CROSSTALK BETWEEN AKI &ALI

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INVASIVE MECHANICAL VENTILATION AS A RISK FACTOR FOR ACUTE KIDNEY INJURY IN THE CRITICALLY ILL

Mechanical ventilation (MV) is commonly regarded as a risk factor for acute kidney injury (AKI) in the critically ill.

Acute lung injury (ALI) and acute kidney injury (AKI) are complications often encountered in the setting of critical illness.

Both forms of end-organ injury commonly occur in similar settings of systemic inflammatory response syndrome, shock, and evolving multiple organ dysfunction.

(VIKI)

TABLE 103-1 NGAL as a Biomarker of AKI in the ICU

SITUATION	N	STUDY	AREA UNDER THE ROC CURVE	REF
Adults	632	NGAL measured at ICU admission predicted the development of severe AKI, similar to serum creatinine-derived eGFR.	0.77-0.88	26
Adults	301	Plasma NGAL was a good diagnostic marker for AKI development and for RRT use.	0.78-0.82	24
Adults	109	NGAL was higher in non-survivors than in survivors. Serum NGAL was a strong independent predictor for 28-day survival.	ND	23
Adults	700	Urine NGAL performed better than cystatin C for the prediction of sustained AKI.	ND	22
Adults	88	Urine NGAL was more useful than serum NGAL in predicting AKI. Urine NGAL levels were not elevated in septic patients without AKI.	0.86	21
Adults	65	NGAL at ICU admission was an early biomarker of AKI.	0.96	20
Adults	88	Plasma NGAL at ICU admission was an early biomarker of AKI. Plasma NGAL increased 48 hours before RIFLE criteria.	0.92	20
Children	140	Urine NGAL increased in AKI patients 2 days before a 50% or greater rise in serum creatinine.	0.78	17
Children	168	Serum NGAL increased in AKI patients compared with that in patients without AKI.		19
Adults	88	Serum NGAL predicted the development of AKI.	0.96	18
Children with sepsis	143	A significant difference was found in the serum NGAL between healthy children, critically ill children with SIRS, and critically ill children with septic shock.		19
Emergency department	635	Elevated urine NGAL in AKI patients was compared to prerenal azotemia, CKD, or normal kidney function. Urine NGAL was highly predictive of clinical outcomes.	0.948	91
Critically ill/Trauma	31	Urinary NGAL was a predictor of AKI.	0.98	92

AKI, acute kidney injury; CKD, chronic kidney disease; CPB, cardiopulmonary bypass; eGFR, estimated glomerular filtration rate; ND, not determined; NGAL, neutrophil gelatinase-associated lipocalin; RRT, renal replacement therapy; SCr, serum creatinine; SIRS systemic inflammatory response syndrome.

TABLE 103-2 Urinary IL-18 as a Biomarker of AKI in the ICU

SITUATION	N	STUDY	AREA UNDER THE ROC CURVE	REF
Adults on RRT	101	A strong correlation was found between serum IL-18 and the hospital mortality of ICU patients with dialysis-dependent AKI.	ND	40
ARDS adults	138	Urinary IL-18 predicted the development of AKI 24 and 48 h later. Urinary IL-18 on the day of initiation of mechanical ventilation was a strong predictor of mortality.	0.73	37
Children	137	The peak levels of IL-18 correlated with the severity of AKI. In nonseptic AKI patients, urinary IL-18 increased 2 days prior to serum creatinine.	ND	38
Infants	47	NGAL, IL-18, and cystatin C, but not KIM-1, differentiated patients with good versus poor outcomes in the early postoperative period.	0.62	93
Adults	451	Urinary IL-18 did not reliably predict AKI development but did predict poor clinical outcomes.	0.67	39
Adults	101	A strong correlation was found between serum IL-18 and the hospital mortality of ICU patients with dialysis-dependent AKI.	ND	40
Adults	4512	IL-18 predicted AKI.	0.66	41

ATN, acute tubular necrosis; ICU, intensive care unit; IL-18, interleukin-18; KIM-1, kidney injury molecule-1; ND, not determined; NGAL, neutrophil gelatinase-associated lipocalin; SCr, serum creatinine.

TABLE 103-3 KIM-1 as a Biomarker of AKI

SITUATION	N	STUDY	AREA UNDER THE ROC CURVE	REF
Adults	150	KIM-1 increased significantly by 6 hours after ICU admission, peaked at 24 hours, and remained significantly elevated until 48 hours.	ND	45
Infants	49	KIM-1 did not differentiate patients with good versus poor outcomes in the early postoperative period.	ND	93
Adults	700	KIM-1 increased at the time of AKI, not earlier.	0.73	46

KIM-1, kidney injury molecule-1.

TABLE 103-5 Cystatin C in AKI in the ICU

SITUATION	N	STUDY	AREA UNDER THE ROC CURVE	REF
Adults septic shock	6	Serum cystatin C showed limited value in determining the residual renal function in septic patients.	ND	95
Noncardiac children	160	NGAL was most diagnostic of AKI as defined by cystatin C. Combining serum creatinine and serum cystatin C improved the diagnostic performance.	0.69	63
Adults	151	Serum and urine cystatin C were poor biomarkers for AKI and RRT in the ICU.	0.66	62
Adults	327	Cystatin C or creatinine did not differ significantly between septic and nonseptic patients. Cystatin C predicted a composite outcome.	0.78-0.80	61
Adults	47	Serum cystatin C outperformed serum creatinine for the detection of an impaired GFR in critically ill patients.	0.94	60
Adults	50	Serum cystatin C correlated better with GFR (creatinine clearance) than serum creatinine.	0.927	57
Adults	422	Cystatin C rapidly detected AKI in the ICU and predicted sustained AKI.	0.80	59
Children	25	Serum cystatin C and B2M were better than creatinine in the identification of a creatinine clearance of under 80 mL/min.	0.792-0.851	58

AKI, acute kidney injury; B2M, beta-2 microglobulin; GFR, glomerular filtration rate; NGAL, neutrophil gelatinase-associated lipocalin; RRT, renal replacement therapy; SCr, serum creatinine.

TABLE 103-6 Cytokines as Biomarkers of AKI in the ICU

SITUATION	N	STUDY	AREA UNDER THE ROC CURVE	REF
Adults	879	Increased levels of IL-6, sTNFR1, sTNFR2, and PAI-1 were independently associated with the development of AKI.		71,72,73
Adults	103	Patients with AKI had significantly higher levels of plasma IL-6, IL-8, and IL-10 than patients without AKI.	ND	70
Adults	98	IL-1β, TNFα, IL-6, IL-8, and IL-10 were significantly elevated. Increased serum IL-6, IL-8, and IL-10 at baseline was correlated with increased in-hospital mortality in AKI patients.	ND	69
Severe sepsis patients	547	Increased log plasma IL-6 and APACHE II score were significant risk factors of AKI.		68
Septic shock	537	Elevated serum TNF-RI and RII were associated with the development of ARF. TNF-R was an independent predictor of mortality in AKI patients.		96

TABLE 103-7 L-FABP as a Biomarker of AKI in the ICU

SITUATION	N	STUDY	AREA UNDER THE ROC CURVE	REF
Adults	80	Urinary L-FABP levels in patients with septic shock were significantly higher than those in patients with severe sepsis without shock, patients with ARF, and healthy subjects.	ND	76
Adults	145	AKI patients had significantly higher levels of urinary NGAL and L-FABP, as well as higher mortality. Urinary L-FABP was an independent predictor for 90-day mortality.	0.73-0.78	77
Adults	337	Mortality in AKI patients diagnosed by serum creatinine was increased remarkably when urinary L-FABP and NAG were positive.	0.75	97

L-FABP, L-type fatty acid binding protein; NAG, N-acetyl glucosaminidase; NGAL, neutrophil gelatinase-associated lipocalin.

