Cause and Management of Acute Renal Failure in ICU

Natalie Leung

QMH ICU

- Causes & Classification of ARF
- RIFLE Criteria and its implication
- Fluid Therapy in ARF
- Common Renal Problems in ICU
  - Sepsis & ARF
  - Contrast Induced Nephrotoxicity
  - Drug induced Nephrotoxicity
  - Rhabdomyolysis
  - Abdominal Compartment Syndrome
  - Hepatorenal Syndrome

Cause of ARF

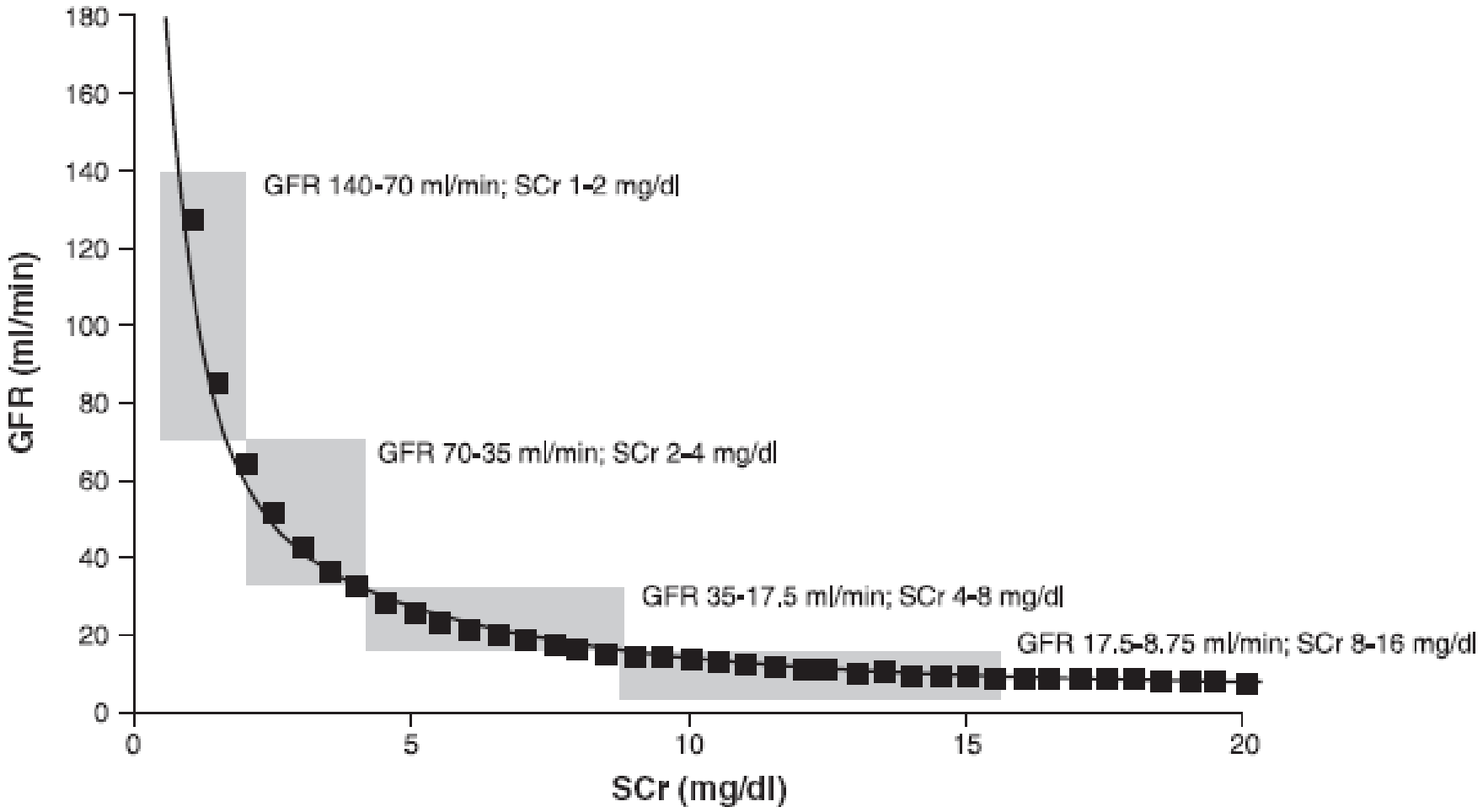
- Traditional classification:
  - pre-renal
  - renal (intrinsic)
  - post-renal (obstructive uropathy)
- prompt identification and treatment of pre-renal and post-renal causes may prevent the development of protracted ARF

Should prerenal ARF be included in the definition of ARF?

- According to **Acute Dialysis Quality Initiative's** (ADQI) recommendation, prerenal ARF is not strictly a failure, but a way the kidney responds under maximum stress, with no function loss.
- severity and prognosis of prerenal azotemia are very different from ATN
- Hence comparison of series that include prerenal ARF may lead to error, resulting from its relative frequency in each series.

Unifying Definition of ARF

- A standardized case definition is necessary for comparisons of outcome across studies, for development of prognostic scoring systems, for interpretation of therapeutic interventions, and for design of multicenter studies.
- Classically, ARF is defined an “abrupt and sustained decrease in renal function”.
- Glomerular filtration, serum creatinine and urine output are used as a measurement of renal function



GFR, glomerular filtration rate; SCr, serum creatinine

Relationship between SCr and GFR

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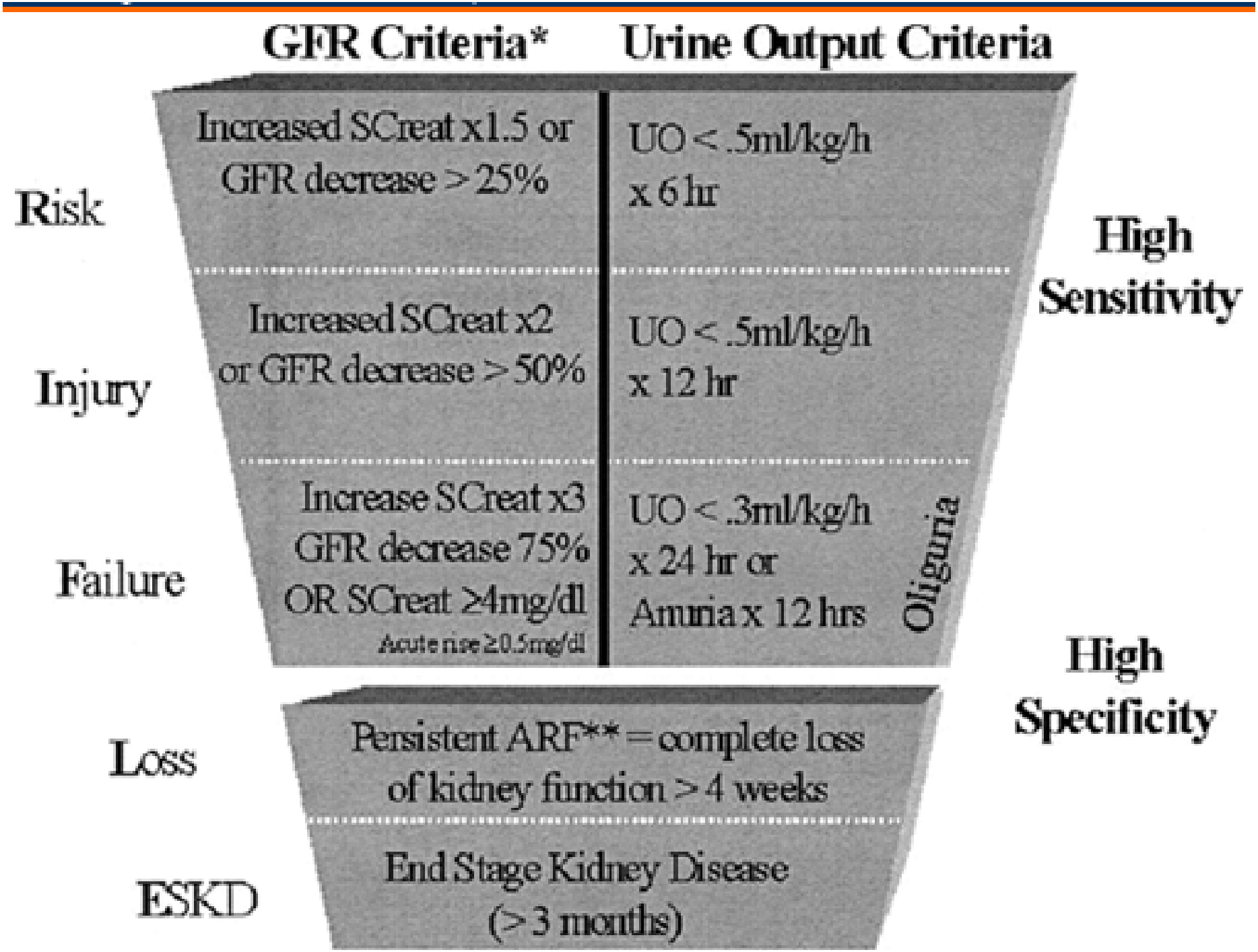
RIFLE Criteria

- The ADQI consensus criteria for ARF
- The classification of ARF is divided into 3 levels, “risk”, “injury” and “failure” based on either GFR, SCr or urine output whichever is more severe.
- a patient with no urine output for 12 hrs has RIFLE-F regardless of the SCr
- a patient with a baseline SCr of 44 mcmol/L that increases to 133 mcmol/L has RIFLE-F even if UO is > 0.5ml/kg/h.
- For patients with oliguric or non-oliguric failure, both can be simply designated as RIFLE-F


GFR Criteria*
Urine Output Criteria
Risk
Increased SCreat x1.5 or
GFR decrease > 25%
UO < .5ml/kg/h
x 6 hr
Injury
Increased SCreat x2
or GFR decrease > 50%
UO < .5ml/kg/h
x 12 hr
Failure
Increase SCreat x3
GFR decrease 75%
OR SCreat ≥4mg/dl
Acute rise ≥0.5mg/dl
UO < .3ml/kg/h
x 24 hr or
Anuria x 12 hrs
Oliguria
Loss
Persistent ARF** = complete loss
of kidney function > 4 weeks
ESKD
End Stage Kidney Disease
(> 3 months)
High
Sensitivity
High
Specificity

- For “acute-on chronic” renal failure any acute (1-7 days) increase in SCr by at least 44 mcmol/L such that the new SCr is 350 mcmol/L is considered to be RIFLE-F and designated as RIFLE-FC
- There is no need to designate acute-on-chronic disease for RIFLE-R or I since these conditions can only occur in the setting of normal baseline function
- The RIFLE criteria also include two clinical outcomes “loss” and “end-stage renal disease” (ESRD).

ADQI Review-Risk Definition

- Dr Lombardi raised the issue regarding the use of the term *Risk* to define the first level.
- Traditionally risk refers to the odds for an event to occur. Hence patients with risk of ARF identify a situation in which there is a chance to prevent renal damage and improve prognosis.
- Risk (RIFLE criteria) is defined by a >25% reduction of GFR, which indicates there is already renal injury.
- The difference between level 1 (risk) and level 2 (injury) is quantitative and not conceptual.

Risk Definition

- Risk may be better defined by the description of potentially harmful situations (low blood pressure, low cardiac output, hypovolemia, use of potentially nephrotoxic agents, pre-existing renal failure, sepsis, diabetes etc).
- crucial to identify reversible causes early - associated with high morbidity and mortality, and the therapeutic window is narrow

ARF after Cardiac Surgery
in an university hospital in Finland

RIFLE criteria	Percentage of patients	Mortality compared to patients with no AKI
Risk	10.9%	8%
Injury	3.5%	21.4%
Failure	5%	32.5%

Multivariate logistic regression analysis identified the RIFLE classification as an independent risk factor for 90 day mortality. (*Ann Thorac Surg 2006:81:542-546*)

RIFLE criteria for AKI are associated with hospital mortality in critically ill patients: a cohort analysis. Crit Care 2006;10:R73-83

- 14% of patients reaching RIFLE “F” received renal replacement therapy, yet these patients experienced a hospital mortality more that 5 times that of the same ICU population without AKI
- Is renal support underutilized or delayed?

Implications

- Levy examined outcomes of>1000 patients enrolled in the control arms of 2 large sepsis trials. (Crit Care Med 2005;33:2194-2201)
- Early improvement in CVS, renal or respiratory function was significantly related to survival
- Outcomes for patients with severe sepsis are closely related to early resolution of AKI
- Rapid resolution of AKI not only represent a marker of good prognosis, but also indicate a window of therapeutic opportunity to improve outcome

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Fluid Therapy in ARF

- The aim of fluid therapy is to assure adequate tissue perfusion, fluid resuscitation should be targeted to a specific preload, stroke volume and/or cardiac output rather than to a specific mean arterial pressure (MAP).
- The ultimate goal of fluid therapy is to maintain or to restore tissue perfusion and organ function

Techniques For Assessing And Achieving Fluid Balance In ARF

- Contemporary management of critically ill patients increasingly recognizes the importance of accurate assessment of volume status and use of fluid therapy to optimize patient outcomes.
- Studies suggest that excess fluid is related to adverse outcomes in critically ill patients.
- However standard volume assessment is not always applicable for patients with acute renal dysfunction

Which monitoring tool should be used to detect volume deficit or excess?

1. Clinical signs

- Hypotension, tachycardia, oliguria, poor capillary refill, core peripheral temperature gradient, altered mental state are poor and late indicators that only detect overt hypovolemia
- Even lesser degrees of hypovolemia compromise tissue perfusion and may result in organ dysfunction.

2. Filling Pressure

- Central venous pressure (CVP) and pulmonary capillary wedge pressure (PCWP) obtained from pulmonary artery catheter are the most popular surrogate markers of preload
- Low filling pressures are sensitive indicators of hypovolemia, but high values do not necessarily mean that the patient is well filled
- The relation between filling pressures and ventricular end-diastolic volume (EDV) is often obscured by changes in ventricular compliance or changes in the pericardium or the thorax

3. Volume-related Preload Indices

- show a better correlation with stroke volume
- Ventricular EDV can be measured with transesophageal echocardiography
- Right ventricular EDV can be measured with a pulmonary artery catheter equipped with a fast-response thermistor
- Intrathoracic blood volume measured with the COLD or PiCCO system (transpulmonary thermo-dye dilution or transpulmonary thermodilution) has also been shown to be a good preload indicator. They also allow determination of extravascular lung water (EVLW)

4. Dynamic Tests

- A positive response to fluid administration or preload responsiveness can be predicted by the presence of (mechanical ventilation-induced) respiratory variations of systolic pressure, pulse pressure, stroke volume, or aortic flow velocity, that are currently considered the most reliable parameters to diagnose volume deficit
- Fluid challenges or straight leg raising with observation of trends in filling pressure and stroke volume responses give much more information

5. Markers of Tissue Perfusion

- Parameters of global tissue perfusion include lactate, pH, BE or SvO2.
- They are non-specific markers of volume status since organ dysfunction and derangement in cellular metabolism may occur in the absence of tissue flow abnormalities
- Parameters of regional perfusion and/or organ function are gastric tonometry, sublingual tonometry and hepatic vein O2 saturation
- The gut mucosa is one of the earliest tissues to be compromised and is especially vulnerable to hypoperfusion. Gastric tonometry has been shown to be more sensitive than global parameters in detecting occult hypovolemia

Excess Fluid

- Fluid management during critical illness must be aimed at improving perfusion, but may have the disadvantage that, in severe inflammation, major fluid shifts occur in the extravascular space resulting in tissue edema despite ongoing intravascular volume depletion.
- There are currently no methods that allow determining the presence of capillary leak, apart from the absence of an effect of fluid administration on intravascular volume.
- In patients with pulmonary edema monitoring of pulmonary capillary pressure can be helpful. During acute lung injury, PAOP is a poor estimate of pulmonary capillary pressure and monitoring of ESVL can be used instead.

What should be the end-point of fluid resuscitation?

- Fluid resuscitation should be targeted to a specific preload, stroke volume and/or cardiac output rather than to a specific MAP until the optimal dose of fluid is achieved.
- This is particularly important in patients with ARF because of the limited capacity to eliminate fluid excess.

Choice of Fluid for patients with or at risk of ARF

- Little evidence to suggest that the choice of fluids should be any different from other critically ill patients.
- However using larger volume of crystalloids may represent a problem in patients with limited capacity to eliminate fluid excess. Large amounts of saline may induce metabolic acidosis
- Colloids result in a more rapid restoration of circulating volume
- Isotonic saline has been shown to be superior to half-isotonic saline in prevention of radiocontrast nephropathy
- In patients with liver cirrhosis, albumin has only been proven to be successful in the prevention of deteriorating renal function after large volume paracentesis, in SBP and in hepatorenal syndrome

What are the consequences of volume deficit and excess and what is the relationship to renal impairment?

- Volume depletion is associated with decreased cardiovascular performance, impaired organ perfusion and renal impairment.
- Non-oliguric ARF can contribute to volume depletion particularly in the recovery phase if volume replacement does not keep pace with urine output.
- Excess IV volume can contribute to pulmonary edema, cardiac failure and tissue edema, however the effects of increase in total body water on organ function are not well defined.

What are the consequences of volume deficit and excess and what is the relationship to renal impairment? (2)

- Studies have demonstrated the influence of increased extravascular lung water (EVLW) on increased mortality in patients with pulmonary edema and ARDS
- Studies have demonstrated a 3-8 fold increased risk of mortality in patients with ARF in the ICU due to an increased incidence of infection, respiratory failure and bleeding

Is the effect of volume deficit or excess time dependent?

- the development of ARF is affected by the duration of deficit.
- Two epidemiologic studies of ARF have demonstrated that the time of development of ARF influences outcomes from ARF
- Mortality increased with increasing duration of ARF and delayed patients had a larger amount of fluid accumulation.
- There is a time dependent effect of ARF on outcome with volume a possible factor.

