NATIONAL INITIATIVE IN SEPSIS EDUCATION

Hemodynamic Assessment, Monitoring, and Support of the Patient with Shock:

An Evidence Based Approach

Issues Discussed in This Module

- Differential diagnosis of shock
- Hemodynamic assessment and monitoring
- The importance of early goal-directed therapy
- Crystalloids vs colloids and volume resuscitation requirements in sepsis
- The role of the PAC in acute lung injury
- What is the best pressor?
- The limited value of pH modification in septic shock

Differential Diagnosis of Shock

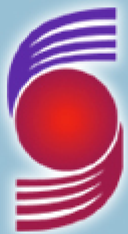
Sepsis

Hypovolemic

Obstructive

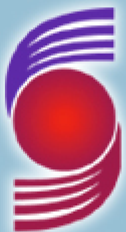
Cardiogenic

Kortisol

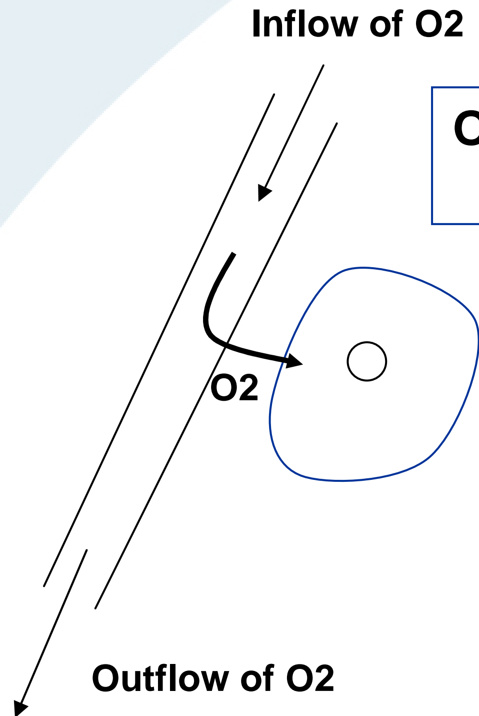


Hemodynamic Monitoring in the Patient with Severe Sepsis

- Monitor
  - Heart rate
  - Mean arterial pressure (MAP)
  - Urine output (UOP)
  - Mental status
  - Skin color/temperature
- Perhaps monitor
  - Cardiac index (CI)
  - Cardiac filling pressure (CVP, PAOP)
  - Capillary refill
- Tissue Hypoxia
  - Lactate
- Mixed venous oxygen saturation

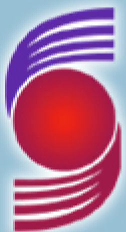


Venous Oxygen Saturation (Central)



Oxygen Consumed $\sim$ [CO x CaO_2] – [CO x $Cv0_2$]
$\sim$ CO x [Hgb (SaO_2 – SvO_2)]

Assuming SaO2 is optimal
If CO decreases or Hgb decreases, then to maintain oxygen consumption, Sv02 needs to decrease.



Tissue Hypoxia

Zone of Tissue Hypoxia

As Oxygen Delivery decreases, SvO2 decreases

Oxygen Uptake

Oxygen Delivery ~ CO x %Sat x Hgb

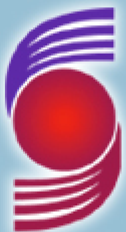
Commonly Accepted Hemodynamic Management Goals

- Achieve adequate perfusion pressure: (MAP >60 mm Hg)
- CI ≥2.5 L/min/m^2
- U/O ≥0.5 mL/kg/hr
- Normal mental status
- Sv02 > 70%
- Trends may be more important than absolute values
- Lowest filling pressure and vasoactive drug dose necessary to achieve MAP, CI and U/O goals

Hemodynamic Trade-Offs

- Perfusion pressure
- Cardiac output
- UOP
- Brain function
- Acceptable acid-base status

- Arrhythmias
- Myocardial ischemia
- Peripheral ischemia
- Pulmonary edema

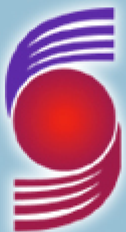


Early Goal-Directed Therapy for Septic Shock

- Randomized, non-blinded trial of traditional vs early goal-directed therapy (EGT)
  - Septic shock unresponsive to 20 mL/kg crystalloids, *or*
  - Lactate ≥4 mmol/L