TABLE 103-8 Other Biomarkers of AKI in the ICU

BIOMARKER	SITUATION	N	STUDY	AREA UNDER THE ROC CURVE	REF
Urinary TIMP-2 and IGFBP7 combined	Adults	728	Urinary TIMP-2 and IGFBP7 predicted the primary endpoint: moderate to severe AKI (KDIGO stage 2 to 3) within 12 hours of sample collection.	0.80	78
Urinary TIMP-2 and IGFBP7 combined	Adults	692	[TIMP-2][IGFBP7] measured early on in the setting of critical illness may identify patients with AKI at increased risk for mortality or receipt of RRT over the next 9 months.		80
sCD163	Adults	80	There is a potential value of urine sCD163 levels for identifying sepsis and AKI.	0.83	82
sTREM-1	Adults	104	The sepsis group had higher levels of urine sTREM-1 and APACHE II scores. Urine sTREM-1, SCr, and BUN levels increased at 48 h before AKI.	ND	84
RBP4	Adults	123	RBP4 was significantly decreased in critically ill patients and was associated with hepatic and renal function, insulin resistance, and acute mortality.	ND	85
Ang-2	Adults on RRT	117	Ang-2 levels were higher in AKI patients with RIFLE category—injury or failure. Ang-2 was a strong and independent predictor of mortality in dialysis-dependent ICU patients.	ND	86
Resistin	Adults	230	Serum resistin was elevated in sepsis and was associated with renal failure and unfavorable outcomes.	ND	87

Table 1. Comparison of Recent Consensus AKI Definitions

AKI Stage	Urine Output[a]	KDIGO	AKIN	RIFLE
1	<0.5 mL/kg/h for 6-12 h	Scr to 1.5-1.9 × baseline over 7 d or ≥0.3 mg/dL absolute increase over 48 h	Scr to 1.5-2 × baseline or ≥0.3 mg/dL absolute Scr increase within 48 h	*Risk*: Scr to ≥1.5 × increase within 7 d, sustained for ≥24 h
2	<0.5 mL/kg/h for ≥12 h	Scr to 2.0-2.9 × baseline	Scr to >2-3 × baseline	*Injury*: Scr to ≥2 × increase
3	<0.3 mL/kg/h for ≥24 h or anuria for ≥12 h	Scr to ≥3.0 × baseline, or Scr increase to ≥4.0 mg/dL or initiation of RRT	Scr to >3.0 × baseline, or Scr increase to ≥4.0 mg/dL (with increase of 0.5 mg/dL) or initiation of RRT	*Failure*: Scr to ≥3.0 × increase or Scr increase to ≥4.0 mg/dL (with increase of 0.5 mg/dL) or initiation of RRT
				Loss: Complete loss of kidney function for >4 wk
				ESKD: ESKD for >3 mo

Table 2. Causes of AKI

Type	Examples of Specific Causes
Decreased kidney perfusion ("prerenal" states)	
Hypovolemia	Increased losses (hemorrhage, burns, massive vomiting or diarrhea), poor oral intake
Reduced cardiac output	Heart failure, cardiac tamponade, massive pulmonary embolism
Renal vasomodulation/shunting	Medications (NSAID, ACEi/ARB, cyclosporine, iodinated contrast), hypercalcemia, hepatorenal syndrome, abdominal compartment syndrome
Systemic vasodilation	Sepsis, SIRS, hepatorenal syndrome
Intrarenal causes	
Vascular	Renal artery stenosis, arterial/venous cross-clamping
Microvascular	Thrombotic microangiopathies (TTP, HUS, aHUS, DIC, APS, malignant hypertension, scleroderma renal crisis, preeclampsia/HELLP syndrome, drug-induced), cholesterol emboli
Glomerular	Rapidly progressive (crescentic) GN: anti–glomerular basement membrane; immune complex diseases: IgA nephropathy, postinfectious, lupus, mixed cryoglobuminemia with MPGN; pauci-immune glomerulonephritis: ANCA-associated vasculitides: GPA, MPA, EGPA (Churg-Strauss); ANCA-negative; nephrotic-range proteinuria with associated AKI: HIV-associated nephropathy (secondary FSGS); other causes of nephrotic-range proteinuria that commonly associate with AKI: minimal change disease with ATN/AIN; membranous nephropathy + crescentic GN or renal vein thrombosis; myeloma + multiple different pathologies, but in particular light chain cast nephropathy
Tubulointerstitium	AIN: medications, infection, lymphoproliferative disease; pigment nephropathy: rhabdomyolysis (myoglobin), massive hemolysis (hemoglobin); crystal nephropathy: uric acid (tumor lysis), acyclovir, sulfonamides, protease inhibitors (indinavir, azatanavir), methotrexate, ethylene glycol, acute phosphate nephropathy, oxalate nephropathy; myeloma-associated AKI (cast nephropathy); ATN: ischemia (shock, sepsis), inflammatory (sepsis, burns), medications (see Box 1; osmotic nephrosis in setting of sucrose, mannitol and hydroxyethylstarch use)
Postrenal causes	
Bladder outlet	Benign prostatic hypertrophy, cancer, strictures, blood clots
Ureteral	Bilateral obstruction (or unilateral with one kidney): stones, malignancy, retroperitoneal fibrosis
Renal pelvis	Papillary necrosis (NSAIDs), stones

Box 1. Medications Commonly Associated With Acute Tubular Necrosis

- Aminoglycosides (tobramycin, gentamycin)
- NSAIDs (ibuprofen, naproxen, ketorolac, celecoxib)
- ACEi (captopril, lisinopril, benazepril, ramipril)
- ARB (losartan, valsartan, candesartan, irbesartan)
- Amphotericin
- Cisplatin
- Foscarnet
- Iodinated contrast
- Pentamidine
- Tenofovir
- Zolendronic acid

Box 2. Key Medications Requiring Dose Adjustment (or Cessation) in AKI

- Analgesics (morphine, meperidine, gabapentin, pregabalin)
- Antiepileptics (lamotrigine)
- Antivirals (acyclovir, gancyclovir, valgancyclovir)
- Antifungals (fluconazole)
- Antimicrobials (almost all antimicrobials need dose adjustment in AKI, with important exceptions of azithromycin, ceftriaxone, doxycycline, linezolid, moxifloxacin, nafcillin, rifampin)
- Diabetic agents (sulfonylureas, metformin)
- Allopurinol
- Baclofen
- Colchicine
- Digoxin
- Lithium
- Low-molecular-weight heparin
- NOACs

MECHANICAL VENTILATION/ACUTE LUNG INJURY

- mechanical ventilation (MV) has been devised
- based upon the four pathophysiologic patterns of respiratory failure
- Type I respiratory failure (acute hypoxemia)
- Type II respiratory failure (hypoventilatory)
- occurs in the setting of the failure of alveolar ventilation leading to the retention of carbon dioxide (hypercapnia).
- Type III respiratory failure
- ('perioperative') relates to the susceptibility of the pulmonary
- system to atelectasis in the perioperative period.
- type IV respiratory failure (shock)
- fall outside the specific definitions of the first three categories categories,
- and require MV for support in the setting of systemic
- hypoperfusion (cardiogenic, hypovolemic, septic,
- or other forms of shock) associated respiratory muscle
- fatigue and increased minute ventilation requirements
- (systemic inflammation, hypermetabolism, metabolic
- acidosis).

