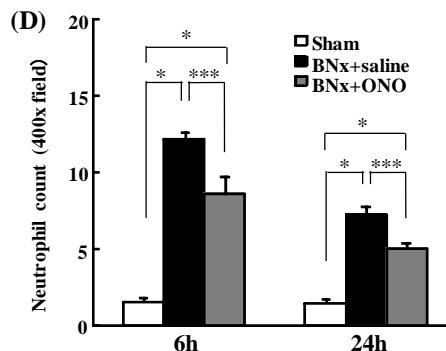
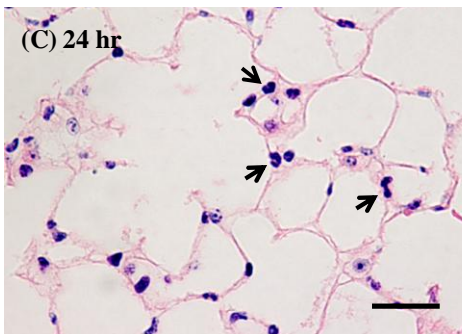
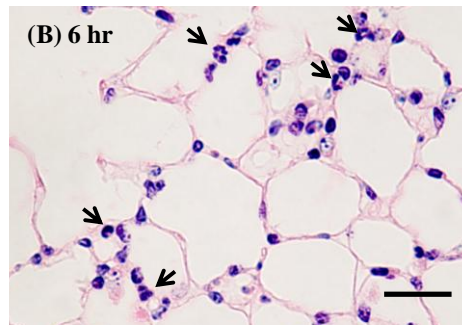
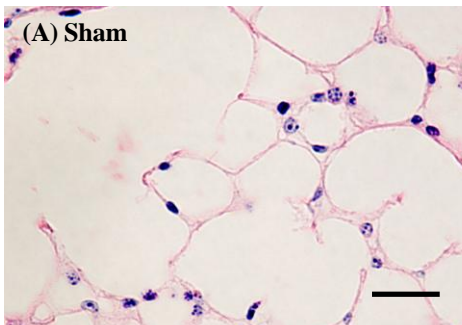
Lung injury in AKI

- Pulmonary neutrophil infiltration (=margination) in mouse "renal" ischemia reperfusion injury model

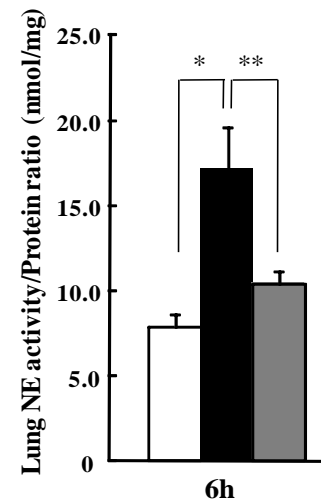


Lung injury in AKI

- Pulmonary neutrophil infiltration in mouse bilateral nephrectomy was reduced by a neutrophil elastase (NE) inhibitor.



Pulmonary NE activity





Lung injury in AKI

What is the “language” in lung-kidney crosstalk?

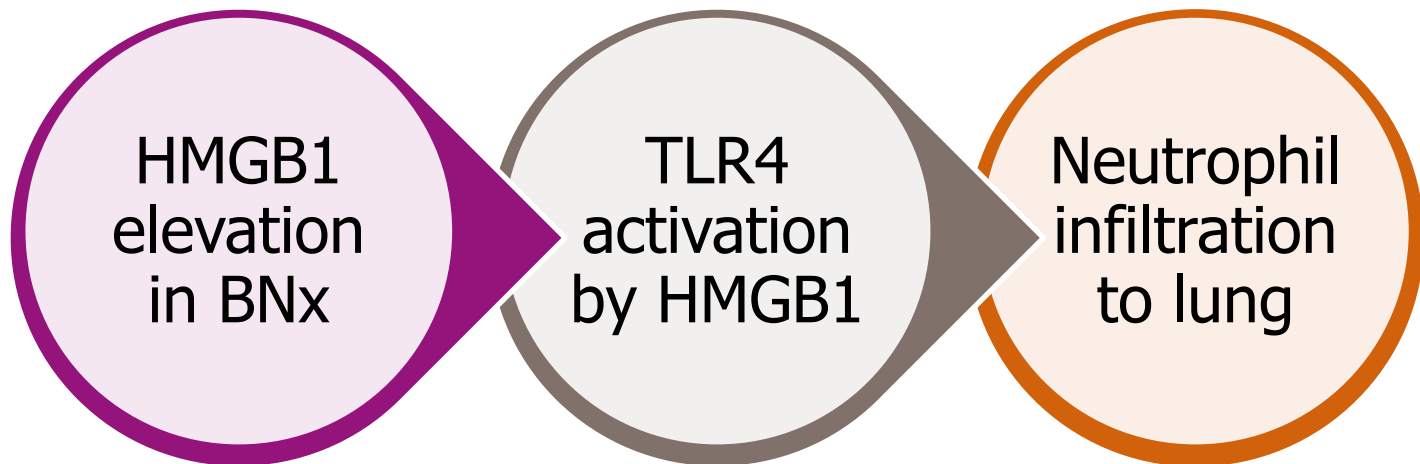
- High-mobility group protein B1 (HMGB1)
 1. DNA-binding protein in nucleus.
 2. Secreted from Mono/MΦ as an inflammatory mediator
 3. Be increased in renal dysfunction.
- Toll-like receptor 4 (TLR4)
 1. Recognize pathogen-associated molecular patterns (PAMPs) such as LPS, HSPs, etc.
 2. Activates innate immunity.



Lung injury in AKI

What is the “language” in lung-kidney crosstalk?