What is the Role of Diuretics in patients with ARF?

- Diuretics are used to enhance urine output, convert oliguric to non-oliguric ARF or to maintain urine volume
- Despite the frequent use of diuretics, there is no evidence that this intervention shortens the duration of ARF, reduces the subsequent need for dialysis or improves outcomes in patients with ARF
- Loop diuretics might even be deleterious for the kidney because they disturb the protective corticomedullary redistribution of blood flow
- The choice of diuretic, frequency and route of administration and timing of intervention are subject to wide variation.

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Sepsis and ARF

Condition	Moderate Sepsis (N=649)	Severe Sepsis (N=467)	Septic Shock (N=110)
		percent	
Acute renal failure			
Positive culture	19	23	51
Negative culture	5	16	38
Acute respiratory distress syndrome			
Positive culture	6	8	18
Negative culture	3	4	18

- ARF occurs in 19% of patients with moderate sepsis, 23% with severe sepsis, and 51% with septic shock when blood cultures are positive
- With moderate & severe sepsis and septic shock, there is increase in rate of ARDS
- The combination of ARF and sepsis is associated with a 70% mortality, as compared with a 45% mortality among patients with ARF alone

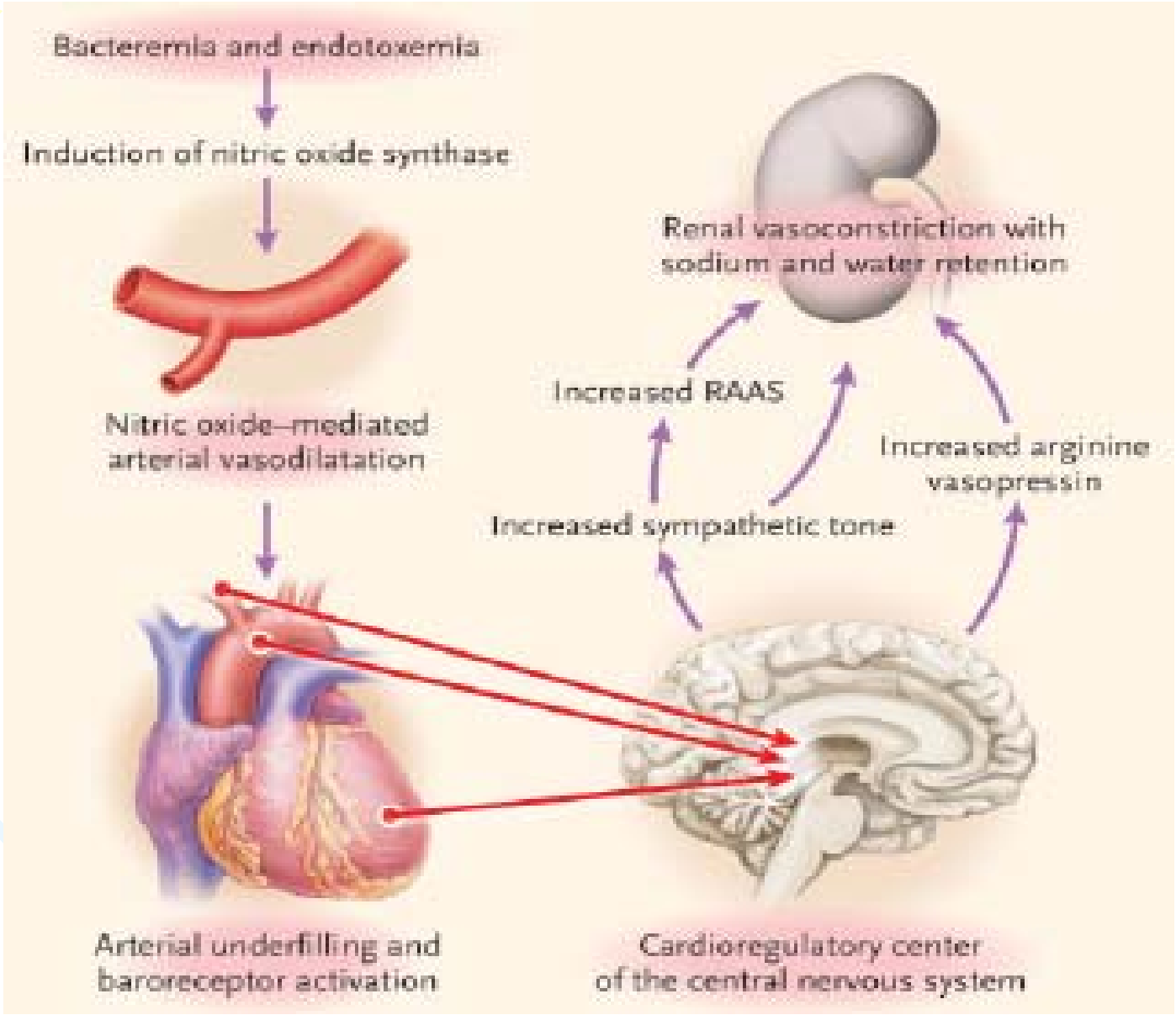
Pathogenesis of ARF in Patients with Septic Shock

- Multifactorial
- Vascular effects
- Hemodynamic effects
- Neuroendocrine effects
- Direct endotoxin effects

Arterial Vasodilatation & Renal Vasoconstriction in Septic Patients

- Endotoxemia stimulates the induction of nitric oxide synthase, which leads to NO–mediated arterial vasodilatation and hypotension.
- Glomerular filtration is determined by the net difference in arterial pressure between the afferent and efferent arterioles across the glomerular capillary bed. Hence hypotension leads to decrease glomerular filtration and ARF.
- Vascular resistance to the pressor response to norepinephrine and angiotensin II occurs during sepsis and is attributable in part to the potent vasodilatory effect of nitric oxide.

- Generalized vasodilatation results in arterial underfilling, which is sensed by the baroreceptors
- results in an increase in sympathetic outflow and the release of vasopressin from the CNS, leading to activation of the renin–angiotensin–aldosterone system (RAAS) and renal vasoconstriction
- increases in renal Na and water retention and a predisposition to ARF

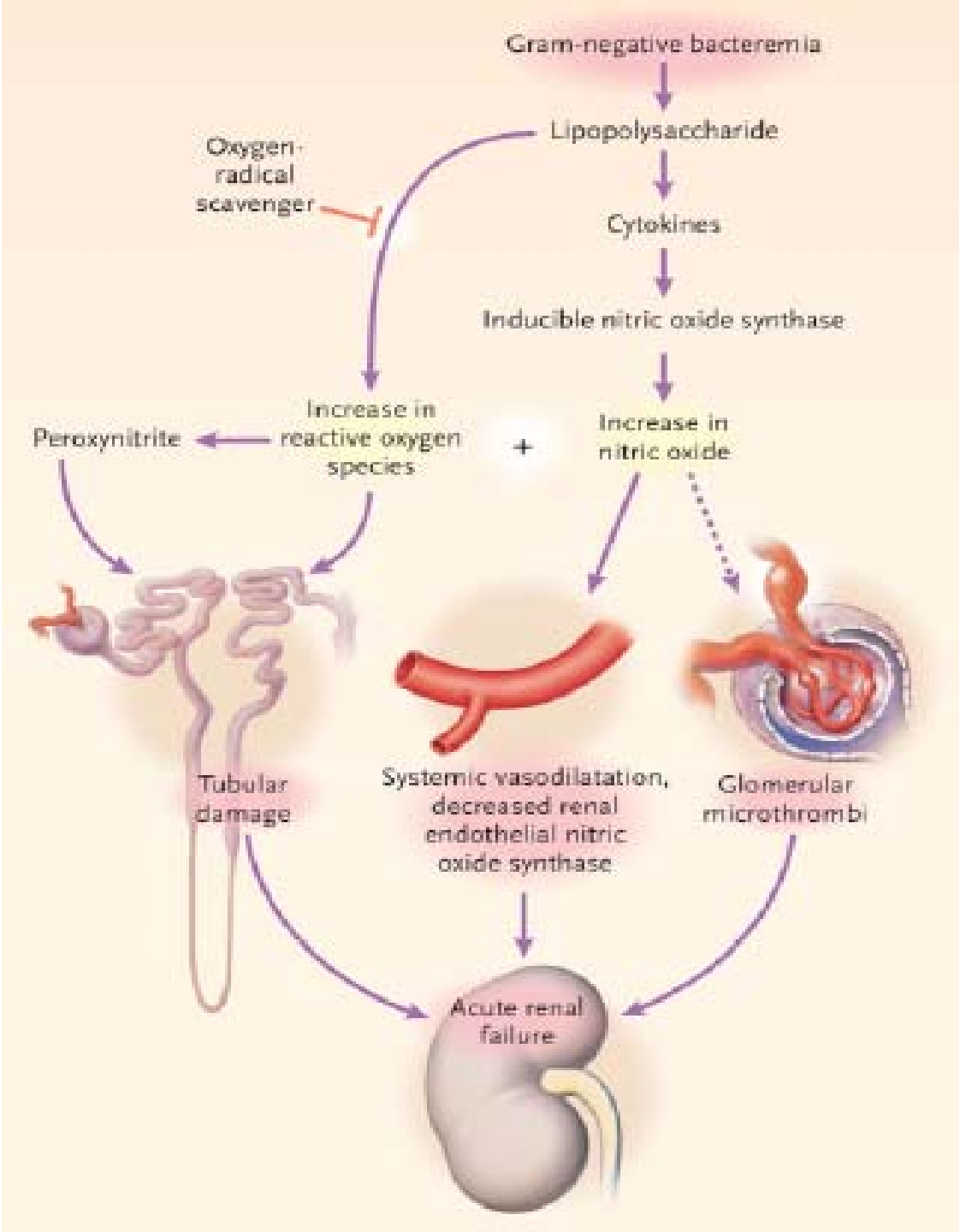


Arterial Vasodilatation & Renal Vasoconstriction in Septic Patients

Effects of Nitric Oxide on the Kidney during Sepsis

Solid arrows indicate activation

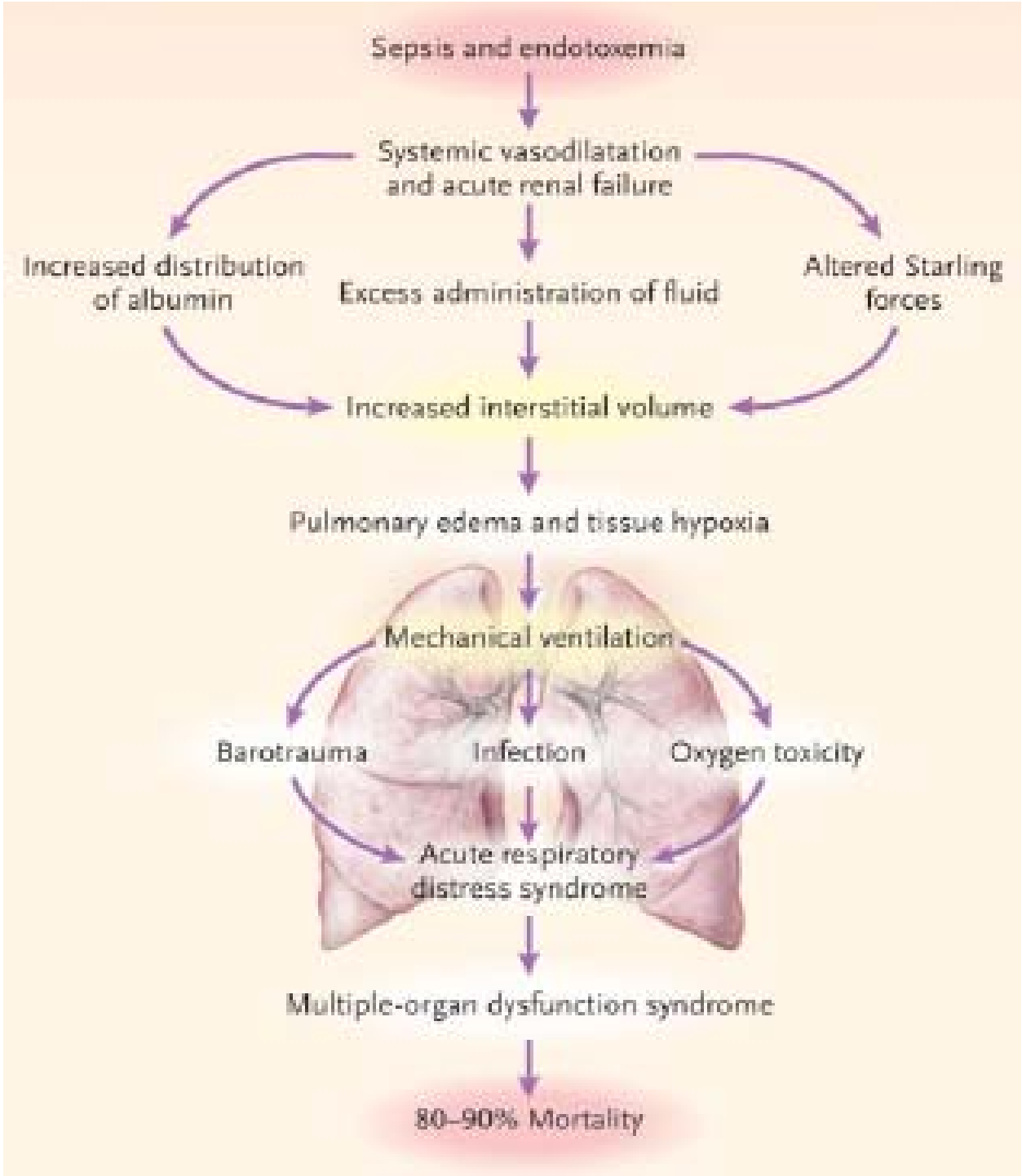
Dashed arrow and T bar indicate inhibition



Good and Bad Effects of Nitric Oxide on the Kidney during Sepsis

- Endotoxemia increases renal cortical inducible NO synthase, with a resultant increase in NO.
- NO may afford protection to the kidney by inhibiting platelet-aggregation–related glomerular microthrombi and causing cyclic guanosine onophosphate–mediated vasodilatation (to counteract renal vasoconstriction secondary to activation of sympathetic nervous system and angiotensin II)
- During sepsis, induction of NO synthase and the generation of oxygen radical cause peroxynitrite-related tubular injury, systemic vasodilatation, and down-regulation of renal endothelial NO synthase.

Effect of Vasodilatation on the Body Fluid, Lungs and Overall Mortality



Effects of Systemic Arterial Vasodilatation in Patients with Sepsis and Acute Renal Failure

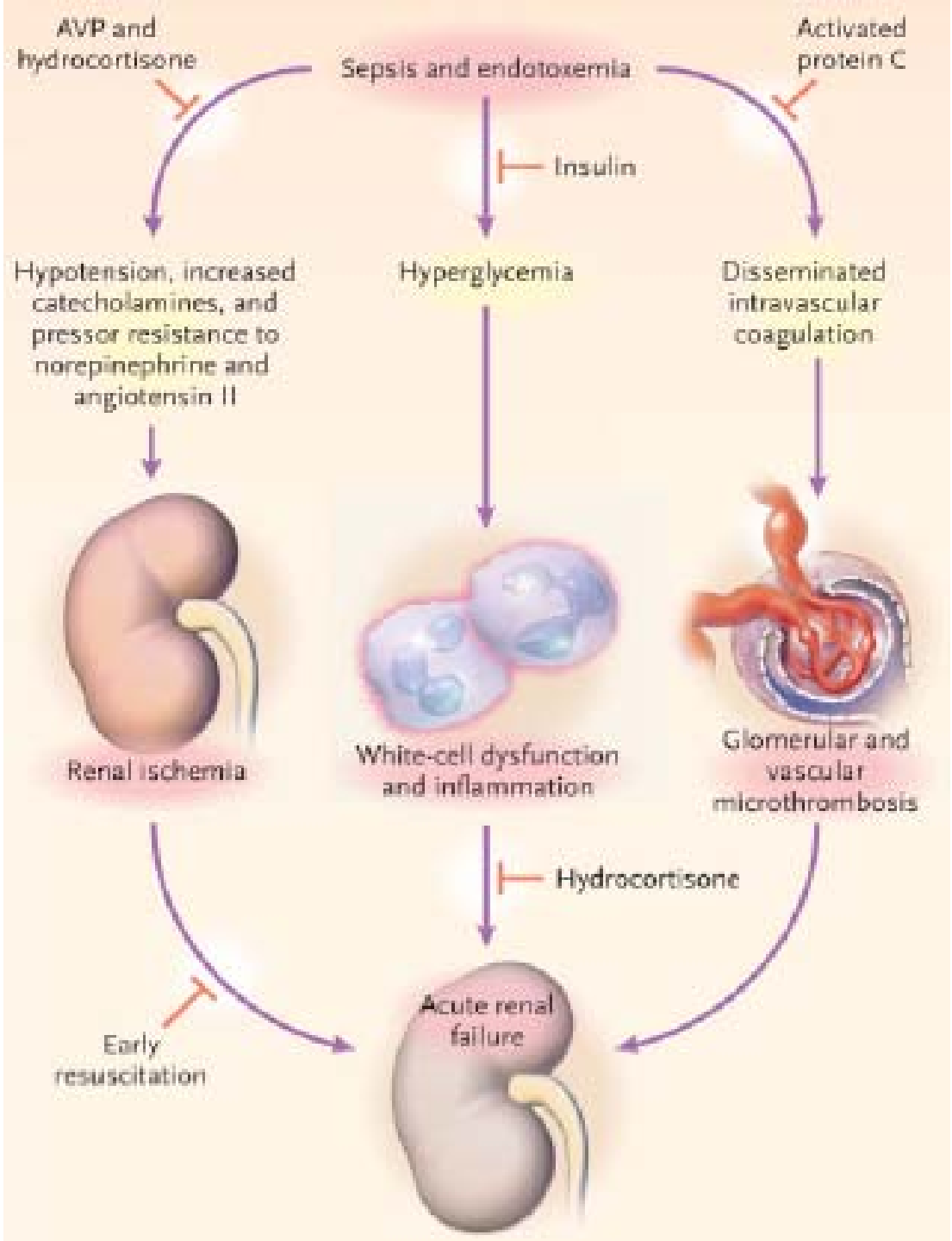
- Sepsis and endotoxemia with ARF can lead to early noncardiogenic pulmonary edema, hypoxia, and the need for mechanical ventilation.
- With prolonged ventilatory support, ARDS, multiple-organ dysfunction syndrome, and an extremely high mortality can occur.
- The goal is to intervene early to prevent excessive fluid administration and to lessen fluid overload by renal replacement therapy.
- This will prevent the need for long-term mechanical ventilation that could lead to damage to the pulmonary capillaries and may also prevent tissue hypoxia, ARDS and reduce the risk of death.