MECHANICAL VENTILATION/ACUTE LUNG INJURY

- ALI is a clinical syndrome characterized by acute (less than 7 days) onset of severe hypoxemia and bilateral pulmonary infiltrates in the absence of elevated left atrial pressures.

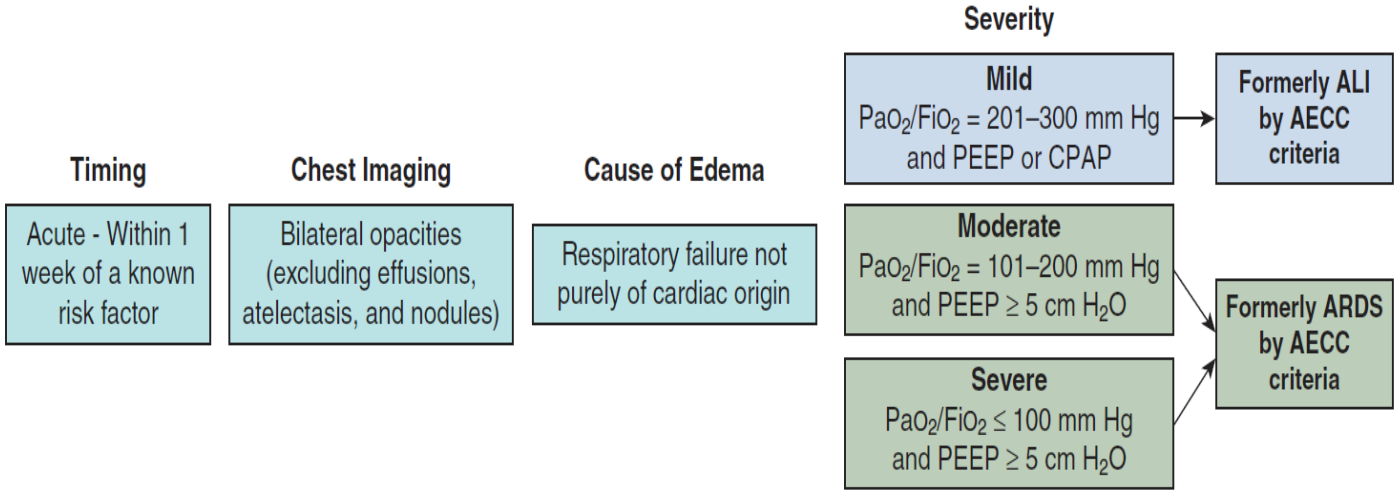

FIGURE 67-2 ■ The Berlin Definition of ARDS.

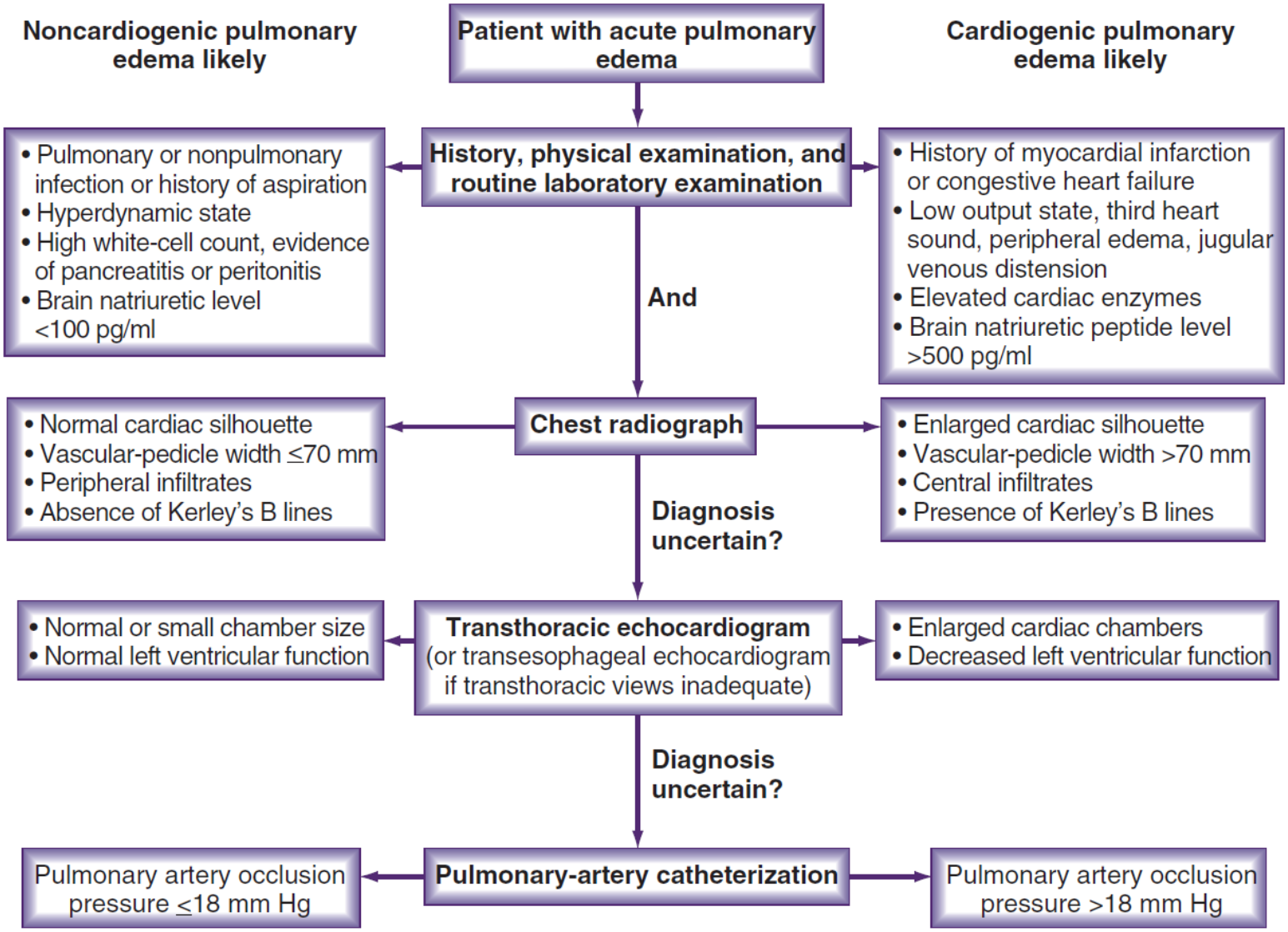

FIGURE 67-3 ■ Algorithm for differentiating between cardiogenic and noncardiogenic pulmonary edema. (With permission from Ware LB, Matthay MA. Clinical practice. Acute pulmonary edema.

