London Acute Kidney Injury Network

AKI and Organ Cross-Talk

Second AKI Academy

London, October 18th – 19th 2014

St George's Healthcare NHS

NHS Trust

St George's University of London

Dr Barbara Philips

Reader and Honorary Consultant

Intensive Care Medicine

St George's University of London

Table 6. Multivariate logistic regression analysis: Impact of risk factors on risk of death in hospital

Variables	B	p	OR (95% CI) for Hospital Mortality
Admission after cardiac surgery	−0.698	.000	0.5 (0.44–0.57)
Male gender	−0.070	.036	0.93 (0.87–0.995)
No. of failed organs at admission to ICU	−0.085	.001	0.92 (0.87–0.97)
Age	0.023	.000	1.02 (1.02–1.03)
APACHE II score at admission to ICU	0.092	.000	1.097 (1.09–1.104)
Preexisting chronic end-stage disease	0.153	.000	1.17 (1.08–1.26)
Mechanical ventilation	0.42	.000	1.52 (1.41–1.65)
Renal function			
No AKI			
Risk	0.335	.000	1.40 (1.28–1.53)
Injury	0.675	.000	1.96 (1.80–2.14)
Failure	0.461	.000	1.59 (1.43–1.76)
ESRD	−0.99	.330	0.91 (0.74–1.11)
Maximum no. of failed organ systems	0.754	.000	2.13 (2.03–2.23)
Admission after emergency surgery	1.124	.000	3.08 (2.77–3.42)
Nonsurgical admission	1.367	.000	3.92 (3.58–4.30)
RRT for AKI	−0.014	.84	0.99 (0.86–1.13)
Constant	−4.951	.000	0.007

OR, odds ratio; CI, confidence interval; ICU, intensive care unit; APACHE, Acute Physiology and Chronic Health Evaluation; AKI, acute kidney injury; ESRD, end-stage dialysis-dependent renal failure; RRT, renal replacement therapy.

Acute kidney injury in the intensive care unit according to RIFLE *. Ostermann, Marlies; MD, MRCP; Chang, Rene; BSc, MS Critical Care Medicine. 35(8):1837-1843, August 2007. DOI: 10.1097/01.CCM.0000277041.13090.0A

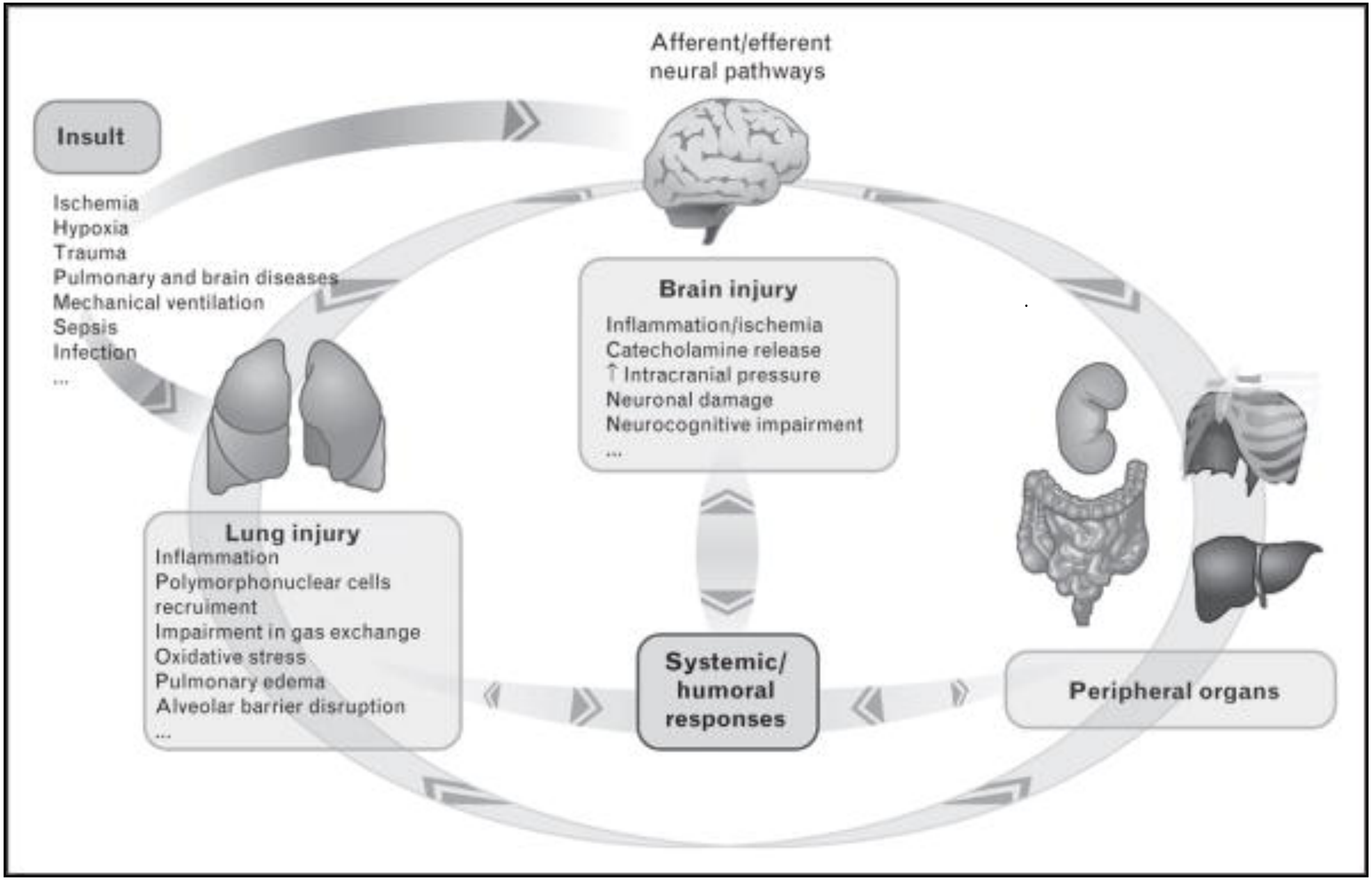
Increased mortality with acute kidney injury

Table 6 Impact of associated maximum organ failure and presence of preexisting chronic illness

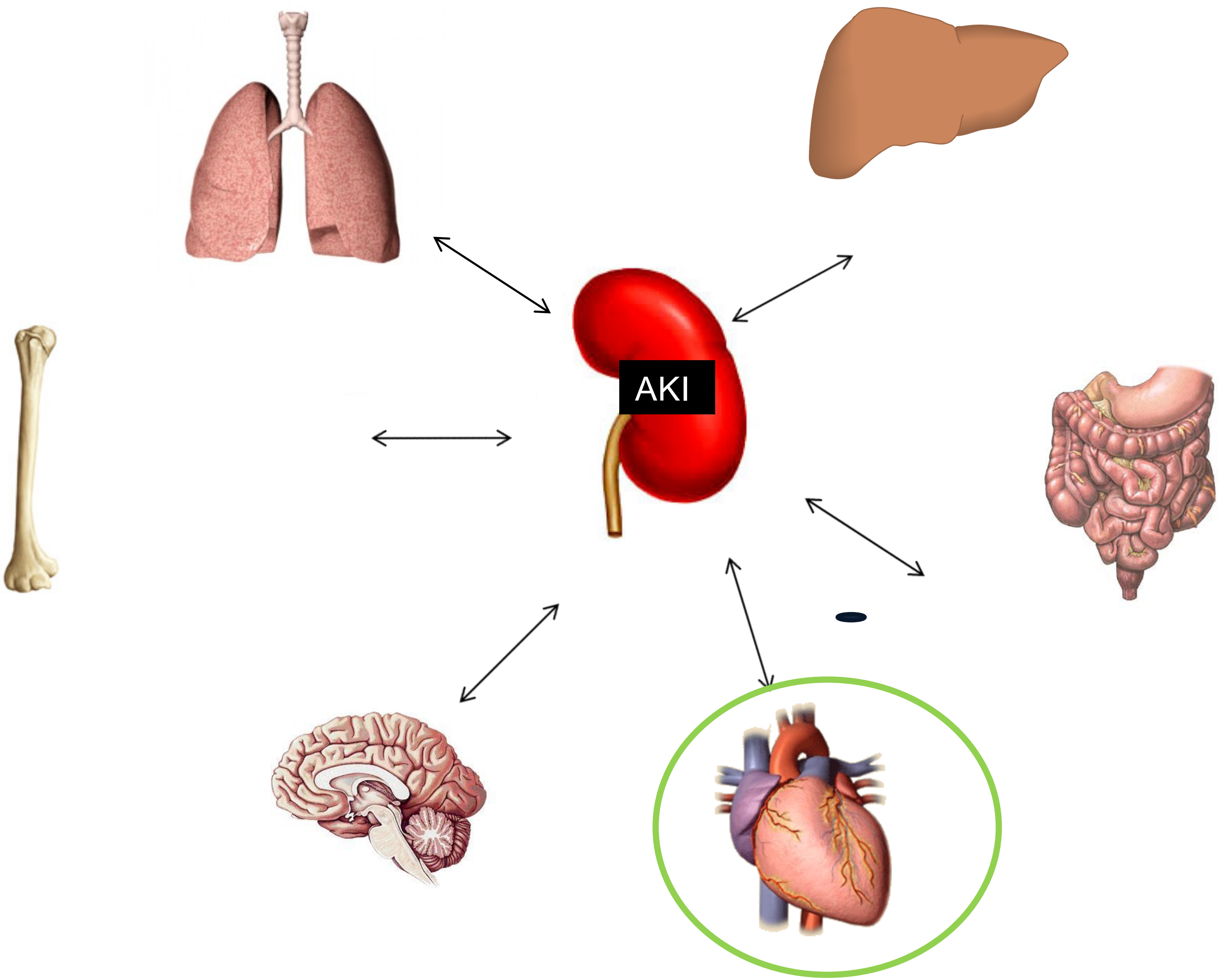
Associated maximum OF during stay in ICU [a]	No preexisting chronic illness		With preexisting chronic illness		*P*
	n (%)	ICU mortality	n (%)	ICU mortality	
	No AKI (n = 14 405)				
0	5184 (35.98)	1.7%	872 (6.1)	2.9%	.033
1	4637 (32.2)	7.8%	1033 (7.2)	11.6%	<.0001
2	1694 (11.8)	28.2%	441 (3.1)	36.1%	.002
≥3	425 (2.95)	54.6%	119 (0.8)	68.9%	.006
	AKI I (n = 4259)				
0	515 (12.1)	3.1%	114 (2.7)	0.9%	.34
1	1383 (32.5)	9.3%	396 (9.3)	11.6%	.18
2	1023 (24)	27.2%	362 (8.5)	37.8%	<.0001
≥3	346 (8.1)	49.1%	120 (2.8)	64.2%	.006
	AKI II (n = 857)				
0	62 (7.2)	3.2%	16 (1.9)	0	NS
1	256 (29.9)	12.5%	71 (8.3)	18.3%	.24
2	234 (27.3)	27.4%	82 (9.6)	43.9%	.008
≥3	96 (11.2)	52.1%	40 (4.7)	62.5%	.34
	AKI III (n = 2782)				
0	154 (5.5)	7.8%	41 (1.5)	0	NS
1	520 (18.7)	24.2%	165 (5.9)	35.2%	.007
2	784 (28.2)	48%	239 (8.6)	64.4%	<.0001
≥3	617 (22.2)	71.3%	262 (9.4)	81.3%	.002

Ostermann M Chang R. *Journal of Critical Care,* 2011; 26: 635.e1–635.e10.

Organ cross talk



Organ crosstalk during acute lung injury, acute respiratory distress syndrome, and mechanical ventilation.
Quilez, Maria; Lopez-Aguilar, Josefina; Blanch, Lluis Current Opinion in Critical Care. 18(1):23-28, February 2012. DOI: 10.1097/MCC.0b013e32834ef3ea


AKI

Cardiorenal syndrome classification

Cardiorenal Syndrome (CRS) General Definition: A pathophysiologic disorder of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction in the other organ
CRS Type I (Acute Cardiorenal Syndrome) Abrupt worsening of cardiac function (e.g. acute cardiogenic shock or acutely decompensated congestive heart failure) leading to acute kidney injury
CRS Type II (Chronic Cardiorenal Syndrome) Chronic abnormalities in cardiac function (e.g. chronic congestive heart failure) causing progressive and potentially permanent chronic kidney disease
CRS Type III (Acute Renocardiac Syndrome) Abrupt worsening of renal function (e.g. acute kidney ischaemia or glomerulonephritis) causing acute cardiac disorder (e.g. heart failure, arrhythmia, ischemia)
CRS Type IV (Chronic Renocardiac Syndrome) Chronic kidney disease (e.g. chronic glomerular or interstitial disease) contributing to decreased cardiac function, cardiac hypertrophy and/or increased risk of adverse cardiovascular events
CRS Type V (Secondary Cardiorenal Syndrome) Systemic condition (e.g. diabetes mellitus, sepsis) causing both cardiac and renal dysfunction