1. HMGB1 is a possible TLR4 agonist.
2. TLR4 induces inflammation including neutrophil activation.

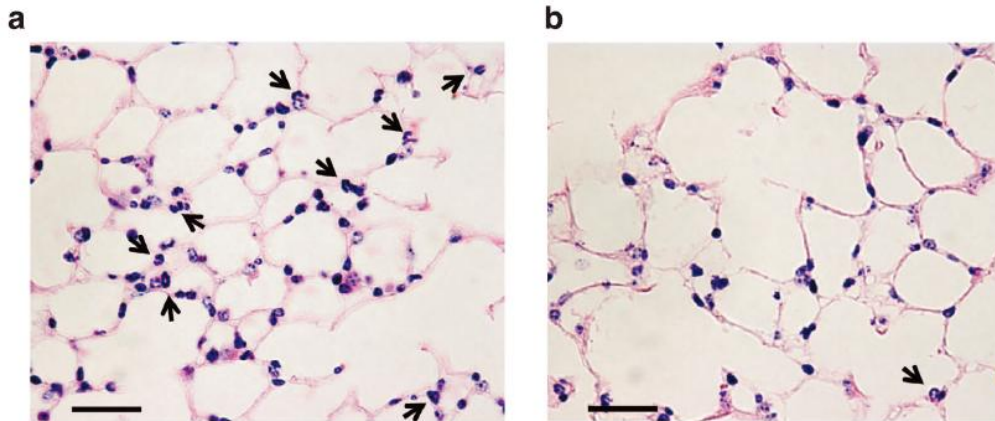


BNx, bilateral nephrectomy

HMGB1/TLR4 in BNx-induced lung injury

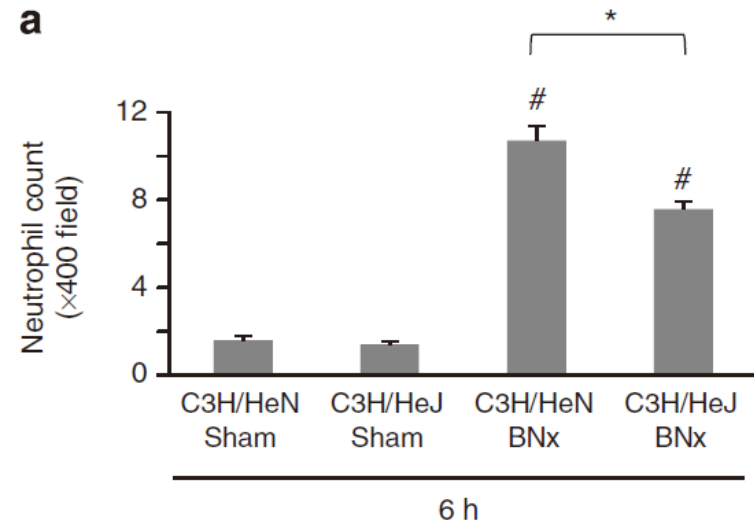
- TLR4-mutant C3H/HeJ mice were more resistant to lung injury caused by bilateral nephrectomy (BNx) compared with TLR4-wild-type C3H/HeN mice

Pulmonary neutrophil infiltration



C3H/HeN
(TLR4-wild)

C3H/HeJ
(TLR4-mutant)

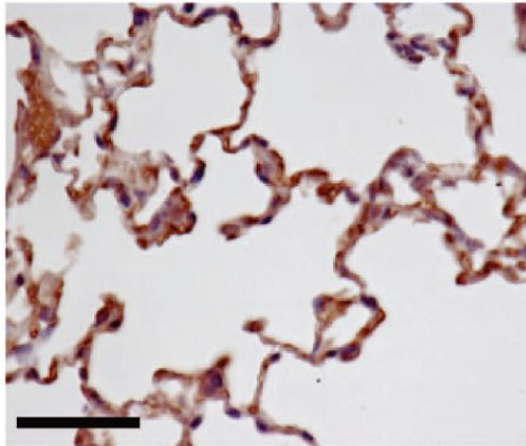


Doi K. Kidney Int (in press)

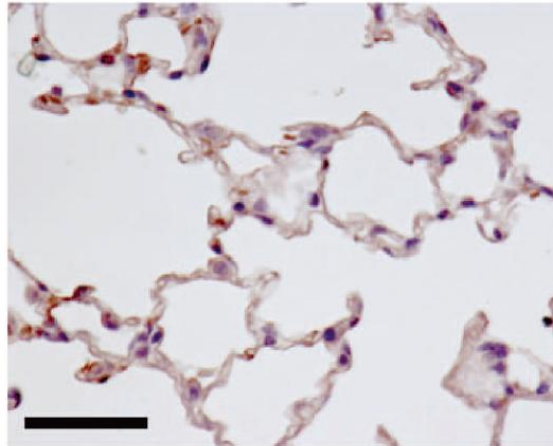
HMGB1/TLR4 in BNx-induced lung injury

- Oxidative stress and vascular leak were reduced in TLR4-mutant C3H/HeJ mice

Oxidative stress
(HHE accumulation)

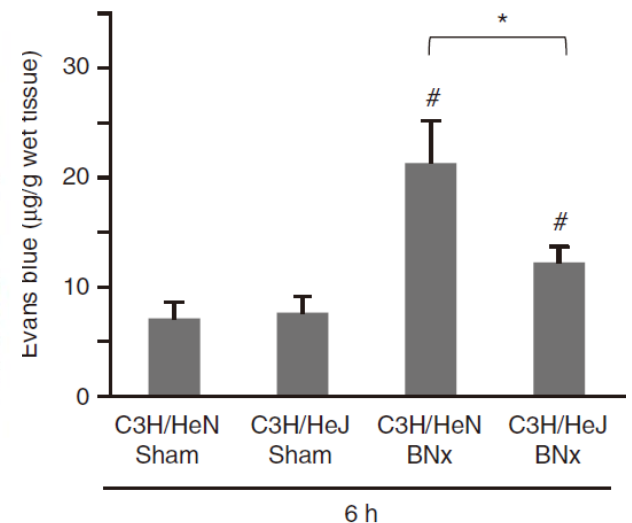


C3H/HeN
(TLR4-wild)



C3H/HeJ
(TLR4-mutant)

Vascular permeability
(Evans blue dye)

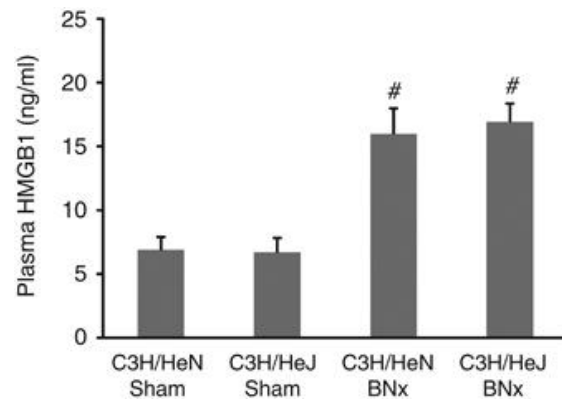


Doi K. Kidney Int (in press)

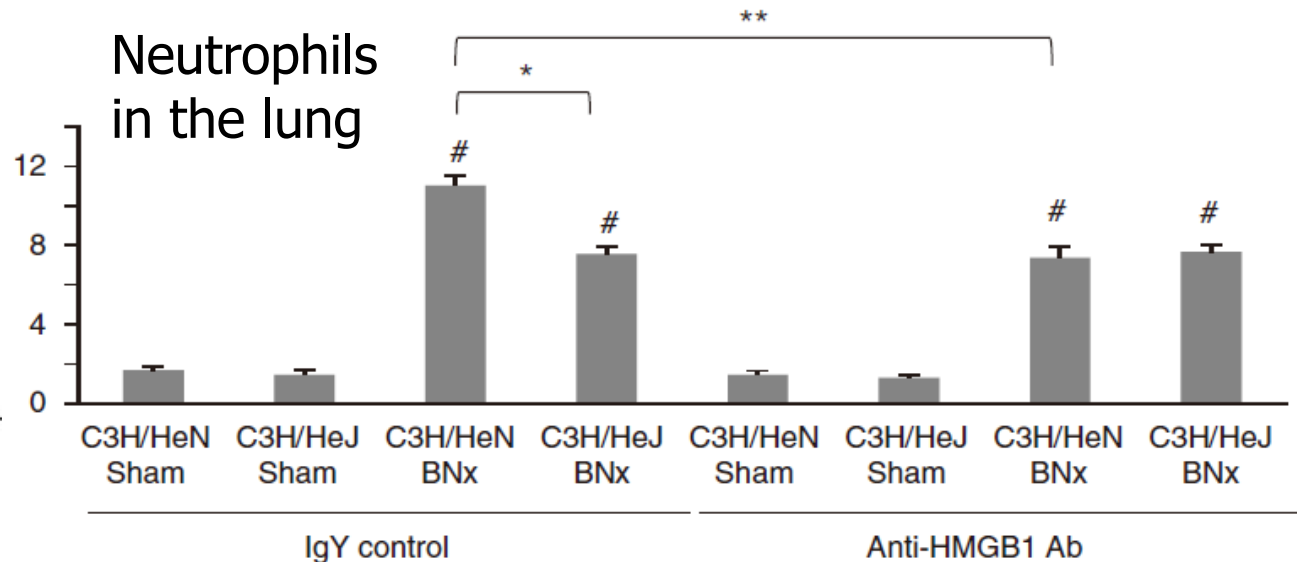
HMGB1/TLR4 in BNx-induced lung injury

- Plasma HMGB1 was increased in wild/mutant mice.
- Treatment with anti-HMGB1 Ab reduced neutrophil infiltration only in TLR4 wild-type C3H/HeN mice.