TABLE 67-2 Ventilator Management of Patients with ARDS

CALCULATE PREDICTED BODY WEIGHT (PBW)

- Males: PBW (kg) = 50 + 2.3 [(height in inches) – 60] or
  50 + 0.91 [(height in cm) – 152.4]
- Females: IBW (kg) = 45.5 + 2.3 [(height in inches) – 60] or
  45.5 + 0.91 [(height in cm) – 152.4]

VENTILATOR MODE

Volume Assist/Control until weaning

TIDAL VOLUME (VT)

- Initial Vt: 6 mL/kg predicted body weight
- Measure inspiratory plateau pressure (Pplat, 0.5 sec inspiratory pause) every 4 hours AND after each change in PEEP or Vt.
- If Pplat > 30 cm H_2O, decrease Vt to 5 or to 4 mL/kg.
- If Pplat < 25 cm H_20 and Vt < 6 mL/kg PBW

RESPIRATORY RATE (RR)

- With initial change in Vt, adjust RR to maintain minute ventilation.
- Make subsequent adjustments to RR to maintain pH 7.30-7.45, but do not exceed RR = 35/min and do not increase set rate if $PaCO_2$ < 25 mm Hg.

I : E Ratio

Acceptable range, 1:1-1:3 (no inverse ratio)

FIO_2, PEEP, AND ARTERIAL OXYGENATION

Maintain PaO_2 = 55-80 mm Hg or SpO_2 = 88%-95% using the following PEEP/FiO_2 combinations:

FiO_2	0.3-0.4	0.4	0.5	0.6	0.7	0.8	0.9	1
PEEP	5-8	8-14	8-16	10-20	10-20	14-22	16-22	18-25

ACIDOSIS MANAGEMENT

- If pH < 7.30, increase RR until pH ≥ 7.30 or RR = 35/min.
- If pH remains <7.30 with RR = 35, consider bicarbonate infusion.
- If pH < 7.15, Vt may be increased (Pplat may exceed 30 cm H_2O).

ALKALOSIS MANAGEMENT

If pH > 7.45 and patient not triggering ventilator, decrease set RR but not below 6/min.

FLUID MANAGEMENT

- Once patients are out of shock adopt a conservative fluid management strategy.
- Use diuretics or fluids to target a central venous pressure (CVP) of <4 or a pulmonary artery occlusion pressure (PAOP) of <8.

LIBERATION FROM MECHANICAL VENTILATION

- Daily interruption of sedation
- Daily screen for spontaneous breathing trial (SBT)
- SBT when all of the following criteria are present:
  (a) FiO_2 < 0.40 and PEEP < 8 cm H_2O
  (b) Not receiving neuromuscular blocking agents
  (c) Patient is awake and following commands.
  (d) Systolic arterial pressure > 90 mm Hg without vasopressor support
  (e) Tracheal secretions are minimal, and the patient has a good cough and gag reflex.

SPONTANEOUS BREATHING TRIAL

- Place patient on 5 mm Hg pressure support with 5 mm Hg PEEP *or* T-piece.
- Monitor HR, RR, oxygen saturation for 30-90 minutes.
- Extubate if there are no signs of distress (tachycardia, tachypnea, agitation, hypoxia, diaphoresis).

PATHOPHYSIOLOGY

- *Renal Effects of ALI and Mechanical Ventilation*
- AKI is an independent predictor of mortality in ICU patients.
- Unfortunately, AKI often develops as a

component of multi-organ system dysfunction in critically ill patients and may lead to mortality rates in excess of 60%.

- Recent advances in critical care, including the implementation of lung-protective ventilatory strategies, have disclosed the role of inflammatory mediators of ALI .
- And specifically ventilator-induced lung injury in the pathogenesis of AKI, which in some cases might appropriately be called ventilator-induced kidney injury (VIKI).

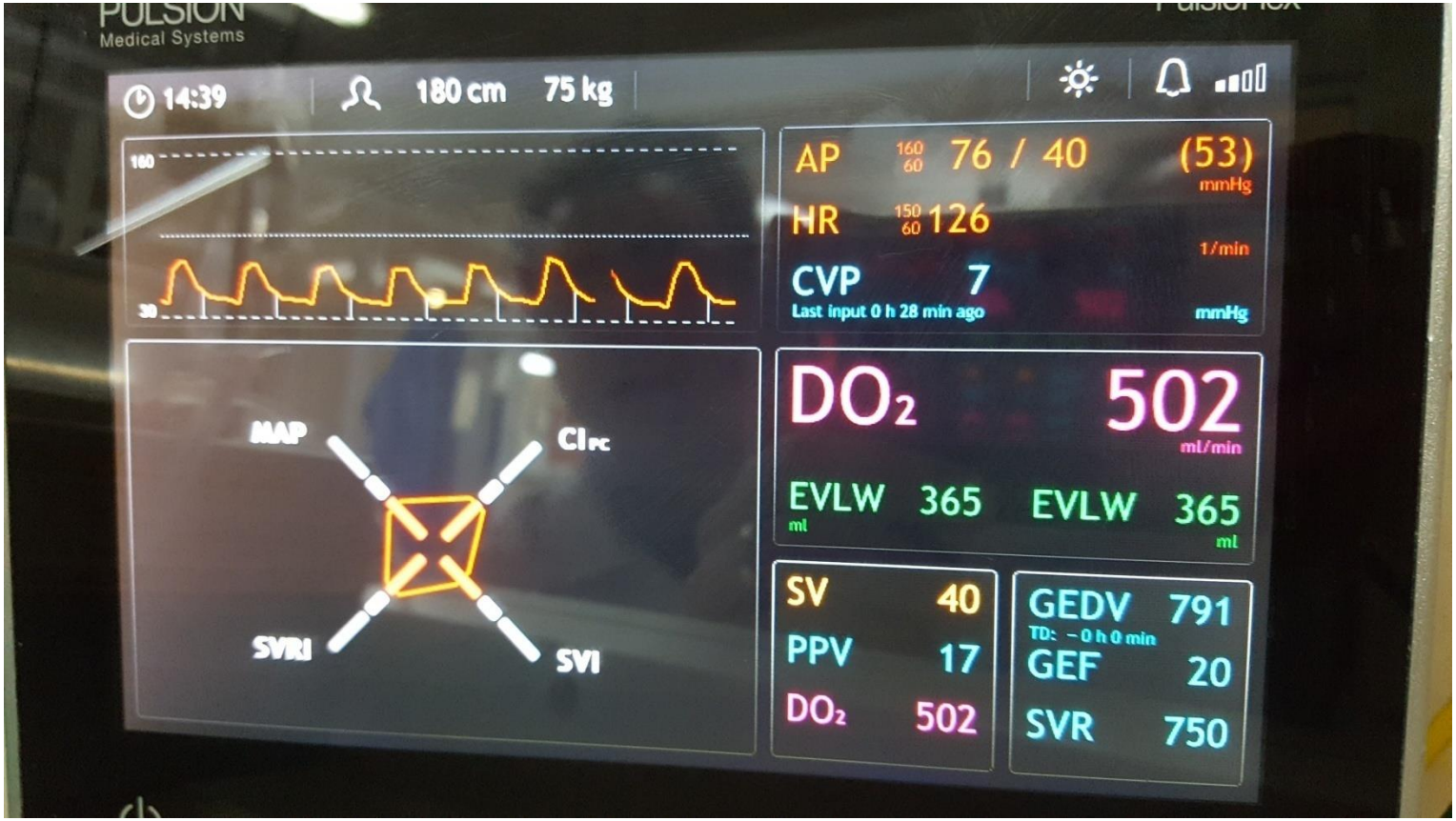
PULSION
Medical Systems
14:39
180 cm
75 kg
160
30
AP
160
60
76 / 40
(53)
mmHg
HR
150
60
126
1/min
CVP
7
Last input 0 h 28 min ago
mmHg
MAP
CI PC
SVRI
SVI
DO2
502
ml/min
EVLW
365
ml
EVLW
365
ml
SV
40
PPV
17
DO2
502
GEDV
791
TD: – 0 h 0 min
GEF
20
SVR
750

Table 1

Summary of the characteristics of the studies comparing patients with and without mechanical ventilation.