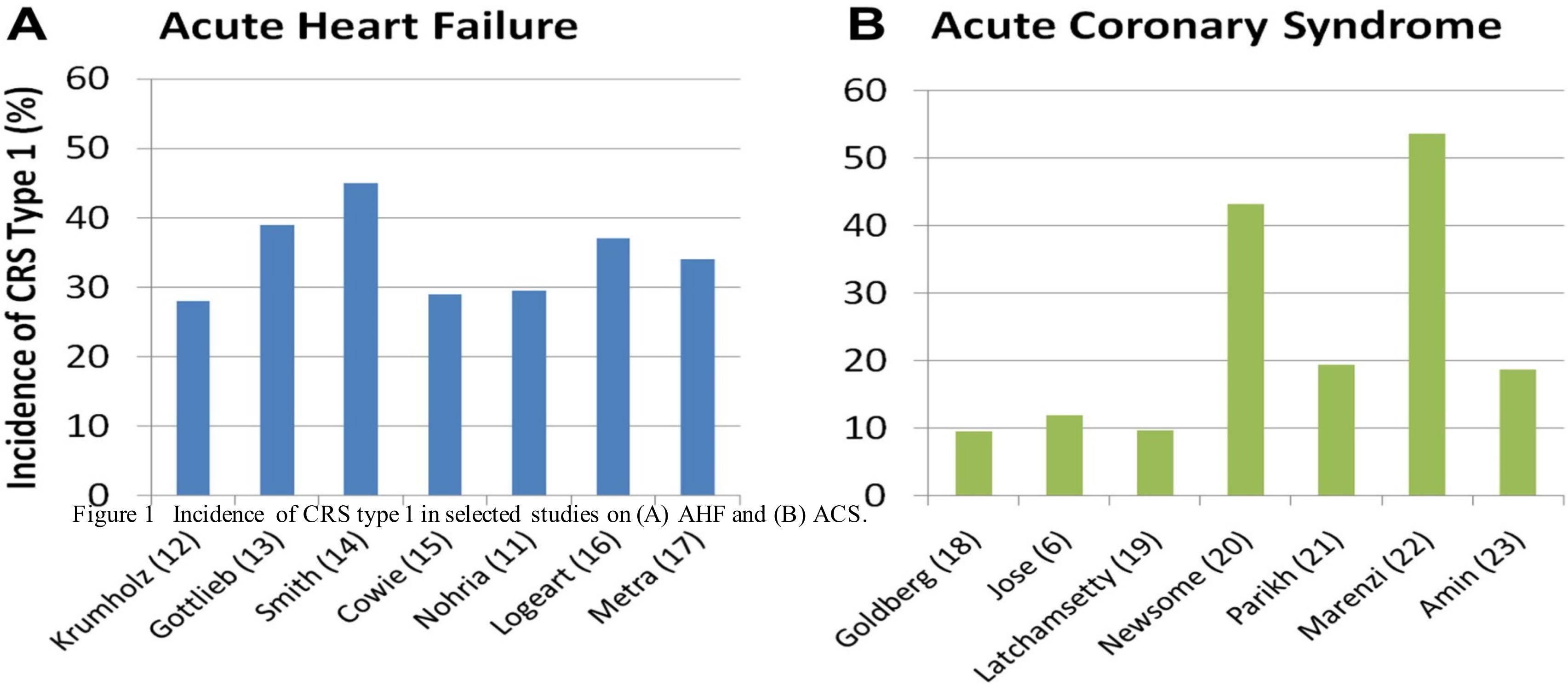


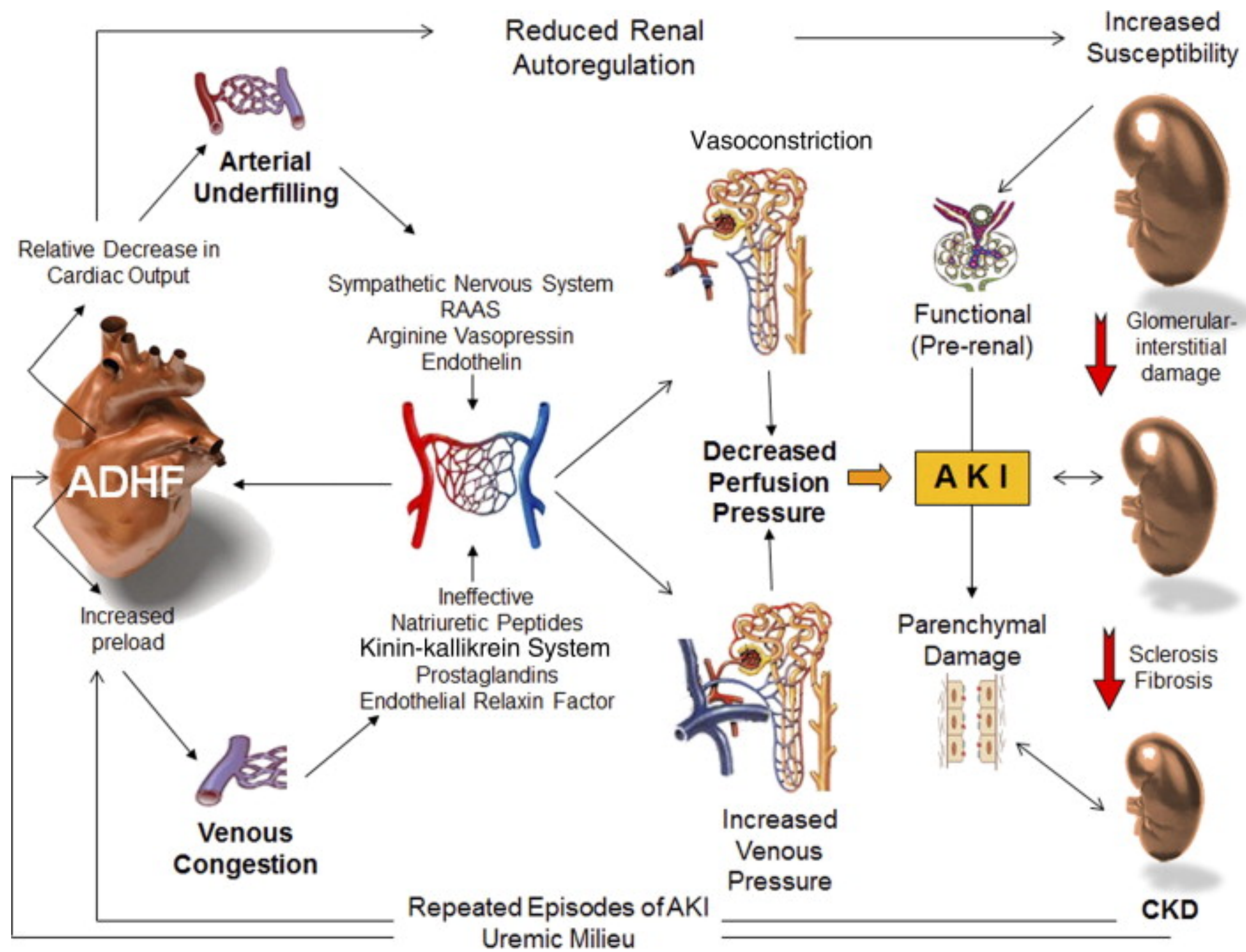
Figure 1 Incidence of CRS type 1 in selected studies on (A) AHF and (B) ACS.

Dinna N. Cruz

Cardiorenal Syndrome in Critical Care: The Acute Cardiorenal and Renocardiac Syndromes

Advances in Chronic Kidney Disease Volume 20, Issue 1 2013 56 – 66 http://dx.doi.org/10.1053/j.ackd.2012.10.005

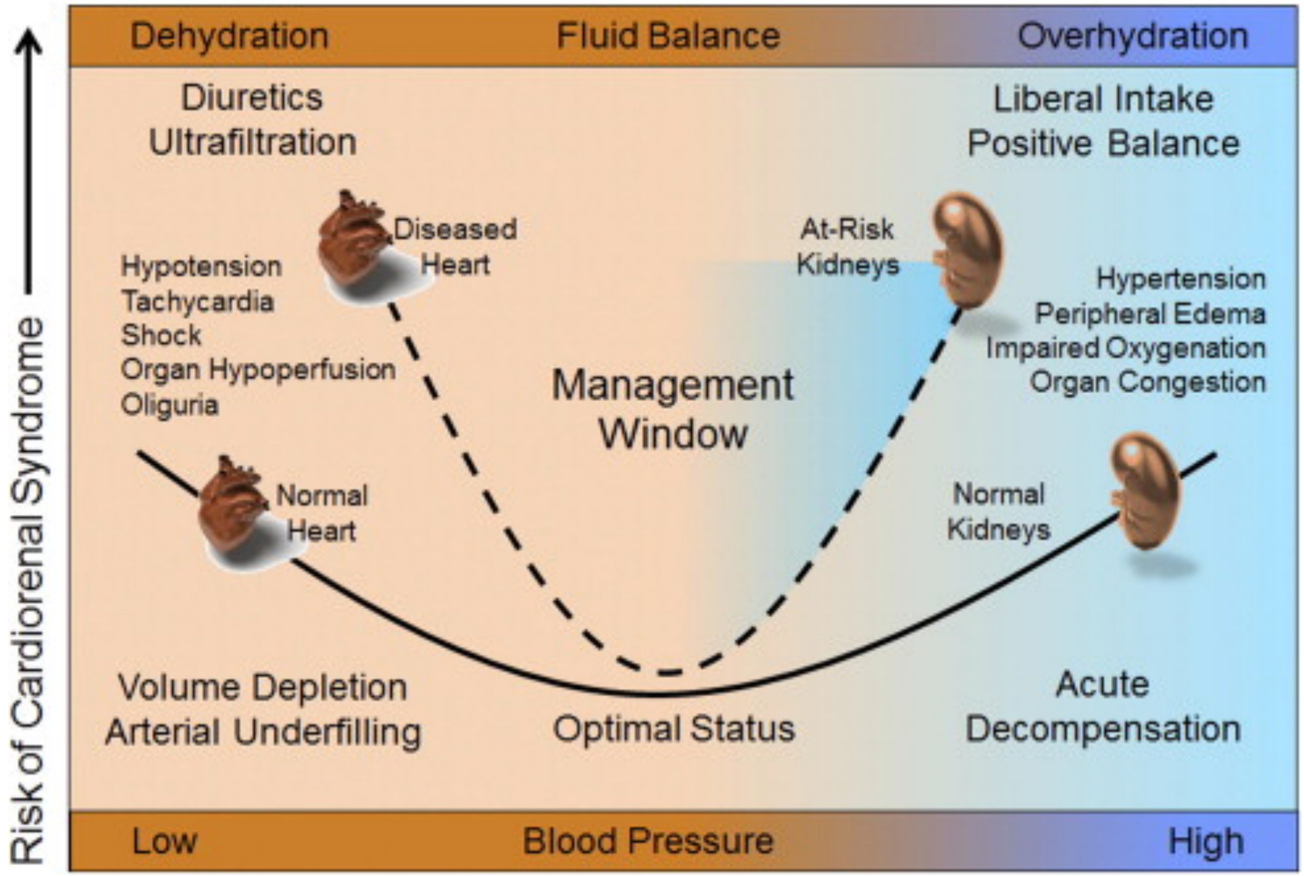
CRS Type 1



Claudio Ronco , Mariantonietta Cicoira , Peter A. McCullough

Journal of the American College of Cardiology, Volume 60, Issue 12, 2012, 1031 – 1042 http://dx.doi.org/10.1016/j.jacc.2012.01.077

Cardiorenal Syndrome Type 1 : Pathophysiological Crosstalk Leading to Combined Heart and Kidney Dysfunction in the Setting of Acutely Decompensated Heart Failure



Claudio Ronco , Mariantonietta Cicoira , Peter A. McCullough
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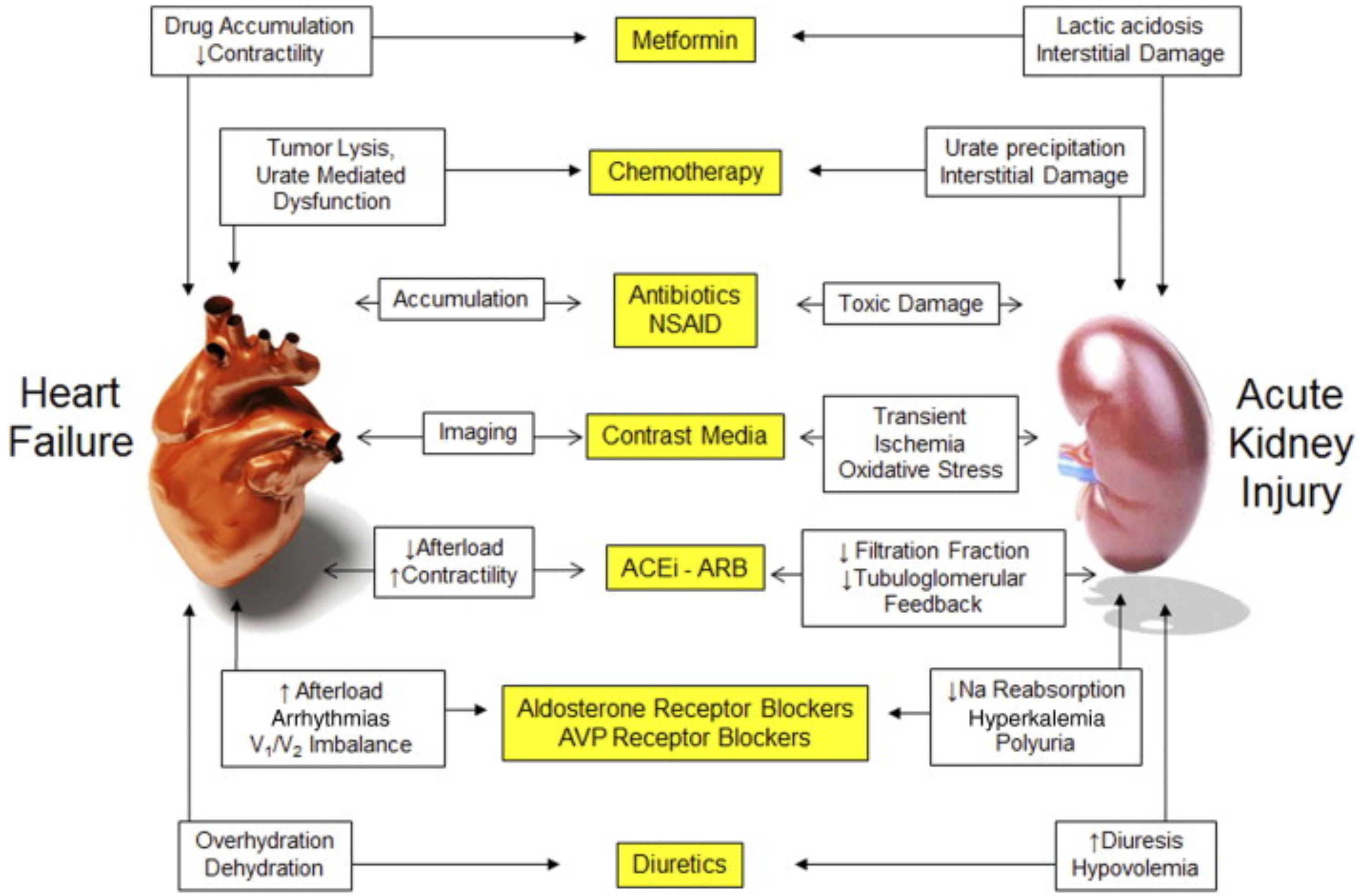

