COME L'ESPERIENZA DEL RIANIMATORE PUÒ INTEGRARSI CON QUELLA DEL CARDIOLOGO, DEL CARDIOCHIRURGO, DEL NEFROLOGO NELLA GESTIONE DEL PAZIENTE IN FASE CRITICA

MILANO, Atahotel Executive
28-29 Novembre 2011

ECOCARDIOCHIRURGIA.it

Come si misura la funzione renale

Come si previene l'IRA

Le soluzioni di rimpiazzo. I diuretici

L'ecografia nella valutazione dello stato volemico

Luca Doroni

Cardiothoracic Anaesthesia & Intensive Care Medicine

University Hospital of Pisa, Italy

Perioperative Acute Renal Failure

- Incidence 5-17%
- The mortality rate exceeds 50% and depends upon the kind of surgery

Uchino S, Kellum JA, Bellomo R et al. Acute renal failure in critically ill patients: a multinational, multicenter study. *The Journal of the American Medical Association* 2005 Aug 17; **294**(7): 813–818.
Chertow GM, Burdick E, Honour M et al. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. *Journal of the American Society of Nephrology: JASN* 2005 Nov; **16**(11): 3365–3370.

Acute Kidney Injury, Mortality, Length of Stay, and Costs in Hospitalized Patients

Glenn M. Chertow,* Elisabeth Burdick,† Melissa Honour,† Joseph V. Bonventre,‡ and David W. Bates†

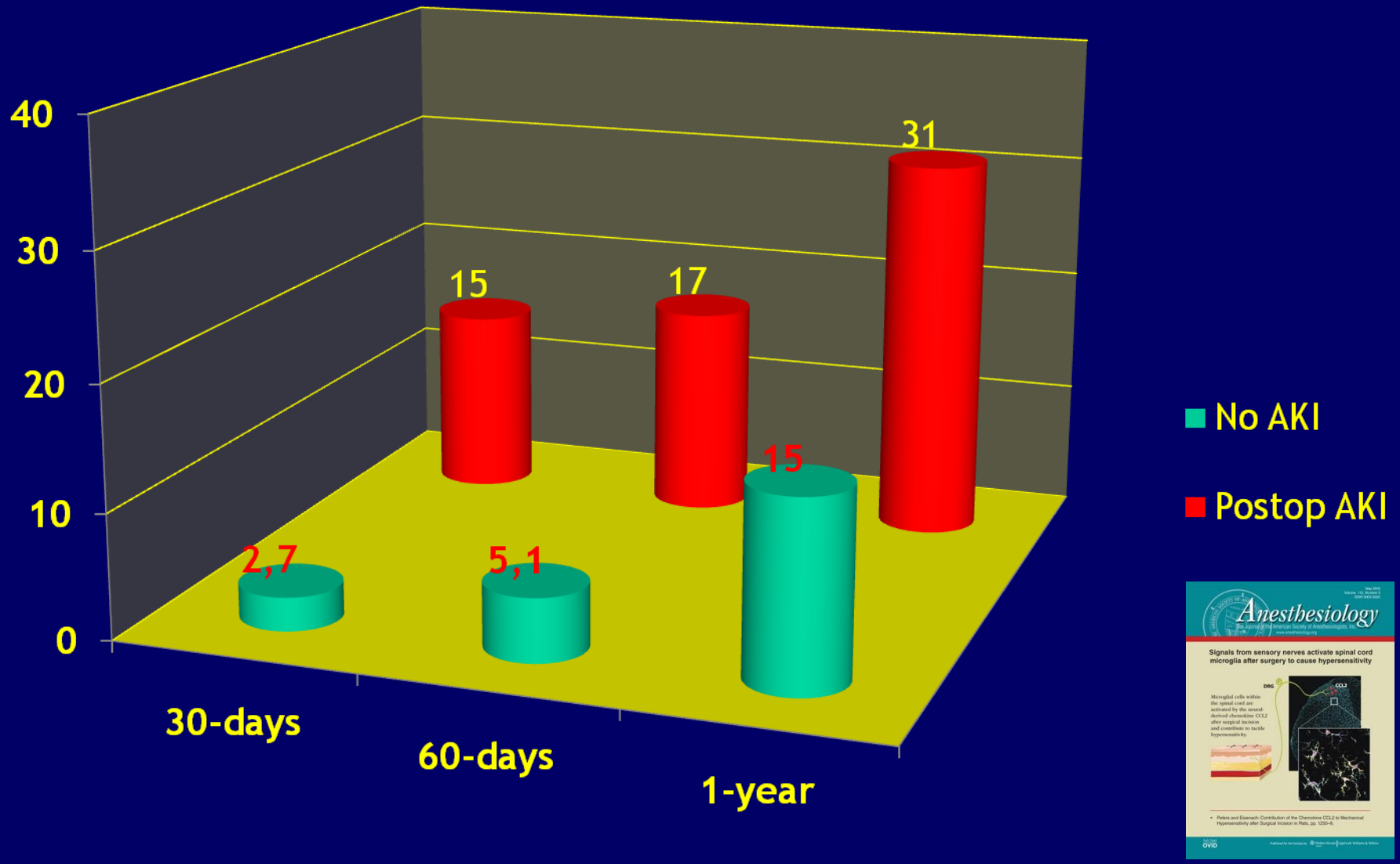
Table 1 | Hospital-acquired AKI: mortality and cost associated with selected changes in SCr

Increase in SCr (mg/dl)	Multivariable OR (95% CI)	Area under ROC curve	Increase in total cost
0.3	4.1 (3.1–5.5)	0.84	$4,886
0.5	6.5 (5.0–8.5)	0.86	$7,499
1.0	9.7 (7.1–13.2)	0.84	$13,200
2.0	16.4 (10.3–26)	0.83	$22,023

AKI, acute kidney injury; CI, confidence interval; OR, odds ratio; ROC, receiving operating characteristic; SCr, serum creatinine.

J Am Soc Nephrol 2005; 16: 3365–3370

Postoperative AKI and mortality



Kheterpal S, Tremper KK, Englesbe MJ, et al. *Anesthesiology.* 2007;107:892–902.

Table 3 Aetiological factors associated with renal dysfunction following cardiopulmonary bypass

Non-bypass factors
1. Significant surgical trauma.
2. Shed blood management.
3. Anaesthesia—increases the pro-inflammatory cytokines (IL-1, IL-8, TNFα, also IL-1ra, CD11b, HLA-DR expression).
4. Heparin–protamine interactions activate complement, also pro-cytokines.
Patient-related factors
1. Genotype—apolipoprotein E4 allele.
2. Pre-morbid conditions—congestive heart failure; diabetes mellitus.
3. Drugs—use of β-agonists/antagonists; use of ACEI.
Bypass related
1. Contact activation.
2. Ischaemia.
3. Endotoxin translocation from the gut to the kidney.

TABLE 2. Clinical conditions causing high risk for cardiac surgery–associated acute kidney injury

Clinical conditions
Preoperative estimated GFR < 60 mL/min/1.73 m^2
Preoperative left ventricular ejection fraction < 35%
Emergency surgery
Cardiogenic shock
Acute myocardial infarction in the week preceding surgery
Left main coronary artery disease
Receiving diuretic or inotropic therapy for decompensated heart failure
CPB time > 3 h

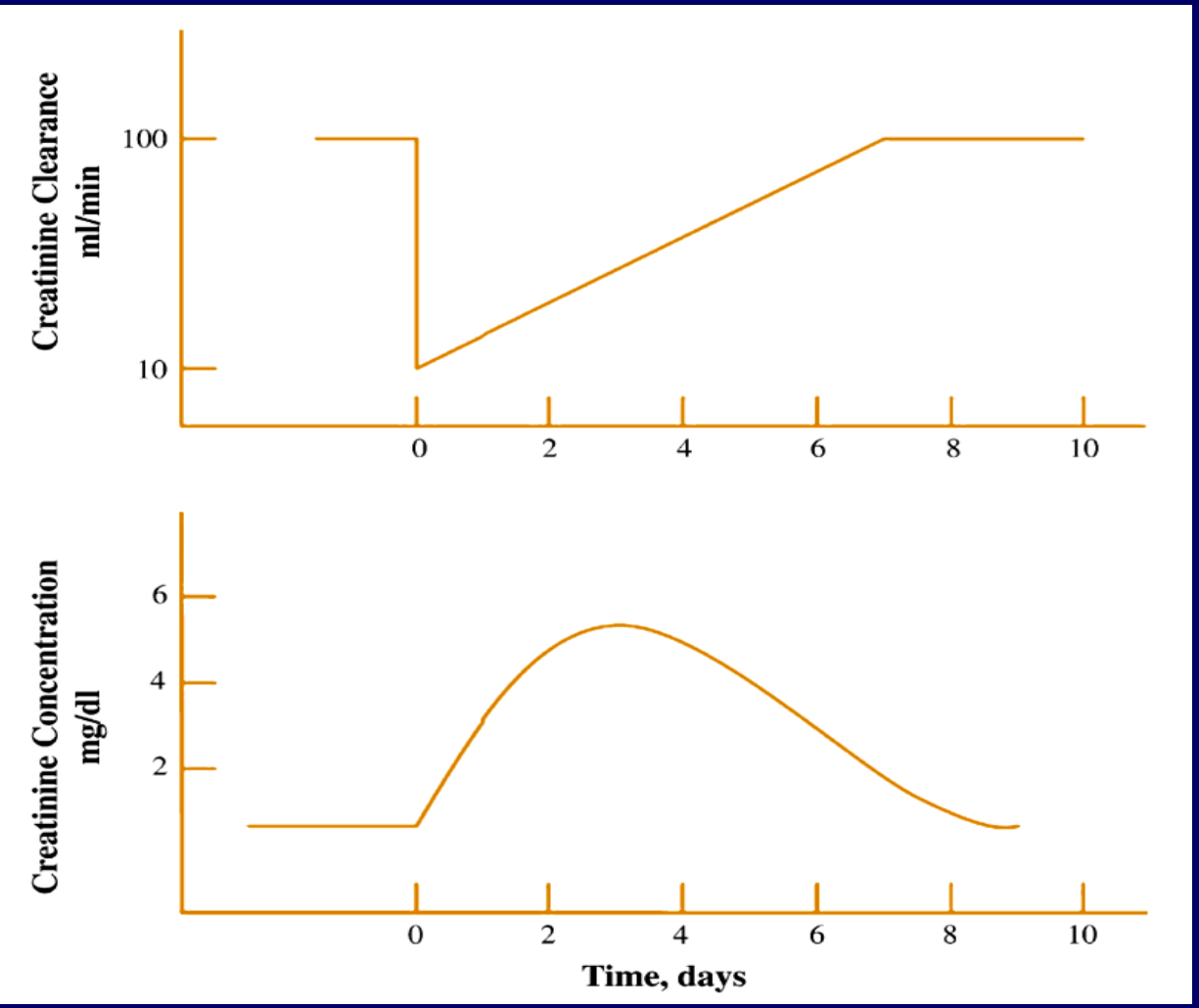
GFR, Estimated glomerular filtration rate; *SCr*, serum creatinine; *CPB*, cardiopulmonary bypass.

What is ARF?

Creatinine Δ 0.1 mg/dL	Creatinine > 3.2 mg/dL or x 2	Δ Creatinine 72h >50µmol/L
Creatinine increase >0.5 mg/dL	Creatinine >5 mg/dL or K^+ > 5.5 mmol/L	Δ Creatinine 72h >100µmol/L
Creatinine ≥ 1.7 mg/dL	Creatinine increase ≥ 25%	Cockcroft-Gault Creatinine Clearance: 30–60 ml/min
Creatinine ≥ 1.5 mg/dL	Creatinine increase ≥ 50%	Δ Cockcroft-Gault 72h <0%
Creatinine ≥ 2 mg/dL	Creatinine increase ≥ 100%	Δ Cockcroft-Gault Creatinine Clearance 72h <-15%
Creatinine ≥ 2.1 mg/dL and x 2	Δ Creatinine 72h >0µmol/L	Δ Cockcroft-Gault Creatinine Clearance 72hr <-25%
Creatinine ≥ 177µmol/L and Δ >62µmol/L	Δ Creatinine 72h >25µmol/L	Δ Cockcroft-Gault Creatinine Clearance 72hr<-50%
Creatinine > 200µmol/L (2.36 mg/dL)	Δ Creatinine 72h >44µmol/L	MDRD: 50% change in GFR

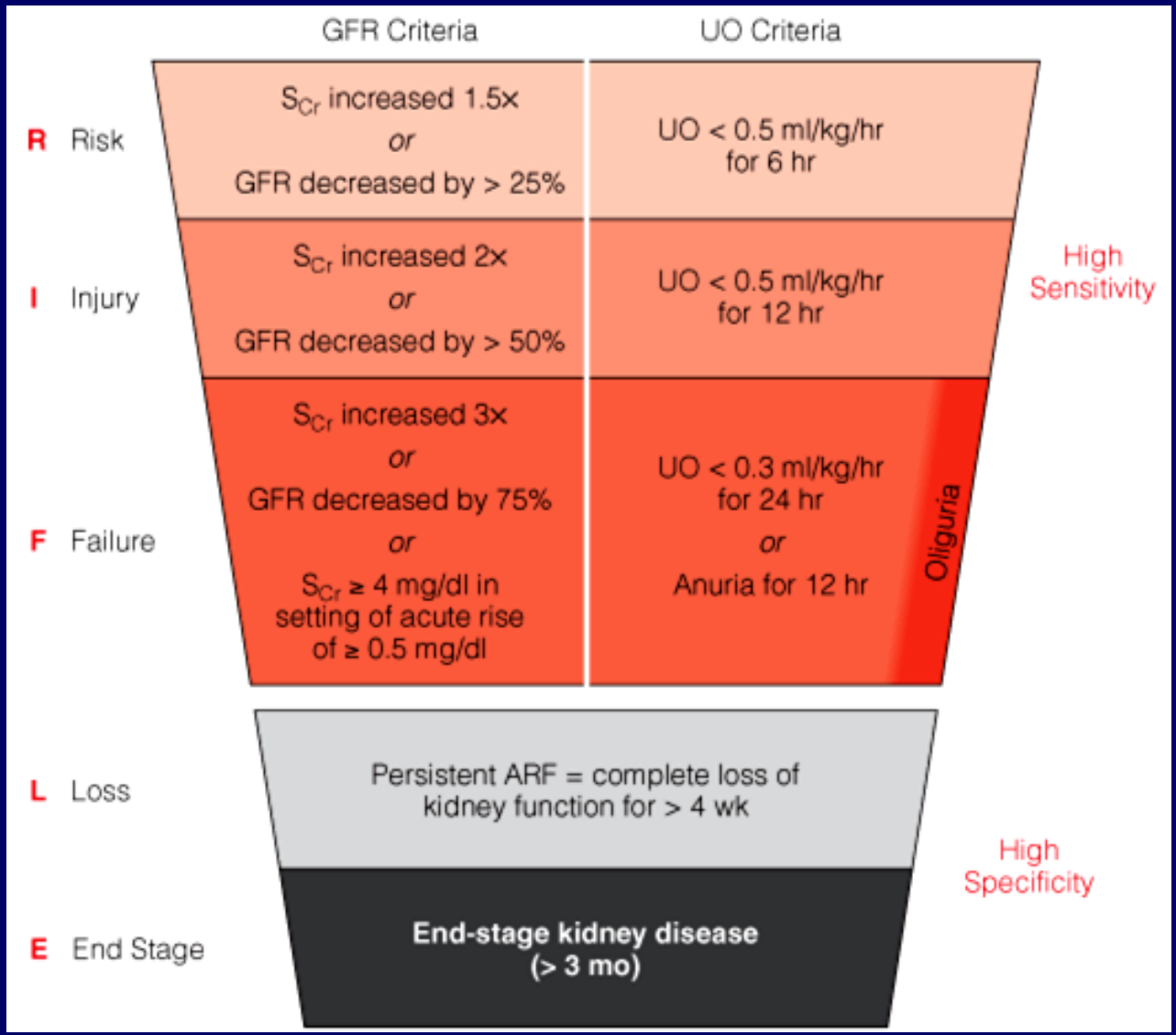
Hoste EA et al Int J Art if Organs 2008 : 31 (2); 158-65

SCr not a sensitive marker of acute changes !!