Author/year	Inclusion diagnosis	Subgroup	Criteria type used	MV precedes AKI
Mataloun 2006 [17]	General population	Mixed	Absolute sCr rise	Yes
Payen 2008 [18]	General population	Mixed	Absolute sCr rise	Unclear
Fonseca Ruiz 2011 [26]	General population	Mixed	AKIN	Unclear
Medve 2011 [30]	General population	Mixed	AKIN	Unclear
Piccinni 2011 [33]	General population	Mixed	RIFLE	Unclear
Brito 2009 [19]	CABG	Cardiac disease	Dialysis, relative and absolute sCr rise	Yes
Marenzi 2010 [24]	STEMI with cardiogenic shock	Cardiac disease	Relative sCr rise	Yes
Iglesias 2010 [22]	Orthotopic liver transplant	Gastro-intestinal	AKIN	Yes
Lopes 2011 [28]	Cirrhosis	Gastro-intestinal	RIFLE	Unclear
O'Riordan 2011 [31]	Paracetamol hepatotoxicity	Gastro-intestinal	AKIN	Unclear
Abdulkader 2010 [21]	2009 Influenza A (H1N1)	Influenza A	RIFLE	Unclear
Jung 2011 [27]	2009 Influenza A (H1N1)	Influenza A	RIFLE	Unclear
Martin-Loeches 2011 [29]	2009 Influenza A (H1N1)	Influenza A	AKIN	Unclear
Pettila 2011 [32]	2009 Influenza A (H1N1)	Influenza A	RIFLE	Unclear

EFFECTS OF MECHANICAL VENTILATION AND ALI ON RENAL FUNCTION
HEMODYNAMIC EFFECTS OF PPV

THE EFFECTS OF CONTINUOUS PRESSURE BREATHING ON KIDNEY FUNCTION [1]

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(Received for publication February 18, 1947)

In 1947, PPV was first shown to affect renal function and perfusion

two main components contributing to the decrease in renal perfusion and function caused by PPV,broadly categorized as hemodynamic and neurohormonal.

Increased intrathoracic pressure associated with PPV decreases the venous return to the heart (preload) and may result in decreased cardiac output.

EFFECTS OF MECHANICAL VENTILATION AND ALI ON RENAL FUNCTION

- The increase in intrathoracic pressure has been shown to correlate with a decrease in renal plasma flow, glomerular filtration rate (GFR) and urine output during PPV.

- PPV has been shown to compress the mediastinal structures and pulmonary vasculature and may result in increased right ventricular afterload.

- PPV in patients with increased intrathoracic pressure (injured, stiff lungs or chest wall) or intra-abdominal pressure (morbid obesity,abdomina compartment syndrome) may act to decrease renal blood flow by increasing renal venous pressure.

- (which diminishes renal perfusion pressure) and by
- compressing the renal vasculature, thus leading to AKI.

NEUROHORMONAL EFFECTS OF PPV

- The end result of all of these neurohormonal pathways is diminished renal blood flow, decreased GFR, and fluid retention (salt and water) with oliguria.

- Despite conflicting data, there is some evidence that fluid retention is caused PPV-induced production of vasoactive substances.

- These mediators shift intrarenal blood flow from the cortex
- to the medulla, resulting in greater fluid retention at any level of renal perfusion.

- PPV has been shown to increase plasma renin activity in both animal
- models and humans.

- PPV has been shown to alter a variety of neurohormonal systems including sympathetic outflow, the reninangiotensi axis, nonosmotic vasopressin (ADH) releas and atrial natriuretic peptide (ANP)production.

- PPV leads to increased sympathetic tone, secondary activation
- of the renin-angiotensin axis, and decreased renal
- plasma flow, GFR and urine output.

- Of course, even
- if ANP suppression does play a role in causing PPV-induced
- sodium retention and oliguria, it may not explain
- the reported decrease in GFR caused by PPV.

Mechanisms of impaired renal function with PEEP

Richard J. Mullins, M.D.[2], Elizabeth J. Dawe, D.V.M.[2], Charles E. Lucas, M.D., FACS[2], Anna M. Ledgerwood, M.D., FACS[2], Steven M. Banks, M.S.[3]

Anesthesiology
V 41, No 5, Nov 1974

Renal Hemodynamics and Function with Continuous Positive-pressure Ventilation in Dogs

Stephen V. Hall, M.D., E. Ernest Johnson, M.D.,* John Hedley-Whyte, M.D.†*

J Nephrol. 2006 Sep-Oct;19(5):556-65.

Acute kidney dysfunction secondary to the abdominal compartment syndrome.

Shear W[1], Rosner MH.

PATHOPHYSIOLOGIC EFFECTS OF AKI ON PULMONARY FUNCTION

Uremic lung: new insights into a forgotten condition

Paul J. Scheel[1], Manchang Liu[1] and Hamid Rabb[1]

September 1, 1956

PULMONARY CONGESTION AND EDEMA IN UREMIA

Skottowe W. DePass, M.D.; Joseph Stein, M.D.; Maxwell H. Poppel, M.D.; et al

- AKI was thought to lead to increas pulmonary vascular permeability and pulmonary congestion; thus, the term ‘uremic lung’ was coined.

- Problems such as refractory hyperkalemia pulmonary edema, or uremic manifestations such as pericarditis are related to AKI when they acutely develop in the appropriate setting.

- (bleeding diathesis and gastrointestinal bleed, leukocyte dysfunction with immunosuppression and nosocomial infection).

INFLAMMATORY MEDIATORS AND VENTILATOR-INDUCED LUNG AND KIDNEY INJURY

- Mounting evidence points to the rol cytokines and chemokines in the pathogenesis of ARDS.
- pro-inflammatory effects of PPV may be source of AKI, especially in the setting of mechanical ventilation and lung-injurious.
- ventilator strategies (higher tidal volumes and lower positive end-expiratory pressure, PEEP).

Mechanical ventilation alters airway nucleotides and purinoceptors in lung and extrapulmonary organs.

Douillet CD, et al. Am J Respir Cell Mol Biol. 2005.
Show full citation

Twenty-eight rats were randomized to: (i) unventilated control animals; (ii) tidal volume (VT; 6 ml/kg); (iii) VT (6 ml/kg) and positive end-expiratory pressure (PEEP; 5 cm H20); (iv) VT (12 ml/kg); or (v) VT (12 ml/kg) and PEEP (5 cm H20).

They demonstrated that injurious mechanical ventilation strategies induced production of a variety of inflammatory cytokines (IL-8 and monocyte chemotactic protein-1, amongst others).

They further demonstrated
that this injurious strategy induced epithelial cell apoptosis in both the kidneys and intestines, providing concrete evidence of injurious distant organ cross talk
initiated by PPV-requiring ALI leading to VIKI

ROLE OF NITRIC OXIDE IN ANIMAL MODELS OF ALI

- lung-injurious ventilation led to a significant increase in renal endothelin-1 production, presumably leading to increased renal vasoconstriction.
- Key roles in a variety of cellular functions, including vascular and epithelial permeability and apoptosis.
- nonselective inhibition of nitric oxide synthase (NOS) leads to elevated systemic blood pressure and marked renal vasoconstriction.
- PPV with injurious high tidal volumes (20 ml/kg) induced NOS expression in both the lung and the kidney.
- Thus, it appears that increased vascular permeability and associated cytokine release are contributors to the development of AKI in the setting of PPV.