Claudio Ronco , Mariantonietta Cicoira , Peter A. McCullough

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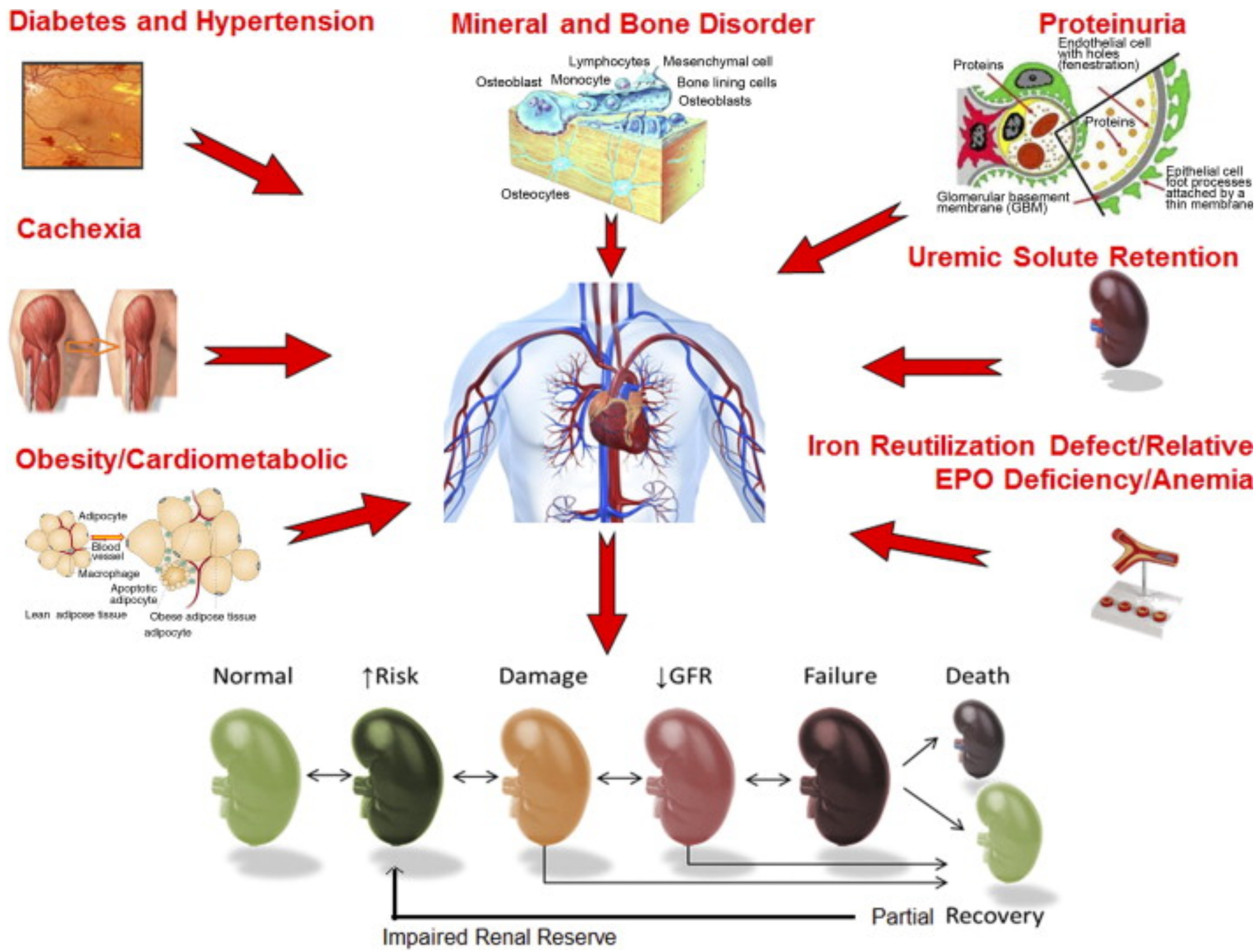
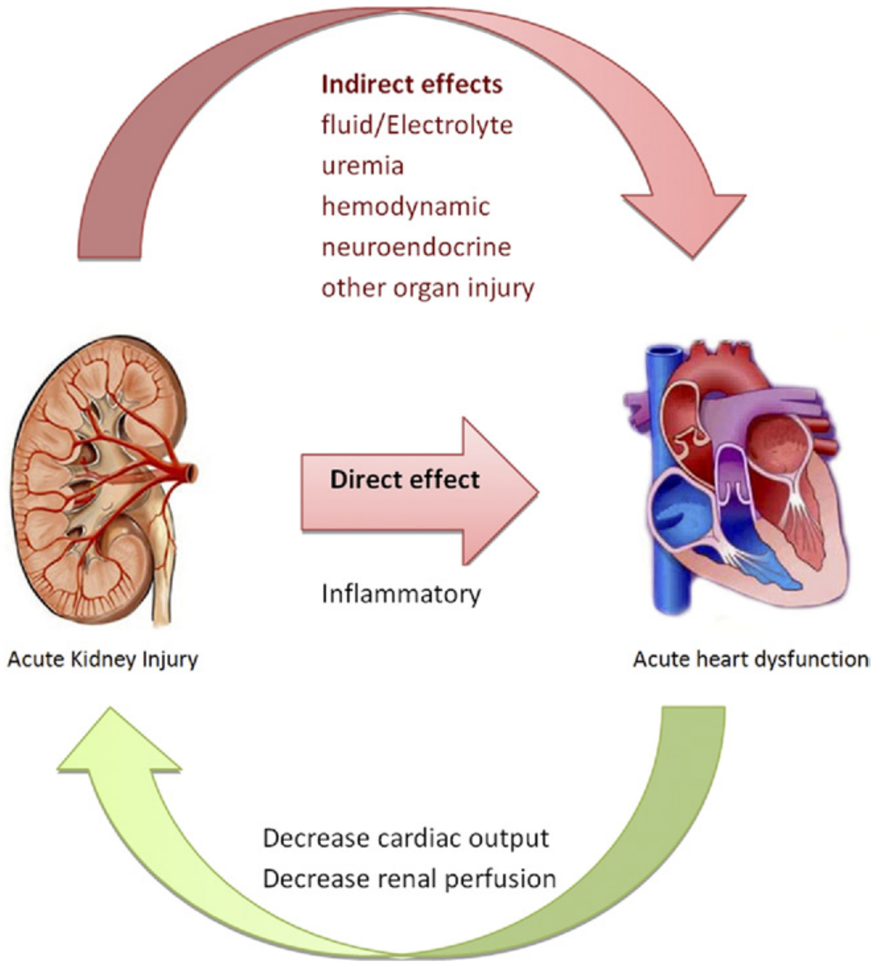


Claudio Ronco , Mariantonietta Cicoira , Peter A. McCullough

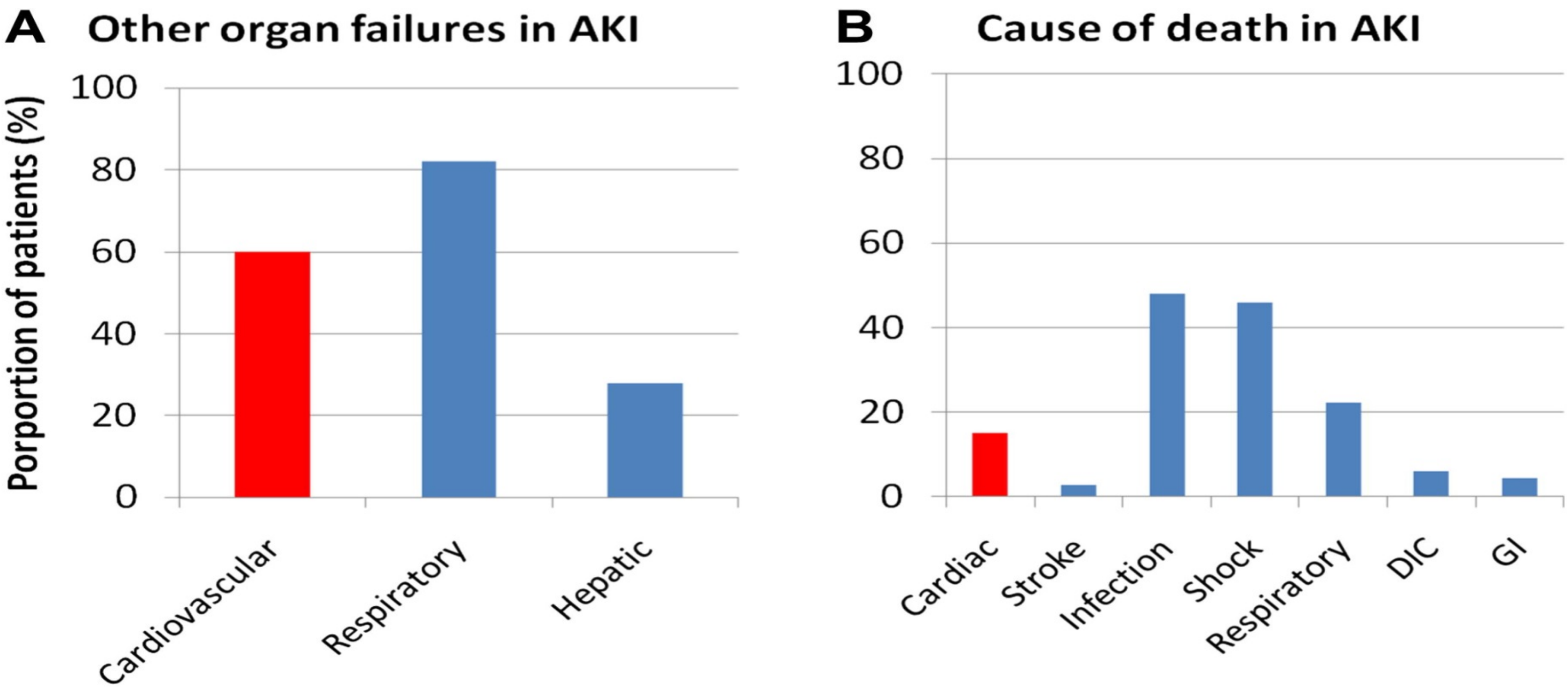
Journal of the American College of Cardiology, Volume 60, Issue 12, 2012, 1031 – 1042 http://dx.doi.org/10.1016/j.jacc.2012.01.077

CRS Type 3



Chuasuwan A, Kellum J: Semin Nephrol 32:31-39 © 2012

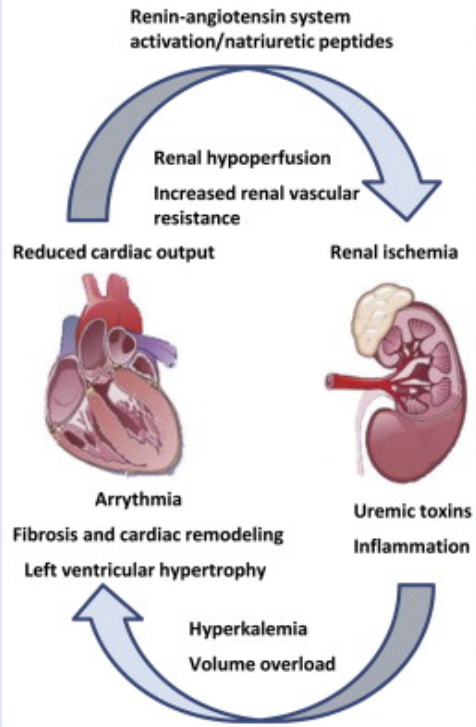
CRS



Dinna N. Cruz

Advances in Chronic Kidney Disease Volume 20, Issue 1 2013 56 – 66 http://dx.doi.org/10.1053/j.ackd.2012.10.005

Markers of myocardial cell damage	cTnI, cTnT
Markers of myocardial strain	BNP, NT-proBNP, midregion pro-atrial natriuretic peptide (MR-proANP), midregion pro-adrenomedullin (MR-proADM), copeptin
Markers of fibrosis and remodelling	Soluble ST2, galectin-3, matrix metalloproteinases (MMPs), collagen propeptides
Markers of atherosclerosis and plaque rupture	Pregnancy-associated plasma protein A (PAPP-A), placental growth factor (PlGF), lipoprotein associated phospholipase A2 (Lp-PLA2), Lp(a), oxidized LDL, growth differentiation factor-15 (GDF-15),
Markers of ischemia	Ischemia-modified albumin (IMA), heart fatty acid binding protein (HFABP)
Inflammatory markers	hsCRP
Renal markers	Cystatin C, NGAL, creatinine, urinary albumin/creatinine ratio
Genetic polymorphisms	9p21.3, PCSK9
MicroRNAs	Mir-1, mir-133, mir-499