Methods of Attenuating or Preventing Sepsis-Related ARF

- Arginine vasopressin (AVP) and hydrocortisone (50 mg every six hours for seven days) may be effective therapy for pressor-resistant hypotension and may decrease the likelihood of acute renal failure during septic shock.
- Early directed resuscitation of patients with sepsis may prevent the progression from prerenal azotemia to acute tubular necrosis.
- Maintenance of blood glucose levels (below 8.0 mmol/L) may decrease the incidence of ARF, multiple-organ dysfunction syndrome, and death.

Methods of Attenuating or Preventing Sepsis-Related ARF

T bars indicate inhibition



Continuous Renal Replacement Therapy

- Start early
- CRRT is better than hemodialysis and peritoneal dialysis: provide more stable hemodynamic, prevent further ischaemic damage, better fluid, electrolytes & acid base control
- High volume hemofiltration (>45ml/kg/hr)
- Removal of inflammatory mediators

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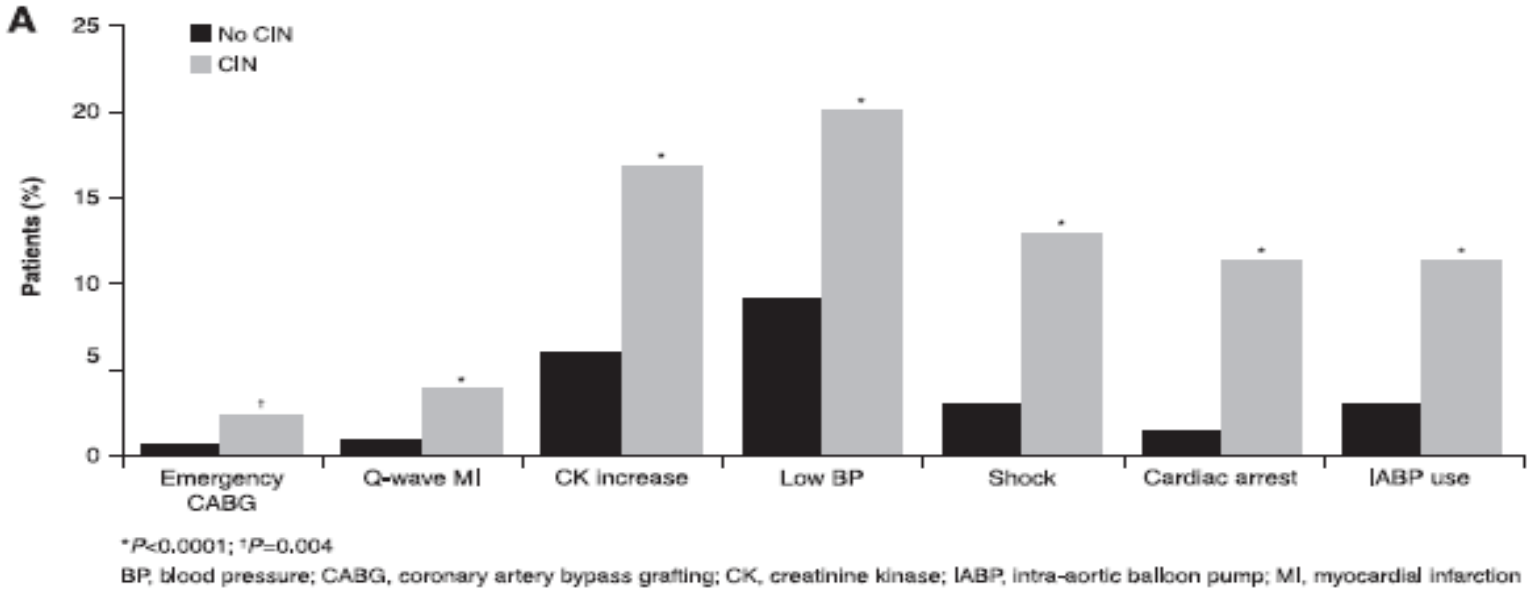
Contrast Induced Nephropathy

- Definition: a relative rise in serum creatinine 25% from the baseline value or an absolute increase 44mcmol/l within 48 h after contrast administration

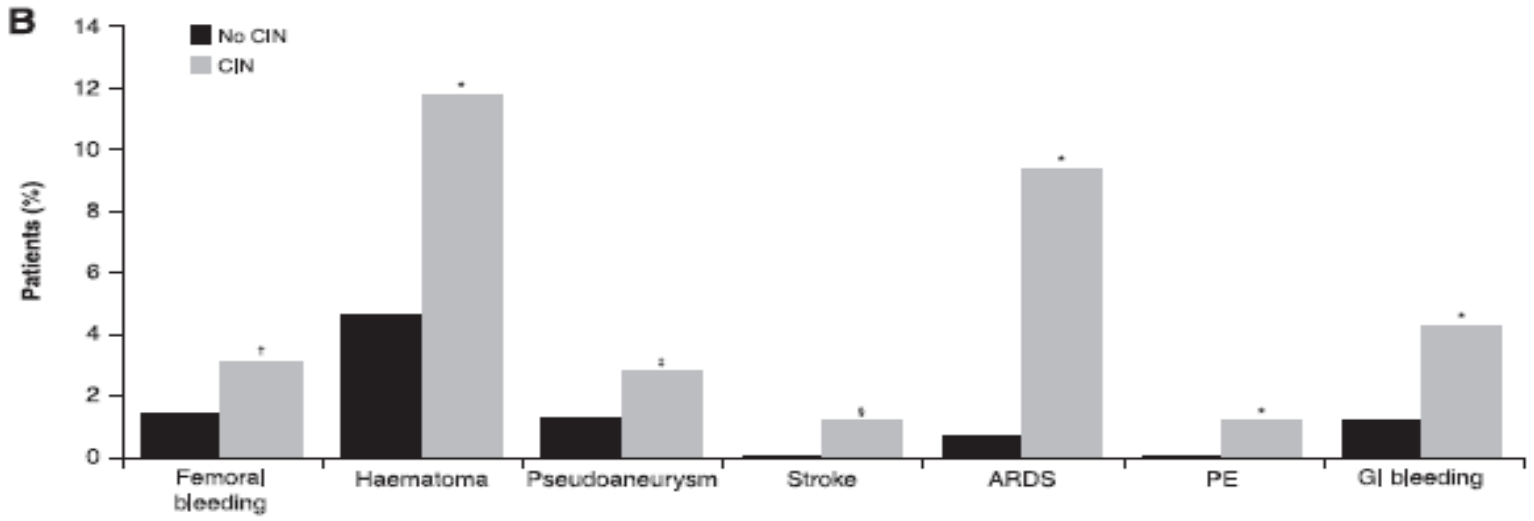
Contrast Induced Nephropathy

- In patients with normal renal function, contrast induced nephropathy (CIN) is a mild disease.
- There is no randomized controlled evidence that any protective intervention achieves biochemically significant renal protection from CIN in such patients -> no protective strategies appear indicated.
- Diabetic patients with normal RFT are still at risk of CIN
- The predictors of renal dysfunction included *volume of contrast* administered, *diabetes* (OR 3.4), *male gender* (OR 2.2) and an *abnormally elevated pre-angiography serum creatinine* (OR 21.1).



*P<0.0001; †P=0.004

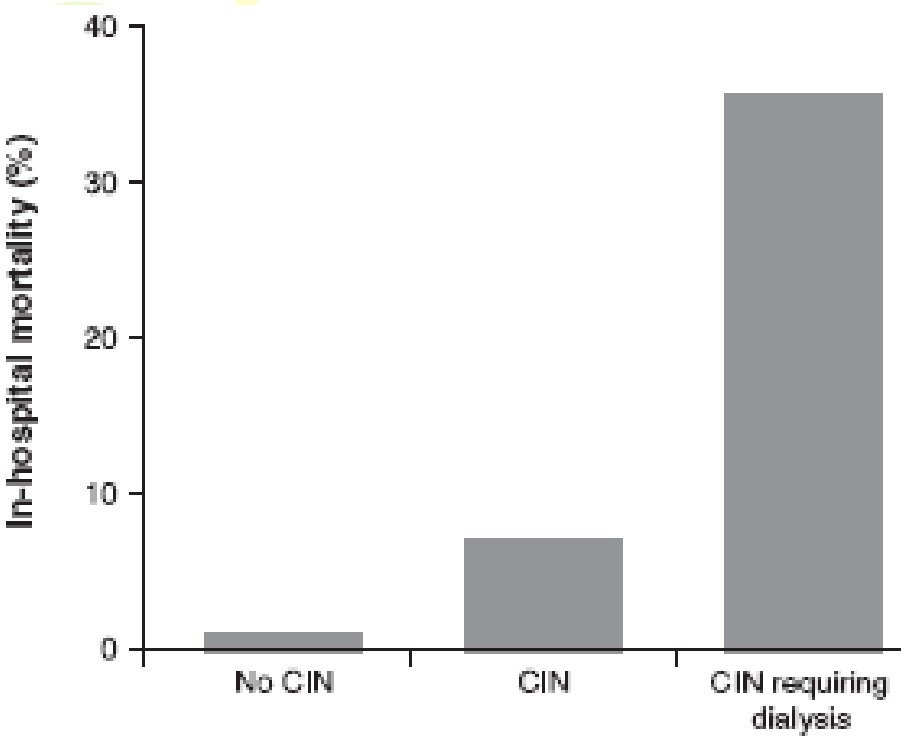
BP, blood pressure; CABG, coronary artery bypass grafting; CK, creatinine kinase; IABP, intra-aortic balloon pump; MI, myocardial infarction

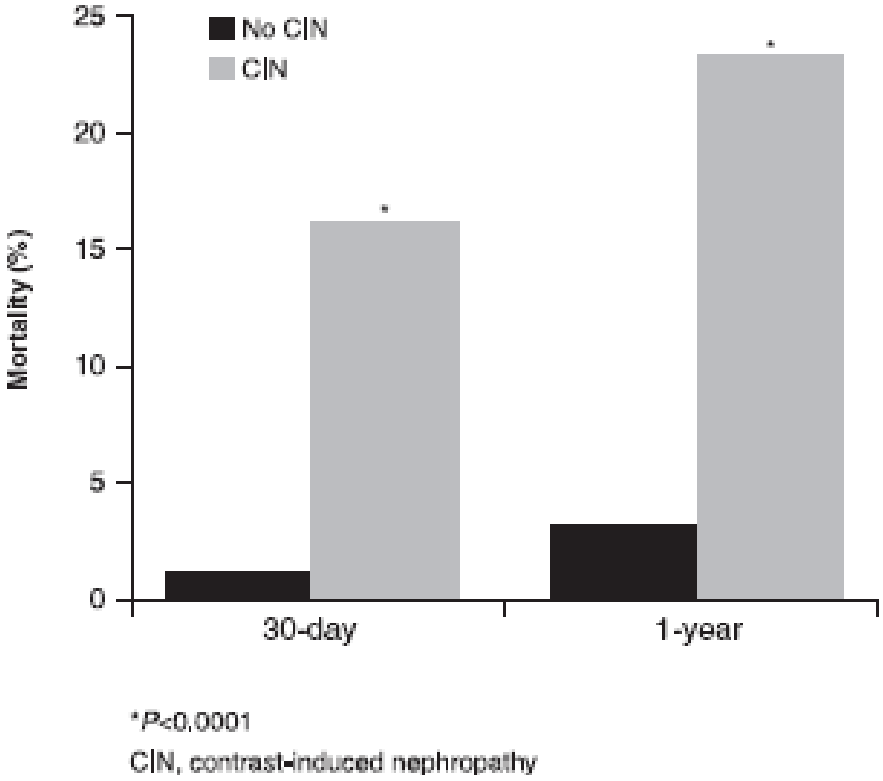


*P<0.0001; †P=0.03; ‡P=0.04; §Not significant

ARDS, adult respiratory distress syndrome; GI; gastrointestinal; PE, pulmonary embolism

Development of procedural complications in 7586 patients in the Mayo Clinic PCI Registry according to the development of CIN; (A) cardiac complications (B) vascular and systemic complications



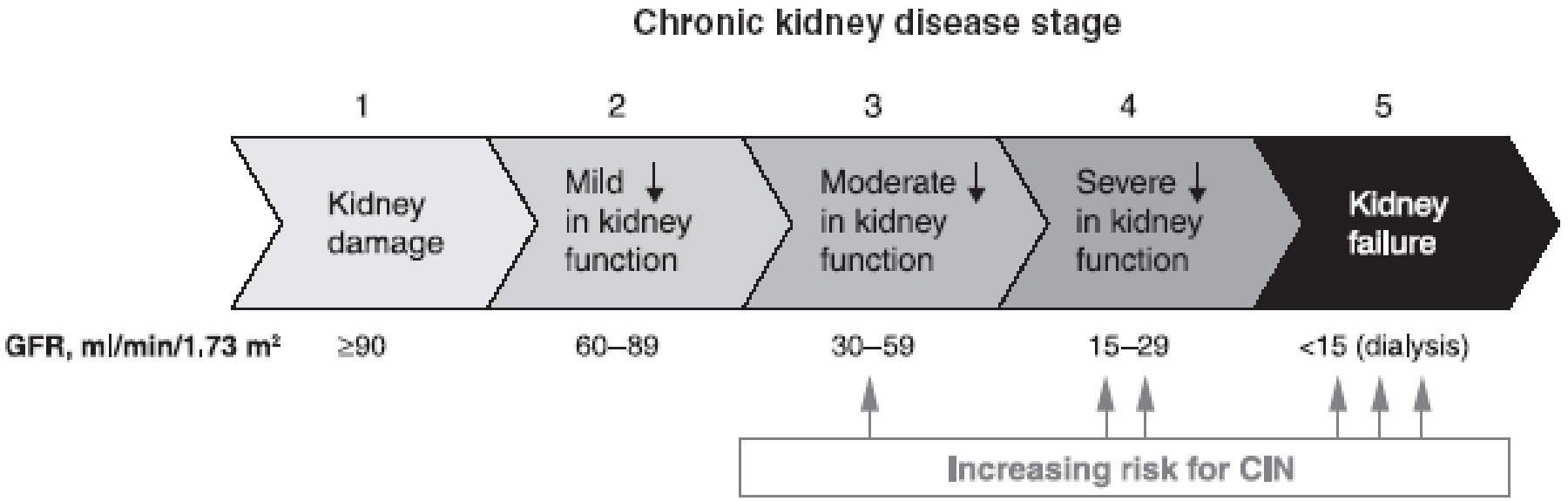


- In-hospital mortality in 1826 patients developing CIN and in those requiring dialysis because of CIN after coronary interventions in a study by McCullough et al.

- 30 day and 1 year mortality rates stratified by the development of CIN from a study of 2082 patients undergoing PCI because of acute MI without shock

Contrast Induced Nephropathy

- For patients with elevated plasma urea and/or creatinine concentration:
- The first step in the prevention of CIN is avoidance of radiocontrast altogether.
- The clinician should carefully consider the risks and benefits of radiocontrast administration in any given patient.
- minimize the amount of radiocontrast administered.
- use non-ionic low osmolality contrast media



CIN, contrast-induced nephropathy; GFR, glomerular filtration rate

Fig. 2. Risk for CIN according to stage of CKD [5–7]. Reprinted with permission [7].

Prevention of CIN

- Isotonic hydration at 1 ml/kg/hr if no clinically significant concerns about fluid overload
- N-acetylcysteine
  - oral preparation administered at 600 mg x 2 doses the day before contrast and with 1 dose the morning of contrast administration and 1 further dose afterwards
  - loading dose of 2 grams over 60 minutes prior to leaving the ICU, followed, upon return to the ICU, by an additional 2 grams given as a slow infusion over a 12 hr
- Sodium bicarbonate
- Aminophylline 250 mg IV over 30 minutes
- Patients with ESRF on chronic dialysis require no treatment

Evidence for Hydration Therapy

- The benefits of this therapy have been shown in patients with pre-contrast renal dysfunction (mean creatinine of 186 mcmol/L) in a randomized controlled trial (N Engl J Med 1994; 331: 1416-1420)
- Such hydration therapy consisted of half normal saline infusion at 1ml/kg/hr beginning 12 hours before and continued for 12 hours after contrast.
- Given its low cost and the fact that ICU patients already have IV access, hydration therapy should probably be administered to all ICU patients about to receive IV radiocontrast, unless contraindicated to fluid bolus (e.g. pulmonary edema).