Plasma HMGB1



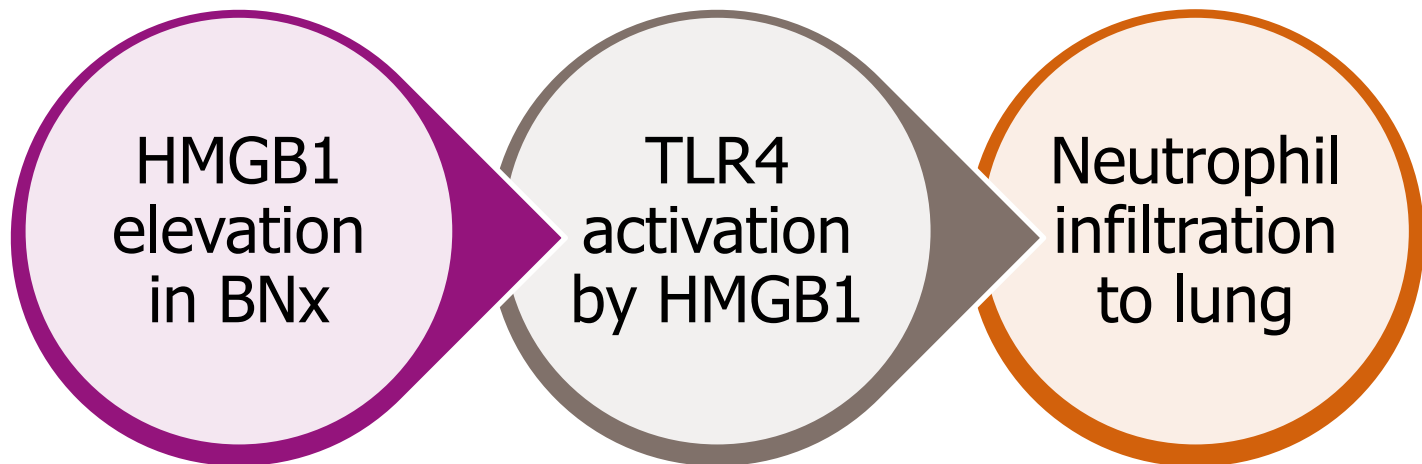
Neutrophils in the lung






Lung injury in AKI

- Possible role of HMGB1–TLR4 pathway in kidney-lung cross-talk



BNx, bilateral nephrectomy

Critical Care Nephrology

High Risk	1	2	3
	Discontinue all nephrotoxic agents when possible		
	Ensure volume status and perfusion pressure		
	Consider functional hemodynamic monitoring		
	Monitor Serum creatinine and urine output		
	Avoid hyperglycemia		
	Consider alternatives to radiocontrast procedures		
	Non-invasive diagnostic workup		
	Consider invasive diagnostic workup		
	Check for changes in drug dosing		
	Consider Renal Replacement Therapy		
	Consider ICU admission		
	Avoid subclavian catheters if possible		



Critical Care Nephrology

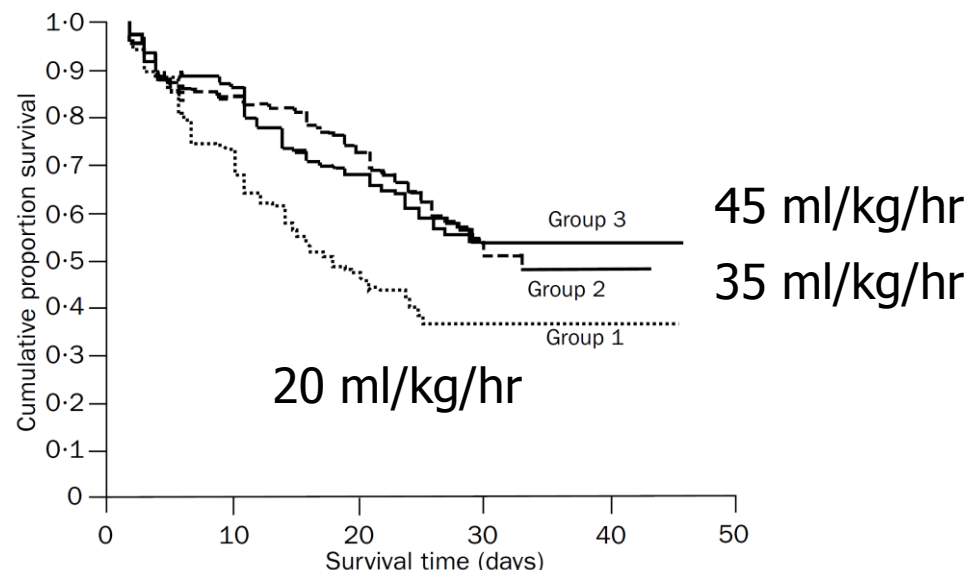
- Renal replacement therapy (RRT) in ICU
 1. How much is enough (“dose”)?
 2. When to start (earlier is better)?
 3. Just for renal support or cytokine removal?
 4. When to stop?

How much is enough for AKI?

- Dose = Qd + Qf (ml/kg/hr) in CHDF/CHF
 - 1000 ml/hr, BW 60kg (=17 ml/kg/hr)
 - Japanese insurance system 15L/day (=10 ml/kg/hr)
 - US survey 1.8[1.2-2.4] L/hr, 80kg (=23 ml/kg/hr)