Functional markers of kidney injury	**Damage markers of kidney injury**
Estimated glomerular filatration rate (eGFR) using •Creatinine •Cystatin C or •Both creatinine and cystatin C	Albuminuria Cystatin C Neutrophil gelatinase associated lipocalin (NGAL) Kidney injury molecule-1 (KIM-1)
RIFLE criteria •Risk •Injury •Failure •Loss •End stage renal disease	Interleukin-18 (IL-18) Liver-type fatty acid binding protein (L-FABP) N-acetyl-beta-D-glucosaminidase (NAG) Beta-2 microglobulin Retinol-binding protein-4 (RBP-4)
AKIN criteria •AKIN-1 •AKIN-2 •AKIN-3	Glutathione-S-transferase (GST) Netrin-1 Clusterin Osteopontin

Karen Tan , Sunil K. Sethi

Translational Research, Volume 164, Issue 2, 2014, 122 - 134http://dx.doi.org/10.1016/j.trsl.2014.04.011

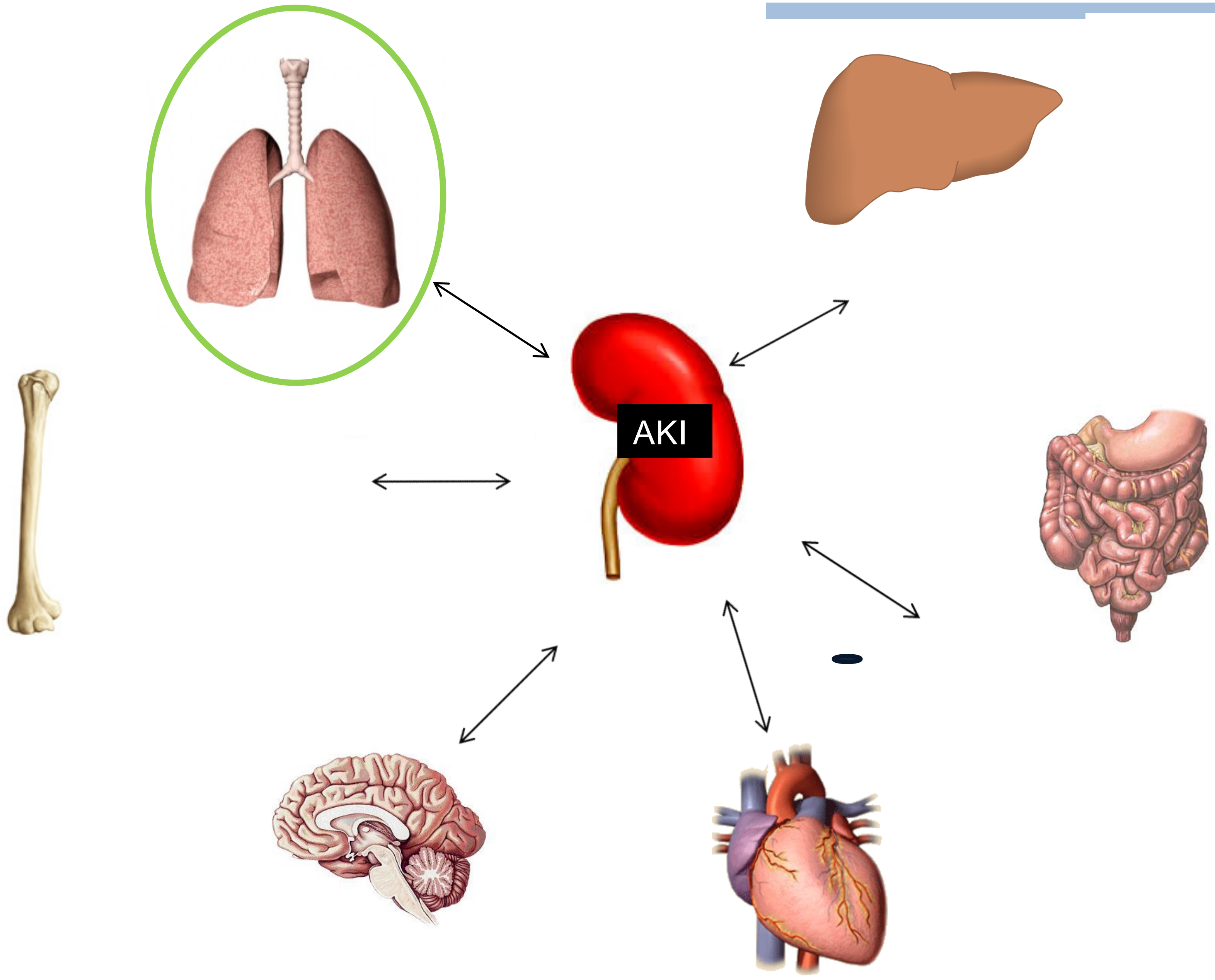
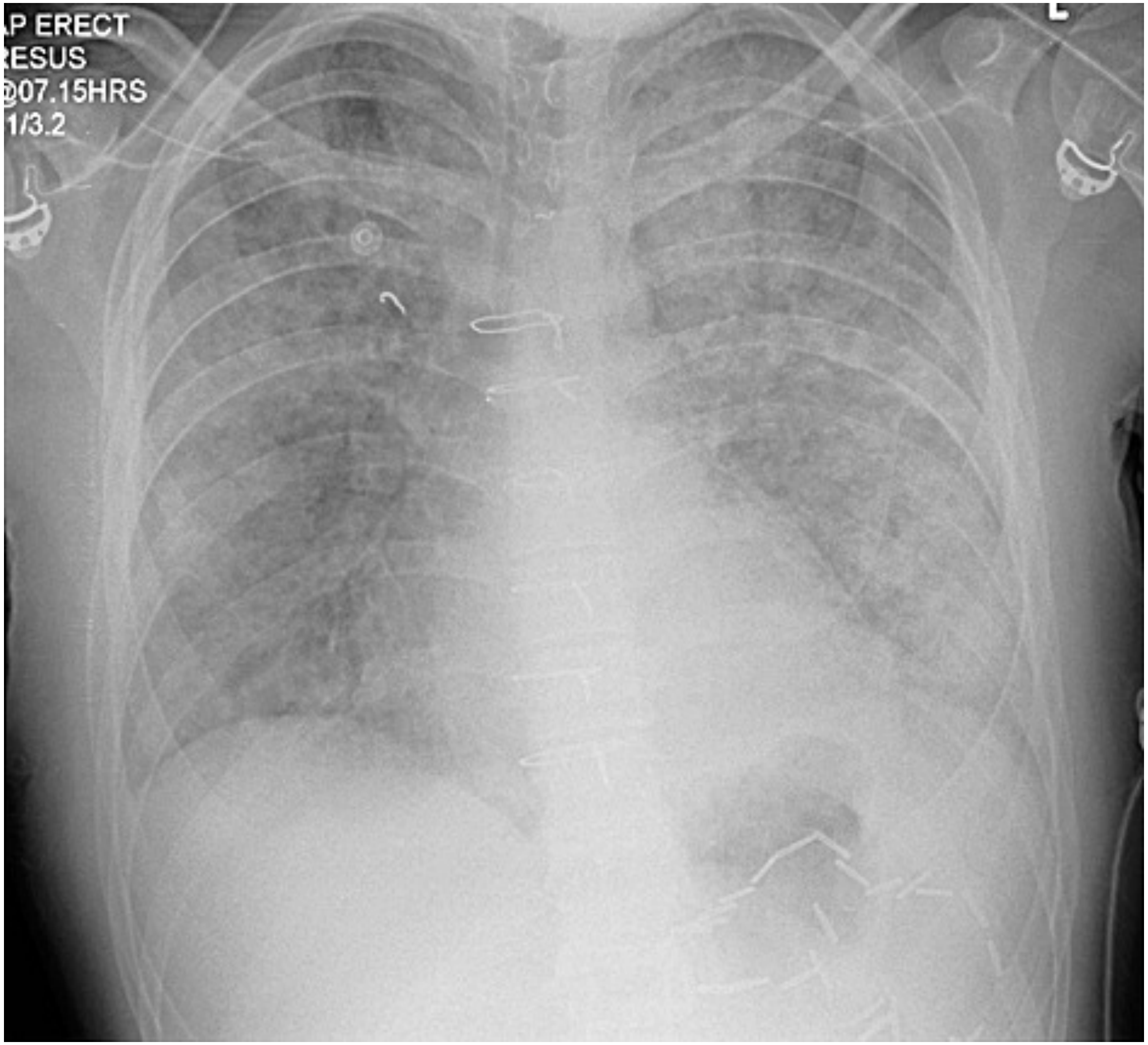

AKI

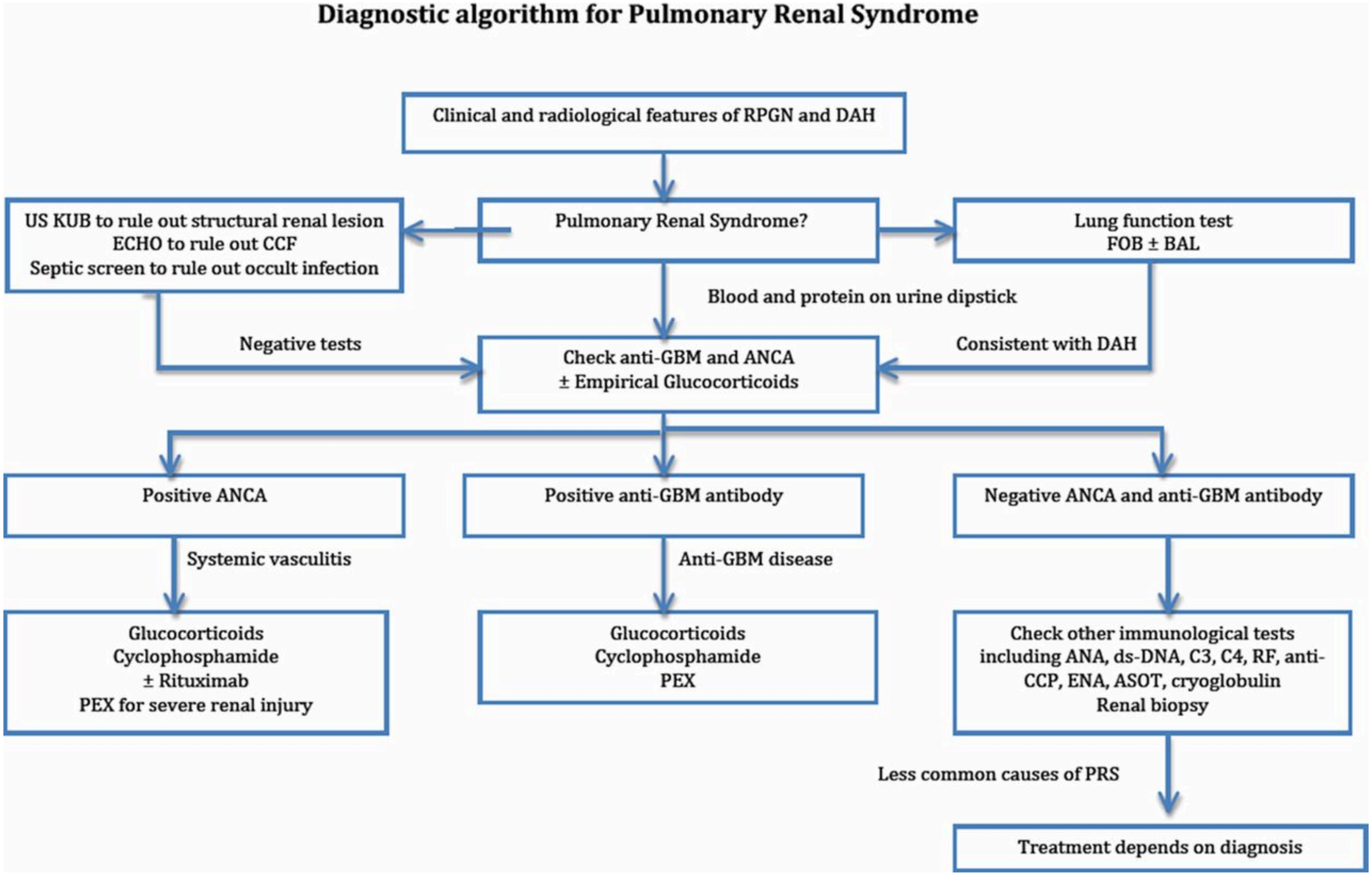
Figure 1



Respiratory Medicine 2011 105, 1413-1421DOI: (10.1016/j.rmed.2011.05.012)

Colm McCabe, Quentin Jones, Aikaterini Nikolopoulou, Chris Wathen, Raashid Luqmani Pulmonary-renal syndromes: An update for respiratory physicians
Respiratory Medicine Volume 105, Issue 10, Pages 1413-1421 (October 2011) DOI: 10.1016/j.rmed.2011.05.012

Diagnostic algorithm for pulmonary renal syndrome.