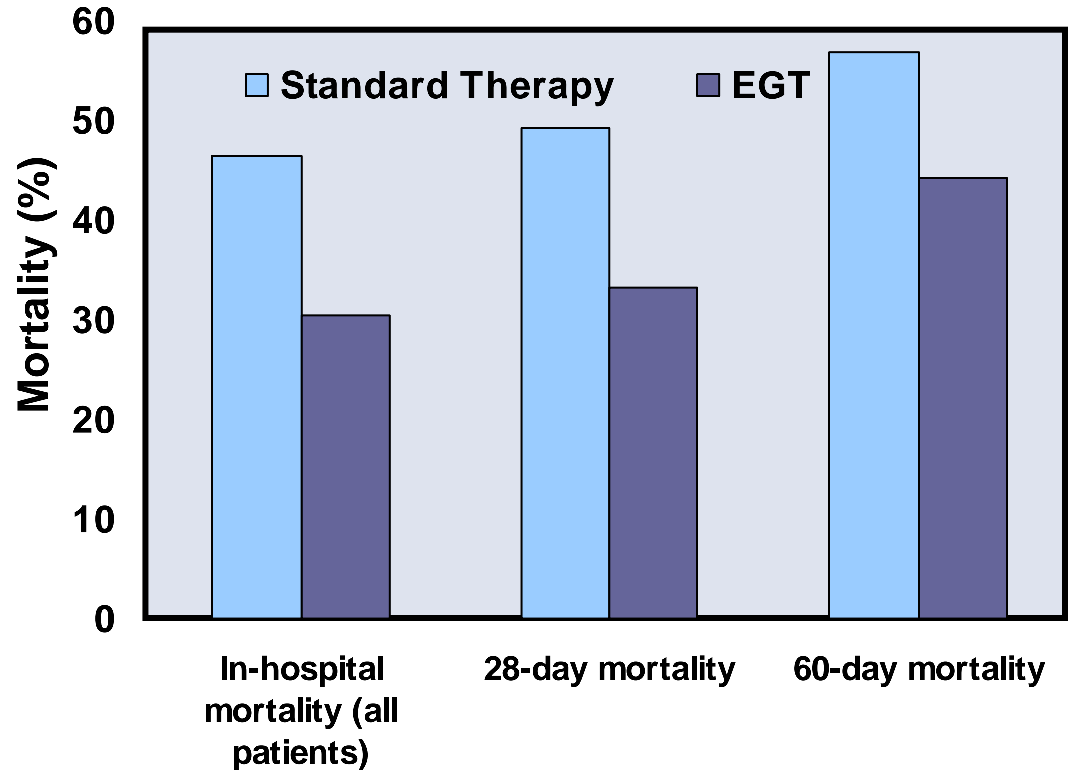
- **Standard**
  - CVP ≥8-12 mm Hg
  - Vasopressors for SBP ≤90 mm Hg
  - Maintain UOP ≥0.5 mL/kg/hr
  - MAP ≥65 mm Hg
- **Goal-directed**
- Above, *plus*
  - *Fluids: 500 cc q30" for CVP*
  - Patients monitored with $ScvO_2$
  - If $ScvO_2$ <70%
    - RBCs until Hct ≥30%
    - If $ScvO_2$ still <70%, add dobutamine to dose of 20 µg/kg/min

Rivers E, et al. *N Engl J Med* 2001;345:1368-77.