Clin J Am Soc Nephrol 2: 623-630, 2007

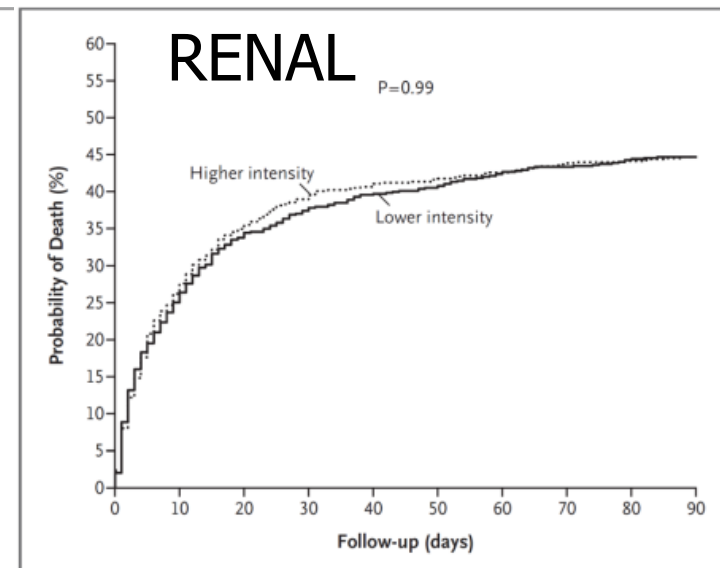
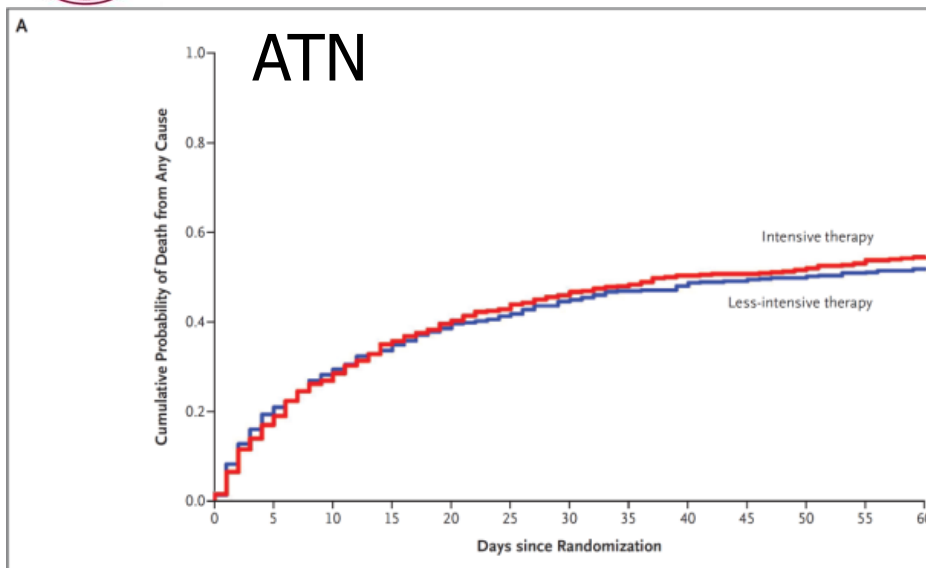
- More is better?



Ronco C et al. Lancet 2000

How much is enough for AKI?

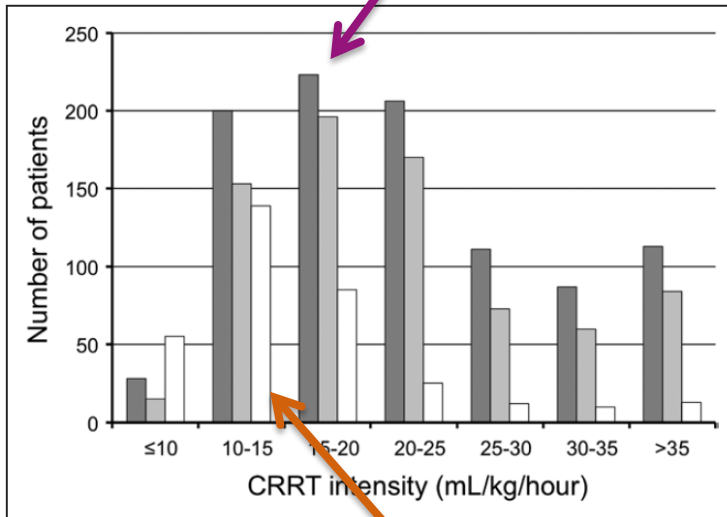
- Dose = $Q_d + Q_f$ (ml/kg/hr) in CHDF/CHF
 - 2 RCTs of "Dose" in NEJM
 - ATN study (2008) and RENAL study (2009)
 - 20-25 ml/kg/hr vs 35-40 ml/kg/hr: no benefit



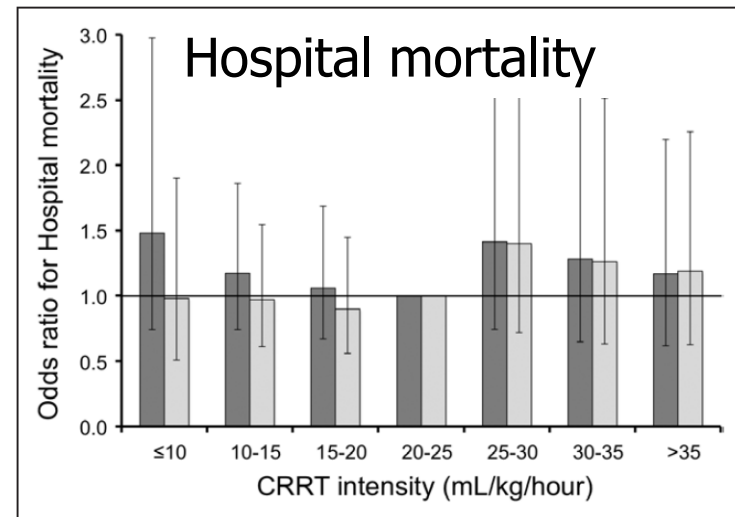
How much is enough for AKI?

- Dose = $Q_d + Q_f$ (ml/kg/hr) in CHDF/CHF
 - BEST cohort (international, n=1006, 2001)
vs JSEPTIC cohort (Japan, n=343, 2010)