Systemic Microvascular Leak in an *In Vivo* Rat Model of Ventilator-induced Lung Injury

Won-Il Choi, Deborah A. Quinn, Kwon Moo Park, Ramzi K. Moufarrej, Behrouz Jafari, Olga Syrkina, Joseph V. Bonventre, and Charles A. Hales

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In summary, the decreased morbidity and mortality of patients with ALI achieved with lung-protectivestrategies for mechanical ventilation are likely mediated not only by amelioration of ventilator-induced lung injury and inflammation but also by diminished injurious cross talk with distant organs, including the kidneys.

PERMISSIVE HYPERCAPNIA AND ITS EFFECTS ON CYTOKINES

- hypercapnic acidosis (type II respiratory failure) has been shown to have a dose-dependent protective effect against myocardial ischemi reperfusion injury.
- The protective effect of hypercapnic acidosis may result from the inactivation of calcium channels (leading to regional vasodilation), a reduction in cellular oxygen demand.
- Hypercapnia can decrease the conversion rate of
- I- to NF- B, and accordingly decrease the release of cytokines (IL-8 and ICAM-1) that are implicated in the pathogenesis of ALI, AKI, and other forms of tissue injury .

ANIMAL MODELS OF ALI AND DISTANT ORGAN EFFECTS

- prophylaxis with IL-10 decreased the intensity of the inflammatory respons induced by nephrectomy.
- Using IL-10, other data suggest the potential utility of anti-inflammatory therapy to diminish ALI secondary to AKI.

- potential role for IL-6 inhibition to
- prevent lung injury in the setting of AKI.

- further investigation of the use of IL-10
- and other anti-inflammatory agents as potential therapeutic options for early AKI.


Backup ventilation on
Insp Hold
Exp Hold
Manual Breath
Spirometry
Mech/Spont
Timing
Pulmonary
Per Weight
Gases
Metabolics
Paw
Pmax
Ppeak
PEEP
A/C PC
10:28
STANDBY
CARESCAPE R860


PetCO2 low
Modes
INTELLIVENT
22
Ppeak
5.0
ExpMinVol
405
VTE
12
fTotal
1:1.5
I:E
97%
SpO2
View 1/2
Auto
Quick Wean
More
CO2 elimination
Ppeak
PetCO2
24 PetCO2 mmHg
10
Target Shift
Quick Wean
Automatic
Disabled
Automatic SBT
SBT settings
SBT time range
08:00
After
15:30
Before
Manually start/stop SBT
Start SBT
Stop SBT
70 %MinVol
5 PEEP/CPAP cmH2O
30 Oxygen %
Controls
Alarms
Monitoring
Graphics
Tools
Events
System
1:19
AC
HAMILTON-C3

JASN

J Am Soc Nephrol. 2008 Mar; 19(3): 547–558.
doi: 10.1681/ASN.2007040469

PMCID: PMC2391061
PMID: 18235097

The Local and Systemic Inflammatory Transcriptome after Acute Kidney Injury

Dmitry N. Grigoryev,* Manchang Liu,* Heitham T. Hassoun,† Chris Cheadle,* Kathleen C. Barnes,* and Hamid Rabb*

Functional genomic analysis of these genes suggested that
IL-10 and IL-6 signaling was involved
in the distant effects of local inflammation, and this was supported by increased serum levels of
IL-10and IL-6 after ischemia-reperfusion

Journal of Gastroenterology and Hepatology
JGHF

Role of interleukin-18 in the development of acute pulmonary injury induced by intestinal ischemia/reperfusion and its possible mechanism

Yong-jie Yang, Song-hua Chen, Xi-rui Ge

These data suggested a role of IL-18 in the activation and sequestration of neutrophils in lungs.
increased sequestration of neutrophils and microvascular leakage might, respectively, relate to the increased IL-18 level and the elevation of TNF-α/iNOS activity, and these two aspects might synergically contribute to intestinal I/R-induced pulmonary dysfunction.

Journal of the American Society of Nephrology
jasn.asnjournals.org

Published online before print September 7, 2005, doi: 10.1681/ASN.2005030236
JASN **October 1, 2005** vol. 16 no. 10 **3046-3052**

Urine IL–18 Is an Early Diagnostic Marker for Acute Kidney Injury and Predicts Mortality in the Intensive Care Unit

Chirag R. Parikh[*], Edward Abraham[†], Marek Ancukiewicz[‡], Charles L. Edelstein[§]
and for the Acute Respiratory Distress Syndrome (ARDS) Network

Urinary IL-18 levels can be used for the early diagnosis of AKI. Urine IL-18 levels also predict the mortality of patients who have ARDS and are in the intensive care unit.

PREVENTION/MANAGEMENT

Crit Care Med. 1992 Jul;20(7):1014-9.

Aggressive hydration during continuous positive-pressure ventilation restores atrial transmural pressure, plasma atrial natriuretic peptide concentrations, and renal function.

Ramamoorthy C[1], Rooney MW, Dries DJ, Mathru M.

Am J Kidney Dis. 2002 Mar;39(3):616-24.

Mechanical ventilation and renal function: an area for concern?

Pannu N[1], Mehta RL.

Anesthesiology. 1993 Oct;79(4):680-4.

Fenoldopam improves renal hemodynamics impaired by positive end-expiratory pressure.

Poinsot O[1], Romand JA, Favre H, Suter PM.

LUNG-PROTECTIVE STRATEGY LED TO FEWER PATIENTS WITH ORGAN SYSTEM FAILURE, WITH A GREATER DECREASE IN THE INCIDENCE OF RENAL FAILURE (P ! 0.04) THAN ANY OTHER ORGAN DYSFUNCTION

Format: Abstract

Full text links

JAMA FULL TEXT

JAMA. 2000 Jul 5;284(1):43-4.

Mechanical ventilation as a mediator of multisystem organ failure in acute respiratory distress syndrome.

Ranieri VM, Giunta F, Suter PM, Slutsky AS.

CLINICAL EFFECTS OF PERMISSIVE HYPERCAPNIA

Intensive Care Med. 1990;16(6):372-7.

Low mortality associated with low volume pressure limited ventilation with permissive hypercapnia in severe adult respiratory distress syndrome.

Hickling KG[1], Henderson SJ, Jackson R.

This approach requires
use of a tidal volume of 6 ml/kg of ideal body weight, and aims to keep static/plateau airway pressure ^ 30 cm H 2 O, requiring permissive hypercapnia as needed to avoid ventilator-induced lung injury.

‘HOW MUCH ACIDOSIS IS TOO MUCH ACIDOSIS?’

- The original ARDSNet low tidal volume trial
- protocol included arterial pH goals and suggested approaches
- arterial pH goal: 7.30 ^ pH ^ 7.45:
- a) Management of alkalemia (pH > 7.45): decrease
- ventilator rate, if possible.
- (b) Management of mild acidemia (7.15 < pH < 7.30):
- (1) increase ventilator rate up to a maximum of 35 or
- until pH > 7.30 or PaCO 2<25 mm Hg;
- (2) if ventilator rate = 35 or PaCO 2 < 25, then bicarbonate infusion may
- be given.
- (c) Management of severe acidemia (pH < 7.15):
- (1) increase
- ventilator rate to 35;
- (2) if ventilator rate = 35 and
- pH < 7.15 and bicarbonate has been considered or infused,
- then tidal volume may be increased by 1 ml/kg
- until pH > 7.15 (under these conditions, target plateau
- pressure may be exceeded).