- SCr varies with age, BSA, status hydration
- SCr not proportional to renal function
- SCr not accurate in the acute setting but in the steady-state

RIFLE criteria for classification of ARF



Bellomo R, Defining, quantifying, and classifying acute renal failure, *Crit Care Clin*. 2005; 21:223–237

Definitions of Acute Kidney Injury

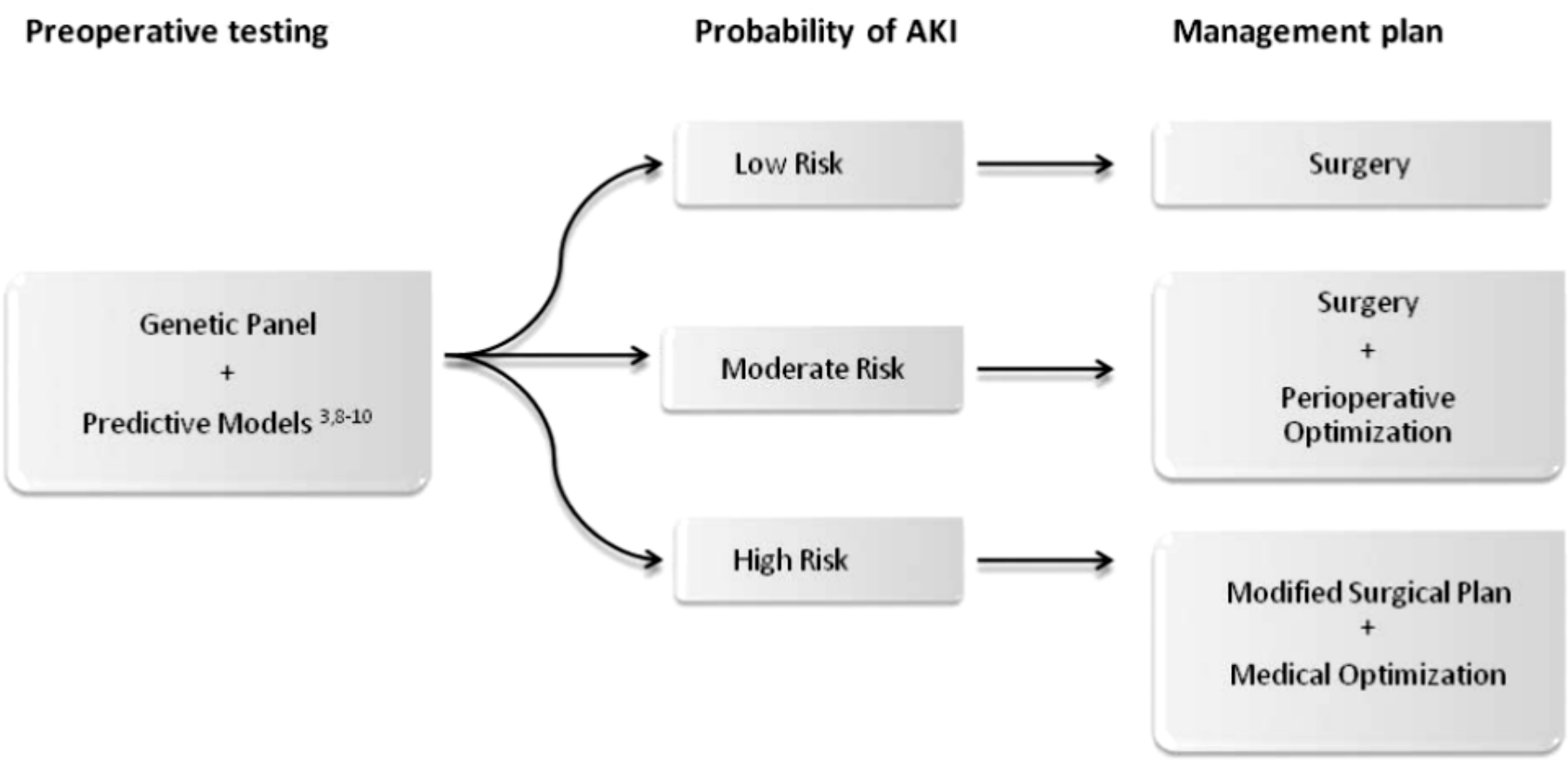
Acute Kidney Injury Network Criteria				RIFLE Criteria	
	Creatinine/ GFR	Urine Output		Creatinine/ GFR	Urine Output
Stage 1	Increased Cr 0.3mg/dL or Cr 150% baseline	UOP<0.5 mL/kg/h for>6h	Risk (R)	Increased Cr 1.5 × or GFR decreased <25%	UOP <0.5mL/ kg/h for >6h
Stage 2	Cr 200%- 300% baseline	UOP<0.5 mL/kg/h for >12h	Injury (I)	Increased Cr 2 × or GFR decreased <50%	UOP <0.5mL/ kg/h for >12h
Stage 3	Cr>300% of baseline or >4mg/dL with 0.5mg/ dL acute increase	UOP<0.3 mL/kg/h for 24 h or anuria for 12h	Failure (F)	Increased Cr 3 × or GFR decreased <75% or Cr >4mg/ dL with 0.5mg/dL acute increase	UOP <0.3mL/kg/ h for 24h or anuria for 12 h
			Loss (L)	Persistent ARF >4wk	
			ESKD (E)	Persistent loss >3mo	

Mehta RL, Kellum JA, Shah SV, et al, and Acute Kidney Injury Network. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care.* 2007;11:R31.

Bellomo R, Ronco C, Kellum JA, et al, and Acute Dialysis Quality Initiative workgroup. Acute renal failure-definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care.* 2004;8: R204–R212.

Ideal characteristics for AKI biomarkers

- Noninvasive
- Highly sensitive for early detection
- Specific for AKI
- Allow monitoring of patient
- Rapidly quantifiable
- Reproducible using standard assays
- Allow for risk stratification
- Allow for identification of AKI subtypes
- Stable production rate
- Circulating levels unaffected by pathologic changes
- Freely filtered at glomerulus without tubular reabsorption/secretion



Seminars in Cardiothoracic and Vascular Anesthesia / Vol. 12, No. 4, December 2008

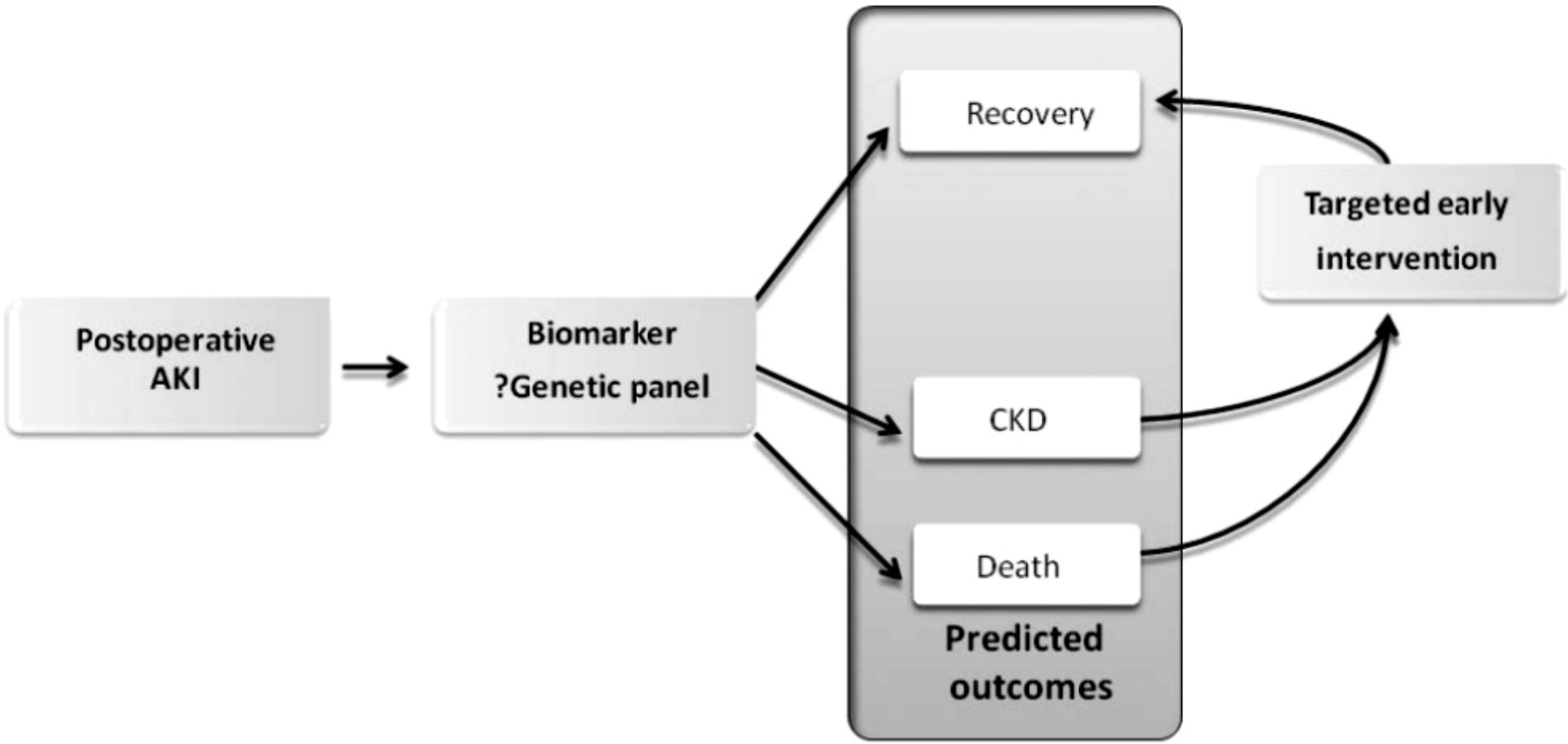
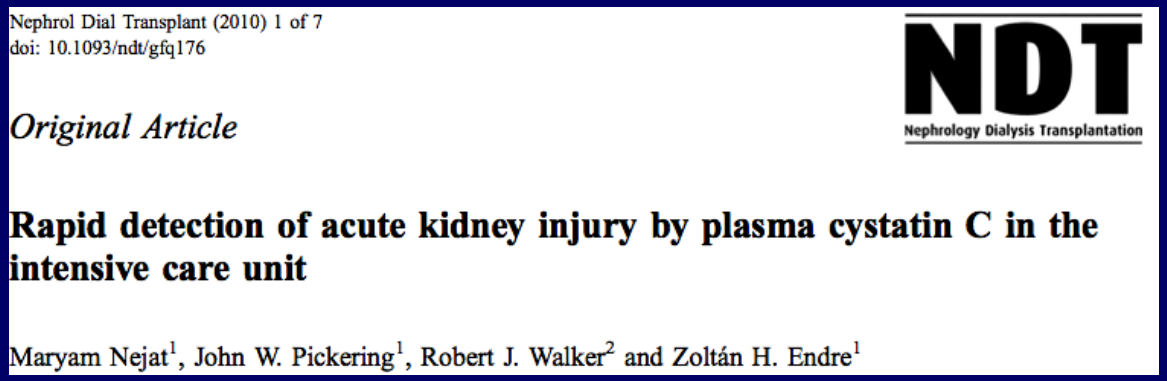


Figure 3. Using biomarkers to predict outcomes and target early interventions following acute kidney injury to improve outcomes.

New Markers: Cystatin C

Produced by all nucleated cells, is freely filtered by the glomerulus, reabsorbed by the proximal tubule, and is not secreted by renal tubules.