Evidence for Hydration Therapy

- In a recent prospective randomized controlled open label study, isotonic hydration (normal saline) was compared to half-isotonic hydration both at 1ml/kg/hr in 1620 patients undergoing angioplasty (Arch Intern Med 2002; 162: 329-336).
- Infusion was begun on the morning of the procedure and continued until the next morning.
- Isotonic hydration decreased the incidence of CIN from 2% to 0.7% ($p=0.04$) with particular benefit in patients receiving > 250 ml of radiocontrast, women or patients with diabetes.
- Thus isotonic hydration appears superior to half-isotonic hydration.

- Several studies show that Frusemide, Dopamine and Mannitol appear to aggravate renal injury in this setting and should probably be avoided in patients receiving radiocontrast.

Evidence for Sodium Bicarbonate

- Isotonic saline has also been compared with isotonic NaHCO3 in two trials:
  - *Merten G, Burgess WP, Gray LV et al.* Prevention of contrastinduced nephropathy with sodium bicarbonate: a randomized controlled trial. JAMA 2004; 291: 2328–2334
  - *Briguori C, Airoldi F, D'Andrea D et al.* Renal insufficiency following contrast media administration trial (REMEDIAL). A raondomized comparison of 3 preventive strategies. Circulation 2007; 115: 1211–1217
- Both found isotonic HCO3 to be superior to NaCl in patients undergoing cardiac angiography, with and without the addition of N-acetylcysteine

Evidence for N Acetylcysteine

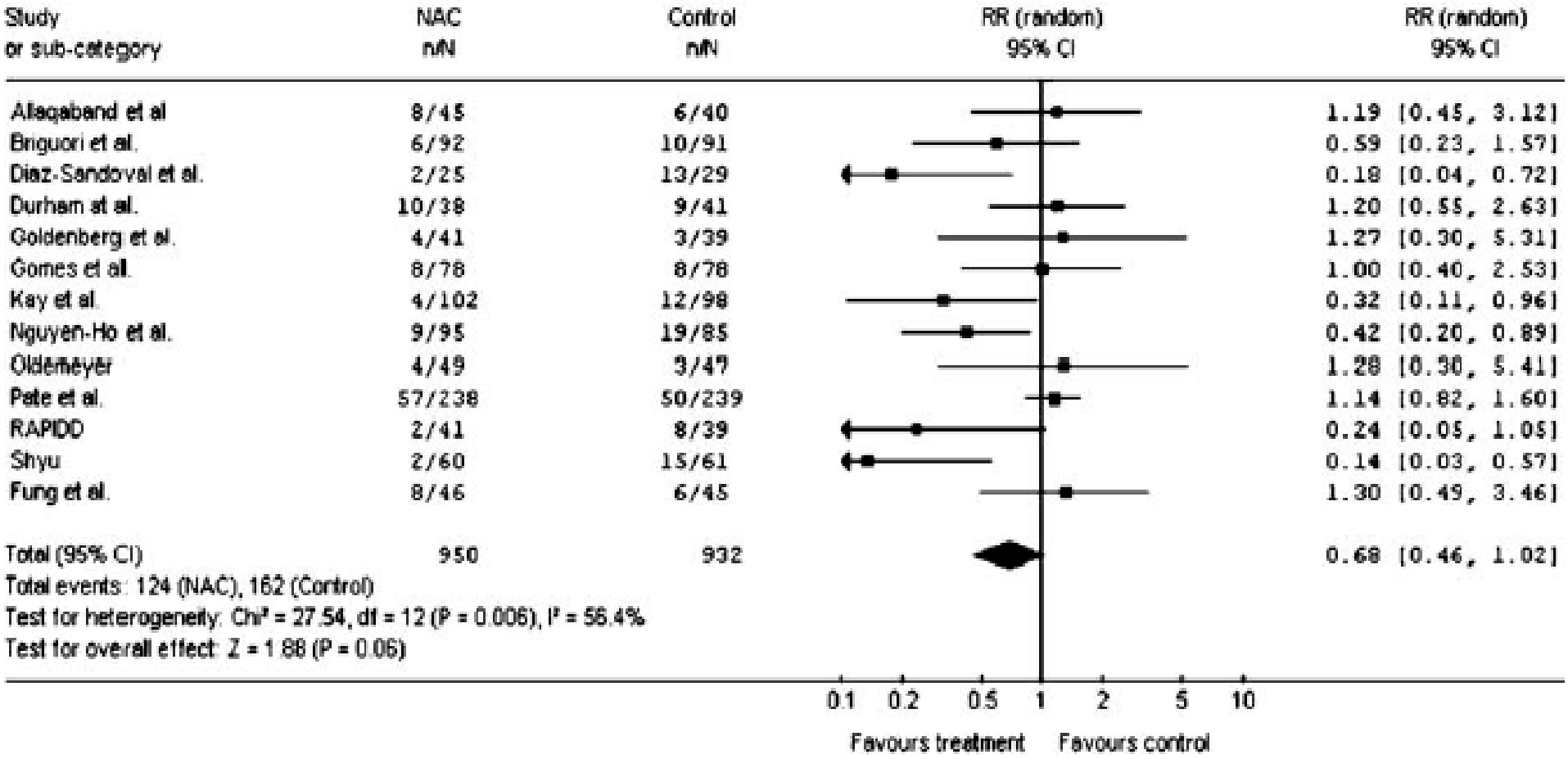
- Since the first study by Tepel suggested that administration of NAC reduced the likelihood of contrast nephropathy, many further studies had been performed to further study the effect of NAC on contrast-induced nephropathy (CIN).
- However most of these studies cannot apply to our patients whom are critically ill patients with multi-organ failure undergoing contrast-enhanced computer tomography.

	n (NAC/C)	Mean age (y)/male (%)	Diabetic patients (NAC/C) (%)	Inclusion Cr (mg/dL) or Cr Cl (mL/min)	Intravenous fluid regimen
Durham et al[16]	38/41	70/66	50/46	Cr >1.7	0.45% saline, 1 mL · kg^{-1} · h^{-1} 12 h before and 12 h after contrast
Allaqaband et al[24]	45/40	71/58	53/43	Cr >1.6 or Cr Cl <60	0.45% saline, 1 mL · kg^{-1} · h^{-1} 12 h before and 12 h after contrast
Shyu et al[14]	60/61	70/68	63/64	Cr >2 or Cr Cl <40	0.45% saline, 1 mL · kg^{-1} · h^{-1} 12 h before and 12 h after contrast
Briguori et al[19]	92/91	64/86	43/32	Cr >1.2 or Cr Cl <70	0.45% saline, 1 mL · kg^{-1} · h^{-1} 12 h before and 12 h after contrast
Diaz-Sandoval et al[17]	25/29	73/80	48/52	Cr >1.4 or Cr Cl <50	0.45% saline, 1 mL · kg^{-1} · h^{-1} 2-12 h before and 12 h after contrast
Kay et al[15]	102/98	69/62	39/36	Cr >1.2 or Cr Cl <60	0.9% saline, 1 mL · kg^{-1} · h^{-1} 2-12 h before and 6 h after contrast
Oldemeyer et al[26]	49/47	76/55	20/23	Cr Cl <50	0.45% saline, 1 mL · kg^{-1} · h^{-1} 12 h before and 12 h after contrast
Goldenberg et al[29]	41/39	70/83	39/49	Serum Cr >1.5	0.45% saline, 1 mL · kg^{-1} · h^{-1} 12 h before and 12 h after contrast
RAPPID	41/39	68/88	41/44	Serum Cr >1.36 or Cr Cl <50	0.9% saline, 1 mL · kg^{-1} · h^{-1} for 12 h pre- and postprocedure
Gomes et al[30]	78/78	64/66	53/47	Serum Cr >1.2 and/or DM	0.9% saline, 1 mL · kg^{-1} · h^{-1} for 12 h pre- and postprocedure
Pate et al[25]	242/245	71/61	31/40	Cr Cl <50	0.9% saline, 200 mL preprocedure and 1.5 mL · kg^{-1} · h^{-1} for 6 h postprocedure or until discharge
Nguyen-Ho et al[27]	95/85	N/A	N/A	N/A	0.45% saline, 1 mL · kg^{-1} · h^{-1} 12 h before and 12 h after contrast
Fung et al[28]	46/45	68/70	23/25	Serum Cr 1.7-4.5	0.9% saline, 100 mL/h 12 h before and 12 h after contrast

Characteristics of 13 trials of NAC in the prevention of CIN in patients undergoing coronary angiography

NAC dosing	Mean baseline serum Cr (NAC/C) (mg/dL)	Mean contrast volume (NAC/C)	Mean 48-h serum Cr (NAC/C)	Patients with CIN (NAC/C)	Patients requiring dialysis (NAC/C)
1200 mg orally 1 h before and 3 h after procedure (2 doses)	2.2/2.3	77.4/84.7 mL	2.2/2.3 mg/dL	10/9	2
600 mg orally twice a day the day before and after the procedure (4 doses)	2.2/2.0	1.52/1.47 mL/kg	2.2/2.0 mg/dL	8/6	2/2
400 mg orally twice a day, the day before and after the procedure (4 doses)	2.8/2.8	119/115 mL	2.5/3.1 mg/dL	2/15	0/1
600 mg orally twice a day, the day before and after the procedure (4 doses)	1.5/1.5	194/144 mL	1.5/1.5 mg/dL	6/10	0/1
600 mg orally twice a day, 1 dose before and 3 doses after the procedure	1.6/1.6	N/A	1.5/1.8 mg/dL	2/13	0/1
600 mg orally twice a day, the day before and after the procedure (4 doses)	1.3/1.3	130/120 mL	1.2/1.4 mg/dL	4/12	0/0
1500 mg orally twice daily, starting on the evening before the procedure (4 doses)	1.6/1.6	134/127 mL	1.6/1.6 mg/dL	4/3	0/0
600 mg orally 3 times a day for 48 h, 24 before and 24 after the procedure	2/1.9	111/121 mL	2/1.9 mg/dL	4/3	N/A
150 mg/kg in 500 mL of saline IV over 30 min immediately before contrast exposure and followed by 50 mg/kg IV for the next 4 h	1.9/1.8	238/222 mL	1.8/1.8 mg/dL	2/8	0/0
600 mg orally twice a day, the day before and after the procedure (4 doses)	1.4/1.2	N/A	1.5/1.3 mg/dL	8/6	1/1
500 mg IV immediately before the procedure	1.6/1.6	120/120 mL	N/A	56/51	0/0
2 g orally twice a day	N/A	N/A	N/A	19/9	1/1
400 mg orally the day before and on the day of the procedure	2.3/2.4	136/121 mL	2.4/2.4	8/6	0/0

Review: Acetylcysteine and CIN
Comparison: 01 NAC on CIN
Outcome: 01 CIN



Relative risk for developing CIN in 13 randomized trials. The overall estimate was obtained by using the random effect model.

Limitation of N Acetylcysteine Studies

- Variable dose of nonionic contrast- as most of them are for coronary angiogram or PCI, doses of nonionic contrast are much higher than that for CT
- Variable baseline creatinine and creatinine clearance- mostly < cr 200μmol/L
- Differences in NAC protocol- oral vs IV preparation, dosage, duration, abbreviated dose
- Variations in hydration protocols
- Differences in the definitions of CIN

Limitations

- Characteristics of study patients are different- Most of them are for coronary angiogram or PCI; hence they have high risk of atherosclerotic disease and are prone to renal impairment other than CIN (eg. Acute tubular necrosis in patients with acute coronary syndrome or atheroemboli triggered by coronary angiography). These patients are clinically well with stable haemodynamics and are admitted as elective procedures.
- Percentages of patients developing CIN after contrast administration are very different between studies. Percentages of CIN in control varied from 3.4 to 44.8%.
- Furthermore because of the multiple analyses performed, conclusions drawn from any particular subsets of studies should be interpreted with caution.

Use of NAC in ICU

- a preponderance of statistically significant evidence now exists to support the use of NAC + hydration prophylaxis in at risk patients who are going to receive IV radiocontrast.
- If NAC therapy simply reduces the risk of transient increases in serum creatinine without improving other clinical outcomes, it might still decrease healthcare costs by reducing the duration of hospitalization in patients receiving IV contrast.
- If the costs associated with the prescription and administration of NAC are low and if the risks are low, then NAC could be given to all patients at risk for CIN.

- Most of the studies used an oral preparation administered at 600 mg x 2 doses the day before contrast and with 1 dose the morning of contrast administration and 1 further dose afterwards.
- however ICU patients usually require immediate NAC therapy for emergency CT scan.
- Christopher et al. had demonstrated that IV infusion of NAC (150mg/kg in 500ml 0.9% NS) immediately before coronary angiography and followed by a 4h infusion of NAC (50mg/kg in 500ml 0.9% NS) was an effective means of preventing CIN.

- Causes & Classification of ARF
- RIFLE Criteria and its implication
- Fluid Therapy in ARF
- Common Renal Problems in ICU
  - Sepsis & ARF
  - Contrast Induced Nephrotoxicity
  - Drug induced Nephrotoxicity
  - Rhabdomyolysis
  - Abdominal Compartment Syndrome
  - Hepatorenal Syndrome

Risk factors for nephrotoxicity

Patient-related factors

- Age, sex, race
- Previous renal insufficiency
- Specific diseases (diabetes mellitus, multiple myeloma, those associated with proteinuria, lupus)
- Sodium-retaining states (cirrhosis, heart failure, nephrosis)
- Dehydration and volume depletion
- Acidosis, potassium and magnesium depletion
- Hyperuricemia, hyperuricosuria
- Sepsis, shock
- Renal transplantation

Risk Factors for Nephrotoxicity

Drug related factors:

- Inherent nephrotoxic potential
- Dose
- Duration, frequency, and form of administration
- Repeated exposure

Drug interactions:

- Combined or closely associated use of diagnostic or therapeutic agents with added or synergistic nephrotoxic potential (eg, radiocontrast agents, NSAID aminoglycosides, cisplatin, ACEI)

FOUR DRUG-RELATED RENAL SYNDROMES

- Acute renal failure
  - Prerenal
  - Intrinsic
    - acute tubular nephritis
    - acute interstitial nephritis
    - thrombotic thrombocytopenic purpura-hemolytic uremic syndrome
  - Postrenal
- Nephrotic syndrome
- Renal tubular dysfunction with renal potassium wasting and acidosis
- Chronic renal failure

Drug-induced toxic renal syndromes

DRUGS	ACUTE RENAL FAILURE					NEPHROTIC SYNDROME	RENAL TUBULAR DYSFUNCTION	CHRONIC RENAL FAILURE
	PRERENAL	INTRINSIC			OBSTRUCTIVE			
		ACUTE TUBULAR NECROSIS	ACUTE INTERSTITIAL NEPHRITIS	TTP-HUS*				
ACE inhibitors*	•							
Acyclovir			•		•			
Aminoglycosides		•					•	
Amphotericin B	•	•					•	
Analgesic abuse								•
Cephalosporins			•					
Chinese herbs							•	•
Cisplatin		•					•	
Ciprofloxacin			•					
Clopidogrel				•				
Cocaine		•	•	•				
COX-2 inhibitors*	•							
Cyclosporine	•			•				•
Diuretics	•		•					
Foscarnet		•			•		•	
Gold			•			•		
Ifosfamide							•	•
Immunoglobulin		•					•	
Indinavir			•	•	•			
Interferon	•							
Interleukin-2	•					•		
Lithium		•	•	•		•		•
Mannitol		•						
Mesalamine			•					
Mitomycin				•				
Nitrosureas								•
NSAIDs*	•		•			•		•
Penicillamine			•			•		
Penicillins			•					
Pentamidine		•					•	
Quinine				•				
Rifampin			•					
Sucrose		•						
Streptozocin		•					•	
Sulfonamides			•					
Tacrolimus	•			•				
Ticlopidine				•				
Triamterene			•		•			
Valproic acid			•					

Prerenal ARF

- Some drugs can cause ARF by reducing the volume or pressure or both of blood delivered to the kidney
- **Drugs implicated** include diuretics, highosmolar radiocontrast media,3–5 the immunosuppressive drugs cyclosporine and tacrolimus, NSAID, interleukin-2, and ACEI
- **Patients at risk** are those who already have compromised renal blood flow such as with bilateral renal artery stenosis, or with decreased effective circulatory volume as with cirrhosis, nephrotic syndrome, or congestive heart failure.
- **Treatment.** Stopping the offending drug usually resolves prerenal acute renal failure.

Drug-induced acute tubular necrosis

- Most of the drugs that can cause ATN are excreted by the kidney; these include aminoglycoside, amphotericin B, cisplatin, radiocontrast agents, pentamidine, cocaine, and IV immunoglobulins
- ATN can also be induced by statin drugs given in combination with immunosuppressive agents such as cyclosporine
- For most drugs that cause ATN, the target is predominantly either the early or late segments of the proximal tubule
- the most critical determinant of nephrotoxicity is the extent of drug or toxin uptake within cellular targets in the kidney
- Treatment: prevention

Acute interstitial nephritis

- presents with systemic manifestations of a hypersensitivity reaction such as fever, rash, and arthralgias
- The onset after drug exposure ranges from 3 to 5 days with a second exposure, to as long as several weeks with a first exposure.
- **Drugs implicated** include penicillins, cephalosporins, cocaine, sulfonamides, NSAIDs (especially fenoprofen, but so far not COX-2 inhibitors), diuretics, lithium, ranitidine, omeprazole, captopril, lithium, phenytoin, valproic acid, amphotericin B, streptokinase, 5-aminosalicylates, allopurinol, rifampin

Diagnosis & Treatment

- Diagnosis can be confirmed only by kidney biopsy, if the diagnosis is uncertain or if the renal failure progresses or persists in spite of stopping the offending drug.
- the major histologic findings are interstitial edema and variable cellular infiltration by eosinophils, plasma cells, T lymphocytes, monocytes, and neutrophils.
- Renal function typically begins to recover within 7 days of stopping the drug, and the serum creatinine concentration eventually returns to baseline values.
- If renal failure persists, steroid therapy is indicated
- If renal function does not recover after 4 to 6 weeks of steroids, immunosuppressive agents such as cyclophosphamide can be tried

Table 1 Common medications associated with acute renal injury.