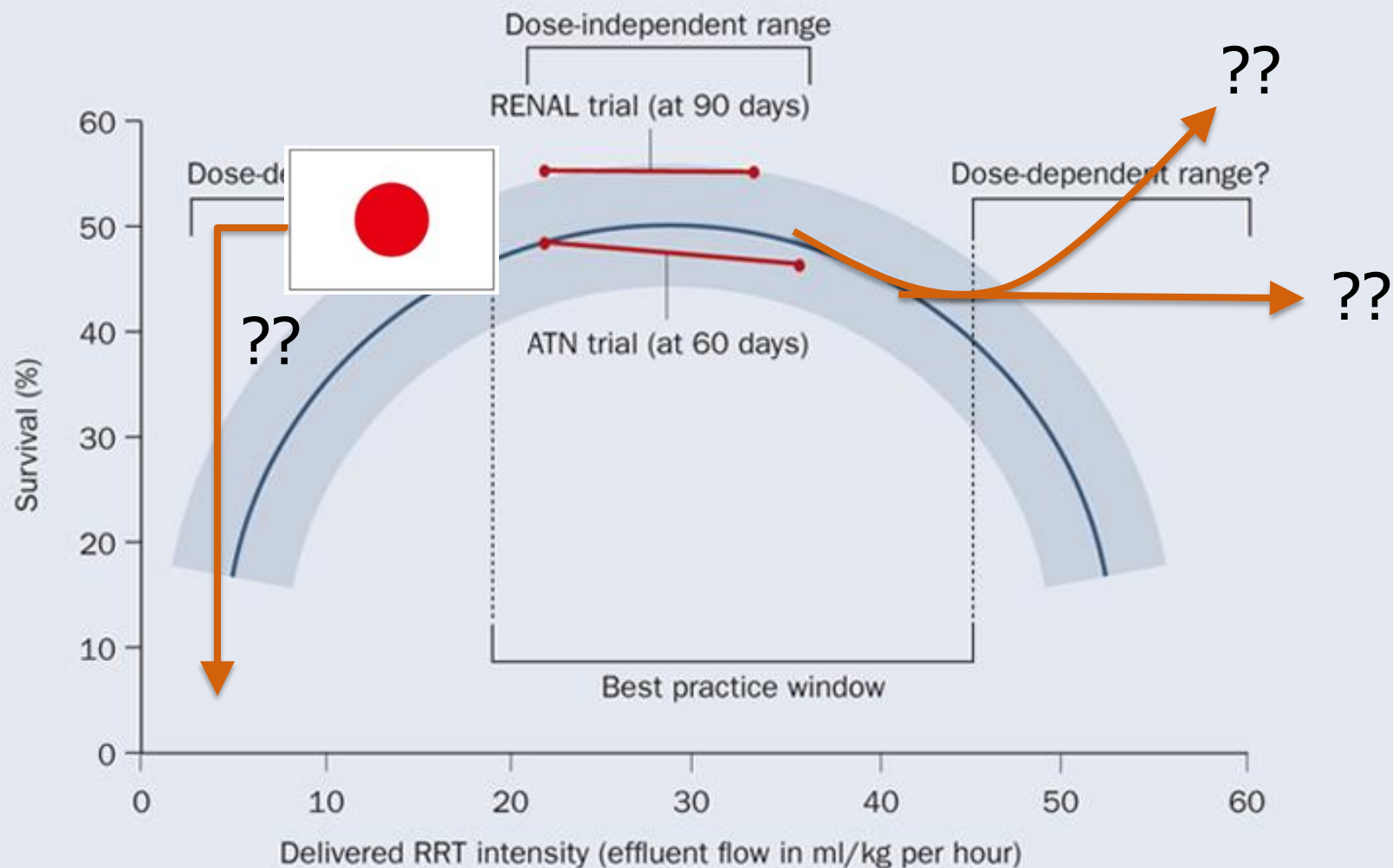
BEST 20.4 ml/kg/hr



JSEPTIC 14.3 ml/kg/hr



How much is enough for AKI?





Critical Care Nephrology

- Renal replacement therapy (RRT) in ICU
 1. How much is enough (“dose”)?
 2. When to start (earlier is better)?
 3. Just for renal support or cytokine removal?
 4. When to stop?



Earlier initiation is better for AKI?

Starting criteria

- “Absolute” indications for CKD/ESRD should be avoided in AKI.
 1. Consider other organ injuries especially the lungs
 2. Increased catabolism and adequate nutritional protein
 3. Fluid space for intravenous medications (antibiotics, vasopressors, etc.)
 4. more sensitive to metabolic derangements (acid-base and electrolyte status)

"An Official ATS/ERS/ESICM/SCCM/SRLF Statement: Prevention and Management of Acute Renal Failure in the ICU Patient" AJR CCM, 2010 (181) 1128-1155.



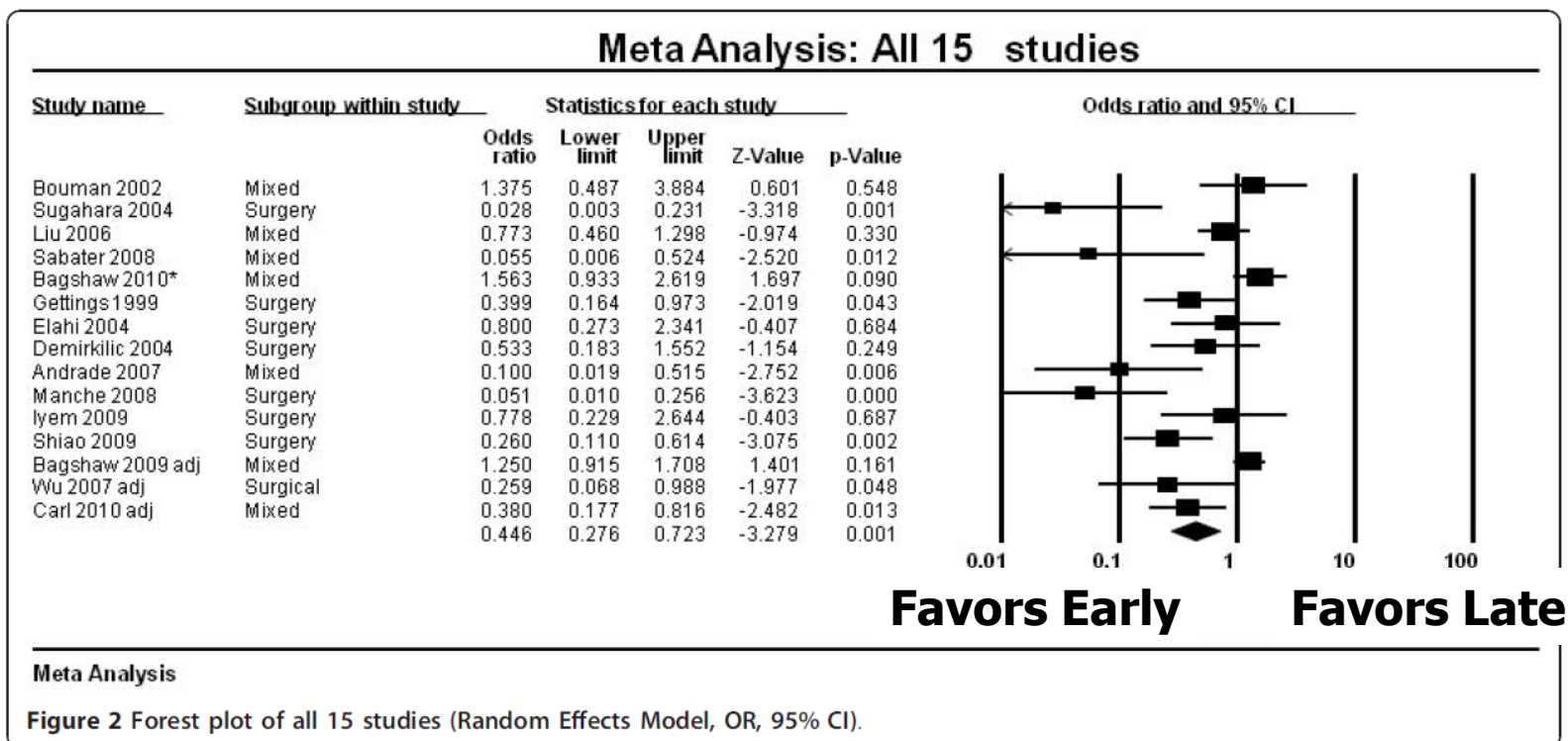
Earlier initiation is better for AKI?

Starting criteria

1. BUN>100, Cre>8, anuria >6hr?
2. KDIGO/AKIN/RIFLE stage 3?
3. Consider the critically ill status with multiple organ dysfunction?
 - Fluid status, metabolic disorders
4. Can we use new AKI biomarkers for decision?
 - NGAL (neutrophil gelatinase-associated lipocalin)
 - L-FABP (L-type fatty acid-binding protein)
 - KIM-1 (kidney injury molecule-1)

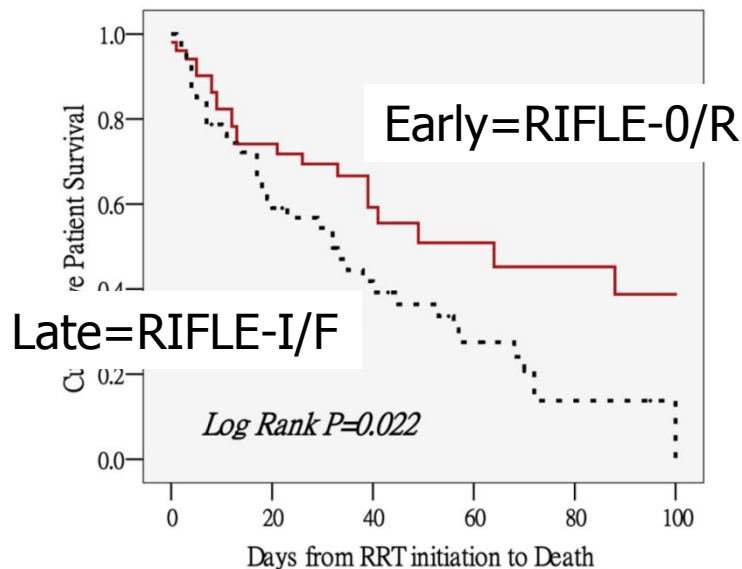
Earlier initiation is better for AKI?