West S C et al. Postgrad Med J 2013;89:274-283

‘Cross talk’ new name for old observations

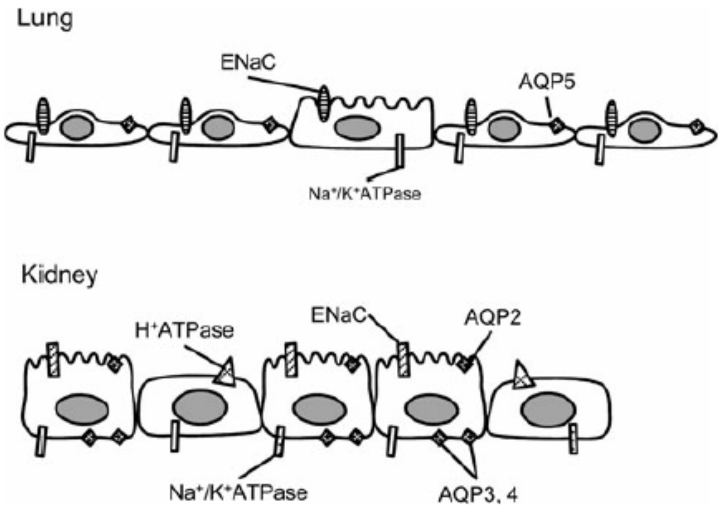
Table 1 History of “uremic lung”

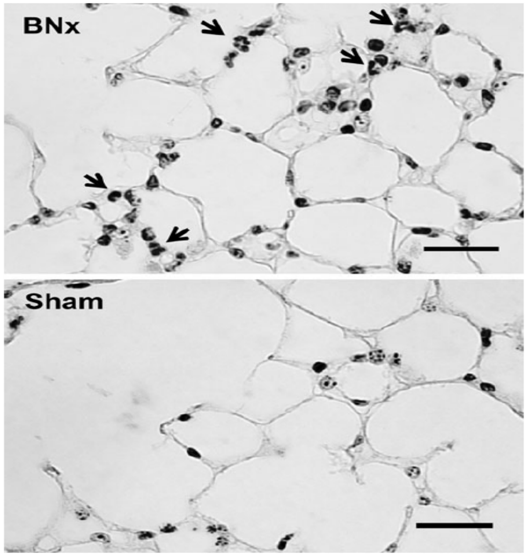
Author	Year	Topics	References
Lange	1901	First description on pulmonary edema in renal failure	[9]
Roubier and Plauchu	1933	Diagnosis of uremic edema by chest X-ray	[10]
Alwall et al.	1953	Description of volume overload (“fluid lung”)	[61]
Bass and Singer	1950	Description of various factors other than volume overload	[62]
Hopps and Wissler	1955	Suggestion of “uremic pneumonitis” by evaluating 536 autopsy cases	[11]
Gibson	1966	Case report of lung edema in renal failure with no increased pulmonary arterial pressure	[63]
Rackow and Fein	1978	Simultaneous measurement of pulmonary arterial pressure and BAL fluid in non-cardiogenic pulmonary edema	[12]
Bleyl et al.	1981	Uremic pneumonitis is a specific characteristic for AKI	[13]

Clin Exp Nephrol (2011) 15:464–470
DOI 10.1007/s10157-011-0459-4

Kent Doi · Tomoko Ishizu · Toshiro Fujita · Eisei Noiri

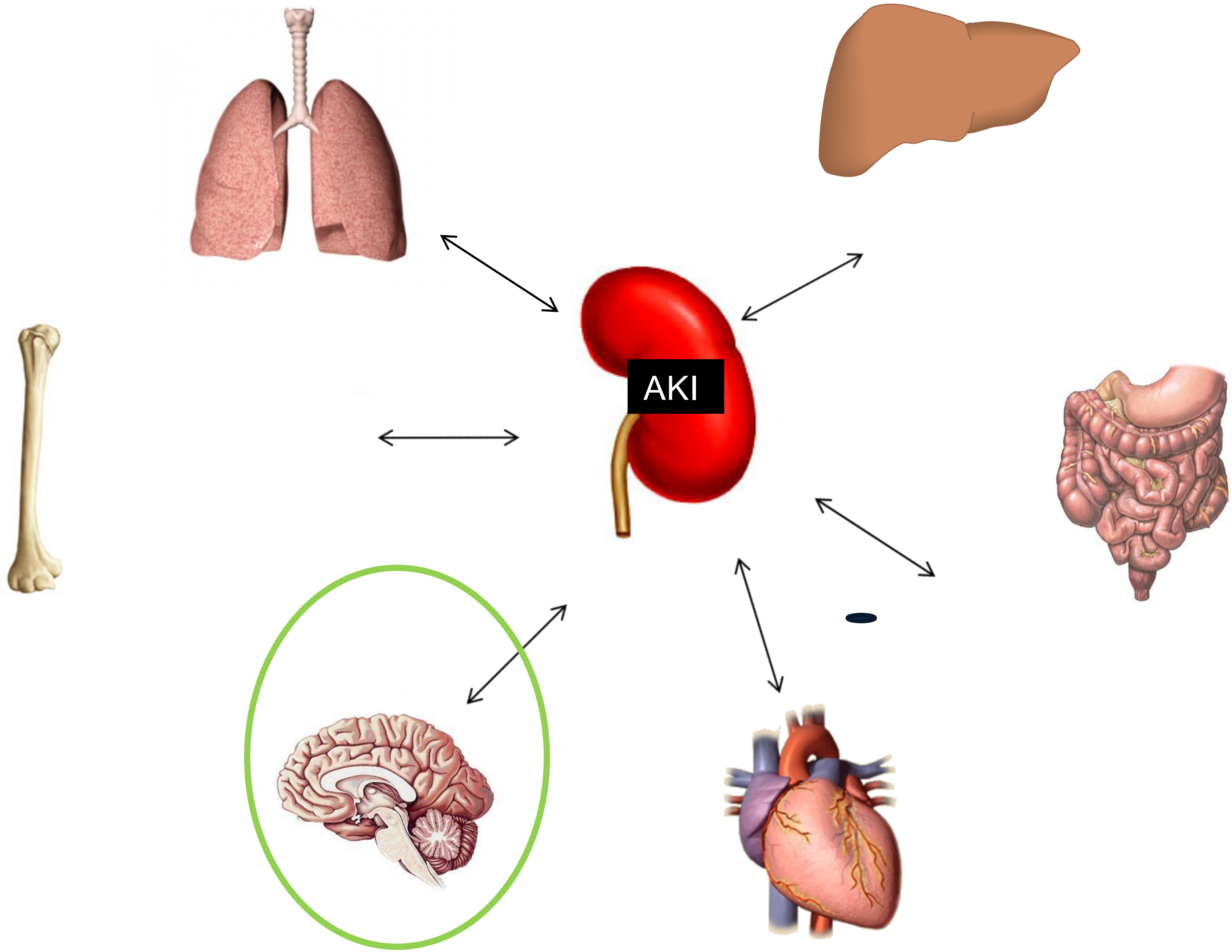
Does AKI cause ARDS?





- Not all related to fluid overload
- Increased pro-inflammatory mediators
  - IL-6 and IL1β
- Inflmammtory responses within lung
  - Activated NFκB, P38 MAP kinase,
- Neutrophil infiltration in to lung
- Increased pulmonary vascular Permeability
  - Down regulation of ENaC, NaK ATPase, AQP5

Clin Exp Nephrol (2011) 15:464–470
DOI 10.1007/s10157-011-0459-4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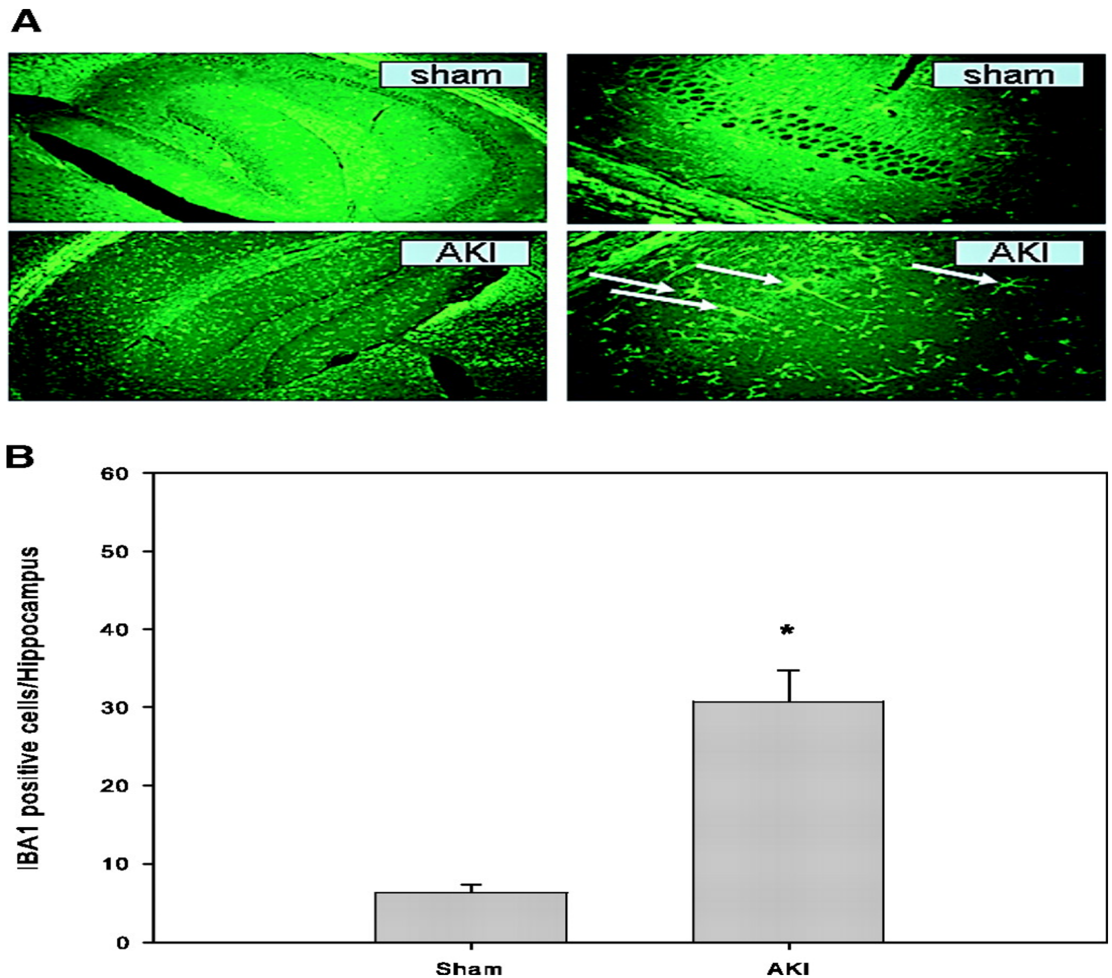
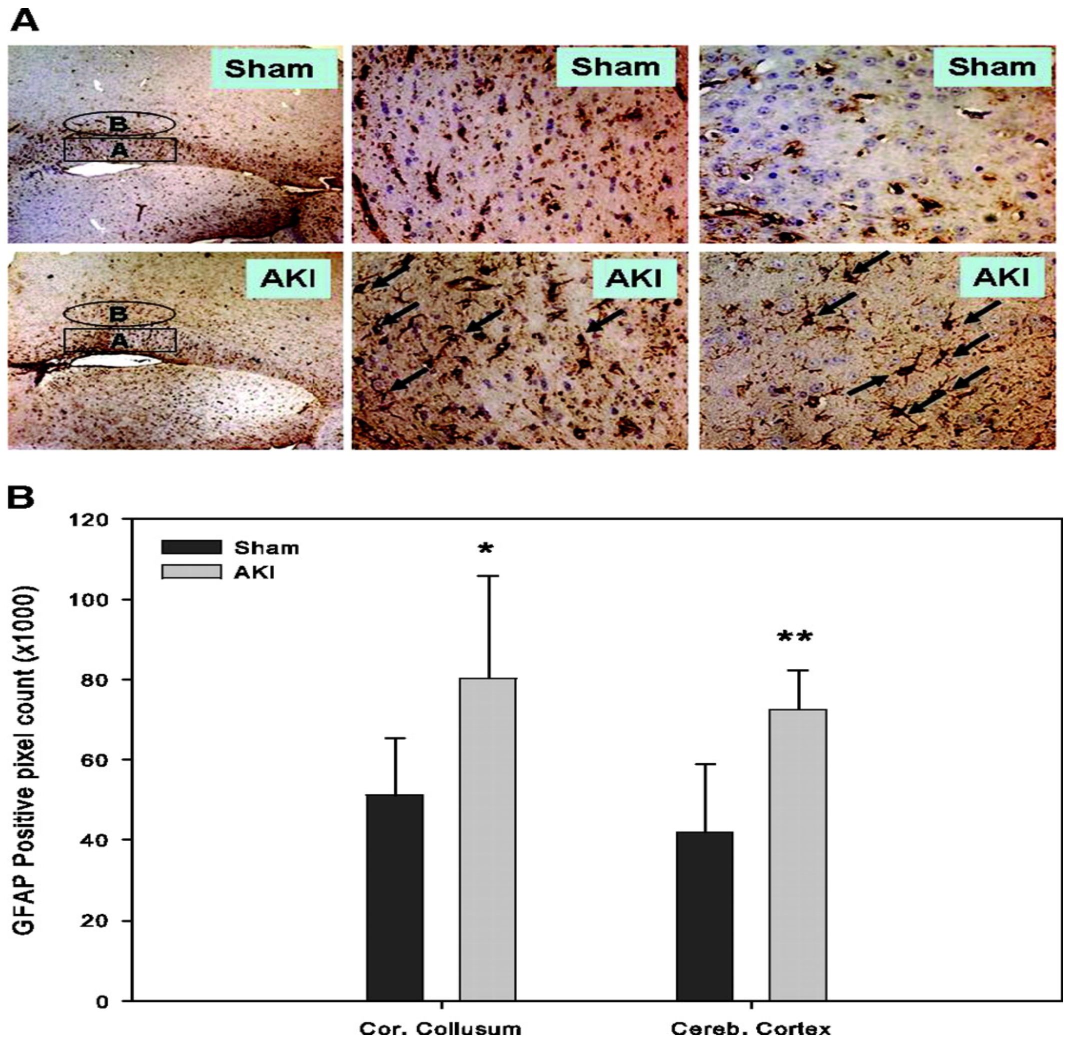
Microglial cells in the hippocampus of mouse brain.