Nephrol Dial Transplant (2010) 1 of 7
doi: 10.1093/ndt/gfq176

Original Article

NDT
Nephrology Dialysis Transplantation

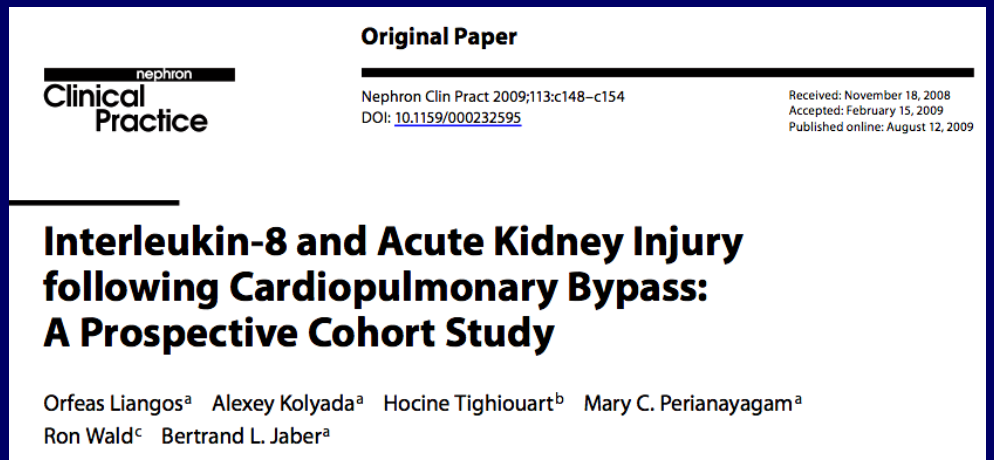
Rapid detection of acute kidney injury by plasma cystatin C in the intensive care unit

Maryam Nejat[1], John W. Pickering[1], Robert J. Walker[2] and Zoltán H. Endre[1]

New Markers: IL-18

Proinflammatory cytokine produced by caspase-1 involved in the pathogenesis of ARF.

In a case-control trial IL-18 was a predictor of AKI and mortality in ARDS patients.



Original Paper

nephron Clinical Practice

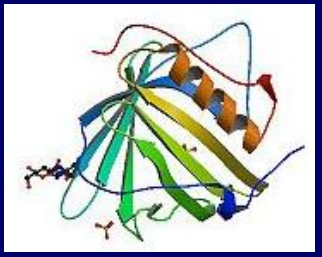
Nephron Clin Pract 2009;113:c148–c154
DOI: 10.1159/000232595

Received: November 18, 2008
Accepted: February 15, 2009
Published online: August 12, 2009

Interleukin-8 and Acute Kidney Injury following Cardiopulmonary Bypass: A Prospective Cohort Study

Orfeas Liangos[a] Alexey Kolyada[a] Hocine Tighiouart[b] Mary C. Perianayagam[a]
Ron Wald[c] Bertrand L. Jaber[a]

New Markers: NGAL



NGAL levels increase in the blood and urine within only a few hours after the injury.

Clinical studies have found that NGAL functions as an early marker of renal function across a wide variety of clinical settings including CKD and cardiac surgery.

Intensive Care Med
DOI 10.1007/s00134-010-1887-4

ORIGINAL

Johan Mårtensson
Max Bell
Anders Oldner
Shengyuan Xu
Per Venge
Claes-Roland Martling

Neutrophil gelatinase-associated lipocalin in adult septic patients with and without acute kidney injury

Clinical Utility of Neutrophil Gelatinase–Associated Lipocalin as an Early Marker for Acute Kidney Injury

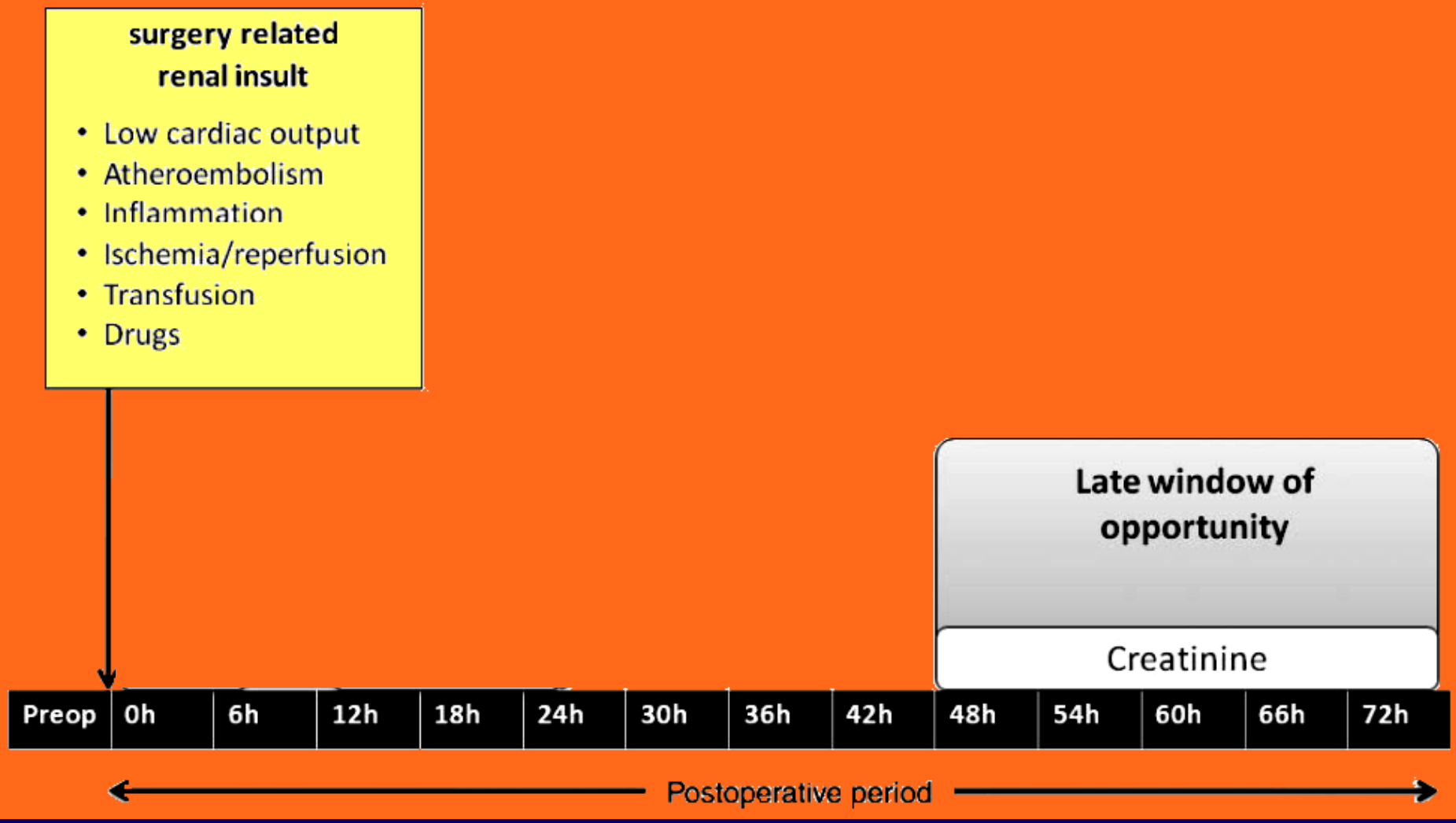
J Thorac Cardiovasc Surg 2010;139:1101-6

In-Depth Review

Blood Purif 2010;29:357–365
DOI: 10.1159/000309421

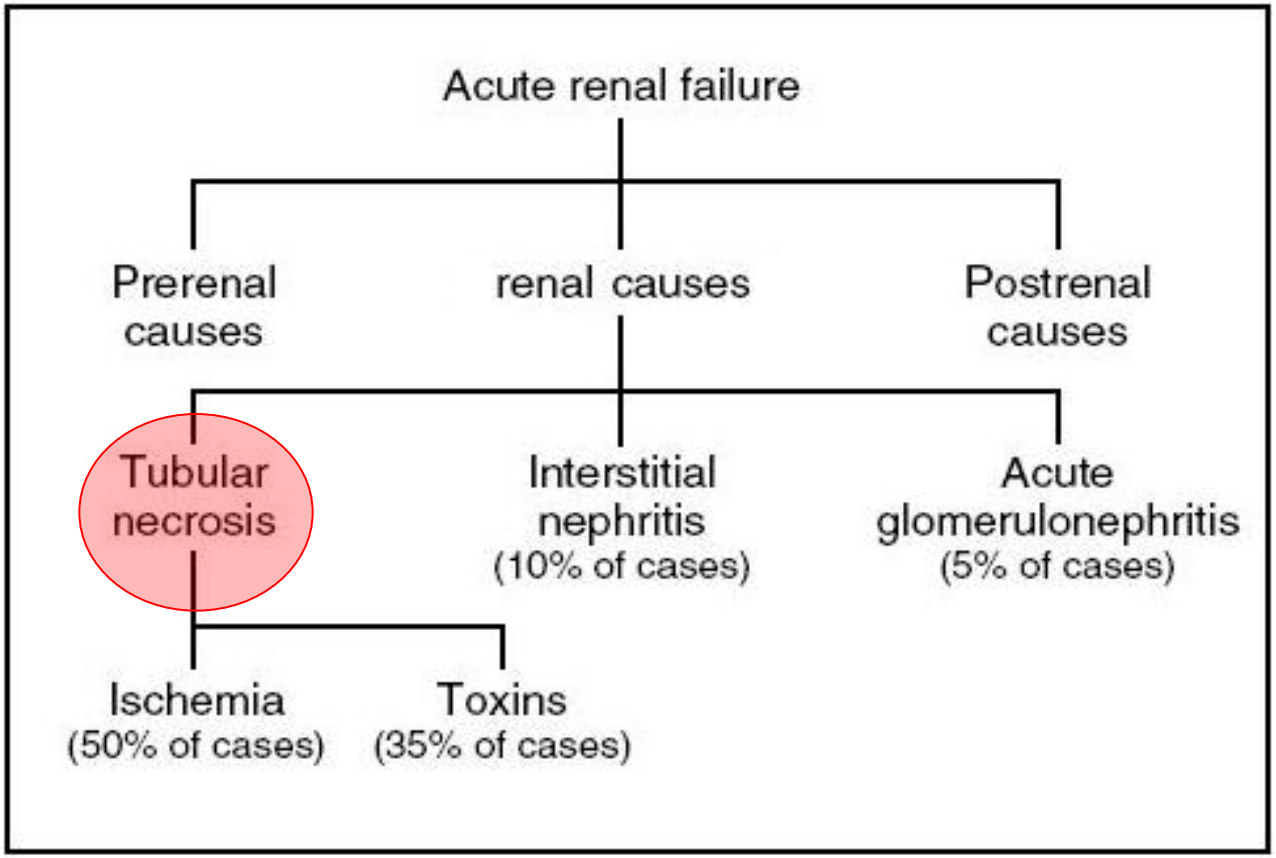
Serum and Urinary Biomarkers of Acute Kidney Injury

Barbara Lisowska-Myjak



Perioperative AKI

- Causes of AKI are classified as prerenal, renal, or postrenal in origin.
- ATN is the most common cause of perioperative AKI.
- The pathogenesis of ATN involves both ischemia and inflammation with cell death due to both necrosis and apoptosis.



Best Practice & Research Clinical Anaesthesiology
Vol. 22, No. 1, pp. 193–208, 2008
doi:10.1016/j.bpa.2007.08.005
available online at http://www.sciencedirect.com