Pathoetiology	Medication	Clinical findings	Treatment
Prerenal injury	Diuretics, NSAIDs, ACE inhibitors, ciclosporin, tacrolimus, radiocontrast media, interleukin-2, vasodilators (hydralazine, calcium-channel blockers, minoxidil, diazoxide)	Benign urine sediment, FENa <1%, UOsm >500	Suspend or discontinue medication, volume replacement as clinically indicated
Intrinsic renal injury (vascular effects: thrombotic microangiopathy)	Ciclosporin, tacrolimus, mitomycin C, conjugated estrogens, quinine, 5-fluorouracil, ticlopidine, clopidogrel, interferon, valaciclovir, gemcitabine, bleomycin	Fever, microangiopathic, hemolytic anemia, thrombocytopenia	Discontinue medication, supportive care, plasmapheresis if indicated
Intrinsic renal injury (vascular effects: cholesterol emboli)	Heparin, warfarin, streptokinase	Fever, microangiopathic, hemolytic anemia, thrombocytopenia	Discontinue medication, supportive care, plasmapheresis if indicated
Intrinsic renal injury (tubular toxicity)	Aminoglycosides, radiocontrast media, cisplatin, nedaplatin, methoxyflurane, outdated tetracycline, amphotericin B, cephaloridine, streptozocin, tacrolimus, carbamazepine, mithramycin, quinolones, foscarnet, pentamidine, intravenous gammaglobulin, fosfamide, zoledronate, cidofovir, adefovir, tenofovir, mannitol, dextran, hydroxyethylstarch	FENa >2%, UOsm <350, urinary sediment with granular casts, tubular epithelial cells	Drug discontinuation, supportive care

Table 1 Common medications associated with acute renal injury.

Pathoetiology	Medication	Clinical findings	Treatment
Intrinsic renal injury (rhabdomyolysis)	Lovastatin, ethanol, codeine, barbiturates, diazepam	Elevated CPK, ATN urine sediment	Drug discontinuation, supportive care
Intrinsic renal injury (severe hemolysis)	Quinine, quinidine, sulfonamides, hydralazine, triamterene, nitrofurantoin, mephenytoin	High LDH, decreased hemoglobin	Drug discontinuation, supportive care
Intrinsic renal injury (immune-mediated interstitial inflammation)	Penicillin, methicillin ampicillin, rifampin, sulfonamides, thiazides, cimetidine, phenytoin, allopurinol, cephalosporins, cytosine arabinoside, furosemide, interferon, NSAIDs, ciprofloxacin, clarithromycin, telithromycin, rofecoxib, pantoprazole, omeprazole, atazanavir	Fever, rash, eosinophilia, urine sediment showing pyuria, white cell casts, eosinophiluria	Discontinue medication, supportive care
Intrinsic renal injury (glomerulopathy)	Gold, penicillamine, captopril, NSAIDs, lithium, mefenamate, fenoprofen, mercury, interferon-α, pamidronate, fenclofenac, tolmetin, foscarnet	Edema, moderate to severe proteinuria, red blood cells, red blood cell casts possible	Discontinue medication, supportive care
Obstruction (intratubular: crystalluria and/or renal lithiasis)	Aciclovir, methotrexate, sulfanilamide, triamterene, indinavir, foscarnet, ganciclovir	Sediment can be benign with severe obstruction, ATN might be observed	Discontinue medication, supportive care
Obstruction (ureteral; secondary to retroperitoneal fibrosis)	Methysergide, ergotamine, dihydroergotamine, methyldopa, pindolol, hydralazine, atenolol	Benign urine sediment, hydronephrosis on ultrasound	Discontinue medication, decompress ureteral obstruction by intrarenal stenting or percutaneous nephrostomy

Drug Induced Nephropathy General Management

- the best clinical approach to drug-induced nephrotoxicity is **prevention**, which starts with the recognition that drug-induced renal injury occurs
- **Identify patients at risk** (those with renal insufficiency, dehydration, salt-retaining states, diabetes, multiple myeloma)
  - Approach the use of any potentially nephrotoxic drugs with caution
  - Analysis the risk and the benefit
  - Be aware of increased risk in elderly patients
  - Polypharmacy increases the risk

General Principles

- **Be vigilant:**
  - Adverse renal effects of drugs are largely silent in the early stages, and only clinical vigilance can ensure early diagnosis.
  - Monitor renal function closely when introducing any drug to patient (especially nephrotoxic drugs)
- **Be aware** of nephrotoxic potential of specific drugs
- **Manage the renal failure:**
  - by replacing fluid volume
  - starting dialysis
  - adjusting drug doses
  - try steroids in cases of acute interstitial nephritis
  - avoiding repeat exposure

General Principles

- Carefully assess the benefits of radiologic procedures or prescribed drugs against potential risk.
- Whenever possible, select diagnostic procedures or therapeutic measures without nephrotoxic potential.
- Avoid dehydration. This is mandatory in high-risk patients.
- Limit total daily dosage and duration of treatment with certain drugs.
- Adjust the daily dosage to ongoing alterations in the GFR.
- Avoid a combination of potentially nephrotoxic drugs.
- **When in doubt about the cause of renal failure, hold all potentially offending drugs.**

Prophylaxis of Drug induced Renal Failure

- **Amphotericin B:** adjust dosage, hydrate with normal saline infusion, use liposomal formulation
- **Aminoglycosides:** Follow levels, correct potassium levels, give once-daily doses, adjust dosage for renal function, avoid use if possible in high-risk patients, possibly give calcium channel blockers
- **Cisplatin:** Hydrate with normal saline, possibly give thiosulfate
- **ACE inhibitors:** Avoid in bilateral renal artery stenosis, use with caution in hypovolemia
- **Acyclovir:** Avoid bolus doses, give intravenous fluids, adjust dose for renal function
- **Lithium:** Monitor levels, amiloride may prevent nephrogenic diabetes insipidus
- **Interleukin-2:** Intravenous saline, albumin infusion
- **Cyclosporine:** Follow levels, avoid drugs that raise levels (erythromycin, verapamil, ketoconazole)

Drugs that cause pseudo-elevation of urea and creatinine

Competitive tubular secretion of creatinine

- Trimethoprim
- Cimetidine
- Probenecid
- Triamterene
- Amiloride
- Spironolactone

Interference with laboratory determination of Creatinine

- Ascorbic acid
- Cephalosporins (cefoxitin and cephalothin)
- Flucytosine
- Levodopa
- Methyldopa

Hypercatabolic effect

- Steroids
- Tetracycline

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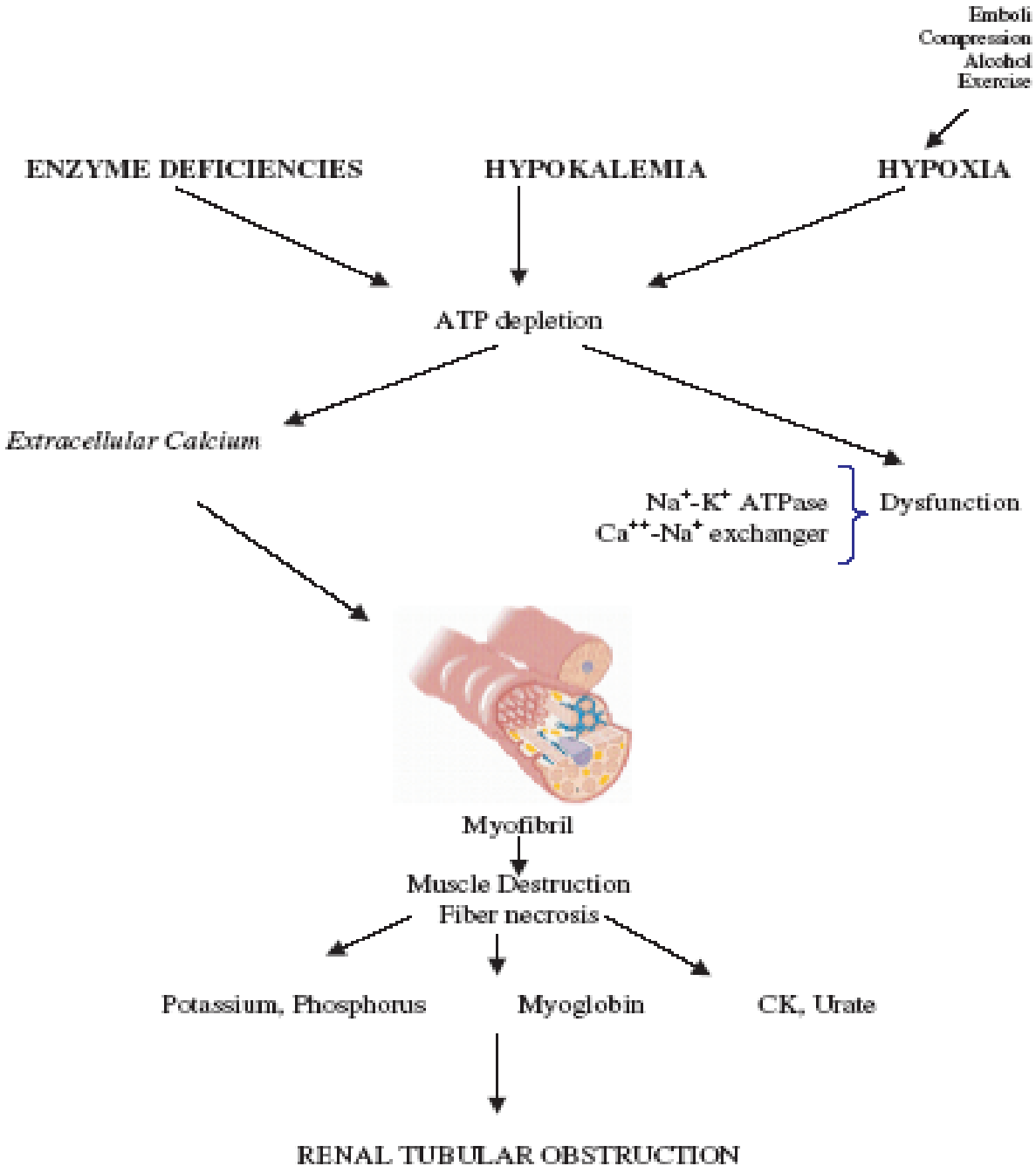
Rhabdomyolysis

- a syndrome caused by injury to skeletal muscle with disruption of sacrolemma resulting in leakage of large quantities of intracellular contents into plasma.
- Presentation: muscle weakness, myalgia, dark urine, renal failure and DIC
- Mechanisms of cell destruction in rhabdomyolysis include cellular membrane injury, muscle cell hypoxia, ATP depletion, and electrolyte disturbances that cause perturbation of Na/K pumps.
- After muscle injury, massive plasma myoglobin levels exceed protein binding and can precipitate in glomerular filtrate. Excess myoglobin cause renal tubular obstruction, direct nephrotoxicity, and ARF.



Overview of the pathophysiology of rhabdomyolysis. CK, creatine kinase.

Diagnosis- Creatinine Kinase

- Creatinine kinase levels rise within 12 hours of muscle injury, peak in 24-36 hours, and decrease at a rate of 36-40% per day. The serum half-life of CK is approximately 36 hours. CK levels decline 3-5 days after resolution of muscle injury.
- Failure of CK levels to decrease suggests ongoing muscle injury.
- The peak CK level, especially when more than 5000 U/L (Normal CK enzyme levels are 45–260 U/l), may be predictive of renal failure.
- CK levels 5 times the reference range suggest rhabdomyolysis

Diagnosis- Myoglobin tests

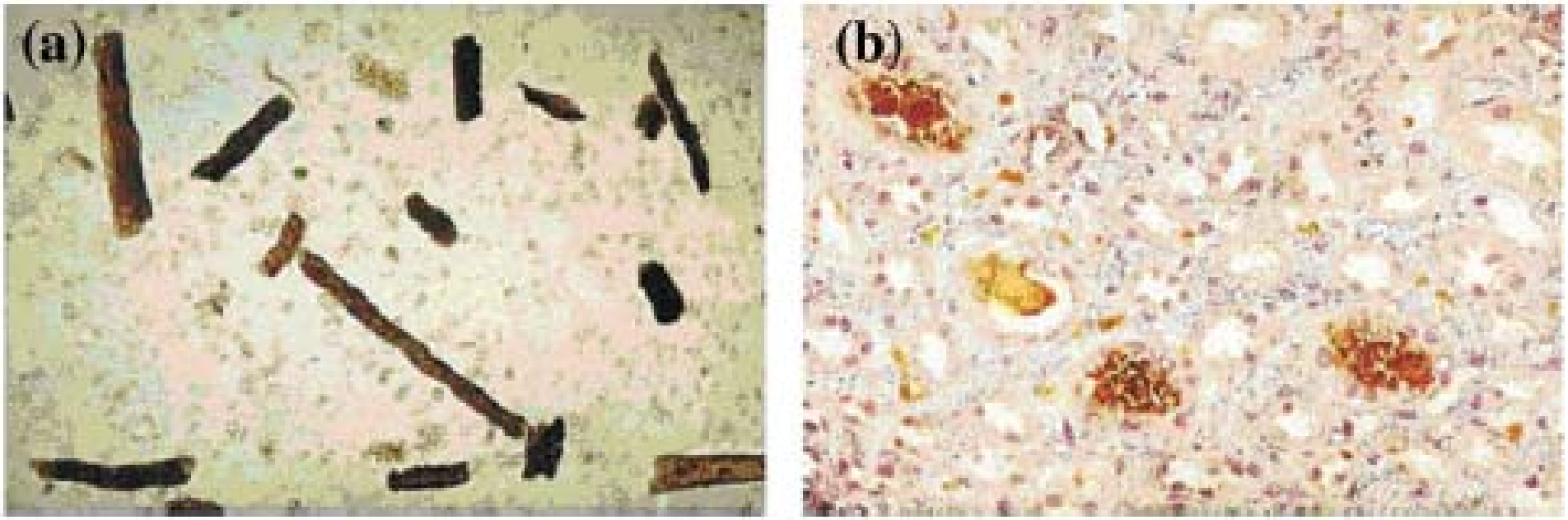
- Plasma myoglobin measurements are not reliable because the half-life of myoglobin is 1-3 hours and it is cleared from plasma within 6 hours. The half-life of CK is 1.5 days and so it remains elevated longer than serum myoglobin levels
- Myoglobin levels not measured at the right time may produce a false-negative result. A positive test result may help to confirm the diagnosis.
- Urine myoglobin is presumed if the urine is positive for blood but negative for RBC
- A urine myoglobin assay is helpful in patients with coexisting hematuria (confirmed with microscopic examination) when myoglobin presence is suspected.

Complications related to Rhabdomyolysis

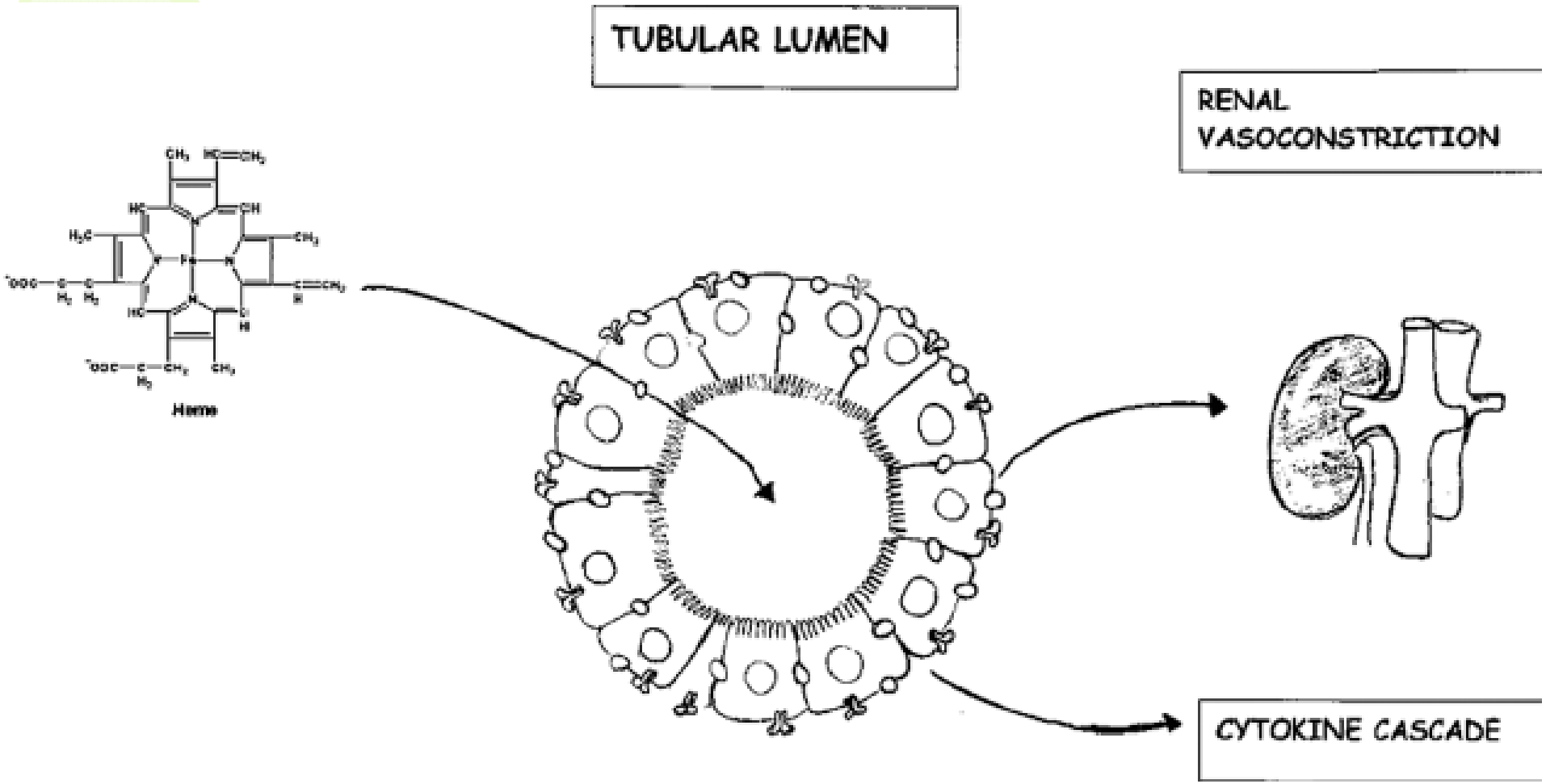
- Hyperkalemia may be a result of both muscle injury and renal insufficiency or failure.
- Hyperphosphatemia
- Hypocalcemia resulting from deposition of calcium phosphate. It may also be due to a decreased level of 1,25-dihydroxycholecalciferol in patients with renal failure. Severe hypocalcemia may lead to cardiac arrhythmias, muscular contractions, and seizures.
- Hypoalbuminemia results from proteinuria and direct leakage of protein
- hyperuricemia is caused by direct damage to muscle and may contribute to renal tubular damage.
- Compartment syndrome

Acute Renal Failure

- 1/3 of patients with rhabdomyolysis develop ARF
- Myoglobin and hemoglobin have no direct toxic effect on the glomerulus in the absence of aciduria and hypovolemia.
- ARF is due to
  - decreased extracellular volume, which results in renal vasoconstriction
  - Myoglobin precipitation in renal tubules causes formation of obstructive casts
  - Ferrihemate, which is formed from myoglobin at a pH <5.6. It produces free hydroxy radicals & causes direct nephrotoxicity. It may enhance renal vasoconstriction & ischemia through interactions with nitric oxide (NO) and endothelin receptors resulting in deplete tubular ATP formation and enhance tubular cell damage.