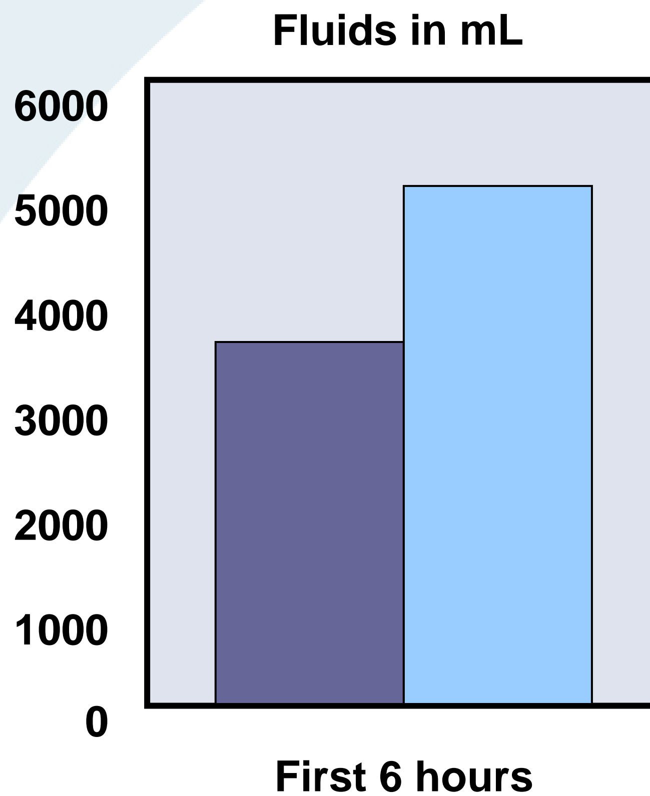
The Importance of Early Goal-Directed Therapy for Septic Shock (cont)

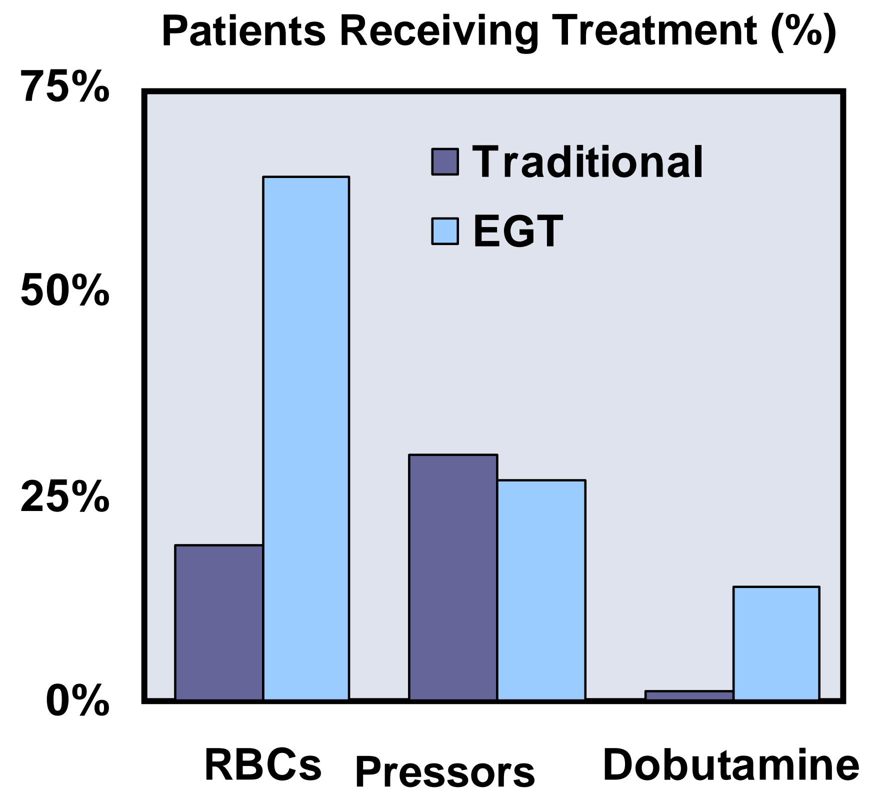
- EGT* in patients with severe sepsis produced the following:
  - 42% ↓ in relative risk of in-hospital and 28-day mortality (P=0.009, P=0.01)
  - 33% ↓ in relative risk of death at 60 days (P=0.03)



*Aggressive resuscitation begun in emergency department.
Rivers E, et al. *N Engl J Med* 2001;345:1368-77.

Patients Treated with EGT Received More Fluids, RBCs and Dobutamine





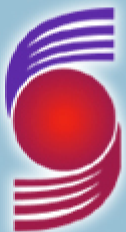
Rivers E, et al. *N Engl J Med* 2001;345:1368-77.