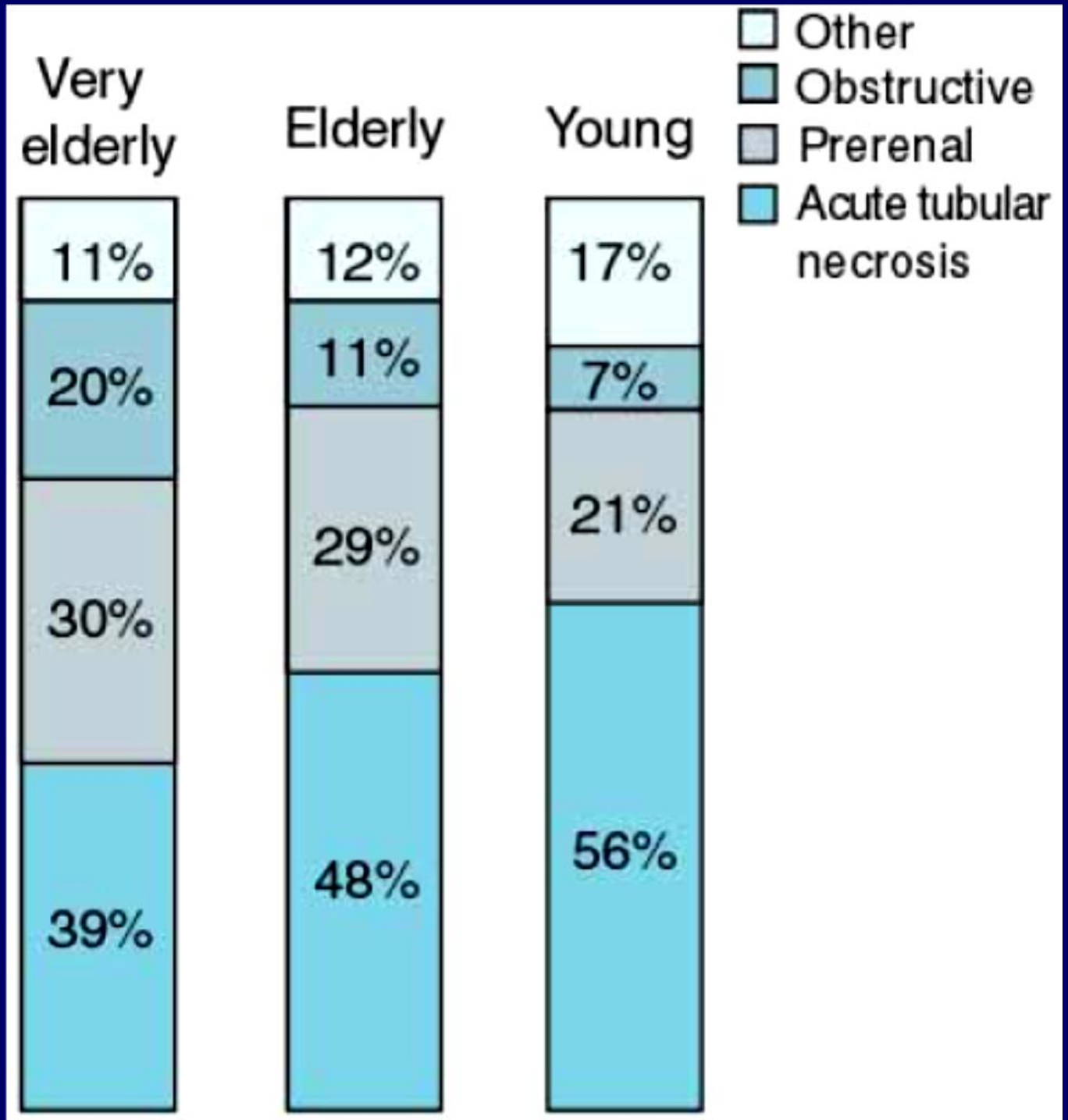
ELSEVIER

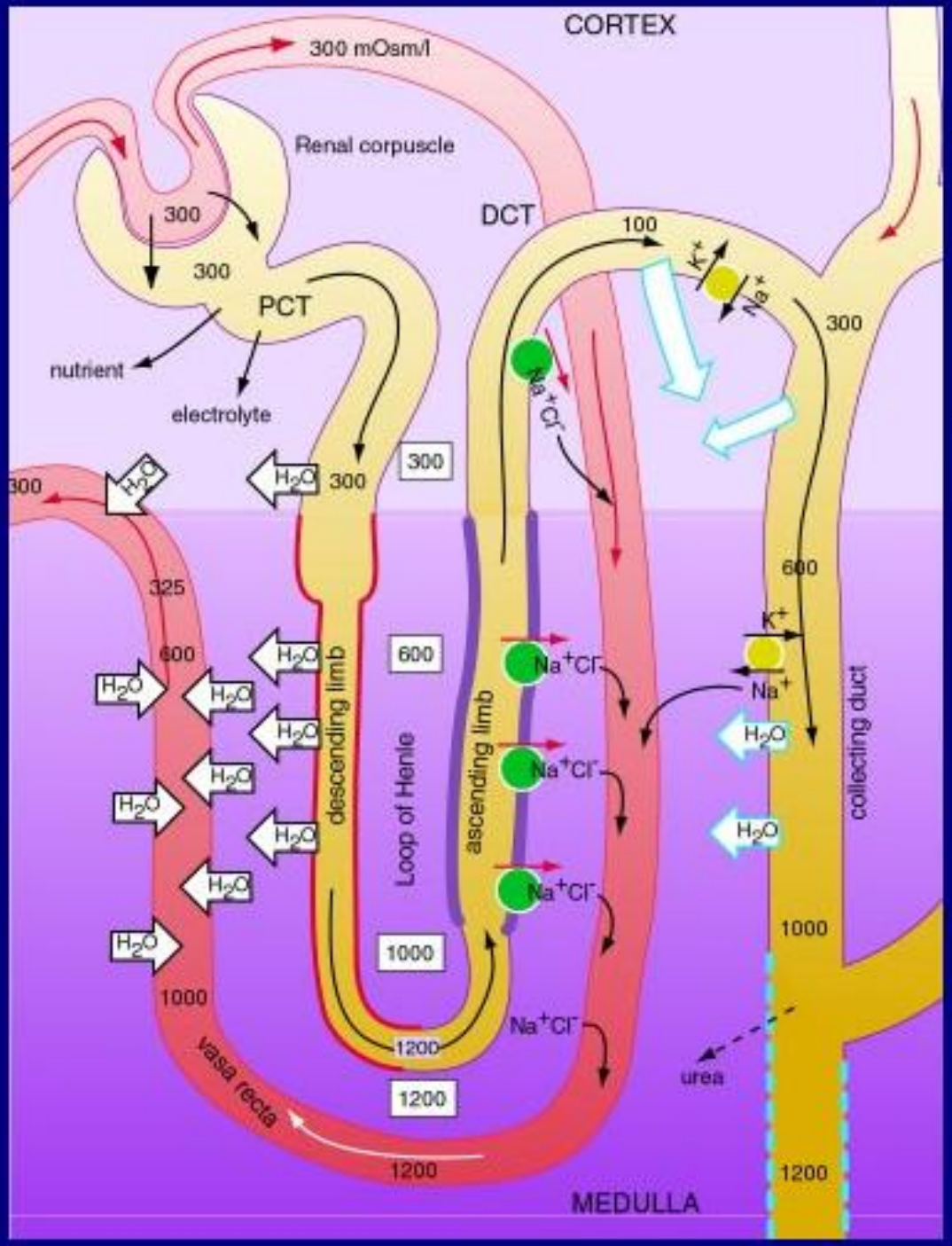
12

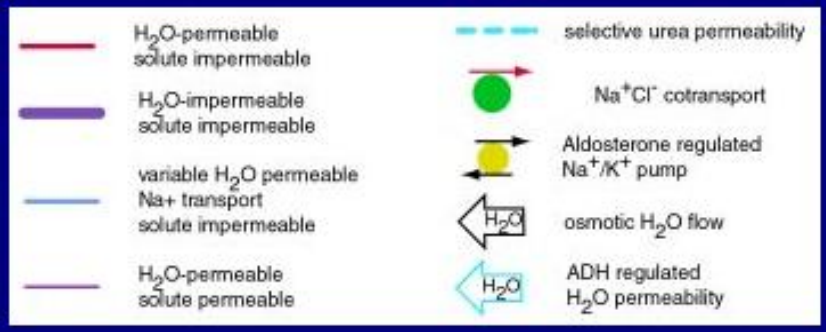
Perioperative renal protection☆

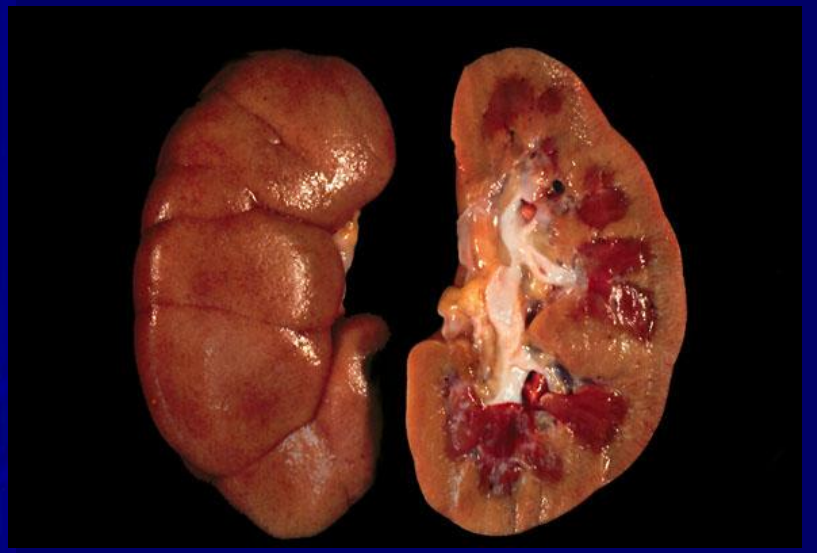
Dean R. Jones M.D., FRCPC
Assistant Professor

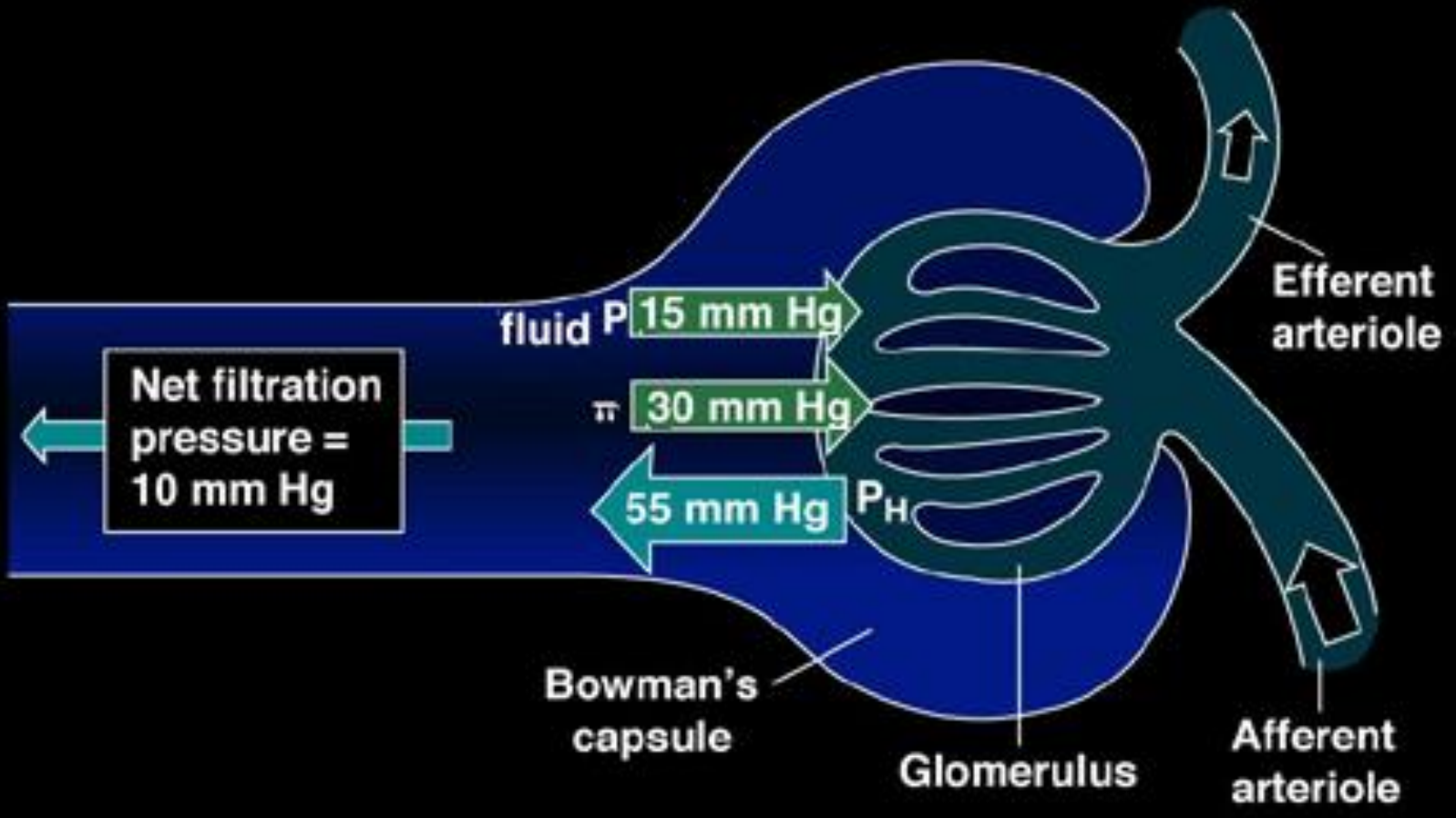
H. Thomas Lee* M.D., Ph.D.
Assistant Professor
Department of Anesthesiology, College of Physicians and Surgeons of Columbia University, New York, NY 10032, USA


Very elderly
Elderly
Young
Other
Obstructive
Prerenal
Acute tubular necrosis
11%
20%
30%
39%
12%
11%
29%
48%
17%
7%
21%
56%


CORTEX
300 mOsm/l
Renal corpuscle
300
300
PCT
nutrient
electrolyte
DCT
100
300
300
300
325
600
600
600
1000
1000
1200
1200
1200
descending limb
Loop of Henle
ascending limb
collecting duct
urea
vasa recta
MEDULLA
H_2O
Na^+Cl^-
K^+
Na^+


H_2O-permeable solute impermeable
H_2O-impermeable solute impermeable
variable H_2O permeable Na+ transport solute impermeable
H_2O-permeable solute permeable
selective urea permeability
Na^+Cl^- cotransport
Aldosterone regulated Na^+/K^+ pump
osmotic H_2O flow
ADH regulated H_2O permeability





net filtration pressure = 55 mm Hg – 30 mm Hg – 15 mm Hg = 10 mm Hg

$$P_H - \pi - P_{fluid}$$

Pathophysiology: pre-renal AKI

- AKI is due to absolute or relative hypoperfusion
- If hypoperfusion is not rapidly corrected ATN occurs

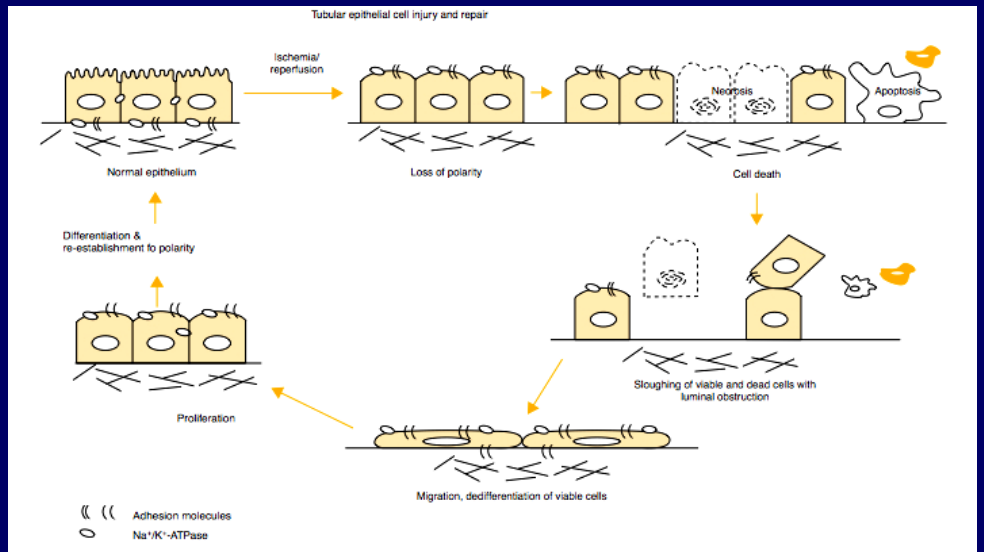
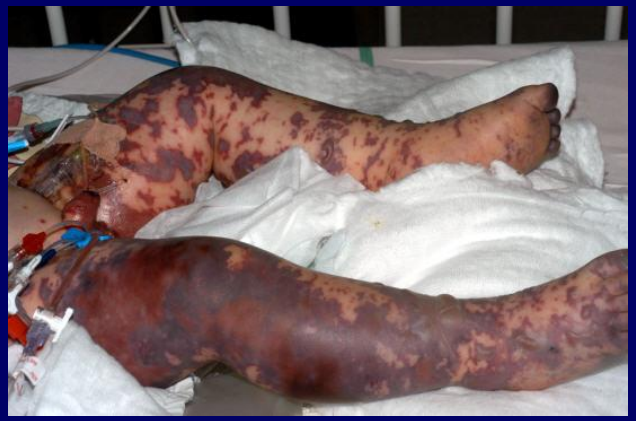


Figure 1. Ischaemia/reperfusion results in reversible and irreversible injury to the proximal tubule epithelial cell. Cells lose their polarity, and viable and non-viable cells are shed into the tubule lumen, contributing to obstruction. The remaining viable cells are de-differentiated and they proliferate, eventually restoring the integrity of the tubule. Reproduced from Sheridan AM and Bonventre JV (2001, *Blood Purification in Intensive Care*, p 11, edited by Ronco C, Bellomo R and La Greca G; Basel: Karger) with permission.