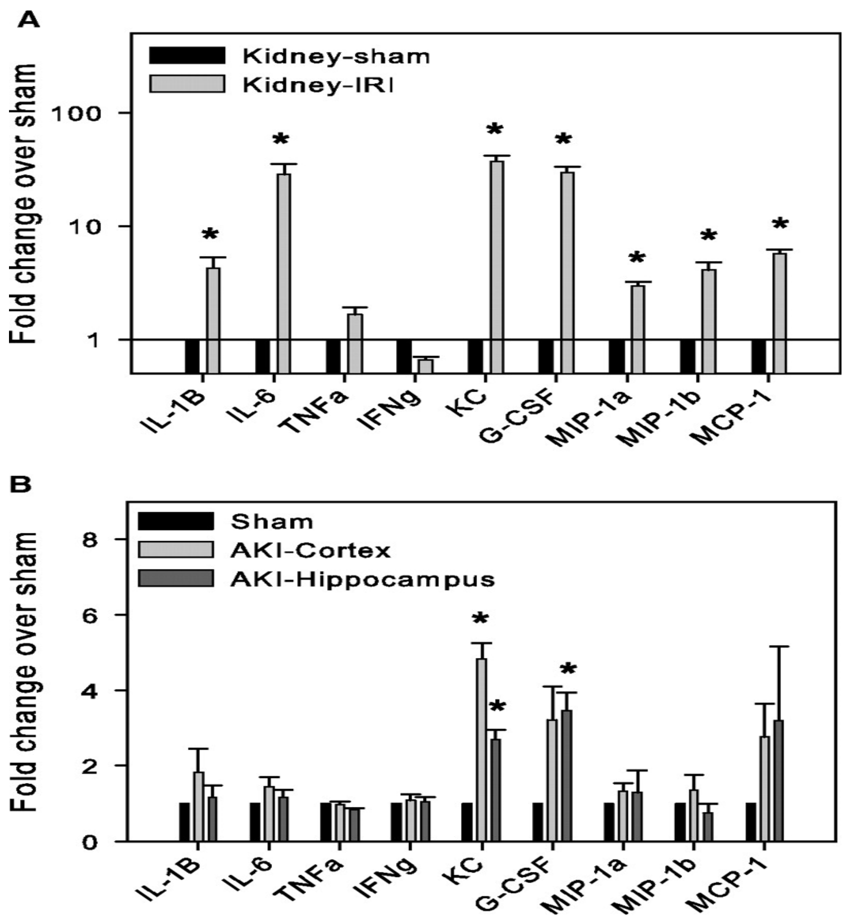
Liu M et al. JASN 2008;19:1360-1370

GFAP expression in the mouse brain astrocytes.

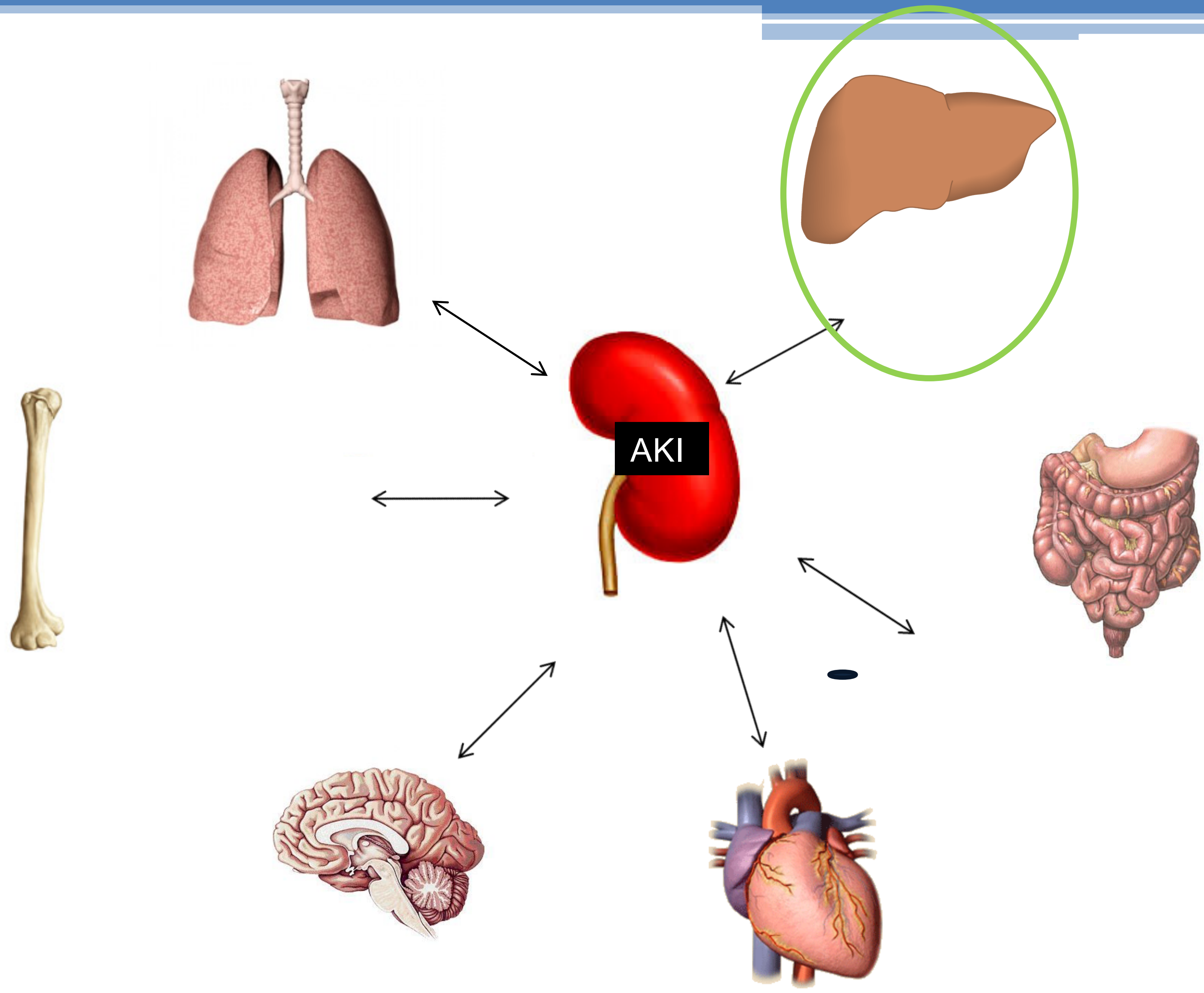


Liu M et al. JASN 2008;19:1360-1370

Cytokine/chemokine protein array in the kidney (A; *P < 0.03 to 0.002 versus sham) and the brain (B; *P < 0.003 to 0.0008 versus sham).



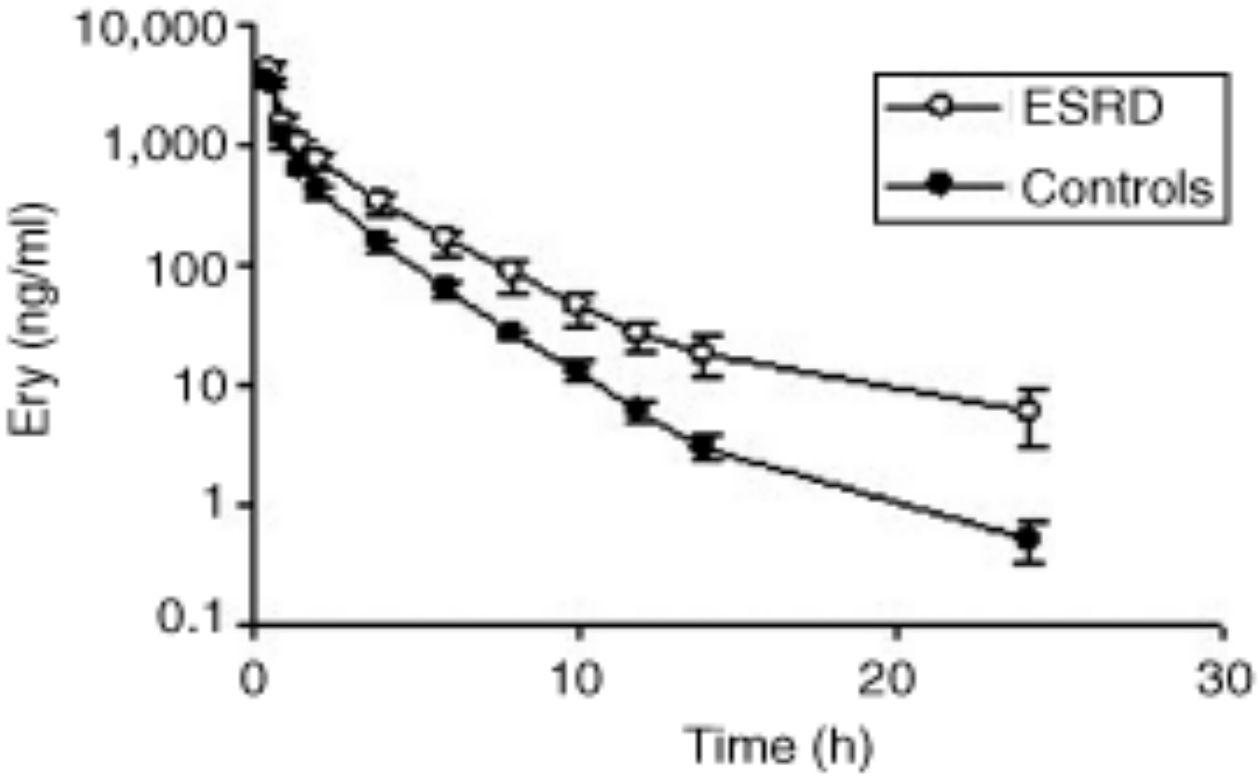
Liu M et al. JASN 2008;19:1360-1370


AKI

CytochromeP450 3A enzymes

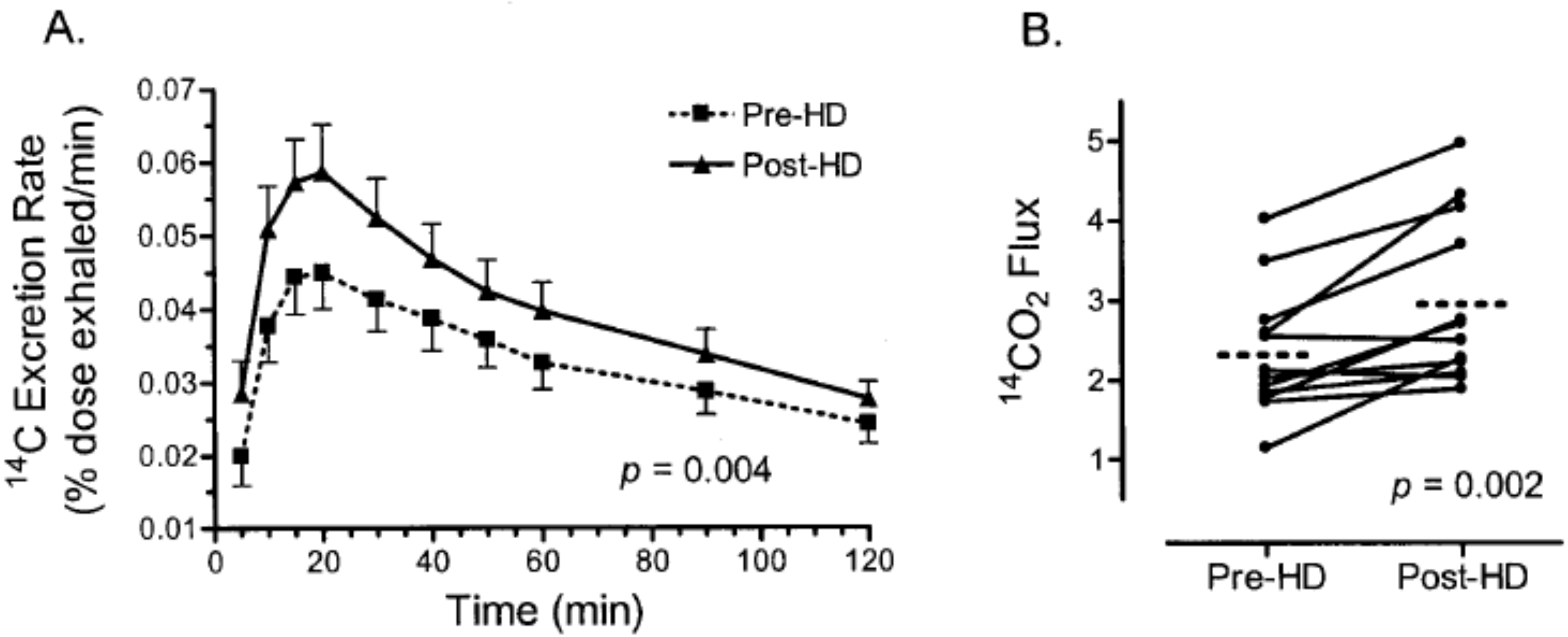
- CYP450
  - phase one reactions
  - oxidation
- CYP 3A
- Two main sub groups CYP3A4 and CYP3A5
- Most abundantly expressed CYP450 enzyme in liver
- Responsible for metabolism of >50% drugs