- Meta-analysis of 2 RCT, 4 pro-, 9 retro-spective

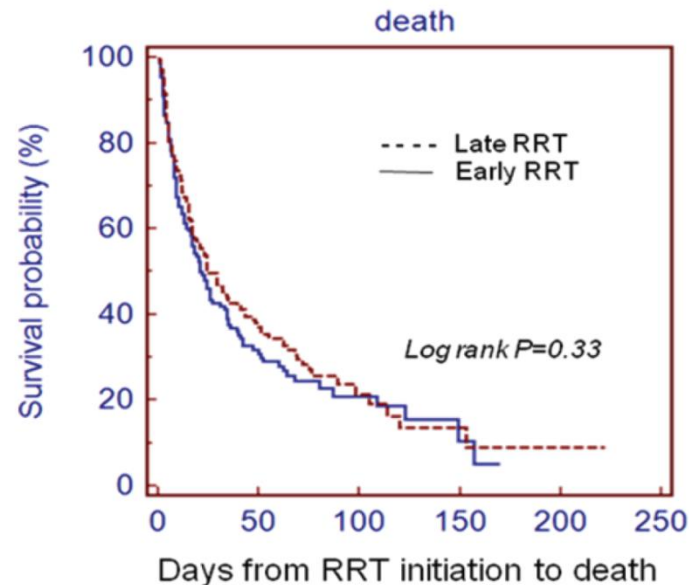


Earlier initiation is better for AKI?

- NSARF (National Taiwan University Hospital Study group on Acute Renal Failure)



Post-major abdo surgery AKI
(n=98)
Crit Care. 2009;13:R171.

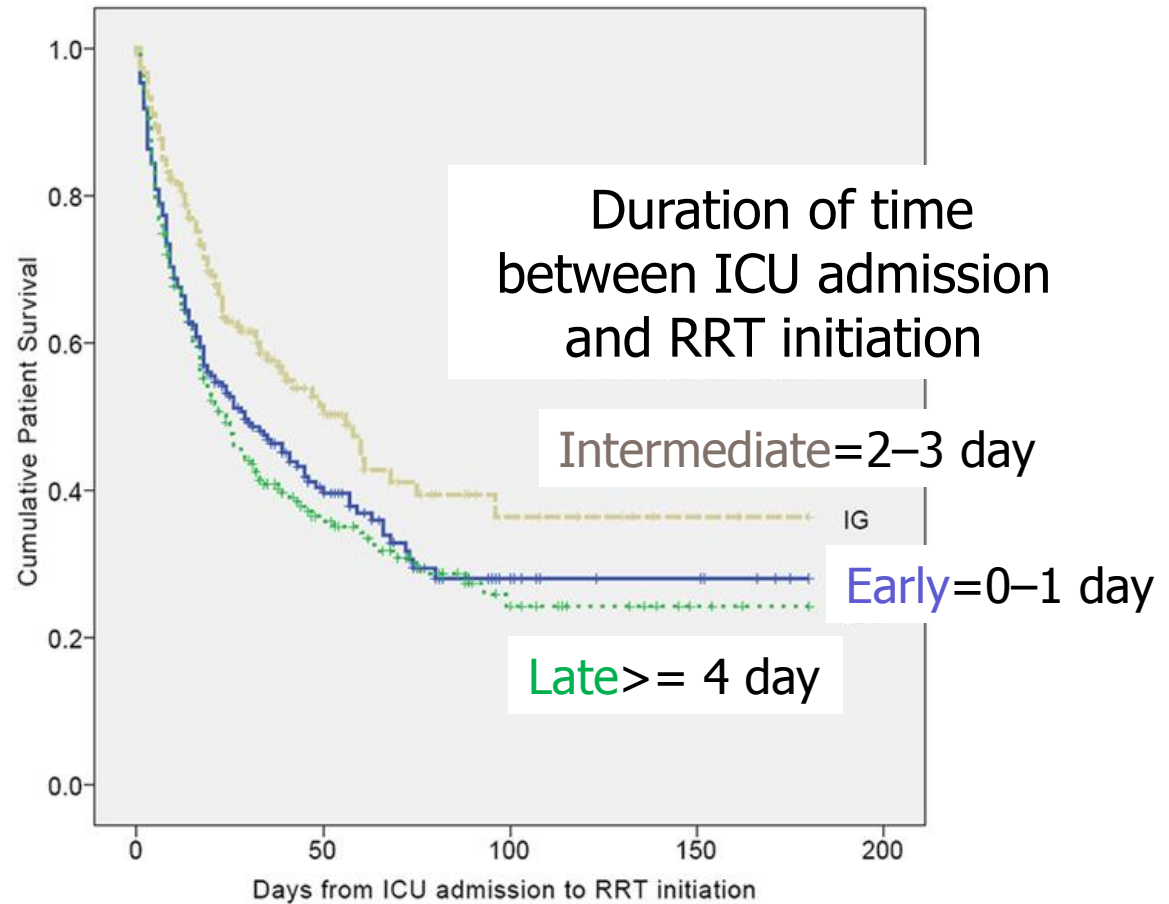


Septic AKI (n=370)
Crit Care. 2011;15:R134

Earlier initiation is better for AKI?