Reduction of circulating volume

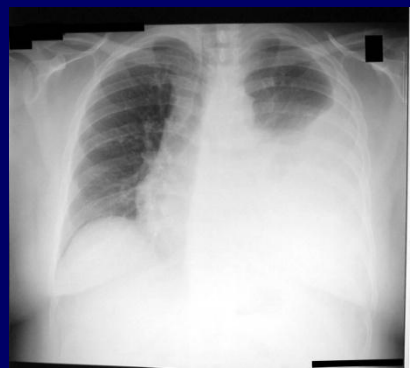
Haemorrhage



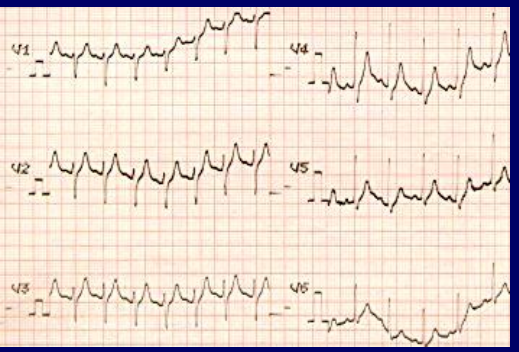
Plasma loss

Dehydration

Third space collection



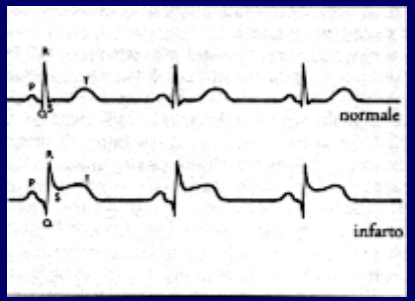
MAP & CO reduction

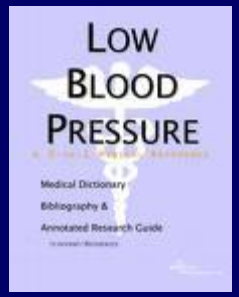


Myocardial ischemia

Arrhythmias

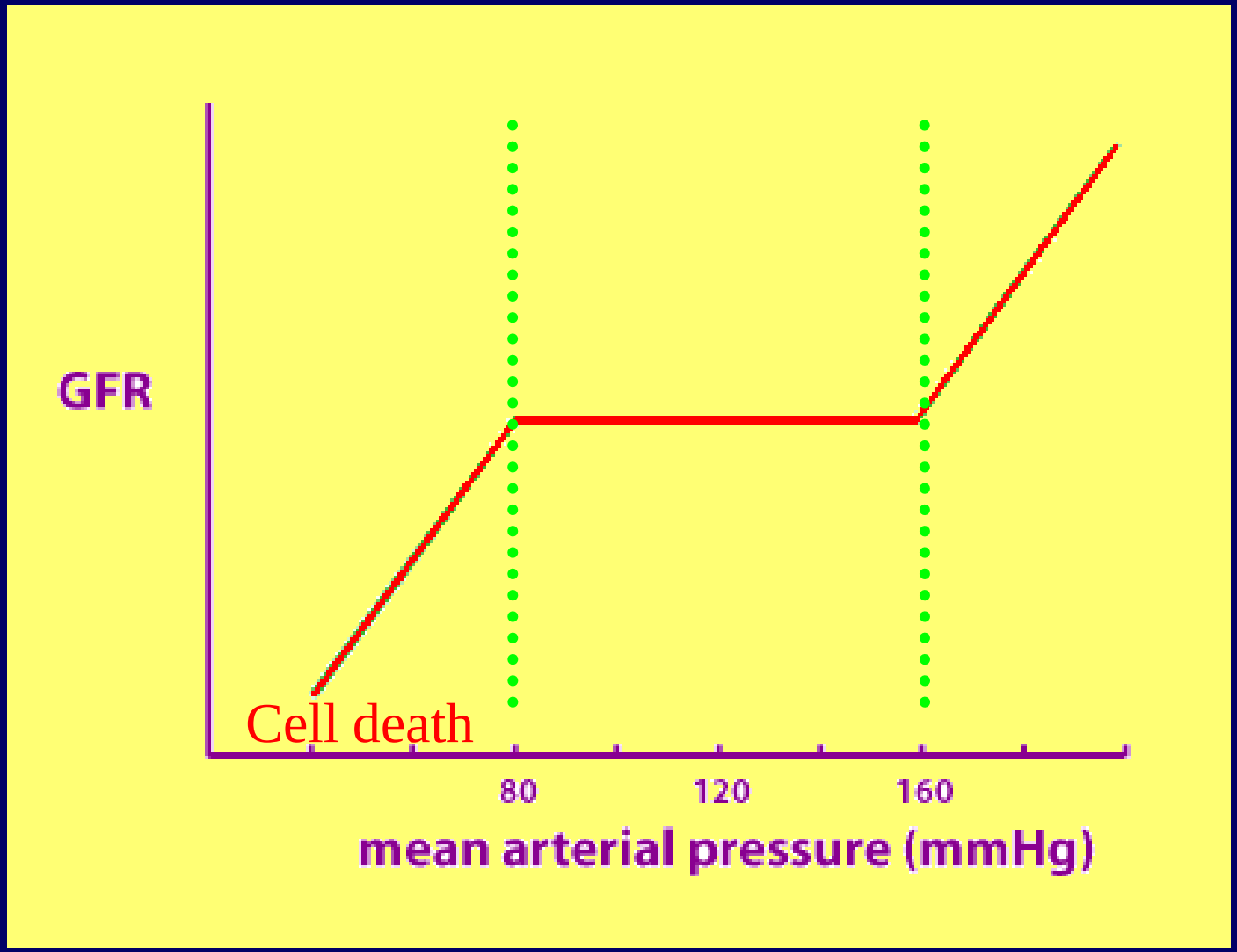
Shock





ECOCARDIOCHIRURGIA.it

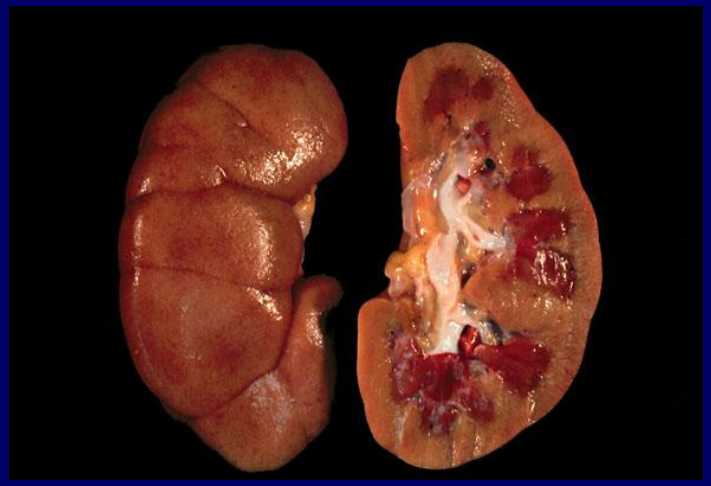
Renal autoregulation



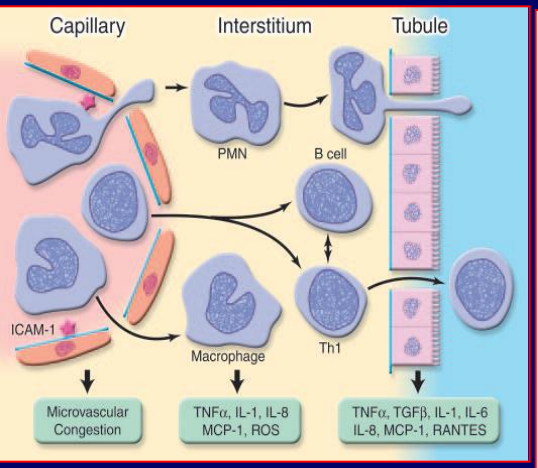
Acute tubular necrosis

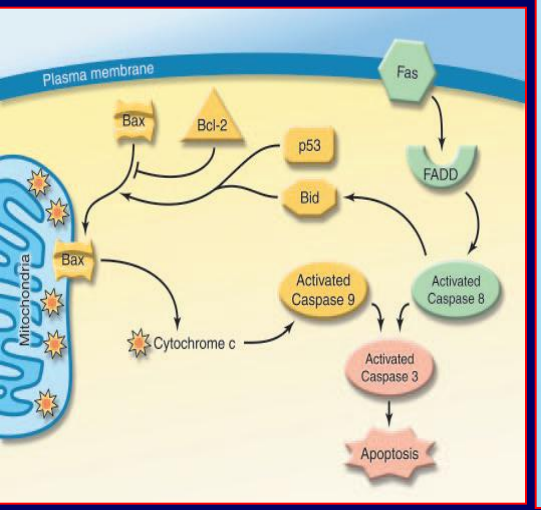
The most frequent AKI (70%)

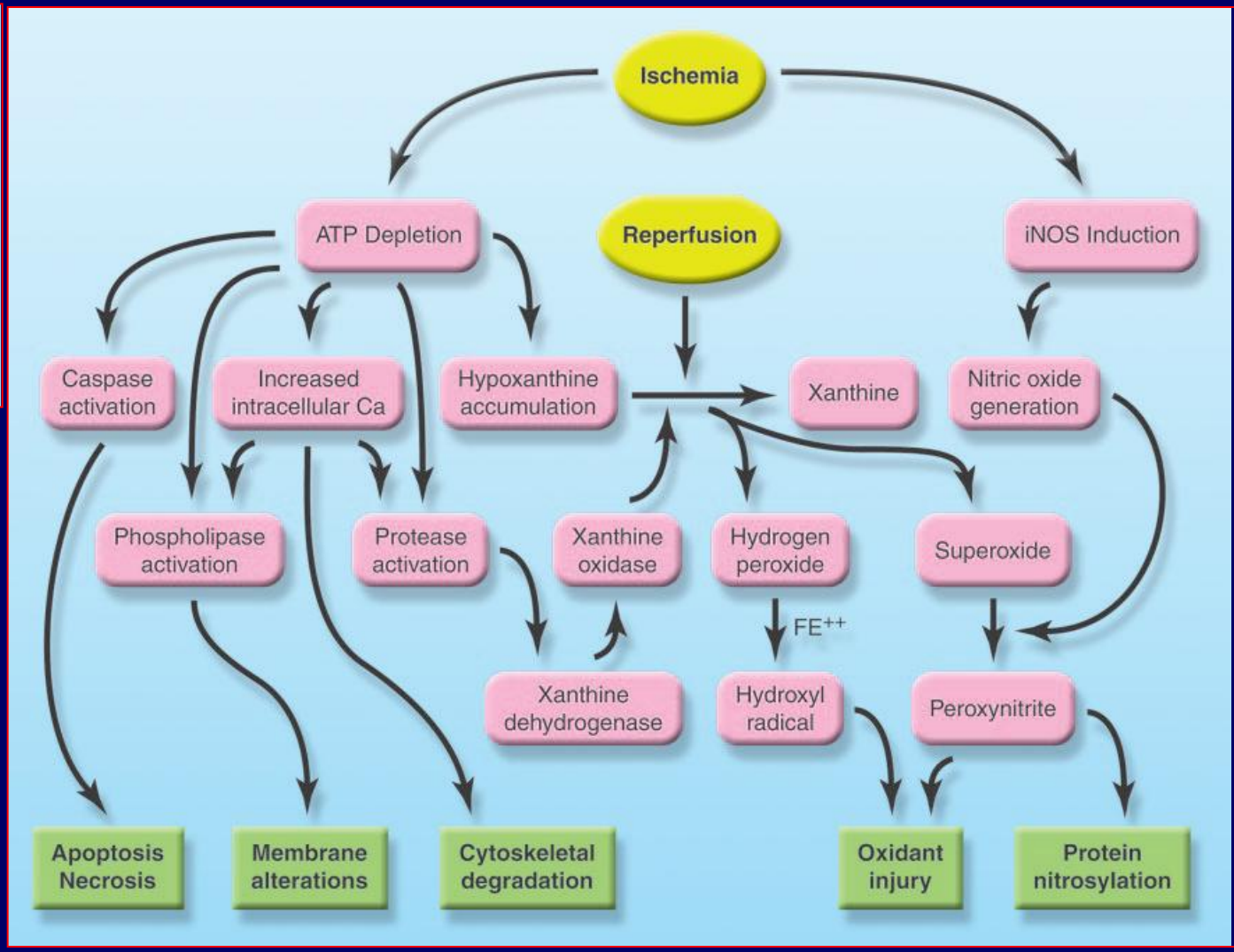
- Ischemic
- Toxic



Ischemic ATN: Pathophysiology

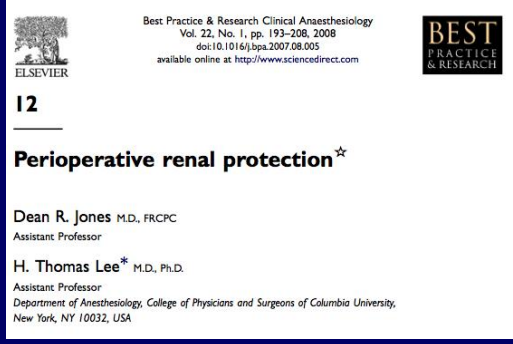






Devarajan P J Am Soc Nephrol 17: 1503–1520

Ischemic ATN: Pathophysiology


Best Practice & Research Clinical Anaesthesiology
Vol. 22, No. 1, pp. 193–208, 2008
doi:10.1016/j.bpa.2007.08.005
available online at http://www.sciencedirect.com