Reduced erythromycin metabolism with end-stage renal disease



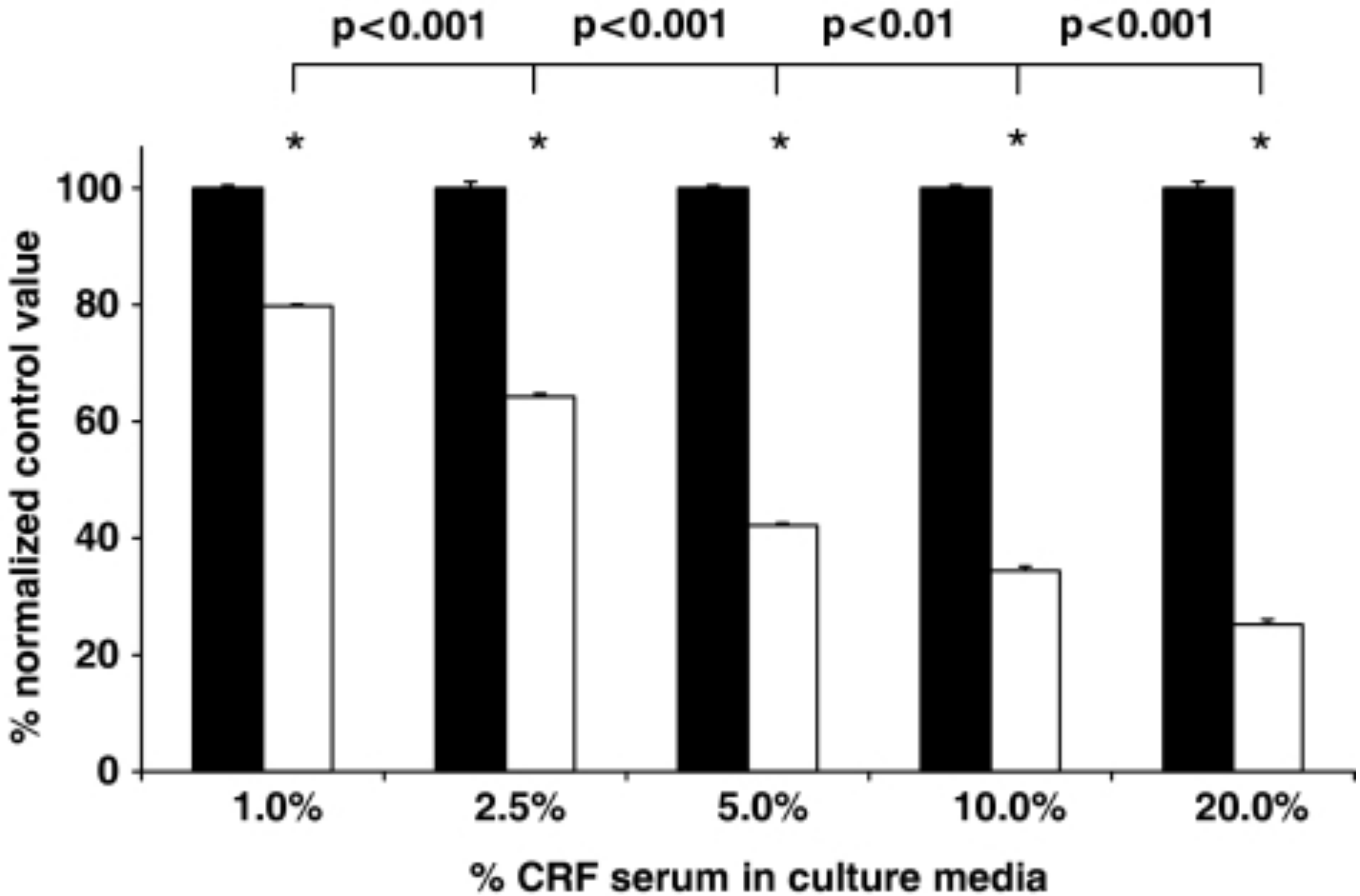
Sun, *et al*. Clin Pharm Ther. 2010;87:465

Increased metabolism of erythromycin after haemodialysis



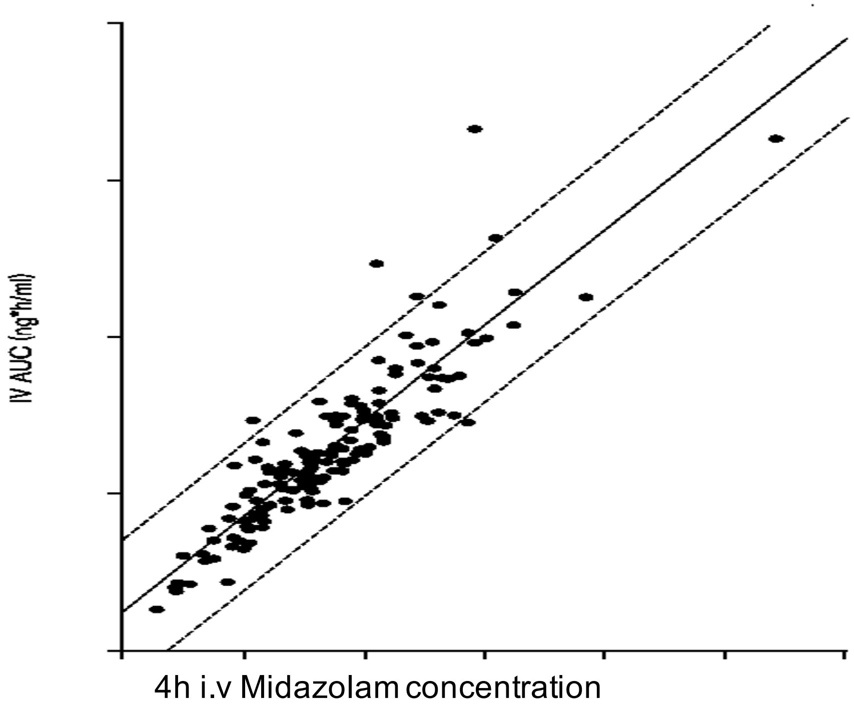
Nolin, et al. JASN 2006;17:2363.

Reduced CYP3A expression in rat hepatocytes incubated with human chronic renal failure serum



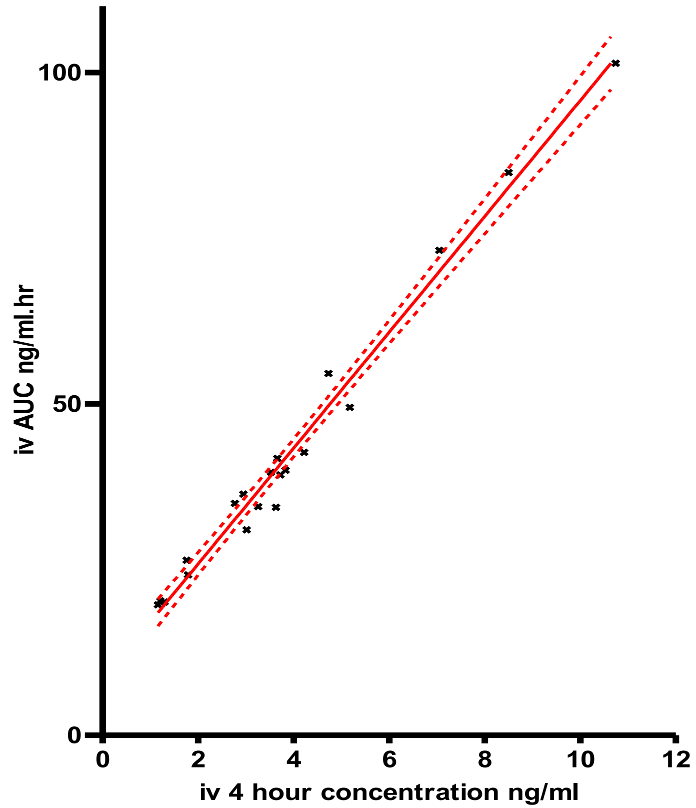
Michaud, *et al*. British Journal of Pharmacology. 2005;144:1067.

Single point determination of midazolam concentrations



Lin *et al*, *Pharmacogenetics* 2001: 781-791

Sample at 4 hours after intravenous midazolam correlates well with AUC

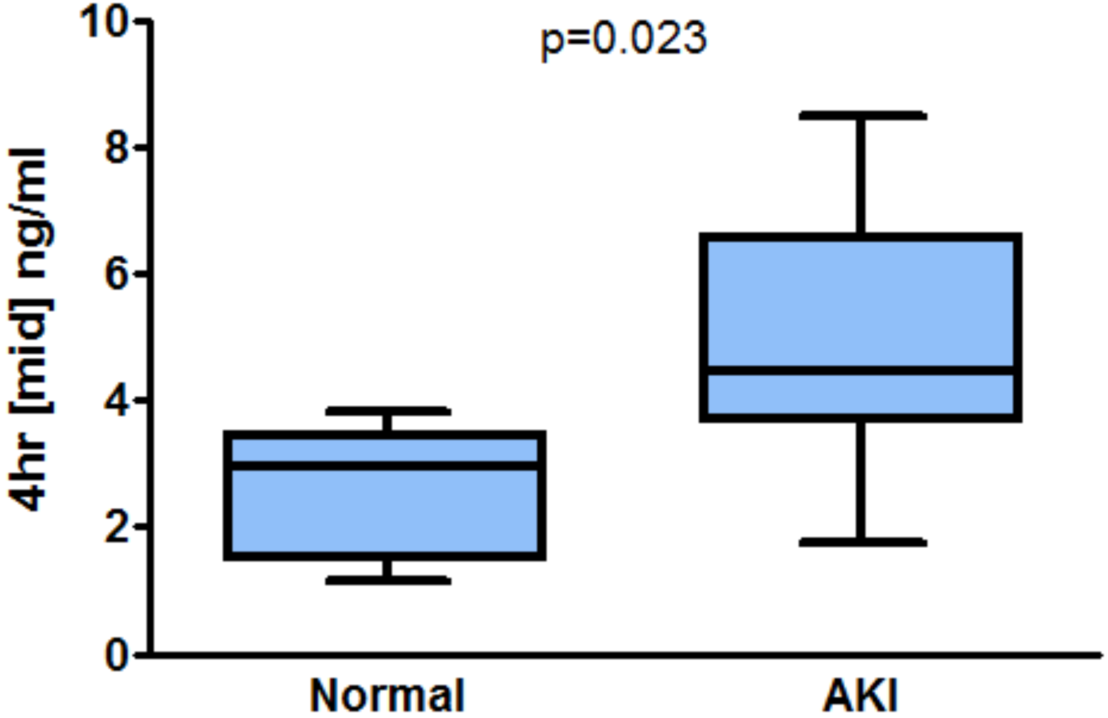


r = 0.956, $p < 0.0001$

AUC = 7.6 + 8.65·[4h IV concentration], $p < 0.001$

Kirwan CJ, Lee T, Holt DW, Grounds RM, MacPhee IA, Philips BJ.
Intensive Care Medicine 2009; 35: 1271.

Inhibition of midazolam metabolism in acute kidney injury



Kirwan CJ, Lee T, Holt DW, Grounds RM, MacPhee IA, Philips BJ.
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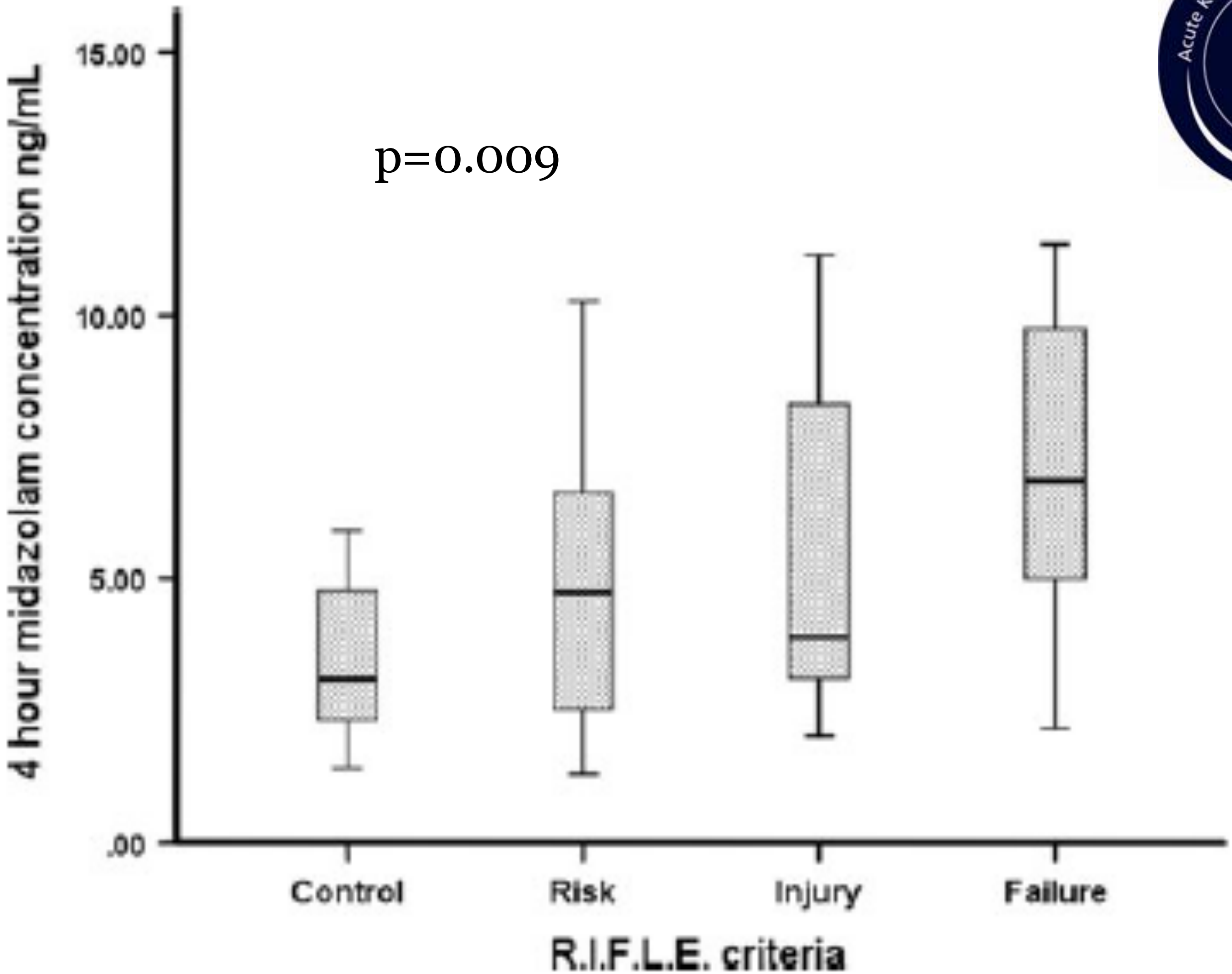
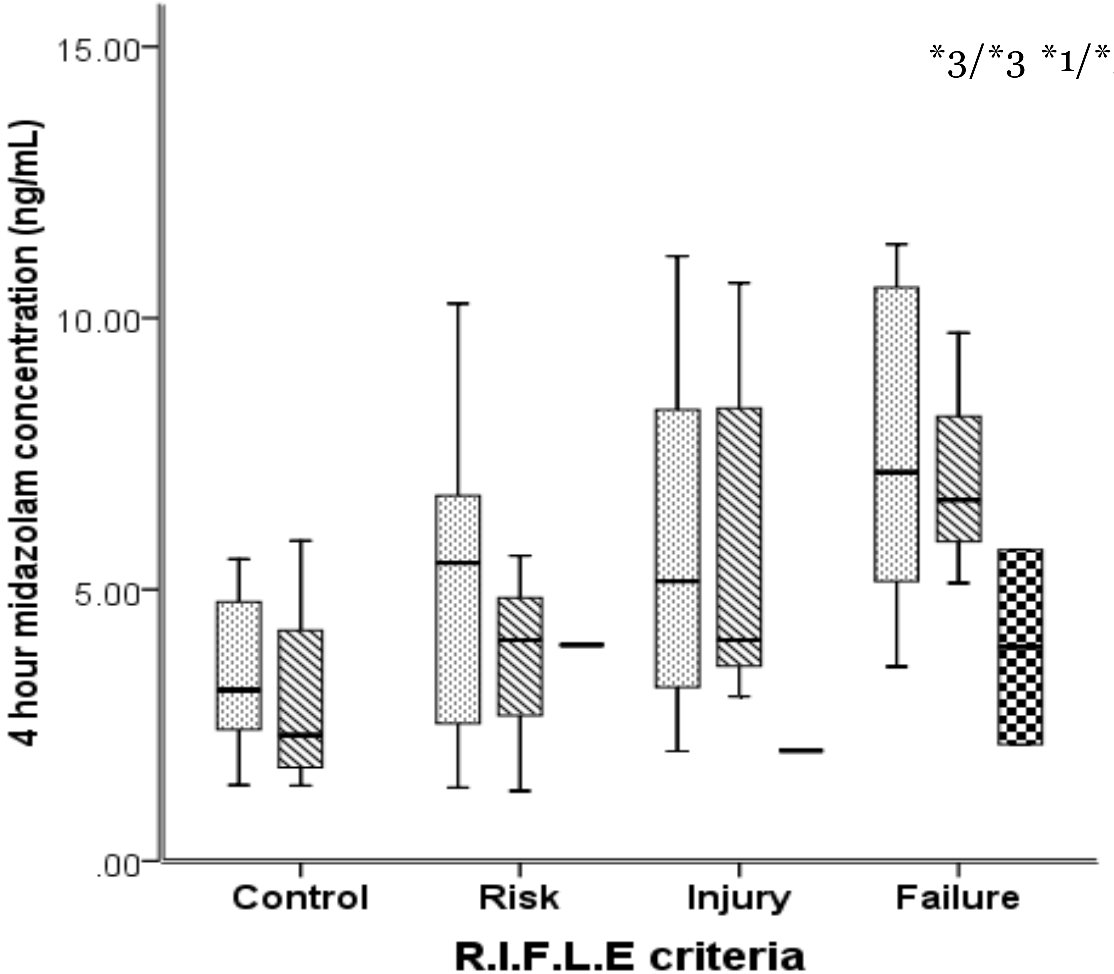
Inhibition of midazolam metabolism in acute kidney injury