HYPERCAPNIC ACIDOSIS

- hypercapnic acidosis may cause or aggravate myocardial depression in critically ill patients, it is generally well tolerated, and
- buffer therapy should probably be reserved for patients with severe acidemia
- (pH < 7.15).
- Particular caution
- use of permissive hypercapnia in patients
- with pulmonary hypertension and right hearfailure, systemic vasodilation may have
- significant adverse hemodynamic effects.

PH MANAGEMENT USED IN THE ARDSNET LOW TIDAL VOLUME TRIAL IS A SENSIBLE APPROACH.

- In summary,,
- permissive hypercapnia may favorably influence the courseof ALI, associated ventilator-induced lung injury, and
- harmful organ cross talk between the injured lung and
- other organs, leading to a protective effect against the development of VIKI.

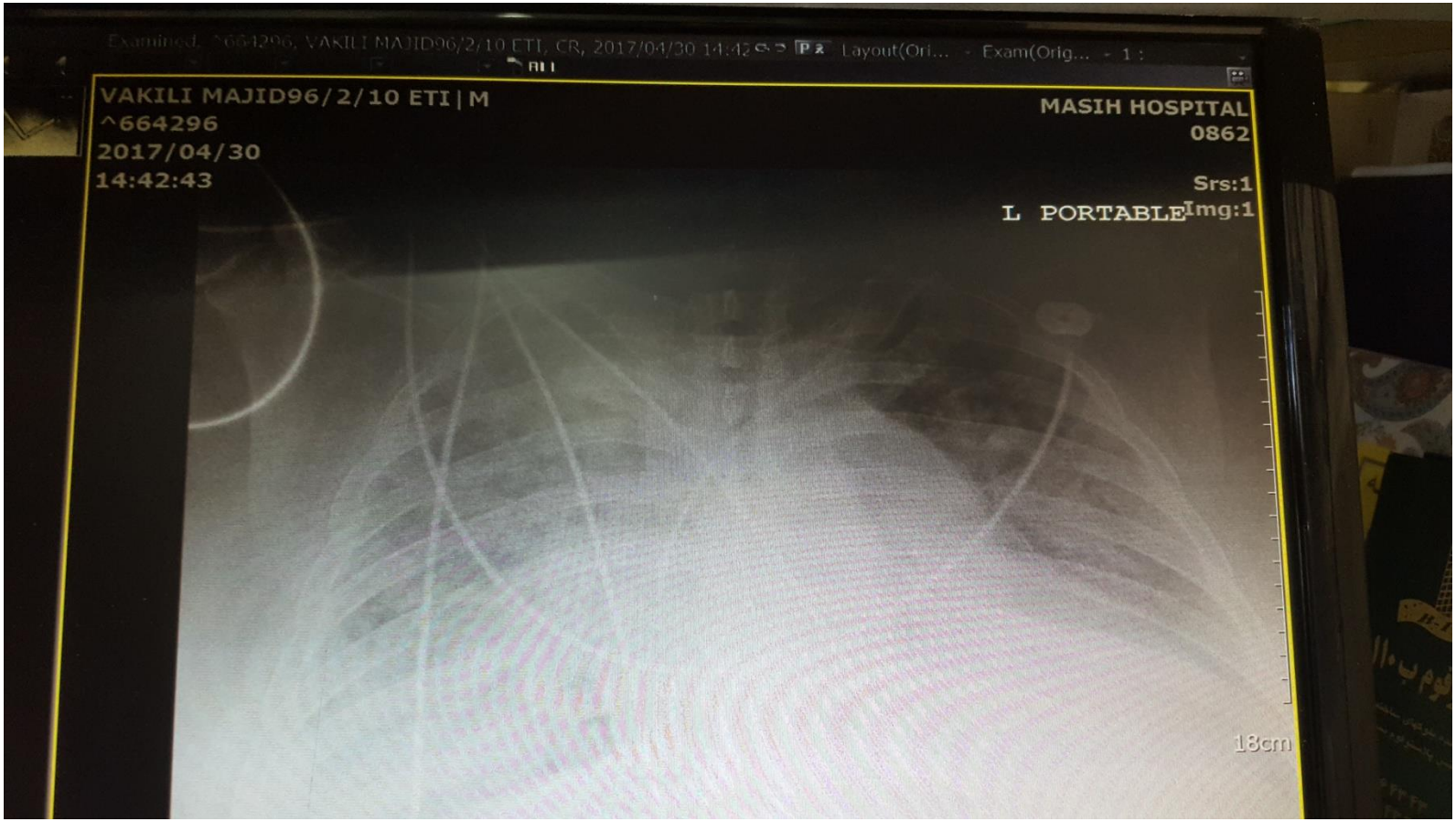
The new england journal of medicine

original article

Comparison of Two Fluid-Management Strategies in Acute Lung Injury

The National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network*

These results support the use of a conserva-tive strategy of f luid management in patients with acute lung injury.
(ClinicalTrials.gov number, NCT00281268.)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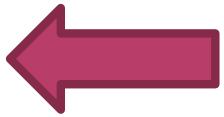
HYPOPROTEINEMIA

- is significantly correlated with fluid retention
- and weight gain, development of ARDS
- and poor respiratory outcome,
- and mortality in patients with sepsis.



Critical Care Medicine.
28(9):3137-3145, SEP 2000
PMID: 11008971
Issn Print: 0090-3493
Publication Date:
2000/09/01

Hypoproteinemia predicts acute respiratory distress syndrome development, weight gain, and death in patients with sepsis

Robert J. Mangialardi; Greg S. Martin; Gordon R. Bernard; Arthur P. Wheeler; Brian W. Christman; William D. Dupont; Stanley B. Higgins; Bridget B. Swindell

Albumin and furosemide therapy in hypoproteinemic patients with acute lung injury*

Martin, Greg S. MD; Mangialardi, Robert J. MD; Wheeler, Arthur P. MD; Dupont, William D. PhD; Morris, John A. MD; Bernard, Gordon R. MD

Critical Care Medicine: October 2002 - Volume 30 - Issue 10 - p 2175-2182
Feature Articles

Albumin and furosemide therapy improves fluid balance, oxygenation, and hemodynamics in hypoproteinemic patients with acute lung injury.

Crit Care Med. 2005 Aug;33(8):1681-7.

Wolters Kluwer

A randomized, controlled trial of furosemide with or without albumin in hypoproteinemic patients with acute lung injury.

Martin GS[1], Moss M, Wheeler AP, Mealer M, Morris JA, Bernard GR.

Author information

The addition of albumin to furosemide therapy in hypoproteinemic patients with acute lung injury/acute respiratory distress syndrome significantly improves oxygenation, with greater net negative fluid balance and better maintenance of hemodynamic stability.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 25, 2006 VOL. 354 NO. 21

Pulmonary-Artery versus Central Venous Catheter to Guide Treatment of Acute Lung Injury

The National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network*

PAC-guided therapy did not improve survival or organ function but was associated with more complications than CVC-guided therapy. These results, when considered suggest that the PAC should not be routinely used for the management of acute lung injury. (ClinicalTrials.gov number, NCT00281268.)