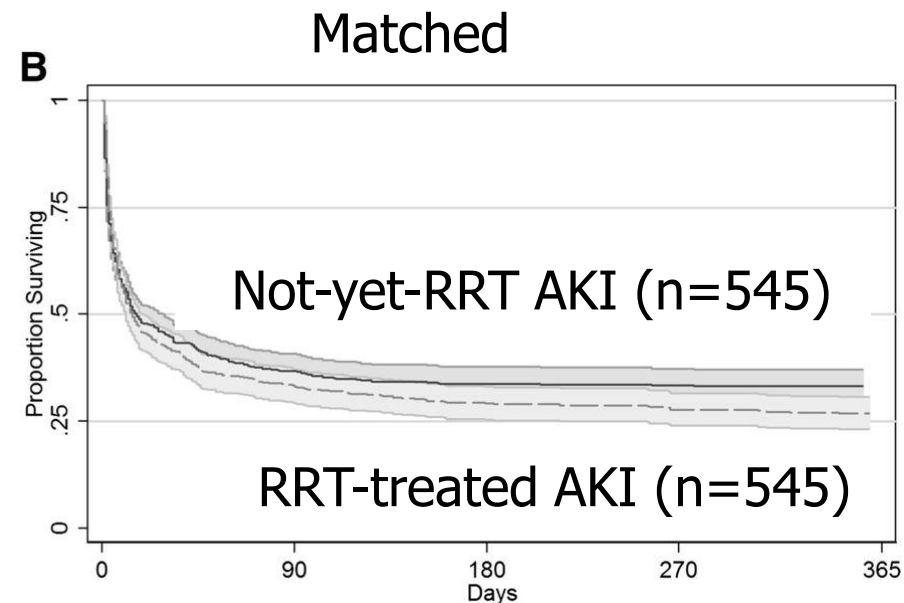
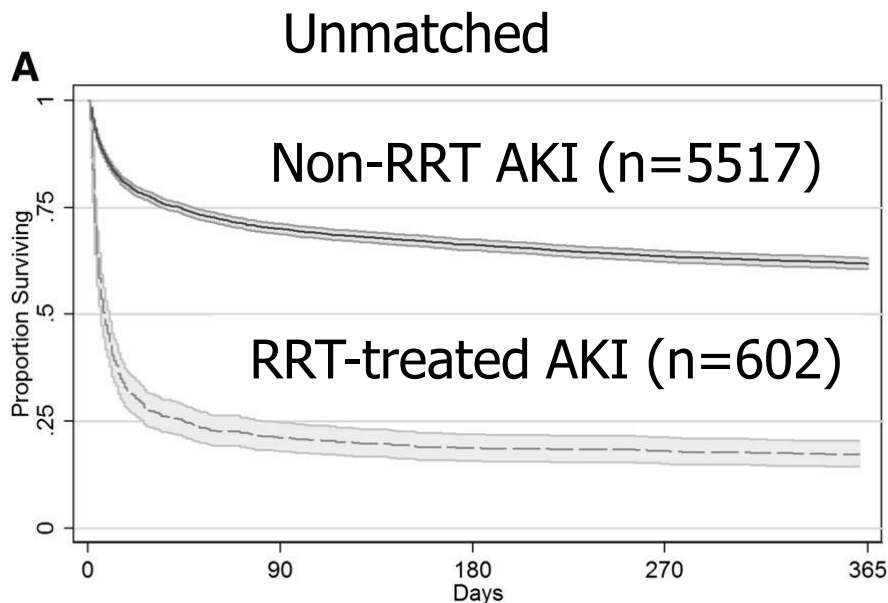
- **NSARF** (National Taiwan University Hospital Study group on Acute Renal Failure)

Post-surgery AKI
(n=648)
Plos One 2012;7:e42952



Earlier initiation is better for AKI?

- Canadian propensity-matched cohort study
 - a time-varying propensity score representing the daily probability of initiation of dialysis for AKI.



In-hospital AKI (n=6119) CJASN 2014;9:673-681



Earlier initiation is better for AKI?

Can AKI biomarkers help us to start RRT?

- NGAL Directed Pediatric Study
 - TAKING FOCUS –
**Trial in AKI using NGAL and Fluid Overload to
optimize CRRT Use
ClinicalTrials.gov Identifier: NCT01416298
Dr. Goldstein@Cincinnati**







Earlier initiation is better for AKI?

- Potentially influencing factors for starting RRT

Bagshaw et al. Critical Care 2009 13:317

Patient-specific	Kidney function/reserve
	Co-morbid disease and physiologic reserve
	Primary diagnosis: severity of illness and trajectory
	Acute kidney injury: severity and trend
Clinician-specific	Goals of therapy
	Clinician threshold for initiation
	Local practice patterns, Prescribing service
Organizational	Country/institution, Health costs
	ICU type
	Machine and nursing availability



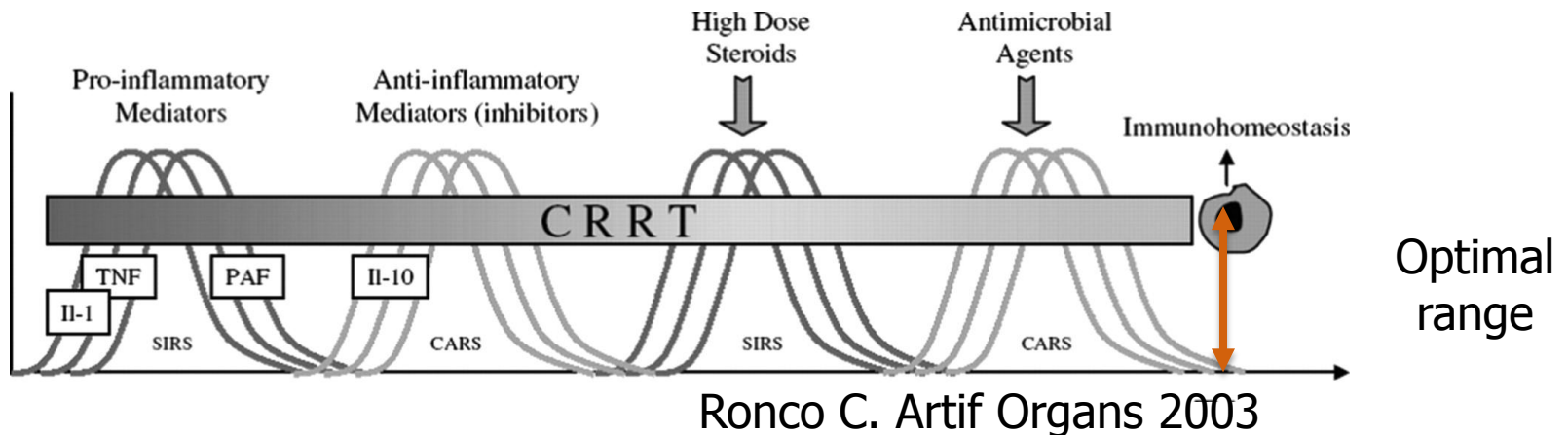
Critical Care Nephrology

- Renal replacement therapy (RRT) in ICU
 1. How much is enough (“dose”)?
 2. When to start (earlier is better)?
 3. Just for renal support or cytokine removal?
 4. When to stop?

Just for renal support?

Purpose of RRT in ICU

1. Replaces kidney function
 - Not 100% → Renal “support”
2. Targets multiple organ failure
 - Removal of the overwhelming cytokines
 - Specific removal or broad elimination?

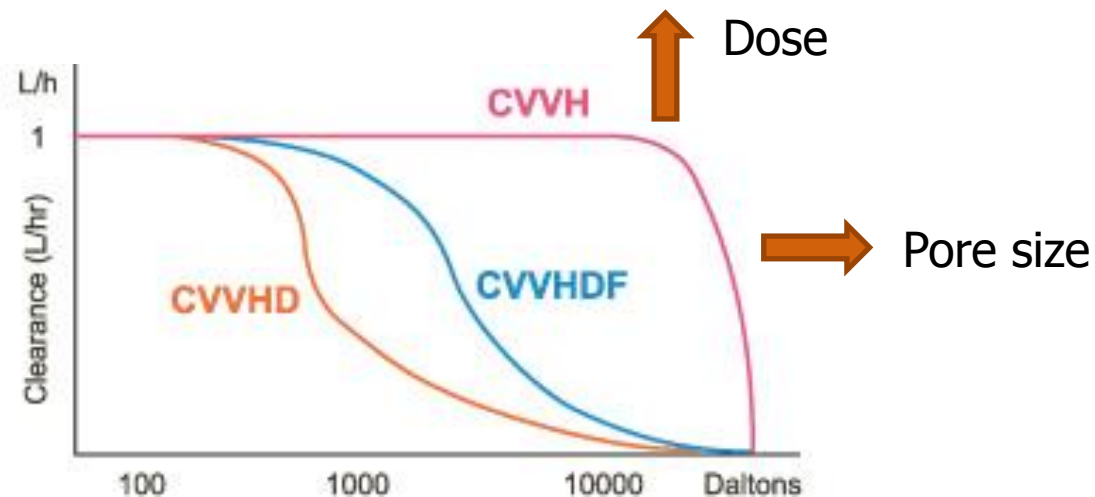


Just for renal support?