12

Perioperative renal protection☆

Dean R. Jones M.D., FRCPC
Assistant Professor

H. Thomas Lee* M.D., Ph.D.
Assistant Professor
Department of Anesthesiology, College of Physicians and Surgeons of Columbia University, New York, NY 10032, USA

- Ischemia and inflammation lead to both vascular and tubular derangements.
- Increased sensitivity to vasoconstrictors, impaired autoregulation and endothelial injury lead to ⇓ GFR.
- Tubules structural changes: loss of cell polarity, shedding of the brush border into the tubular lumen, tubular obstruction, and cell death

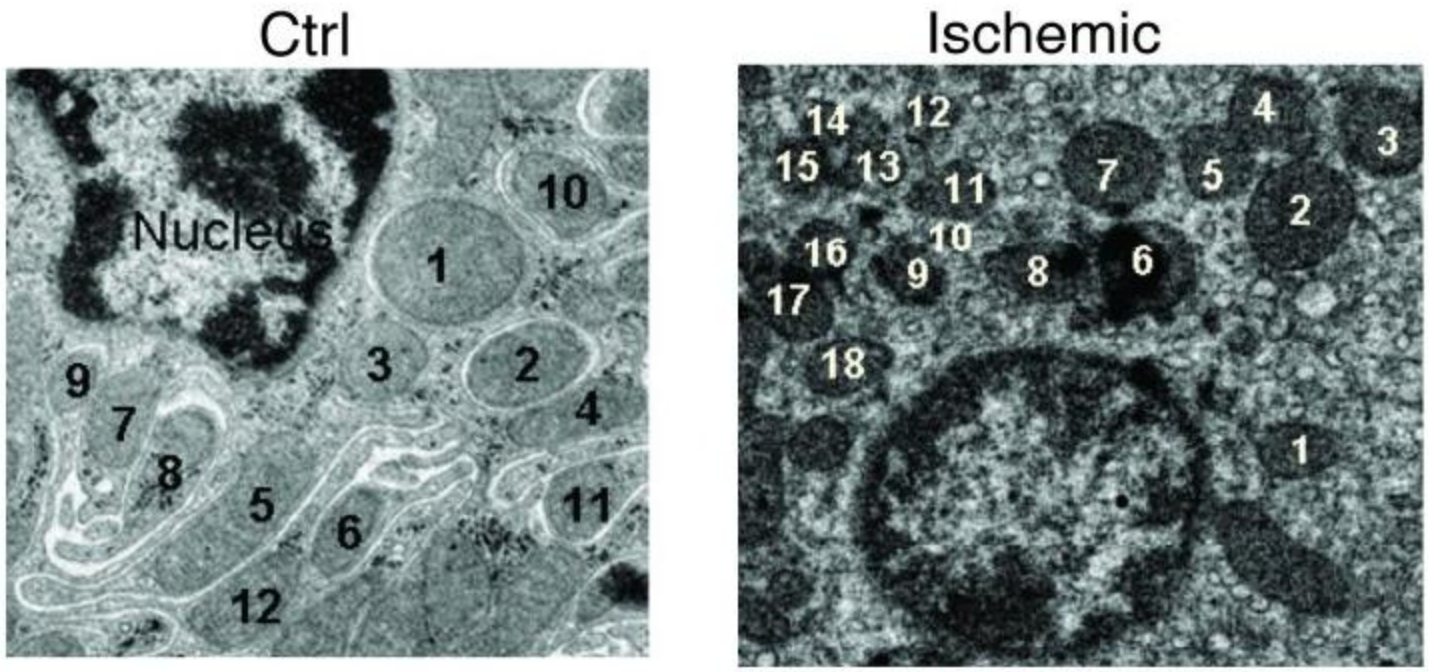
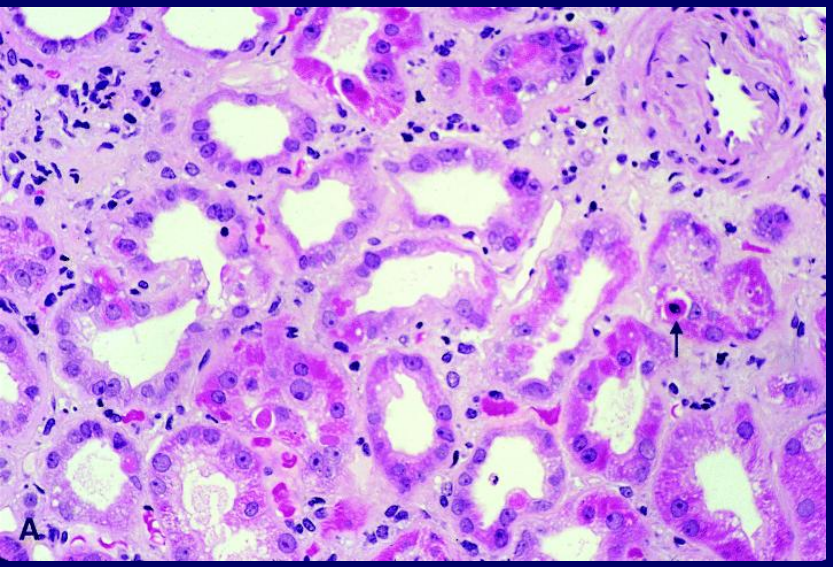


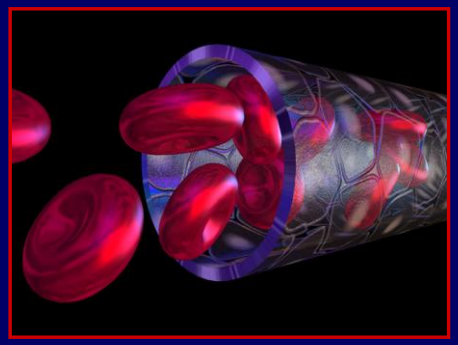
Figure 10
3D image of mitochondria in control and ischemically injured tubular cells.

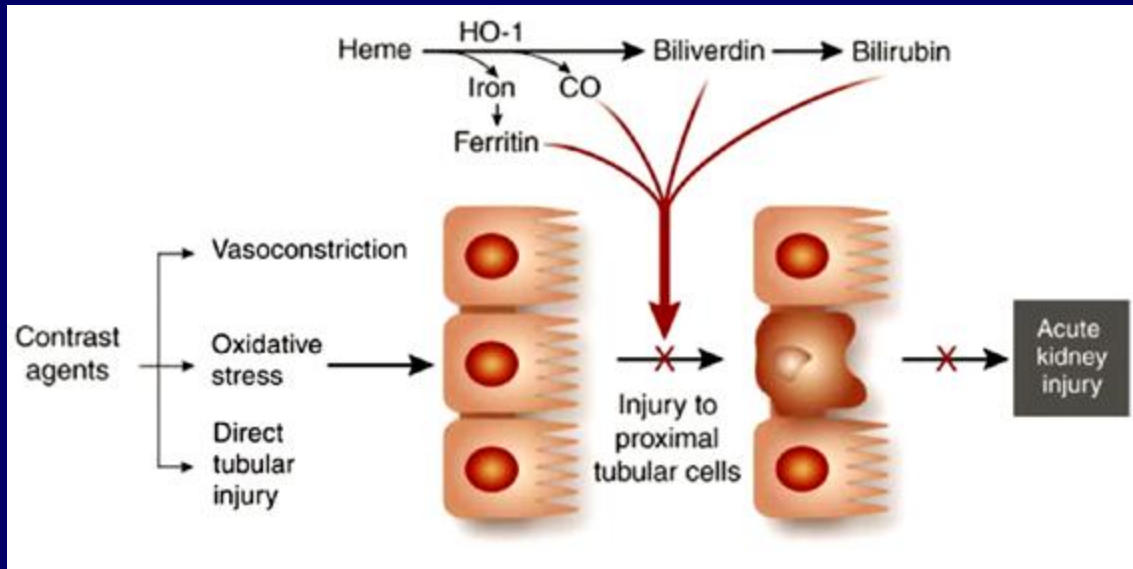
J. Clin. Invest. **119**:1275–1285 (2009).

Toxic acute tubular necrosis



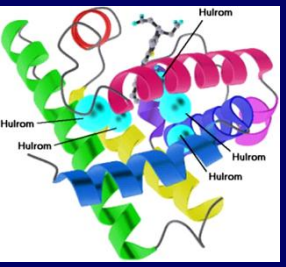
- Exogenous
- Endogenous





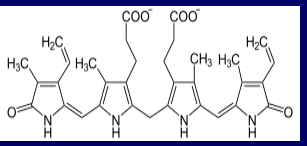
Perioperative toxic ATN: endogenous

Hb → hemolysis



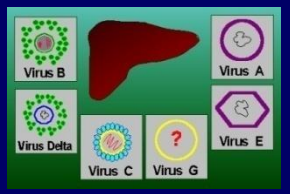
Myoglobin → trauma

tetanus



Bilirubin → Acute hepatitis

Obstructive icterus



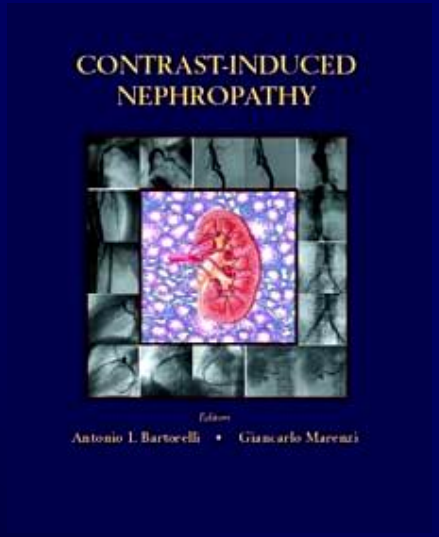
Perioperative toxic ATN: exogenous

- Antibiotics (aminoglycoside, amfotericine)
- Cytostatic (ciclosporine)
- Contrast media

ECOCARDIOCHIRURGIA.it

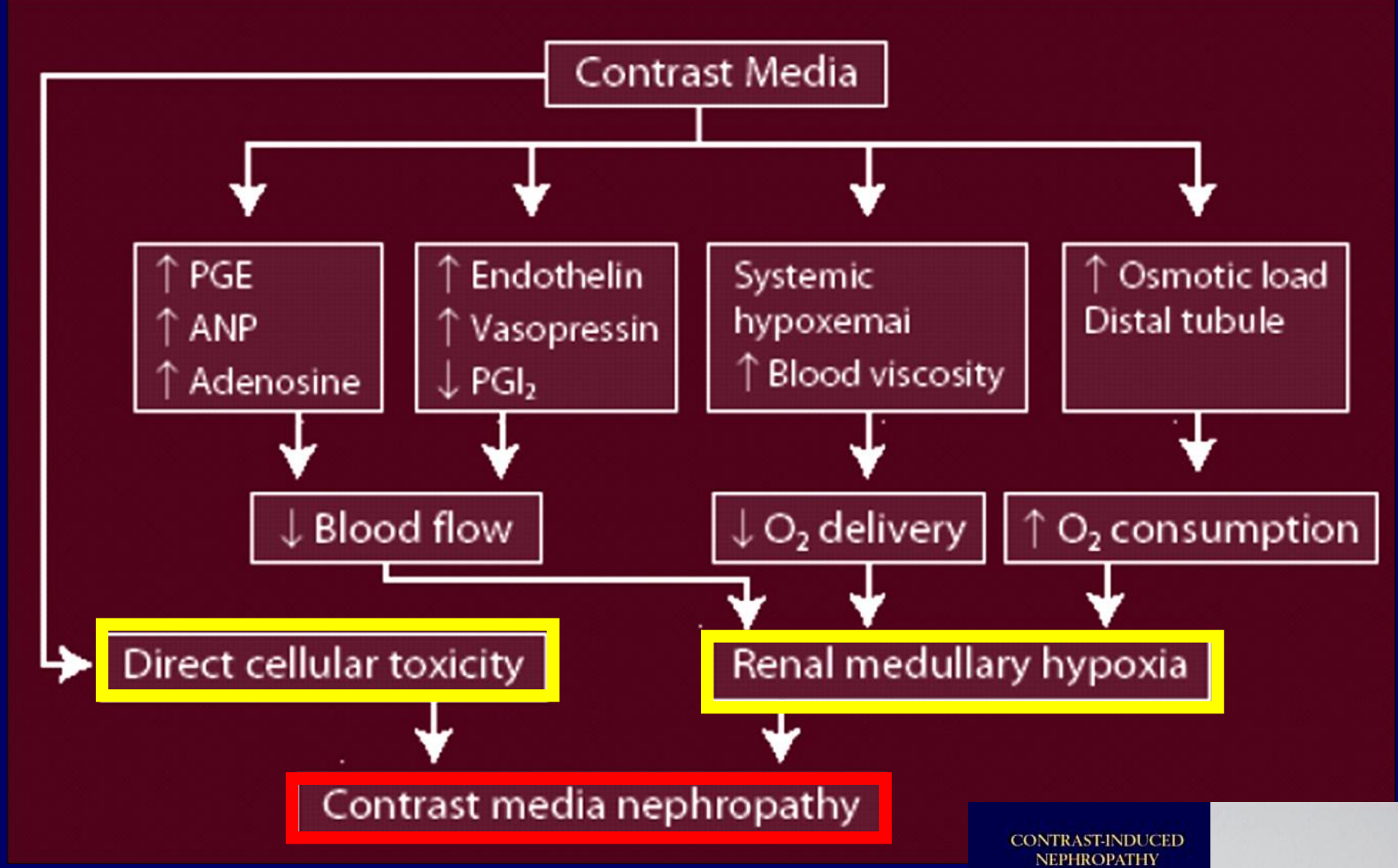
CIN

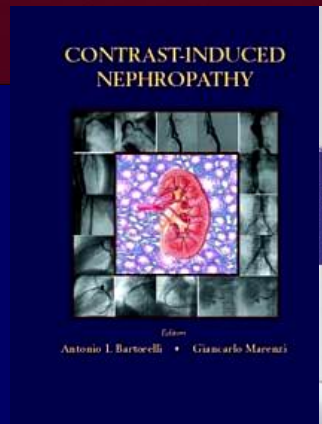
- ARF usually non oliguric



- Variable: from mild creatinine ↑ to need for CRRT

- Serum creatinine behaviour:
  - Increase within 24 h in 60% of cases
  - peak between 3rd and 5th day
  - Recovery in 1 – 2 weeks