Pigmented casts. Analysis of urinary sediment (× 400) pigmented casts, leukocyturia, and hematuria without dysmorphic red cells. **(a)** Pigmented casts, leukocyturia, hematuria with dysmorphic cells; **(b)** with antibody against human myoglobin.



Mechanisms of heme-induced renal failure

Management of Rhabdomyolysis

- Aggressive and early hydration with isotonic sodium chloride solution is important for the prevention of pigment-associated renal failure.
- Alkalinization of urine:
  - Ferrihemate and globin are the breakdown products of myoglobin when pH levels fall to < 5.6
  - Sodium bicarbonate is used with care to achieve a urine pH level of >6.5
- Monitor serum electrolyte levels, urine pH levels, and acid-base status frequently

Management of Rhabdomyolysis

- mannitol may be protective due to the associated diuresis that minimizes intratubular heme pigment deposition
- mannitol can act as a free-radical scavenger, thereby minimizing cell injury
- mannitol reduces blood viscosity and is a renal vasodilator
- Despite mannitol and bicarbonate are considered the standard of care in preventing ARF in patients with rhabdomyolysis, there is little clinical evidence to support the use of these agents and randomized controlled trials are lacking
- Volume expansion, urinary alkalinization, and forced diuresis are not useful in the context of severe oliguria.

General Management

- Treat hyperkalemia by administering insulin and glucose, and a potassium exchange resin by transiently shifting potassium from extracellular to intracellular compartments
- Correct hypocalcemia only if the patient has cardiac dysrhythmias or seizures
- Calcium may combine with phosphate, forming a metastatic calcification
- Control hyperphosphatemia using alkaline diuresis.
- Hypercalcemia may develop during recovery phase.

Removal of Myoglobin

- renal damage is induced by circulating myoglobin, so treatment should aim to replace the failing kidney function, & to prevent further damage due to renal tubular obstruction, altered intrarenal hemodynamics and tubular cell dysfunction.
- ARF is treated by renal replacement therapies
- Removal of myoglobin using blood purification techniques had also be tried. Such as plasma exchange, intermittent hemodialysis, and CRRT, but were met with limited success
- The inefficient removal of myoglobin results in a permanently high myoglobin level & a perpetuation of the pathological insult with prolongation of anuria and delay of renal function recovery.

Why are extracorporeal techniques ineffective in removing myoglobin?

- Myoglobin has a molecular mass of 17 kDa but because it is non-spherical and carries electrical charges, hence its effective radius is greater than expected.
- a very low diffusion coefficient, thus requiring transport by convection
- possesses a steric magnitude that is likely to be rejected by the membrane pores
- The volume of distribution in the human body is not known
- standard cellulosic membranes are practically impermeable to the molecule

Comparison of studies of renal replacement therapy (RRT) in the management of myoglobinuric acute renal failure

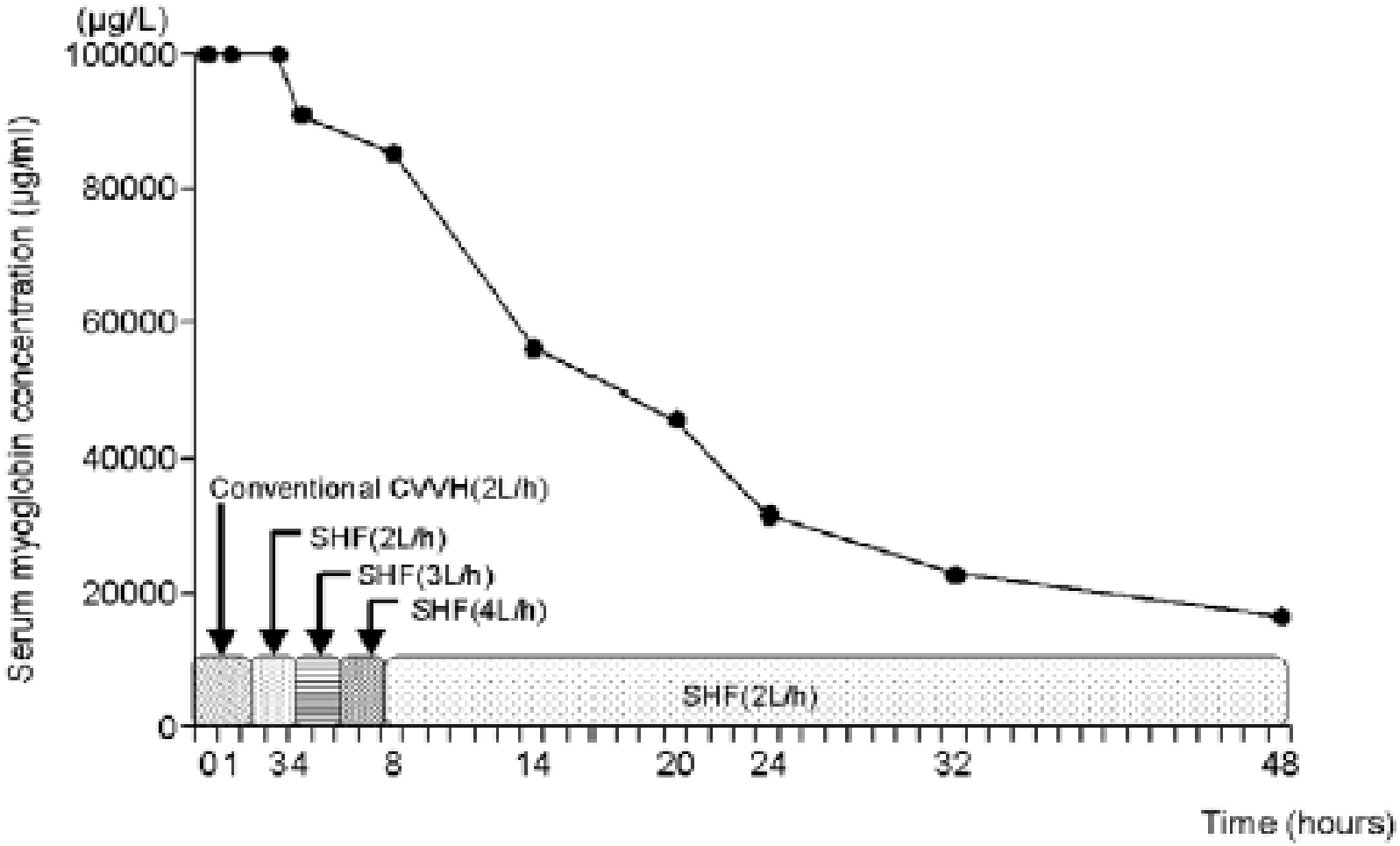
Reference	Subject(s)	Mode of RRT	Filter used	Sieving coefficient (%)	Myoglobin removal (g/day)	Clearance (ml/min)
Present study	Single patient with ARF due to rhabdomyolysis	CVVH, 2 l exchange	Polysulphone (APS)	<0.23	1.1	<8
		SHF CVVH, 3–4 l exchange	Gambro Polyflux P2SH	0.69–0.72	4.3–5.1	30.5–39.2
[8]	Three patients with myoglobinuric ARF	Continuous hemodiafiltration	Hospal AN 69S	0.21*	1.8	4.6
[9]	Swine model of myoglobinuric ARF	CAVH	Hospal AN 69S	0.15	1.64 (0.41 g/6 hours)	1.42 ± 1.03
[10]	Swine model	CVVH	Hospal AN 69HF	0.36–0.55	2.3–3.8 (0.95 g/6 hours)	11.2–25.2
[11]	Single patient with ARF due to rhabdomyolysis	CVVH	Hospal AN69 Multiflow 100	0.40–0.60	1.05 (0.7 g/16 hours)	14–22
[19]	Patient with malignant hyperthermia and rhabdomyolysis	CVVH	Gambro polyflux 11S	0.37	4.3	11*

ARF, acute renal failure; CAVH, continuous arterio-venous haemofiltration; CVVH, continuous veno-venous haemofiltration; SHF, super high-flux. * Calculated from the C_{UF}, V_{UF}, and C_{pre} values provided in these studies

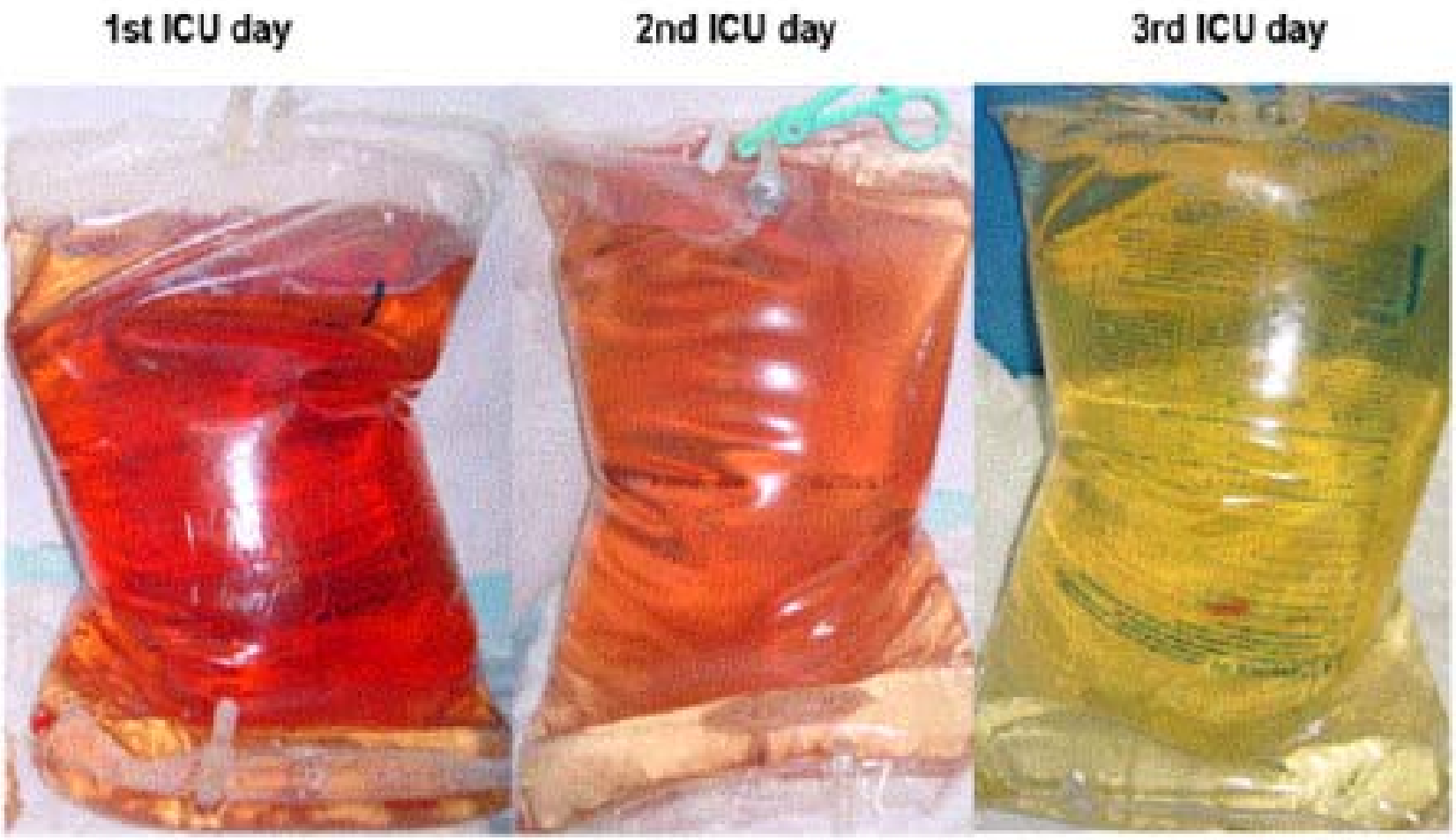
Myoglobin clearance by super high-flux hemofiltration in a case of severe rhabdomyolysis: a case report

- A patient with serotonin syndrome complicated by severe rhabodomyolysis and oliguric ARF
- CVVH is started in to clear myoglobin
- Molecular weight of Myoglobin is 17kDa
- Initially at 2 l/hour ultrafiltration (UF) with a standard polysulphone 1.4 m2 membrane (cutoff point, 20 kDa)

- followed by CVVH at 2 l/hour UF with a super high-flux (SHF) membrane with a pore cutoff size of 100 kDa, which has the ability to dialyze inflammatory cytokines and β2-microglobulin
- then at 3 l/hour UF
- then at 4 l/hour UF



Progressive reduction of serum myoglobin concentration over a 48-hour period using super high-flux (SHF) continuous veno-venous hemo-filtration (CVVH). The serum concentration of myoglobin remained >100,000 µg/l until commencement of SHF CVVH.



Images of ultrafiltration fluid demonstrating progressive reduction in pigmentation over a 3-day period concurrent with treatment using super high-flux continuous veno-venous hemofiltration. ICU, intensive care unit.

Sieving coefficient and clearance of myoglobin using conventional and super high-flux (SHF) continuous veno-venous hemofiltration in a patient with severe rhabdomyolysis secondary to serotonin syndrome

Filter type	Ultrafiltration rate (l/hour)	Myoglobin concentration (μg/l)			Sieving coefficient (%)	Myoglobin removal (g/day)	Myoglobin clearance (ml/min)
		Pre-filter	Post-filter	Ultrafiltrate			
Conventional (polysulphone)	2	>100,000	>100,000	23003	<0.23	1.1	<8
SHF	2	>100,000	>100,000	>100,000	Unable to calculate	>4.8	Unable to calculate
SHF	3	100,000	68,776	60,912	0.722	4.4	30.5
SHF	4	91,058	64,587	53,527	0.688	5.1	39.2

$$\text{Sieving coefficient (SC)} = 2C_{uf}/(C_{pre} + C_{post})$$

where C_{uf} represents the concentration of myoglobin in the ultrafiltrate, and C_{pre} and C_{post} are the pre-filter and post-filter concentrations of myoglobin,respectively.

Sieving Coefficient

- the mathematical expression of the ability of a solute or drug to convectively cross a membrane.
- determined from the ratio of the solute concentration in the ultrafiltrate to the solute concentration in the plasma. Since the arterial and venous concentrations may be different because of solute removal, it is more accurate to estimate the SC using concentration in ultrafiltrate divided by mean of concentrations in pre and post filter blood
- Sieving coefficient (SC) = $2C\text{uf}/(C\text{pre} + C\text{post})$
- An SC of 1 means that the solute freely crosses the membrane and is removed in the same concentration as in the plasma
- An SC of 0 means that there is no solute removal due either to large molecular size or to extensive protein binding

Adverse Effect of SHF Membrane

- A potential adverse effect of SHF (high cutoff point) hemofiltration is the loss of serum albumin (69 kDa).
- Loss of clotting factors or protein-bound drugs such as fentanyl and midazolam may occur.
- monitoring of albumin levels and the clotting status, and adjustment of the drug dosage must be performed regularly.