Removal of the overwhelming cytokines by RRT

1. Hemofiltration (convection)

Removal of middle-weight molecules by convection depends on 1) dose and 2) filter pore size.

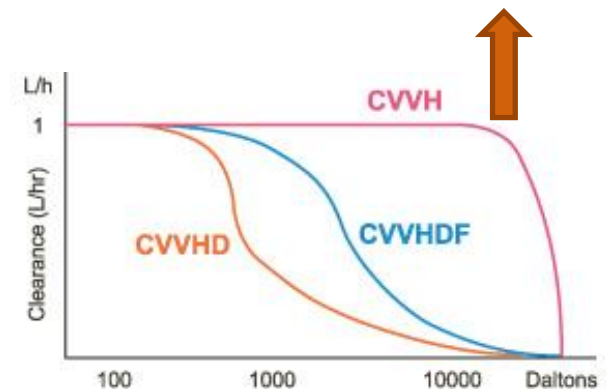
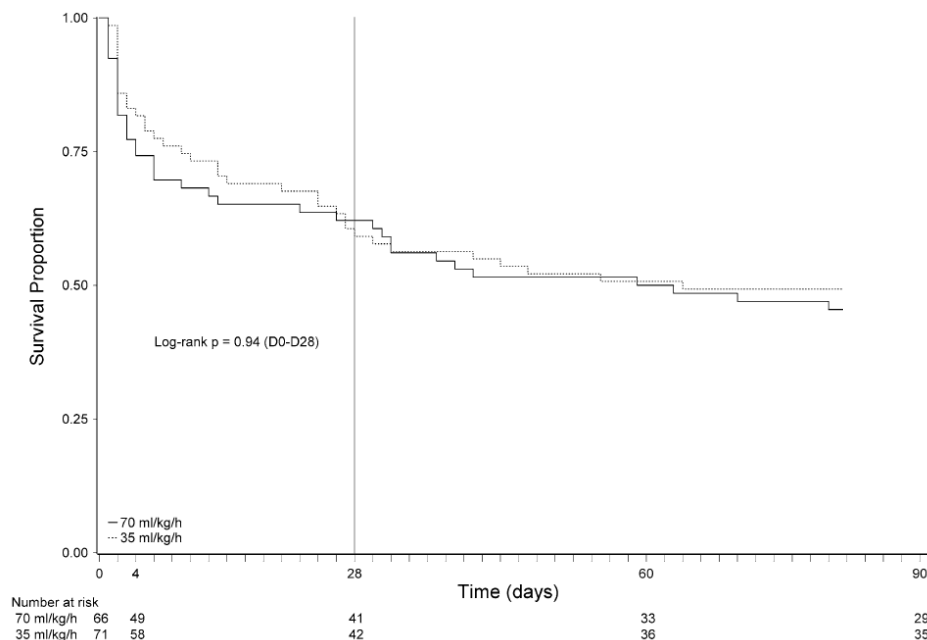


Just for renal support?

Removal of the overwhelming cytokines by RRT

1. Hemofiltration (convection)

IVOIRE study: 70 mL/kg/h vs 35 mL/kg/h: no benefit



Joannes-Boyau O.
Intensive Care Med 2013

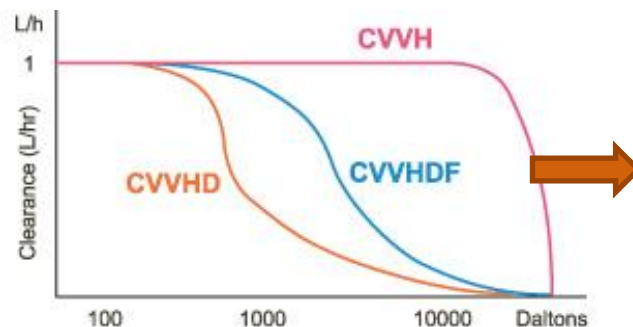
Just for renal support?

Removal of the overwhelming cytokines by RRT

1. Hemofiltration (convection)

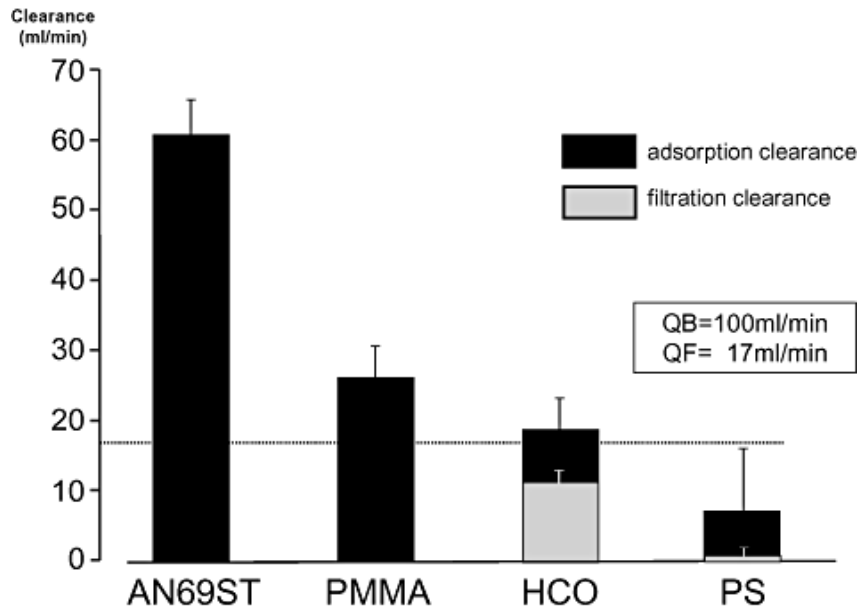
HICOSS study [ClinicalTrials.gov Identifier: NCT00875888](https://clinicaltrials.gov/ct2/show/study/NCT00875888)

- High cutoff membrane (60 kDa), CVVHD 35 ml/kg/h
- This study was stopped prematurely because of no difference in the 28 day mortality (31% vs 33%)



Just for renal support?

- Removal of the overwhelming cytokines by RRT
2. Absorption; removal by using molecular adherence to the surface or interior of the filter membrane.



Nishida O. Ther Apher Dial 2011

A promising in vitro study

- HMGB1 is a 30 kDa protein and an important inflammatory mediator in septic AKI or MOF.
- HMGB1 could be removed by AN69ST and PMMA (absorption filters) more than HCO (high cutoff) and polysulfone filters.



Critical Care Nephrology

- Targets?
 - AKI/ESRD/MOF
- Purpose?
 - Improve patient outcomes
 - Develop novel therapeutics
- Who?
 - Intensivist/Nephrologist/Cardiologist
 - Young brilliant doctors!!



Critical Care Nephrology

- For future critical care nephrologists, we need an integrated training program

Requirement of Critical Care Nephrology

Nephrology fellow One year fellowship in critical care medicine

Critical care fellow One year fellowship in nephrology



東京大学
THE UNIVERSITY OF TOKYO

Task force for AKI clinical management and research program

Large institutions One or more double-board certificated staffs

An integrated critical care nephrology training program

Critical Care Nephrology

Thank you for your attention!



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Emergency and Critical Care Medicine, The University of Tokyo