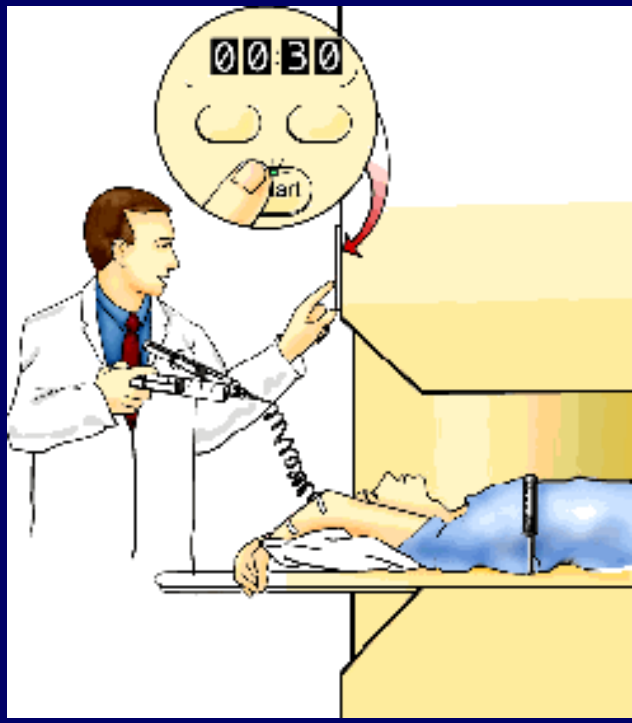


Acute tubular necrosis

Rudnic MR et al, Rev Cardvasc Med 2003

Patient related risk factors

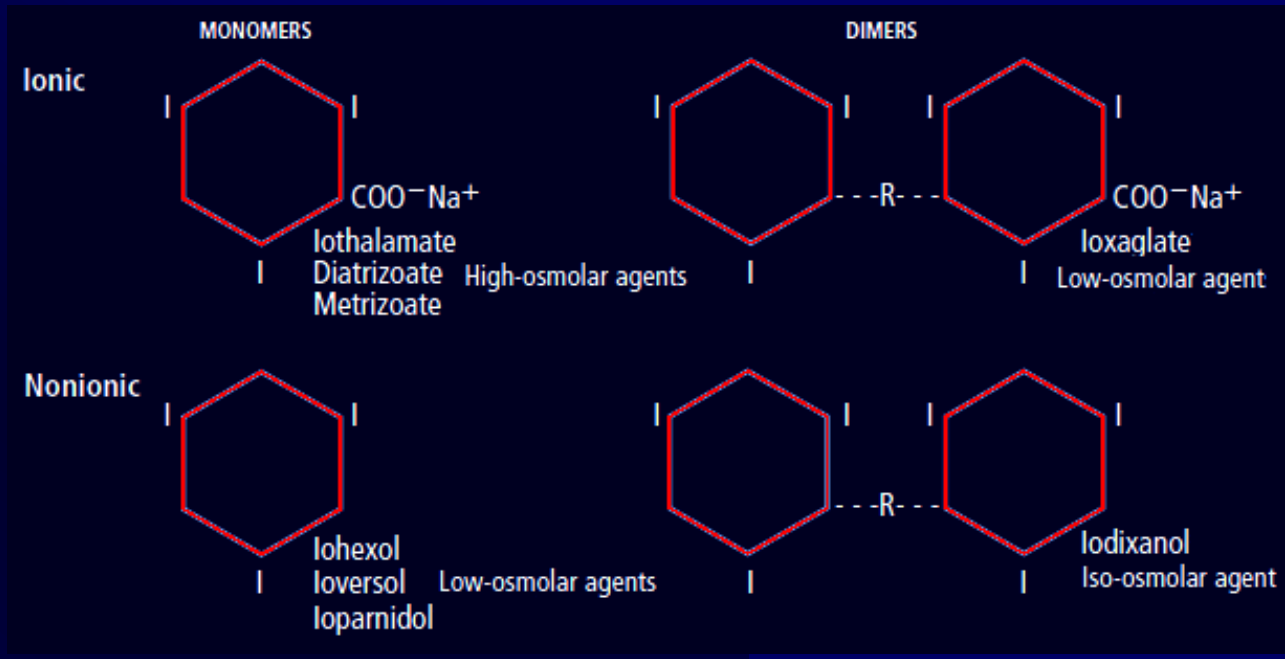
- Age > 70
- CRF 7-27 %
- Dehydratation
- Diabetes & CRF 33-48 %
- Hypovolemia
- CHF
- Nephrotic syndrome
- Nephrotoxic drugs



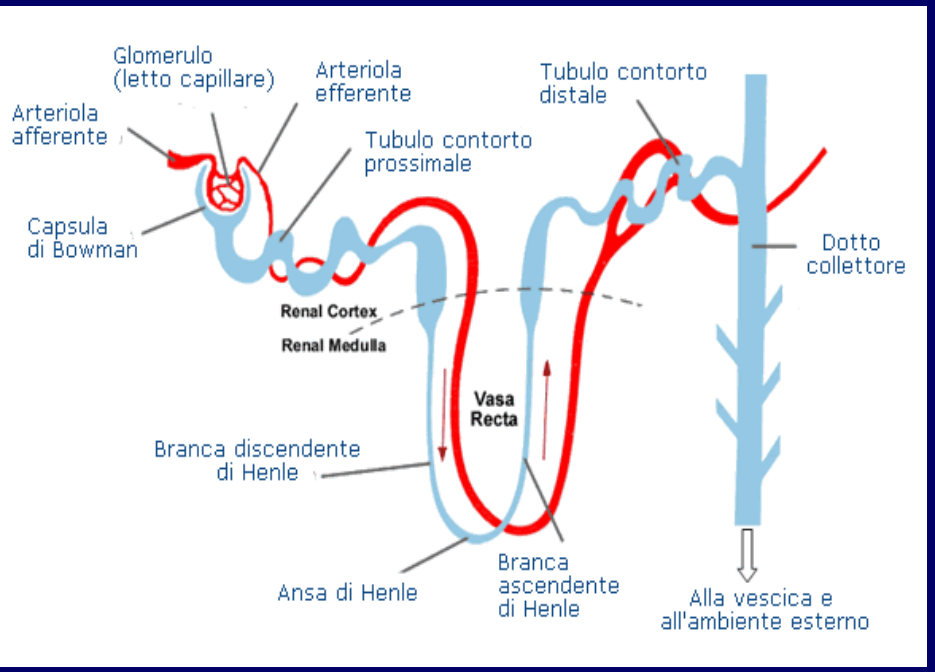
ECOCARDIOCHIRURGIA.it

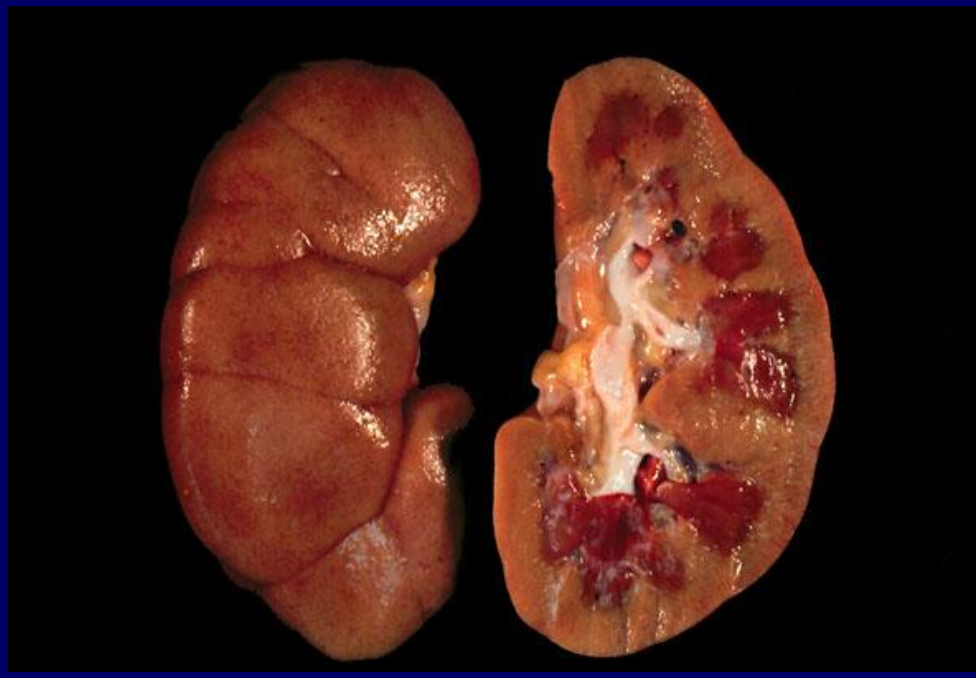
Contrast related factors

- Dose
- Plasma C
- Osmolarity
- Viscosity
- Hydrofilia
- Repeated administration within 72 h



ECOCARDIOCHIRURGIA.it


Glomerulo
(letto capillare)
Arteriola
efferente
Tubulo contorto
distale
Arteriola
afferente
Tubulo contorto
prossimale
Capsula
di Bowman
Dotto
collettore
Renal Cortex
Renal Medulla
Vasa
Recta
Branca discendente
di Henle
Ansa di Henle
Branca
ascendente
di Henle
Alla vescica e
all'ambiente esterno



What to do ?

Treatment of AKI

Hydratation

Loop Diuretics

Dopamine (low doses)

Fenoldopam

N-Acetyl Cystein

Teophylline

Atrial Natriuretic Peptide

Strategies that are likely to be effective
- Isotonic hydration (IV route)
- Once-daily dosing of aminoglycosides
- Use of lipid formulations of amphotericin B
- Use of iso-osmolar nonionic contrast media

Strategies of unknown efficacy
- NAC
- Theophylline
- Low-dose recombinant ANP (in cardiac surgical patients)

Strategies that are not effective
- Loop diuretics
- Dopamine and dopamine receptor agonists
- ANPs
- Prophylactic hemofiltration

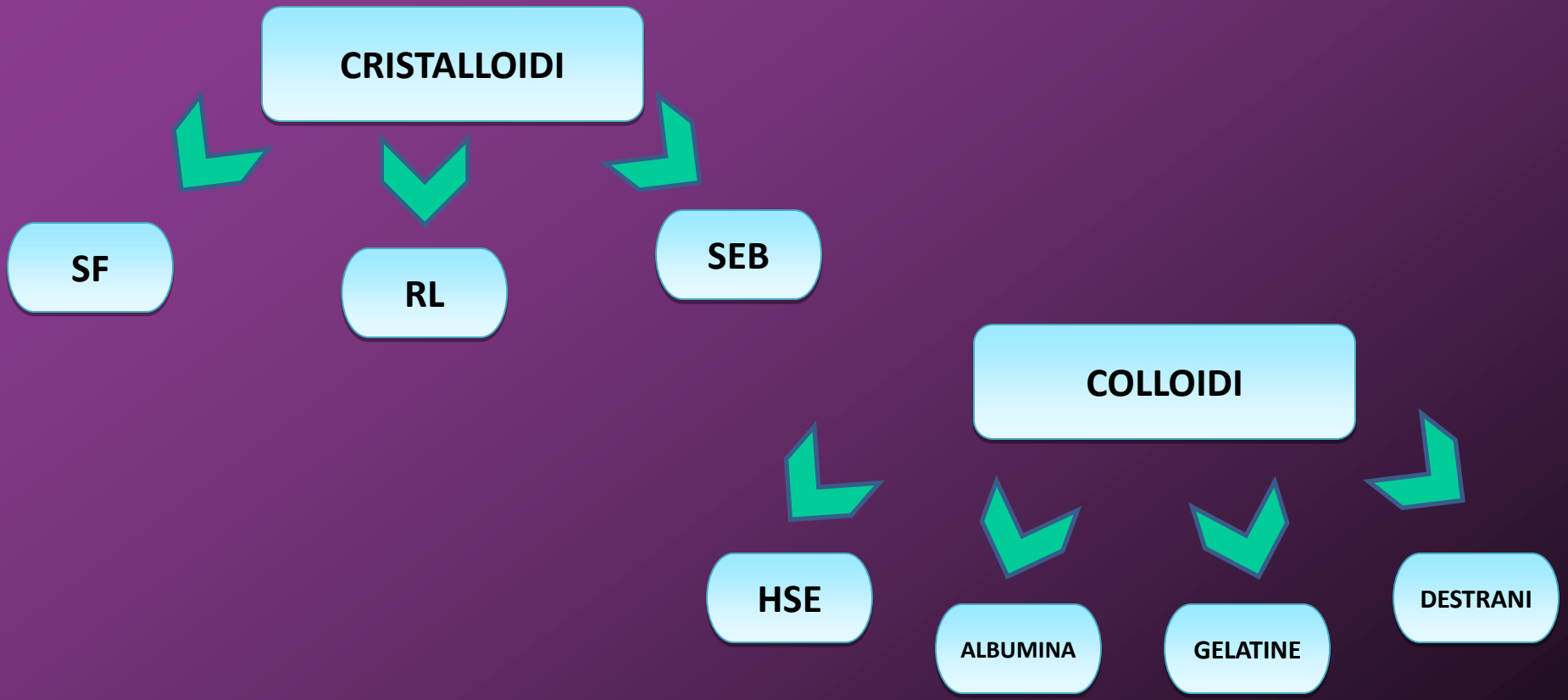
Perioperative renal protection

Best Practice & Research Clinical Anaesthesiology
Vol. 22, No. 1, pp. 193–208, 2008

Prevention of perioperative acute renal failure: what works?