Kirwan CJ, MacPhee IA, Lee T, Holt DW, Philips BJ. ***Intensive Care Medicine*** 2012 Jan;38(1):76-84.

Inhibition of midazolam metabolism in acute kidney injury in CYP3A5 non-expressers

*3/*3 *1/*3 *1/*1



Kirwan CJ, MacPhee IA, Lee T, Holt DW, Philips BJ. Intensive Care Medicine 2012 Jan;38(1):76-84.

CYP3A5 expressers are less affected by factors altering drug metabolism

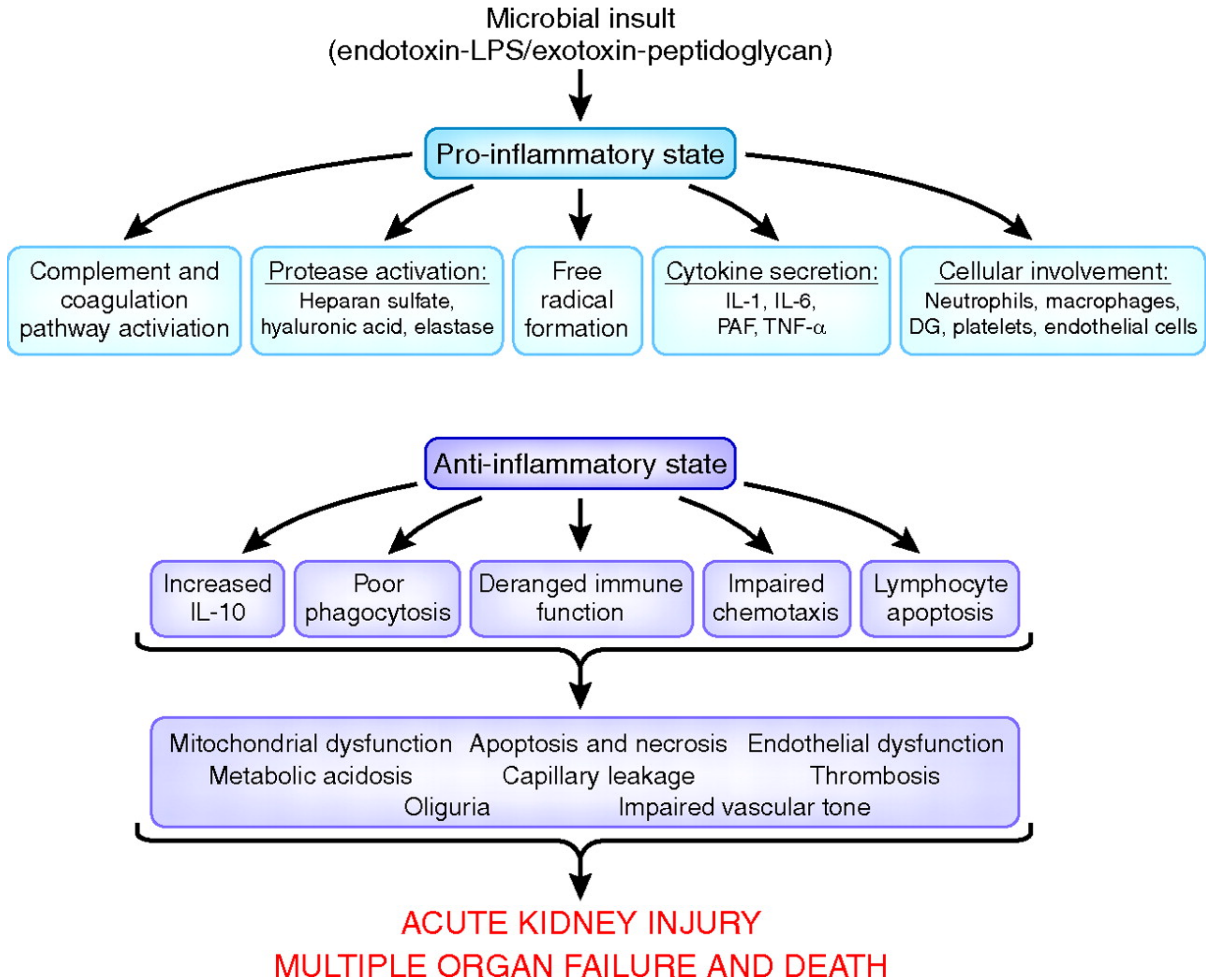
- **Steroid induction of cytochrome P450**
  - Roberts, *et al*. Drug Metab Dispos. 2008;36:1465.
- **Inhibition of cytochrome P450 by imidazole antifungals**
  - Kuypers, *et al*. Pharmacogenet.Genomics :2008;18:861.
  - Chandel, *et al*. Pharmacogenet.Genomics 2009;19:458.

Tramadol as a probe of CYP2D6

Mean [tramadol]$_{t=4}$ (ng mL^{-1}) according to CYP2D6 phenotype (based on genotype)	
Poor metabolizer (n = 2)	34.7
Intermediate metabolizer (n = 2)	33.3
Intermediate/extensive metabolizer (n = 2)	28.0
Extensive metabolizer (n = 4)	25.9
Mean AUC by CYP2D6 phenotype (based on genotype)	
Poor metabolizer (n = 2)	269.4
Intermediate metabolizer (n = 2)	261.2
Intermediate/extensive metabolizer (n = 2)	206.9
Extensive metabolizer (n = 4)	211.2

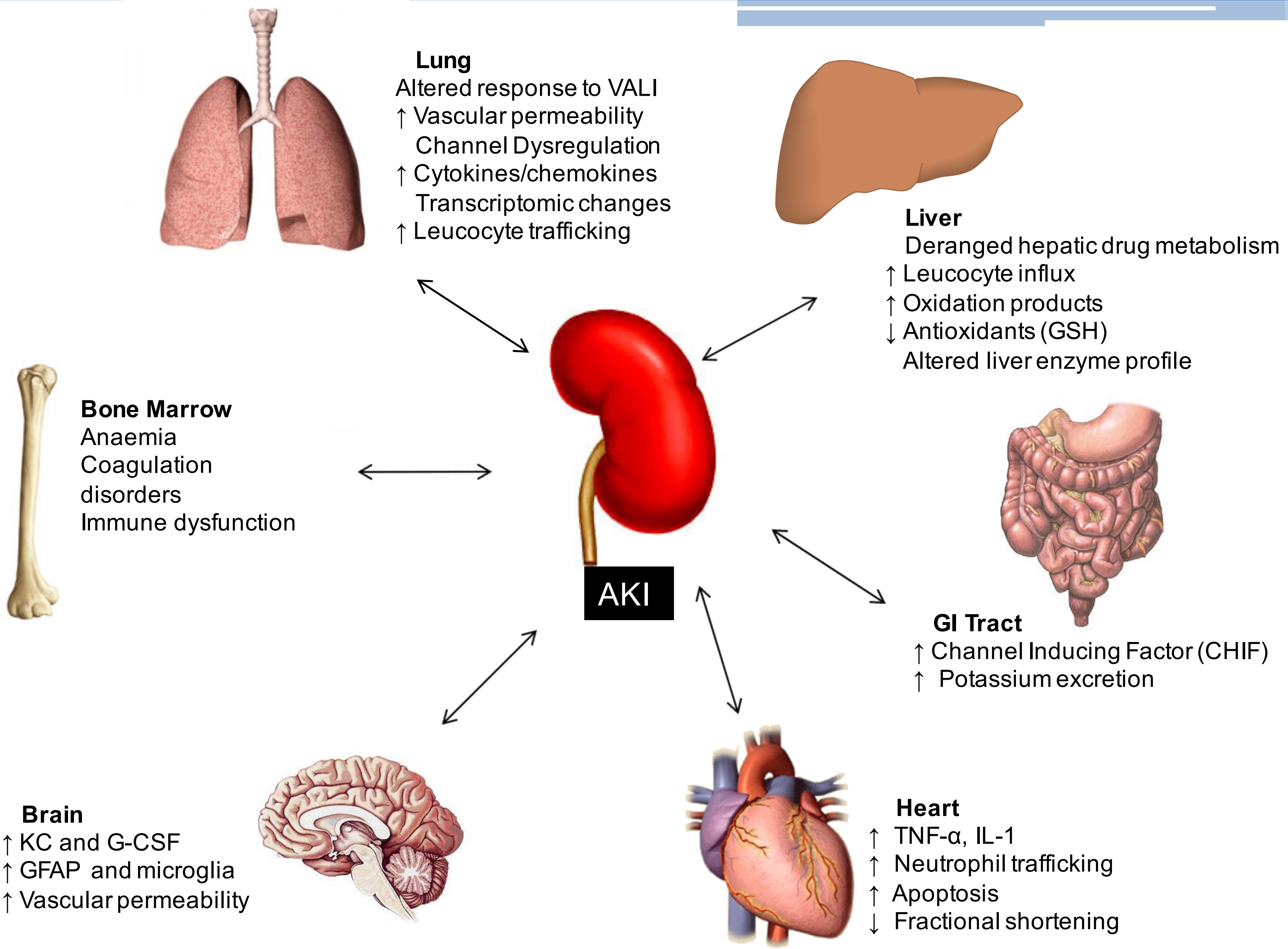
Lane K, Dixon J, McKeown D, Johnston A, van Schaik R, van Fessem M, MacPhee I, Philips B, Using tramadol to measure CYP2D6 metabolism in critically ill adults. *Intensive Care Medicine* 2014

Key pathogenic pathways involved in the clinical course of sepsis that also have implications in the pathophysiology of sepsis-induced acute kidney injury.



Zarjou A , and Agarwal A JASN 2011;22:999-1006

JASN


Lung
Altered response to VALI
↑ Vascular permeability
Channel Dysregulation
↑ Cytokines/chemokines
Transcriptomic changes
↑ Leucocyte trafficking
Liver
Deranged hepatic drug metabolism
↑ Leucocyte influx
↑ Oxidation products
↓ Antioxidants (GSH)
Altered liver enzyme profile
Bone Marrow
Anaemia
Coagulation disorders
Immune dysfunction
AKI
GI Tract
↑ Channel Inducing Factor (CHIF)
↑ Potassium excretion
Brain
↑ KC and G-CSF
↑ GFAP and microglia
↑ Vascular permeability
Heart
↑ TNF-α, IL-1
↑ Neutrophil trafficking
↑ Apoptosis
↓ Fractional shortening

London Acute Kidney Injury Network

St George's University of London

Second AKI Academy

London, October 18th – 19th 2014

Thank You

St George's Healthcare NHS Trust

Any Questions?