Prognosis

- Most important is to preserve renal function
- Retrospective analysis demonstrates that early aggressive fluid replacement with saline is beneficial in minimizing the occurrence of renal failure.
- Forced diuresis, when started within 6 hours of admission, has been reported to minimize the risk of ARF
- Once patients developed renal failure, it may take weeks before renal recovery occurs

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Intraabdominal Hypertension

- Intraabdominal pressure (IAP) is the pressure concealed within the abdominal cavity
- Abdo perfusion pressure (APP) =MAP – IAP
- Normal IAP is approx. 5–7mmHg
- IAH is defined by a sustained or repeated pathological elevation in IAP≥12mmHg.
- IAH is graded as follows:
- grade I: IAP 12–15 mmHg
  grade II: IAP 16–20 mmHg
- grade III: IAP 21–25 mmHg
  grade IV: IAP>25 mmHg

Abdominal Compartment Syndrome

- ACS is defined as a sustained IAP>20mmHg that is associated with new organ dysfunction/failure.
- Primary ACS is a condition associated with abdomino-pelvic pathology that frequently requires early surgical or interventional radiological intervention.
- Secondary ACS refers to conditions that do not originate from the abdomino-pelvic region.
- Development of IAH and ACS are common among the critically ill with a significant associated risk of organ failure and increased mortality

Risk Factors for ACS

1. Diminished abdominal wall compliance
   - Acute respiratory failure, especially with elevated intrathoracic pressure
   - Abdominal surgery with primary fascial closure
   - Major trauma / burns
   - Prone positioning

2. Increased intra-luminal contents
   - Gastroparesis
   - Ileus
   - Colonic pseudo-obstruction

3. Increased abdominal contents
   - Hemoperitoneum / pneumoperitoneum
   - Ascites / liver dysfunction

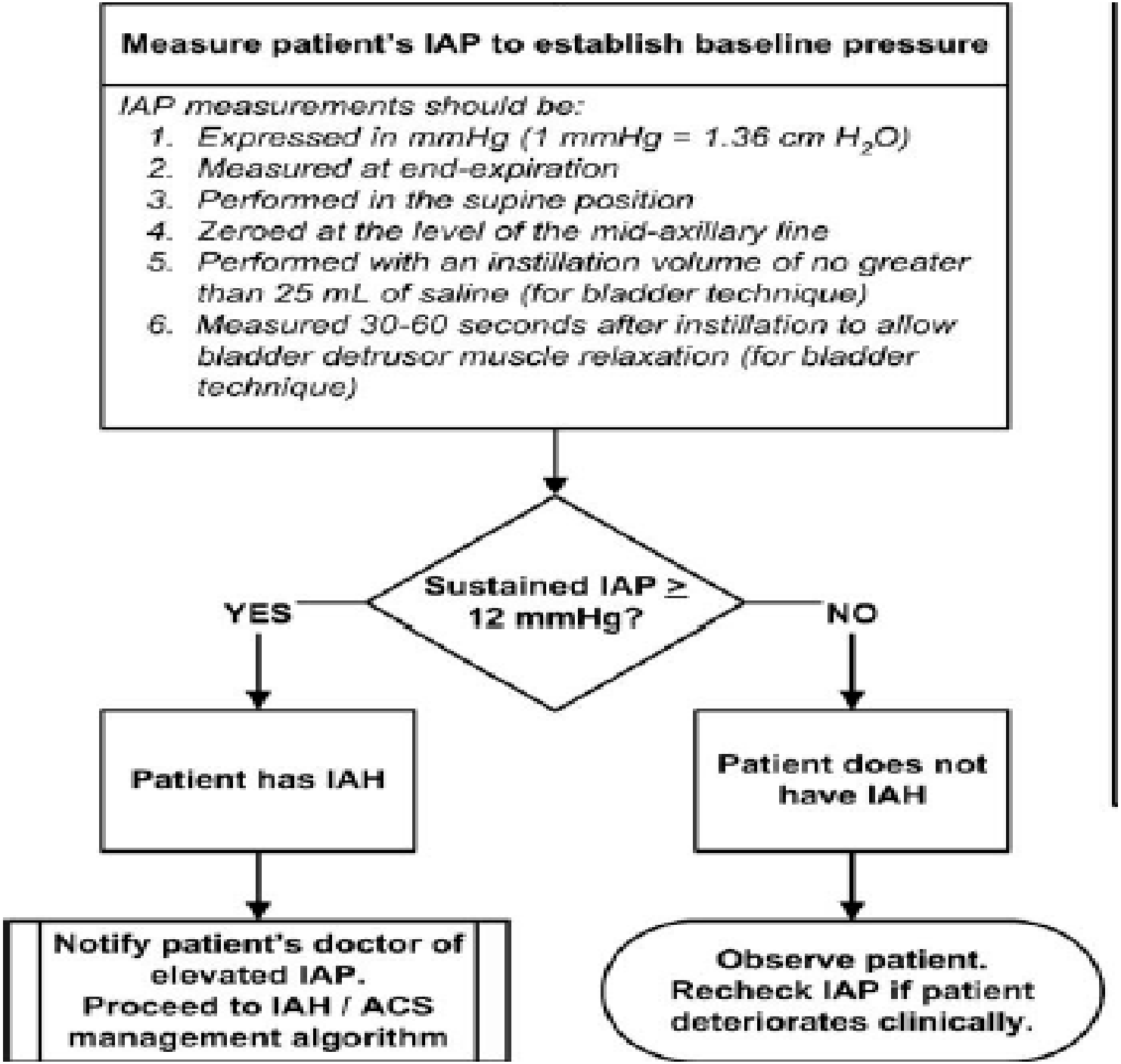
4. Capillary leak / fluid resuscitation
   - Acidosis (pH < 7.2)
   - Hypotension
   - Hypothermia (core temperature < 33°C)
   - Polytransfusion (>10 units of blood / 24 hours)
   - Coagulopathy (platelets < 55000 / mm^3 OR activated partial thromboplastin time (APTT) > 2 times normal OR prothrombin time (PTT) < 50% OR international standardised ratio (INR) > 1.5)
   - Massive fluid resuscitation (> 5 L / 24 hours)
   - Oliguria
   - Sepsis
   - Major trauma / burns
   - Damage control laparotomy

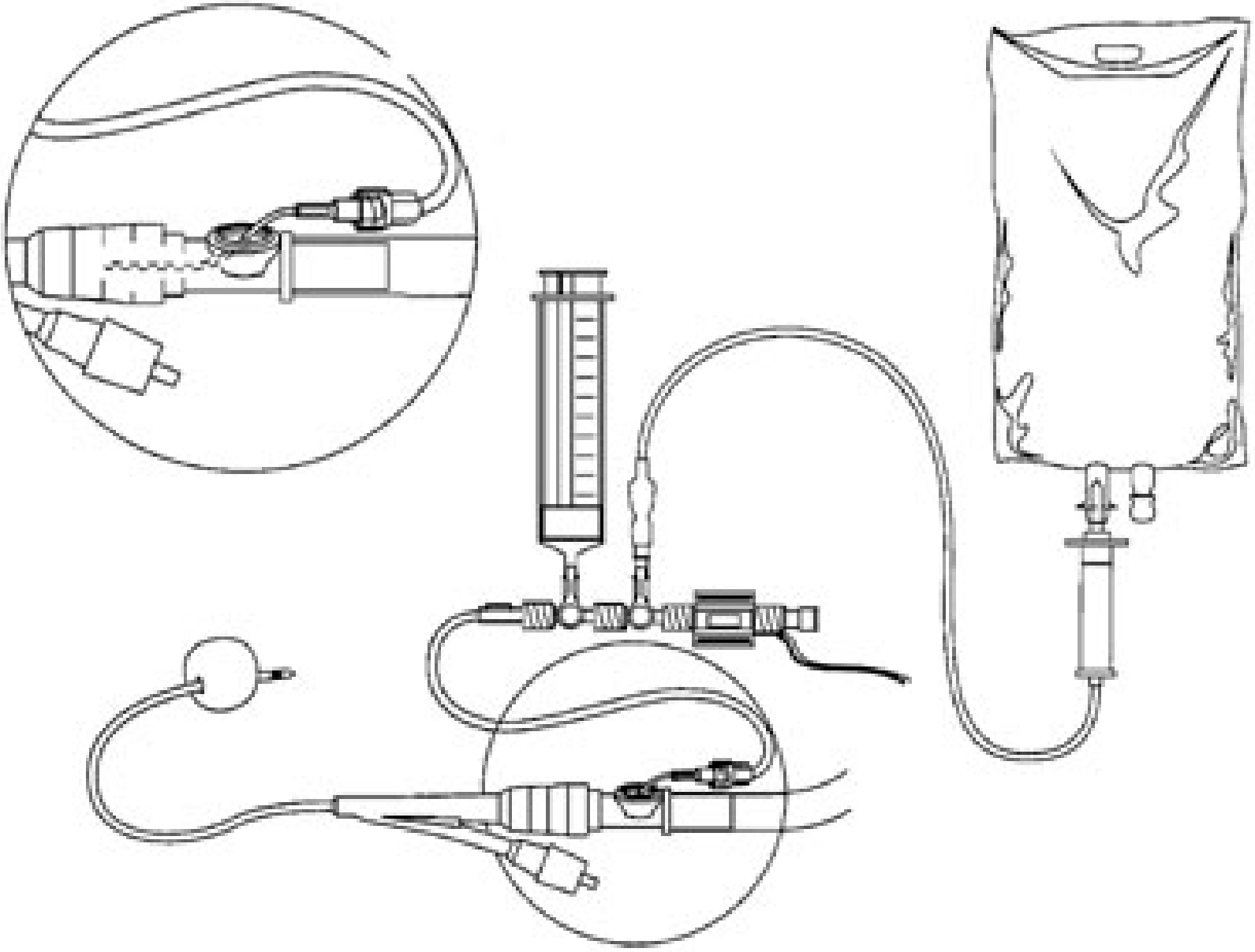
Type of Surgery (N = 263)	Total No. (%) of Patients With an Increased IAP (n = 104)*	Emergency Surgery (n = 174)†	Elective Surgery (n = 89)†	Elective vs Emergency Surgery
Upper gastrointestinal tract (n = 131)	**54** (41.2)	44/96 (45.8)	10/35 (28.6)	$\chi^2 = 2.48$, $P = .12$
Lower gastrointestinal tract (n = 70)	**27** (38.6)	25/54 (46.3)	2/16 (12.5)	$\chi^2 = 4.61$, $P < .05$
Vascular (n = 57)	**24** (42.1)	12/20 (60.0)	12/37 (32.4)	$\chi^2 = 3.00$, $P = .08$
Other (n = 5)	**1** (20.0)	1/4 (25.0)	0/1 (0)	$\chi^2 = 0.70$, $P = .40$

** Percentages are obtained by dividing the number of patients by the total number of patients who underwent that type of surgery (given in the first column).*
† Data are given as number of patients with an increased IAP divided by the total number of patients who underwent that type of surgery (percentage).