Specifically,
although the conservative fluid arm protocol targeted
a CVP of 4 mm Hg
or a pulmonary artery occlusion pressure
(PAOP) of 8 mm Hg

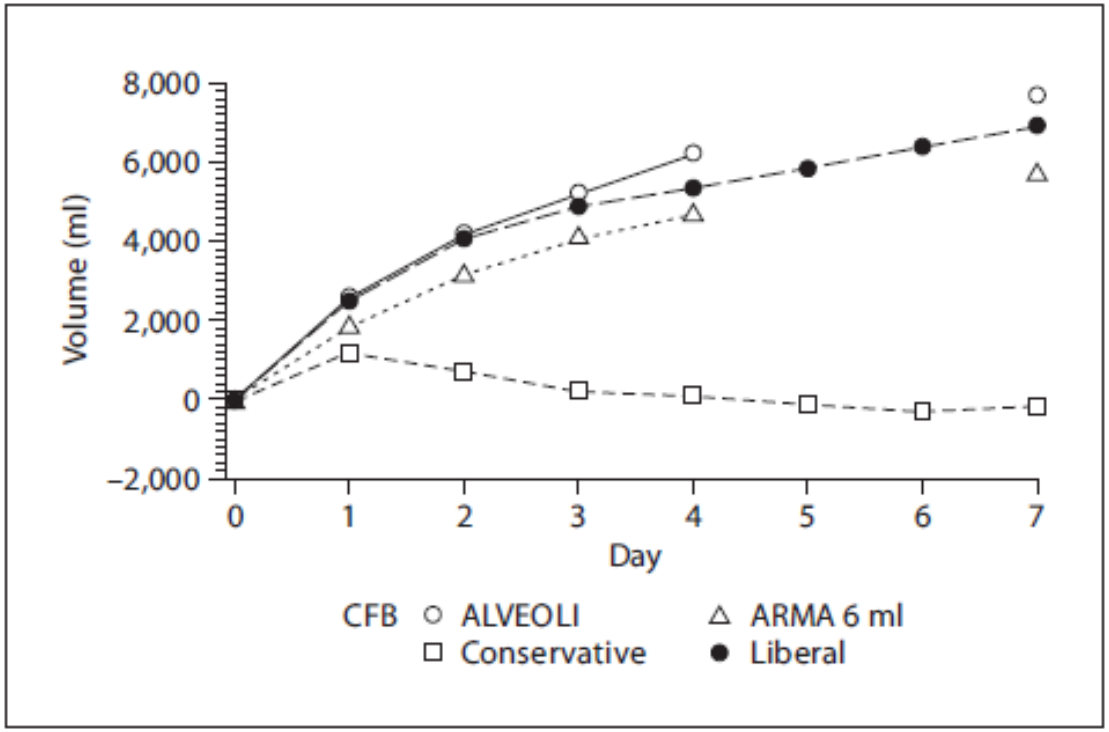


Fig. 2. Net fluid balance for fluid liberal and fluid conservative arms of the FACTT trial as well as for the ALVEOLI trial, and the 6 ml/kg tidal volume of the original ARDSNet trial. The National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome Clinical Trials Network.

Format: Abstract

Full text links

PEDIATRICS

FINAL VERSION

Pediatrics. 2001 Jun;107(6):1309-12.

Outcome in children receiving continuous venovenous hemofiltration.

Goldstein SL[1], Currier H, Graf Cd, Cosio CC, Brewer ED, Sachdeva R.

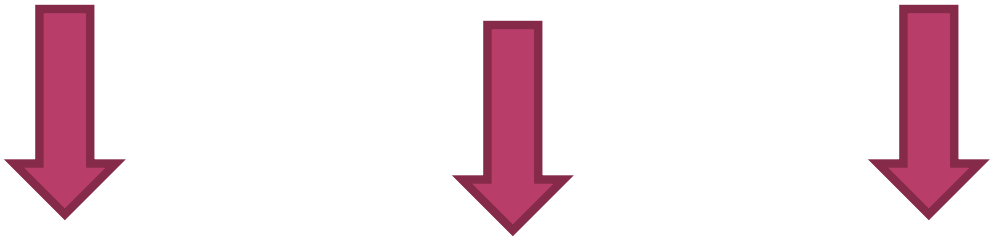
The pattern of early multiorgan system failure and death, minimal relative cost of CVVH/D provision, and potential for improved outcome with initiation of CVVH/D at lesser degrees of fluid overload are factors that

may support early initiation of CVVH/D in critically ill children with acute renal failure.

Springer

Fluid overload and acute renal failure in pediatric stem cell transplant patients

Pediatric Nephrology
January 2004, Volume 19, Issue 1, pp 91–95
| Cite as
Original Article
First Online: 22 November 2003



maintenance of euvolemia (<10% FO) is critical
but not sufficient for survival in SCT patients with ARF,
as all non-euvolemic patients died.
We suggest that aggressive use of diuretics and early initiation of RRT to prevent worsening of FO may improve the survival of SCT patients.

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CRITICAL CARE
this article | search | submit a manuscript | register

Crit Care. 2008; 12(3): R74.
Published online 2008 Jun 4. doi: 10.1186/cc6916
PMCID: PMC2481469
PMID: 18533029

A positive fluid balance is associated with a worse outcome in patients with acute renal failure

Didier Payen,[1] Anne Cornélie de Pont,[2] Yasser Sakr,[3] Claudia Spies,[4] Konrad Reinhart,[3] Jean Louis Vincent,[5] and the Sepsis Occurrence in Acutely Ill Patients (SOAP) Investigators

In this large European multicenter study,
a positive fluid balance was an important factor associated with increased 60-day mortality.
Outcome among patients treated with RRT was better when RRT was started early in the course of the ICU stay.


HF440
infomed

Intensive Care Med. 2006 Jan;32(1):80-6. Epub 2005 Nov 18.

Early isovolaemic haemofiltration in oliguric patients with septic shock.

Piccinni P[1], Dan M, Barbacini S, Carraro R, Lieta E, Marafon S, Zamperetti N, Brendolan A, D'Intini V, Tetta C, Bellomo R, Ronco C.

In patients with septic shock, early isovolaemic haemofiltration(conventional continuous venovenous haemofiltration CVVH) was associated with improved gas exchange, haemodynamics, greater likelihood of successful weaning and greater 28-day survival compared with conventional therapy.

THE RESULTS

PaO_2/FiO_2 ratio increased from 117±59 to 240±50 in EIHF,

while it changed from 125±55 to 160±50 in the control group (p <0.05).

In EIHF patients, mean arterial pressure increased (95±10 vs 60±12 mmHg; p <0.05

norepinephrine dose decreased (0.20±2 vs 0.02±0.2 µg/kg/min; p <0.05).

Among EIHF patients, 28 (70%) were successfully weaned from the ventilator compared with 15 (37%) in the control group (p <0.01).

IN CONCLUSION,

- it is evident that there is a deleterious bidirectional relationship between the AKI and ALI.
- Increasing evidence points to cross talk between these two distant organs, and shows that injury to one organ may initiate and aggravate injury to the other.

- Recent data show that the kidneys play an important role in the production and elimination of mediators of inflammation and ALI.

CONVERSELY, (VIKI).

- exposure to the inflammatory milieu of ALI and mechanical ventilation-induced injury may precipitate the onset of AKI, and we suggest that this
- phenomenon might be termed ventilator-induced kidney injury (VIKI).

THANK YOU FOR YOUR GREAT ATTENTION