Best Practice & Research Clinical Anaesthesiology
Vol. 18, No. 1, pp. 91–111, 2004

COSA ABBIAMO A DISPOSIZIONE



IL caso J. Boldt 89 lavori «Retracted»

Molte metanalisi contenevano i dati del Prof. Boldt

Un nuovo inizio; una cascata di nuovi studi

COSA USIAMO:

IN EUROPA

NEL MONDO

Intensive Care Med (2004) 30:2222–2229
DOI 10.1007/s00134-004-2415-1

ORIGINAL

Frédérique Schortgen
Nicolas Deye
Laurent Brochard
for the CRYCO Study Group

Preferred plasma volume expanders for critically ill patients: results of an international survey

	Crystalloids		Colloids				
	Isotonic	Hypertonic	Starches	Gelatins	Albumin	Plasma	Dextrans
France (n=162)	72	0	51	40	6	2	0
Germany (n=63)	84	0	81	19	5	6	0
United Kingdom (n=40)	60	0	35	68	5	0	0
The Netherlands (n=35)	91	2	66	46	3	3	0
Italy (n=33)	88	0	54	42	6	18	0
European countries (n=517)	80	2	58	35	5	5	3
Non-European countries (n=60)	82	0	25	35	22	10	5

IN SCANDINAVIA

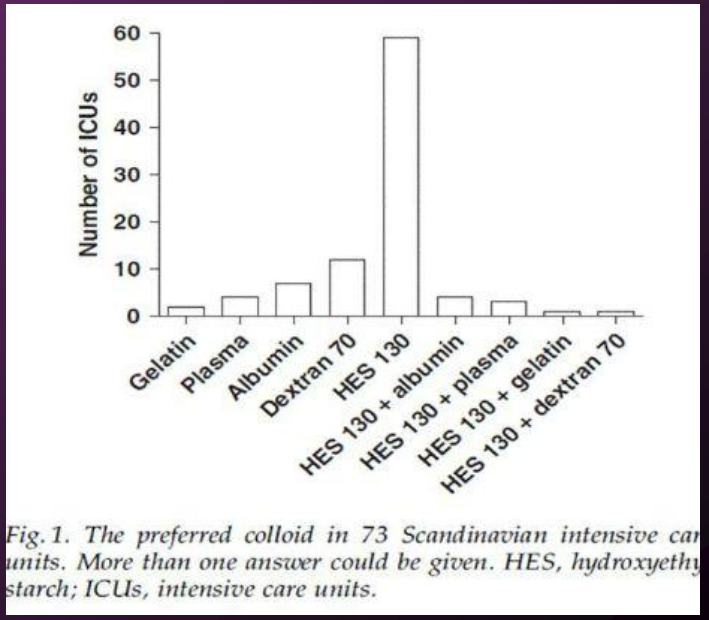


Fig. 1. The preferred colloid in 73 Scandinavian intensive car units. More than one answer could be given. HES, hydroxyethy starch; ICUs, intensive care units.

Alderson P et al, Cochrane 2000

- **18 trial su albumina o plasma o altre frazioni plasmatiche vs/ (641 pz),**
- **7 trials su amido idrossietilico vs/ (197 pz),**
- **4 trial su gelatina modificata vs/ (95 pz),**
- **8 trials su destrano vs/ 668 pz.**

Conclusion

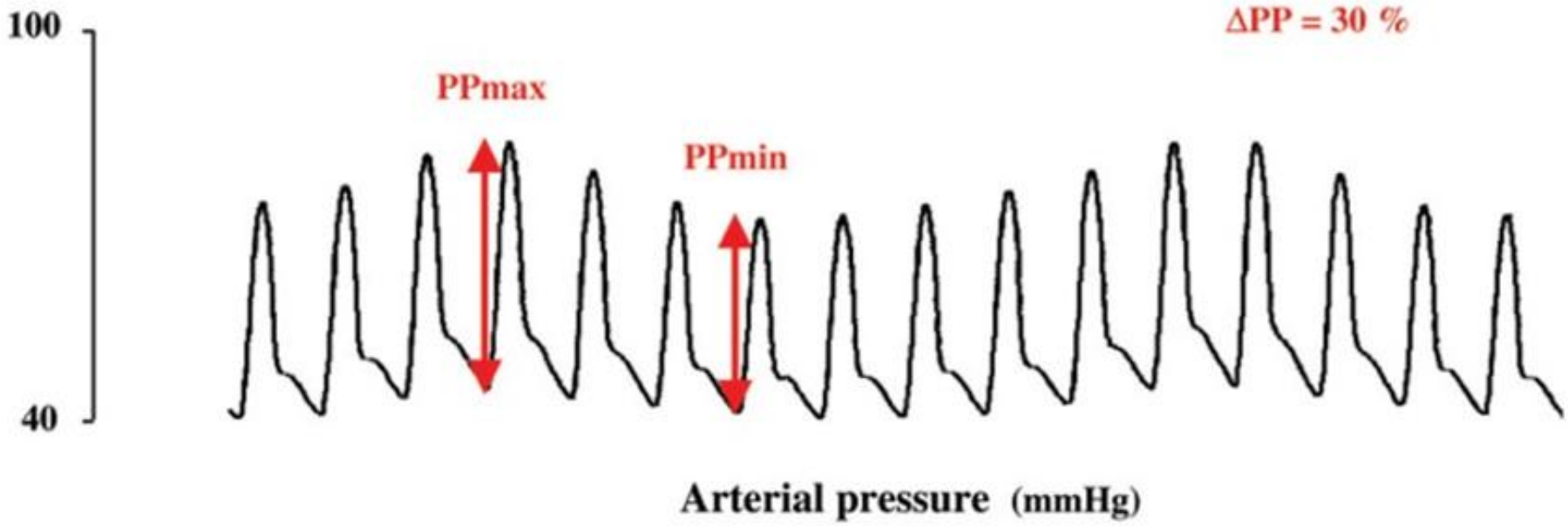
"There is no evidence from randomised controlled trials that resuscitation with colloids reduces the risk of death compared to crystalloids in patients with trauma, burns and following surgery.

As colloids are not associated with an improvement in survival, and as they are more expensive than crystalloids, it is hard to see how their continued use in these patient types can be justified outside the context of randomised controlled

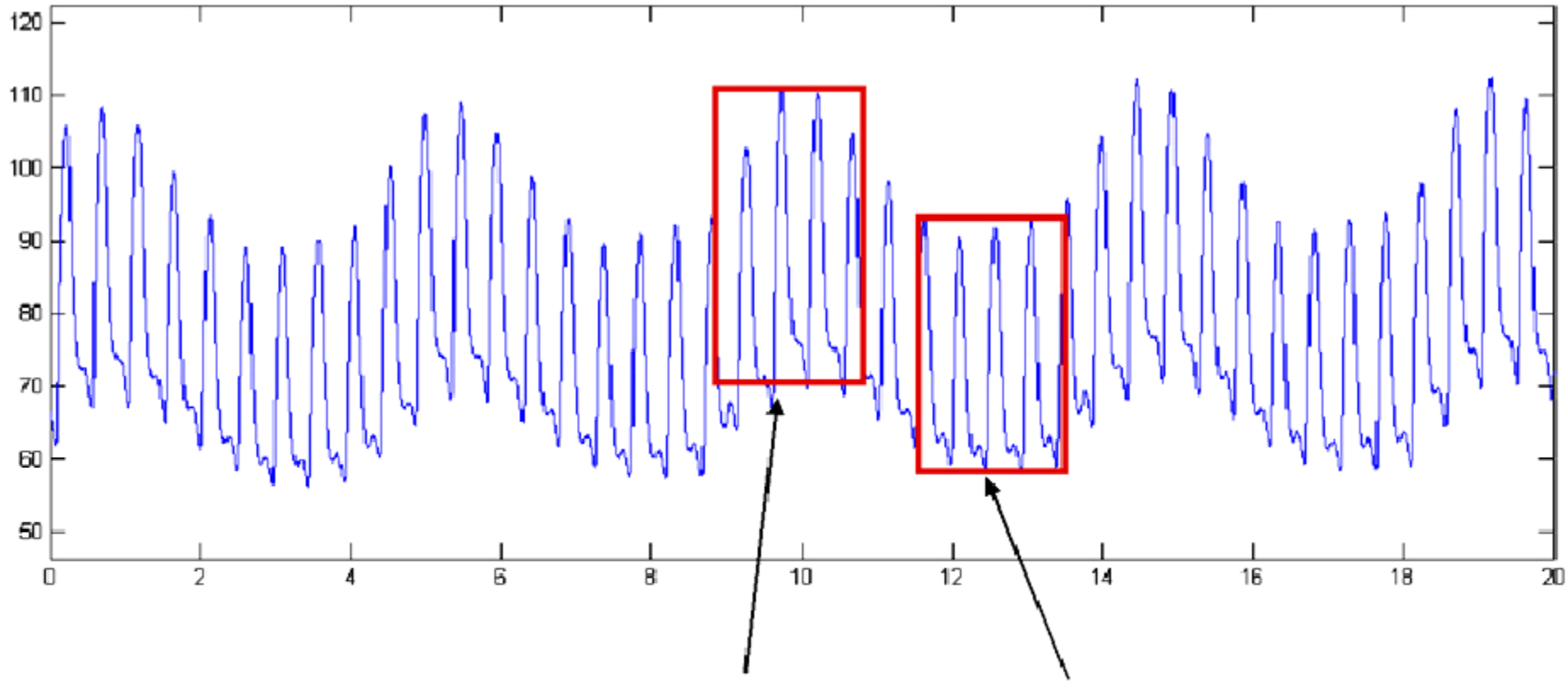
Cosa scegliere

Sicuramente nel paziente critico lungo degente in ICU c'è bisogno di "programmare" un terapia infusionale valutando bene quale sono i rischi e i benefici di ciascun fluido.

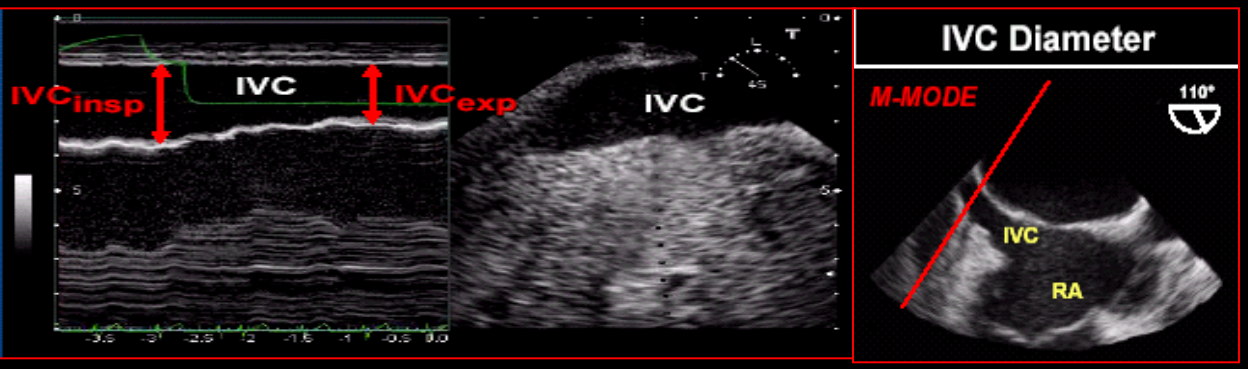
In attesa risultati studio Albios 2008-2012



$$PPV(\%) = \frac{(PPmax - PPmin)}{(PPmax + PPmin)/2} * 100$$



$$SVV = \frac{SV_{max} - SV_{min}}{SV_{mean}}$$



IVC distensibility

$$\Delta IVC = 100 \times \frac{(IVCinsp - IVCexp)}{IVCinsp}$$

Δ IVC > 18%

The Cochrane Library Evidence for healthcare decision-making

Interventions for protecting renal function in the perioperative period

There is no evidence from available RCTs that any of the measures used to protect patients' kidneys during the perioperative period are beneficial

including: dopamine and its analogues, diuretics, Ca^{+} channel blockers, ACE inhibitors or hydration fluids.

There is no difference in morbidity (renal failure) or mortality following the various perioperative interventions.

Therapy: diuretics

- Decreased duration of RRT and increased UO
- no improvement in mortality or independence from RRT in AKI patients.

Crit Care Resusc. 2007 Mar;9(1):60-8.

Loop diuretics in the management of acute renal failure: a systematic review and meta-analysis.

Bagshaw SM, Delaney A, Haase M, Ghali WA, Bellomo R.

Department of Intensive Care, Austin Hospital, Melbourne, VIC, Australia. sean.bagshaw@austin.org.au

Therapy: dopamine

‘Renal dose’ dopamine does not protect patients from AKI and has numerous side effects.

Is There Still a Place for Dopamine in the Modern Intensive Care Unit?

Yves A. Debaveye, MD, and Greet H. Van den Berghe, MD, PhD

Department of Intensive Care Medicine, Catholic University of Leuven, Leuven, Belgium

Therapy: fenoldopam mesylate

A recent meta-analysis of 16 randomized studies found reduced the risk of AKI, RRT, and in-hospital death.

Beneficial Impact of Fenoldopam in Critically Ill Patients With or at Risk for Acute Renal Failure: A Meta-Analysis of Randomized Clinical Trials

JCVA 2010, march

Giovanni Landoni, MD, Giuseppe G.L. Biondi-Zoccai, MD, James A. Tumlin, MD, Tiziana Bove, MD, Monica De Luca, MD, Maria Grazia Calabrò, MD, Marco Ranucci, MD, and Alberto Zangrillo, MD

Perioperative management

- Individualize renal perfusion: a lower MAP >65 mmHg
- Expand intravascular volume

Prevention of perioperative acute renal failure: what works?

Best Practice & Research Clinical Anaesthesiology
Vol. 18, No. 1, pp. 91–111, 2004

Perioperative management

- Avoid hypotensive anesthesia in patients at risk of AKI
- Lower pressures for laparoscopic procedures or gasless laparoscopy should be considered for pts at high risk of AKI
- Antihypertensive medications and NSAID's should be held in patients without adequate intravascular volume
- Adjust perioperative antibiotics based on Cr. clearance

- AKI is associated with increased mortality
- AKI should be looked at as a "preventable" rather than "treatable" clinical entity
- The only management strategy proven to be of value consists in providing adequate volume expansion, adequate renal perfusion, and avoiding nephrotoxins