- Nature of Surgery and Intra-abdominal Pressure

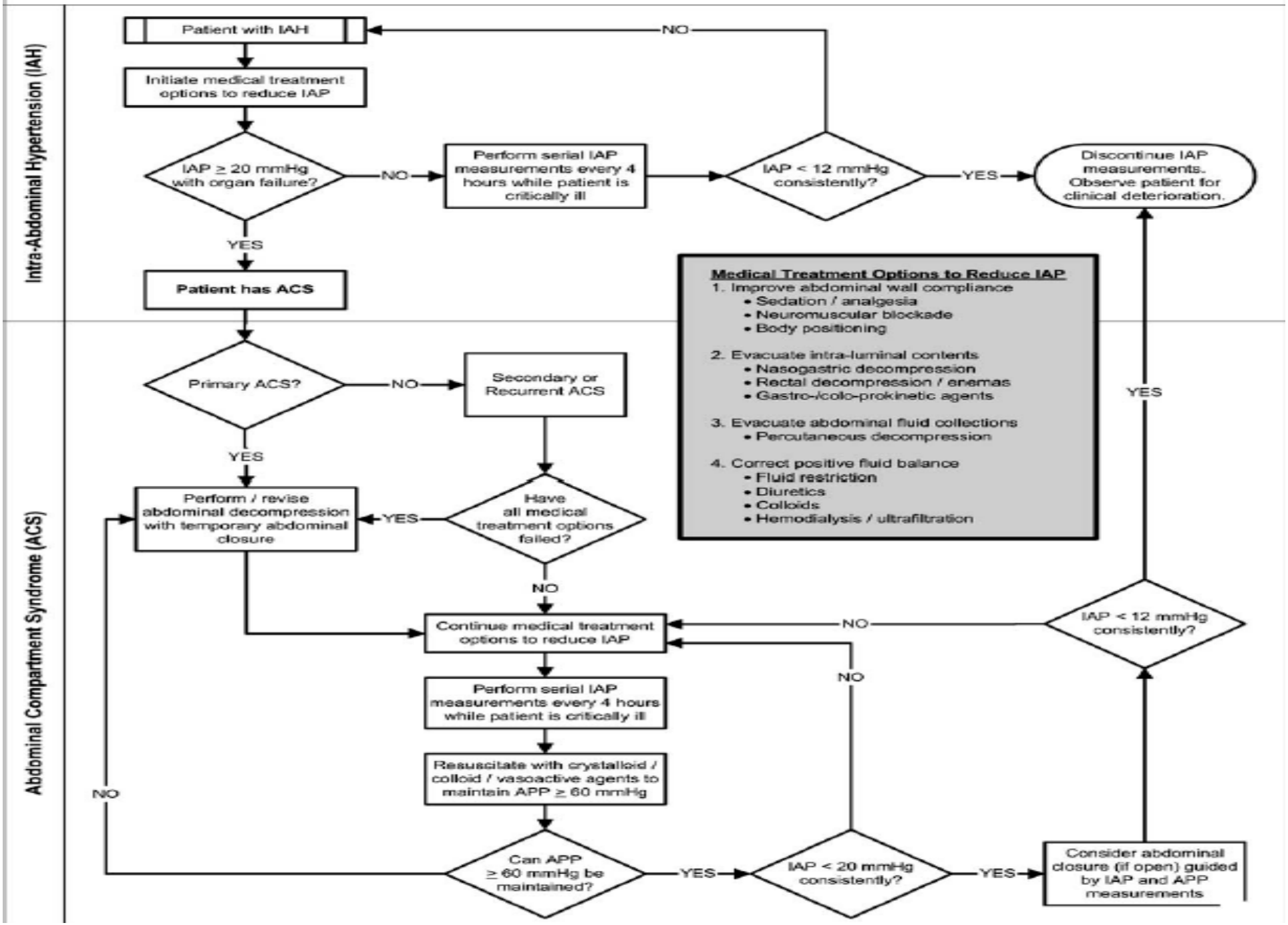
IAP assess-ment Algorithm

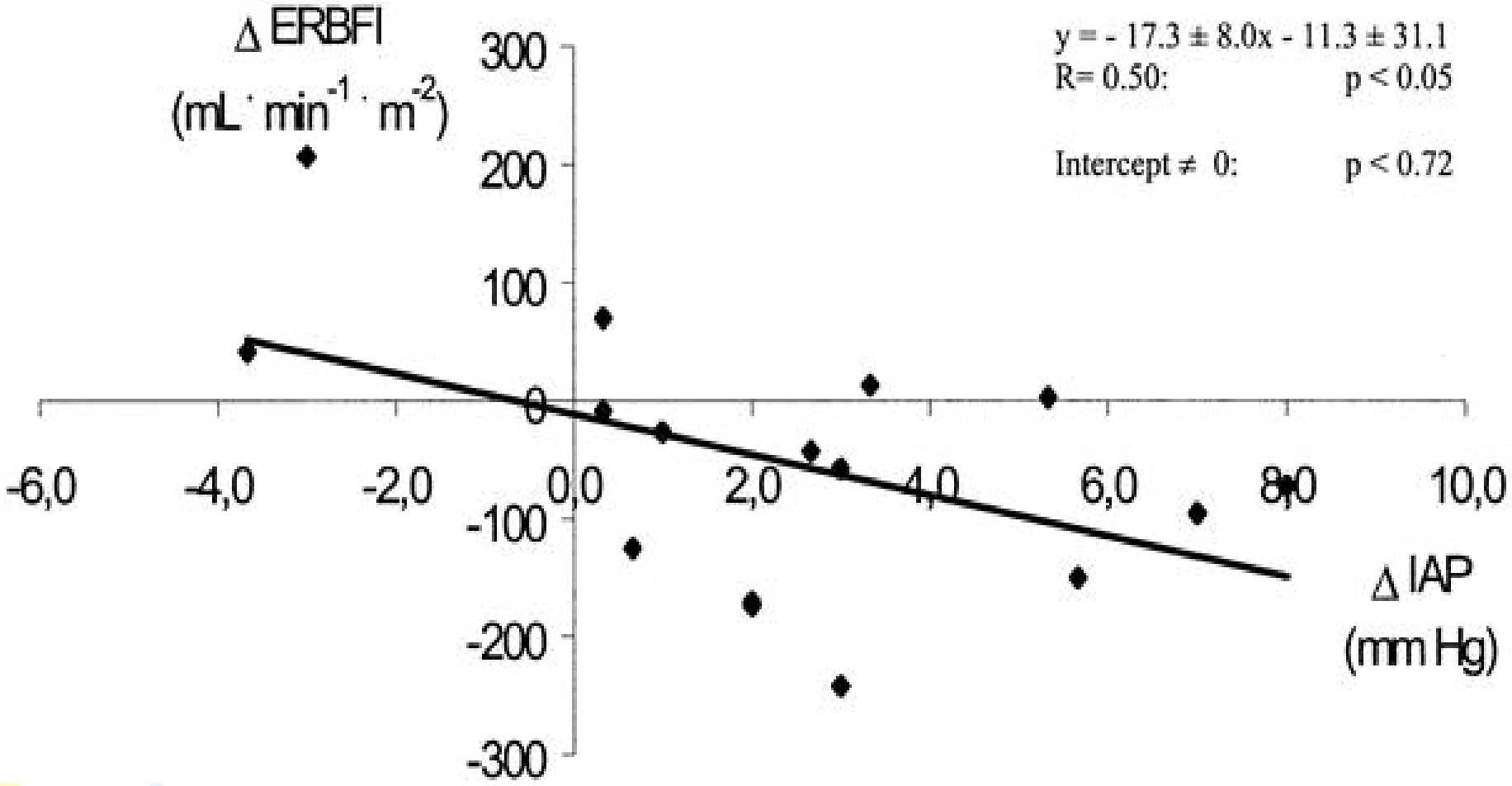




IAP measurement

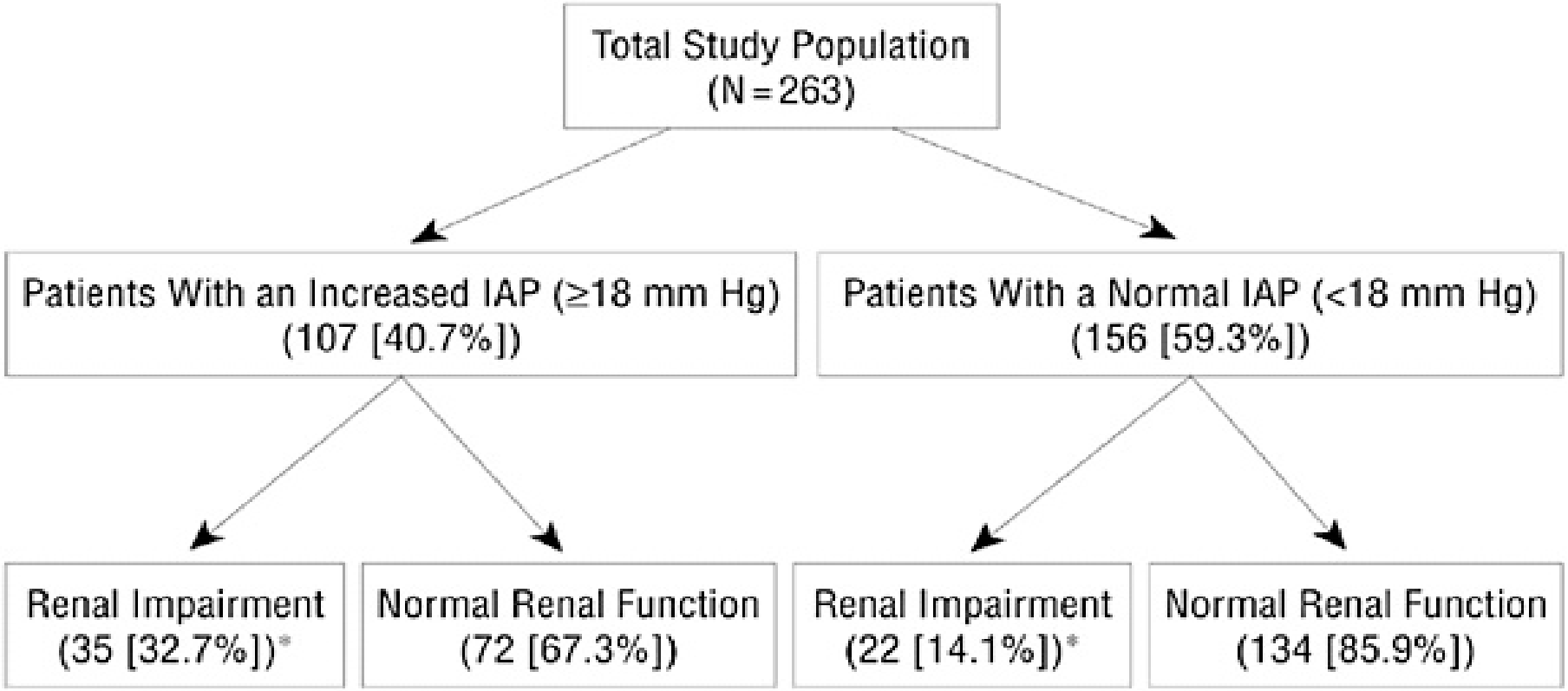
Intra-Abdominal Hypertension / Abdominal Compartment Syndrome Management Algorithm





- Correlation between changes in intraabdominal pressure (Δ IAP) and changes in effective renal blood flow index (Δ ERBFI).
Regression analysis revealed a weak inverse correlation between changes in IAP and ERBFI

From: Hering: Anesth Analg, Volume 92(5).May 2001.1226-1231



- A prospective study of all patients admitted to an ICU following abdominal surgery
- IAP was measured every 8 hours & 18 mm Hg or higher was considered increased

Sugrue: Arch Surg, Volume 134(10).October 1999.1082-1085

Risk Factors Assessed*	Patients With Normal Renal Function (n = 206)†	Patients With Renal Impairment (n = 57)†	Unadjusted Odds Ratio (95% Confidence Interval)
Increased IAP	72 (35.0)	35 (61.4)‡	2.96 (1.62-5.42)§
Hypovolemia	44 (21.4)	20 (35.1)	1.99 (1.05-3.77)
Aminoglycosides	77 (37.4)	33 (57.9)‡	2.30 (1.27-4.18)
Radiocontrast	23 (11.2)	12 (21.0)	2.12 (0.98-4.58)
Sepsis	76 (36.9)	37 (64.9)‡	3.16 (1.71-5.84)§
Hypotension	84 (40.8)	42 (73.7)‡	4.07 (2.11-7.80)§
CCF	7 (3.4)	3 (5.3)	1.58 (0.40-6.31)
Hypertension	49 (23.8)	24 (42.1)‡	2.33 (1.26-4.31)‡
Diabetes	15 (7.3)	5 (8.8)	1.22 (0.43-3.53)
Age >60 y	114 (55.3)	47 (82.4)‡	3.79 (1.82-7.92)§
NSAIDs	27 (13.1)	13 (22.8)	1.96 (0.94-4.10)
ACE inhibitors	18 (8.7)	6 (10.5)	1.23 (0.46-3.26)
Diuretics	23 (11.2)	13 (22.8)	2.35 (1.10-5.00)
Gout	7 (3.4)	3 (5.3)	1.58 (0.40-6.31)
Aortic clamping	35 (17.0)	19 (33.3)‡	2.44 (1.26-4.73)
Dehydration	7 (3.4)	2 (3.5)	1.03 (0.21-5.12)

** IAP indicates intra-abdominal pressure; CCF, congestive cardiac failure; NSAIDs, nonsteroidal anti-inflammatory drugs; and ACE, angiotension-converting enzyme.*

† Data are given as number (percentage) of patients.

‡ P<.01 (bivariate, χ^2 analysis).

§ P<.05 (unadjusted).

Forward stepwise logistic regression determined whether IAH is an independent cause of renal impairment

renal impairment was independently associated with 4 antecedent factors:

hypotension (*P*=.09)

sepsis (*P*=.006)

age older than 60 years (*P*=.03)

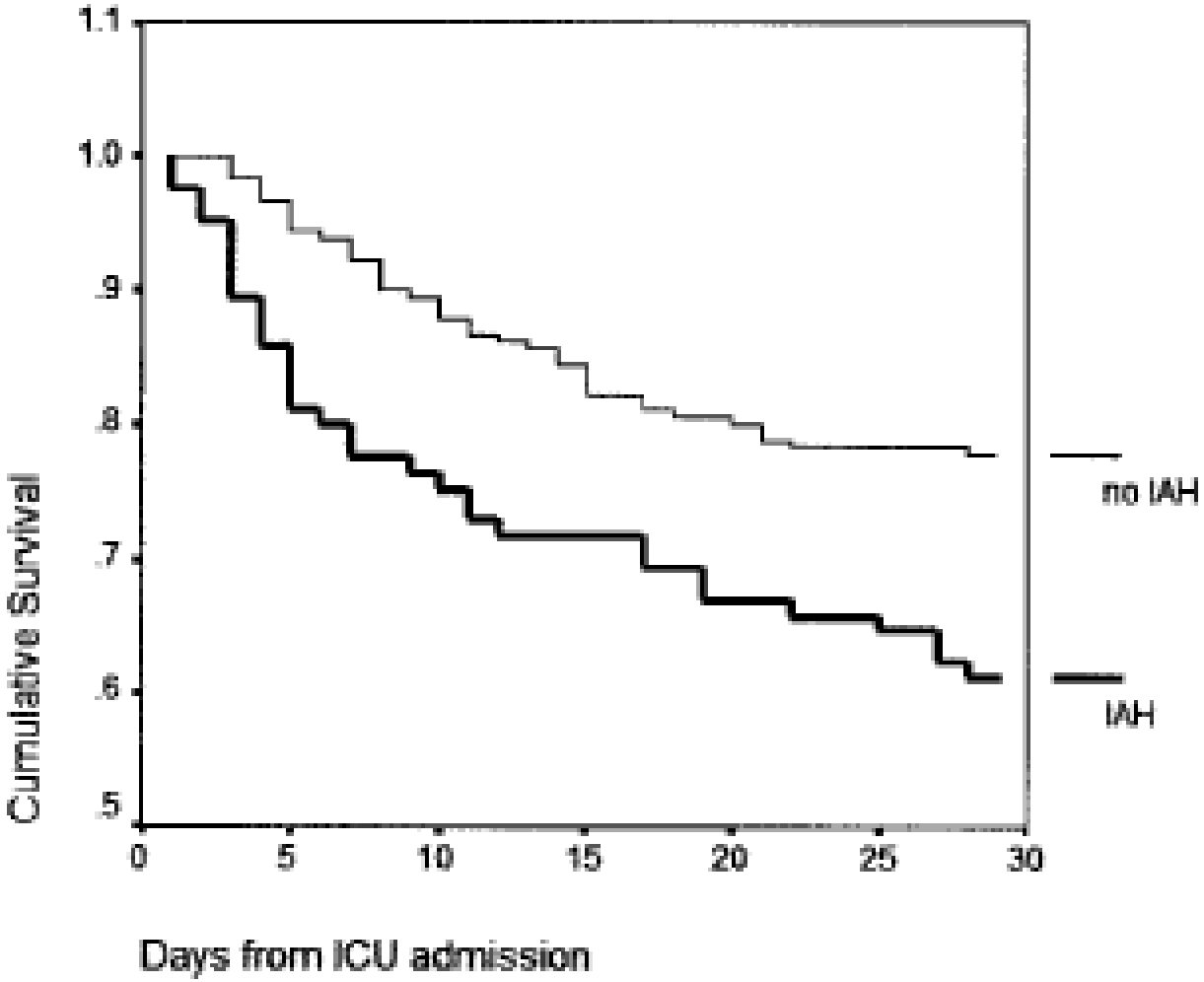
increased IAP (*P*=.004)

IAP, mm Hg (N = 263)	Patients With Renal Impairment (n = 57)*	Patients With Normal Renal Function (n = 206)*
<18 (n = 156)	22 (14.1)	134 (85.9)†
18-25 (n = 86)	22 (25.6)	64 (74.4)†
>25 (n = 21)	13 (61.9)	8 (38.1)†

**Data are given as number (percentage) of patients. Percentages are obtained by dividing the number of patients by the total number of patients with that specific IAP (given in the first column).*

†$\chi^2_3 = 26.06$, P<.001.

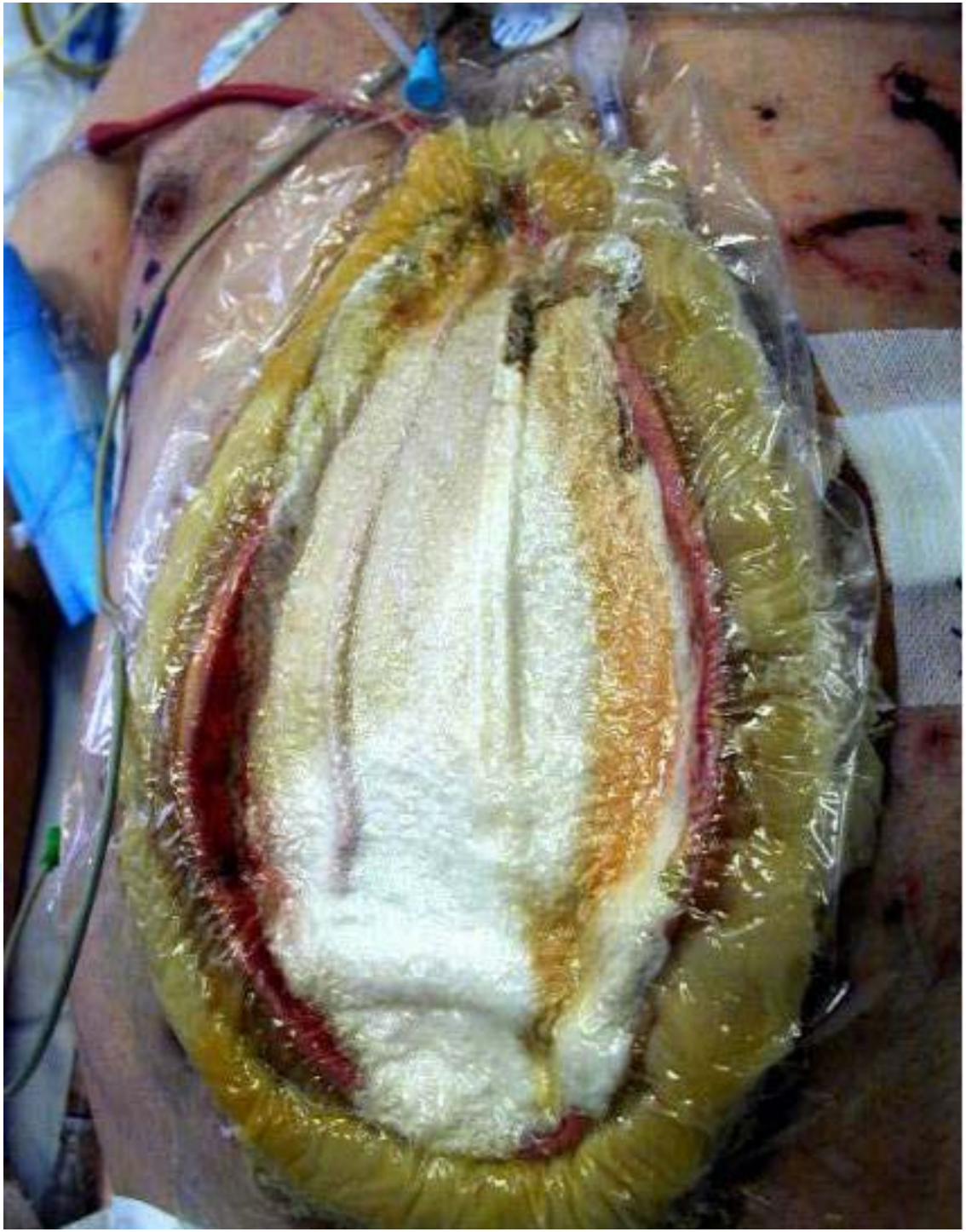
- An Analysis of Renal Function for Different Levels of Intra-abdominal Pressure



Kaplan Meier cumulative survival curve split according to patients with or without IAH
IAH during ICU stay was an independent outcome predictor.
Crit Care Med 2005; 33:315–322

Surgery related

- Cardiac surgery
- Abdominal aortic aneurysm repair



Parameter	Group I Mesh closure (n = 45)	Group II Fascial suture (n = 25)	*p* Value
Abdominal trauma index	29.3 ± 13.3	25.9 ± 18.7	0.375
Injury Severity Score	22.3 ± 9.8	21.1 ± 8.2	0.609
Revised Trauma Score	9.8 ± 2.9	11.1 ± 1.5	0.032
Worst base deficit	12.4 ± 6.6	11.4 ± 5.1	0.545
Worst lactate	6.3 ± 4.1	5.6 ± 3.2	0.489
Blood in 24 hours	13.9 ± 10.6	12.2 ± 6.5	0.512
Developed IAH	10 (22.2%)	13 (52%)	0.012
Mortality	5 (10.6%)	9 (36%)	0.003
MODS points	1.3 ± 2.4	3.1 ± 3.9	0.023

Comparison of mesh closure and fascial suture groups: A mesh fascial prosthesis (nonsuture of the fascia) at the initial surgery in high-risk patients may prevent the development & deleterious effect of IAH

J Trauma. 1998;44:1016-1021

- Causes & Classification of ARF
- RIFLE Criteria and its implication
- Fluid Therapy in ARF
- Common Renal Problems in ICU
  - Sepsis & ARF
  - Contrast Induced Nephrotoxicity
  - Drug induced Nephrotoxicity
  - Rhabdomyolysis
  - Abdominal Compartment Syndrome
  - Hepatorenal Syndrome

Hepatorenal Syndrome

- occurs in patients with chronic liver disease, advanced hepatic failure and portal hypertension.
- characterised by impaired renal function and marked abnormalities in the arterial circulation and activity of the endogenous vasoactive systems in the kidney.
- In the kidney, there is marked renal vasoconstriction which results in a low GFR.
- In the extrarenal circulation, arteriolar vasodilatation predominates resulting in reduced systemic vascular resistance and arterial hypotension

Diagnosis

- low GFR - serum creatinine >140 mcmol/l
  - creatinine clearance <40 ml/min
- absence of shock, ongoing bacterial infection, fluid losses and current treatment with nephrotoxic drugs
- no sustained improvement in renal function despite diuretic withdrawal and fluid resuscitation
- proteinuria <500 mg/day & no evidence of obstructive uropathy or parenchymal renal disease
- urine volume <500 ml/day
- urine Na <10 mmol/l
- urine osmolality >plasma
- urine RBCs <50 per high power field
- serum Na <130 mmol/l

Management

- haemodialysis, renal vasodilators, prostaglandin excretion modifiers, insertion of peritoneovenous shunts and TIPS have all been tried but do not improve survival
- terlipressin may reduce mortality and improve renal function
- uncontrolled studies suggest that the combination of furosemide, albumin and noradrenaline may improve renal function in type I hepatorenal syndrome
- in carefully selected patients liver transplantation improves survival

Conclusion

- ARF is a common problem in critically ill patients and is associated with high morbidity & mortality
- Important to identify those at risk
- Prevention
- Early treatment