What is the Optimal Hematocrit?

Randomized Controlled Trial

- 25 (Canadian) ICUs from 1994-1997
- 838 ICU patients
- Patients Excluded
    - active bleeding, pregnancy, s/p cardiac surgical procedure
- Randomized < 72 hours of admission
    - Restrictive: Hgb < 7.0 (Hgb 7 - 9 g/dL)
    - Liberal: Hgb <10.0 (Hgb 10 - 12 g/dL)

Hebert, N Engl J Med 1999; 340:409



Transfusion Strategy in the Critically Ill

Survival (%)

100
90
80
70
60
50

0 5 10 15 20 25 30

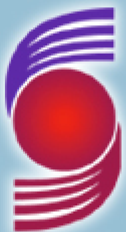
Days

Restrictive transfusion strategy
Hgb < 7 gm%

Liberal transfusion strategy
Hgb < 10 gm%

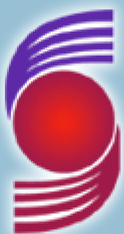
P=0.11

Hebert PC, et al. *N Engl J Med* 1999;340:409-17.



Trial Results

- Restrictive Group vs. Liberal Group
  - Trend towards decreased mortality (p = 0.11)
  - Less blood transfusions: 2.6 vs. 5.6 units/patient (54% reduction)
- Adverse Effects
  - Pulmonary edema and myocardial infarction were more frequent In the liberal group compared with restrictive group



Conclusions

- Transfusion Threshold of Hgb < 7.0 gm/dL
  - is at least as effective as and possibly superior to a liberal transfusion strategy
  - decreases the number of transfusions by 54 %

Autoregulation of blood flow

Flow

Pressure

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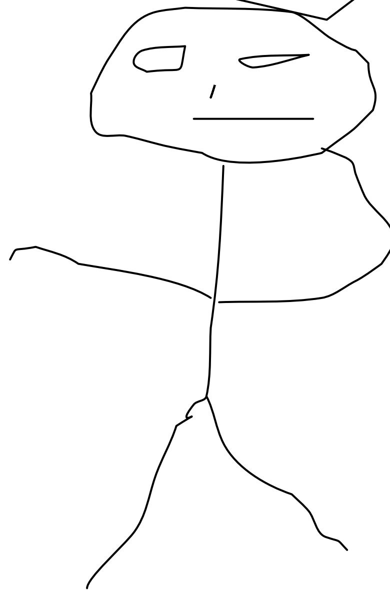
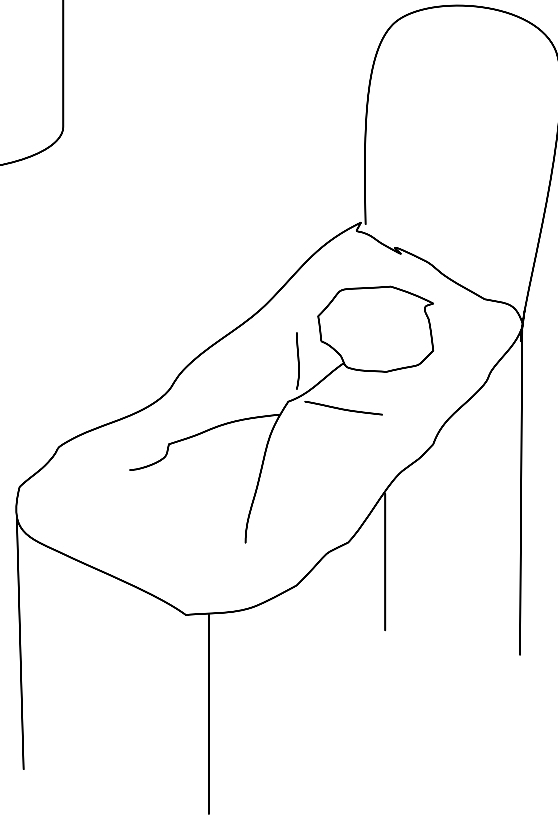
Determination of Volume status

Determination of Volume Status

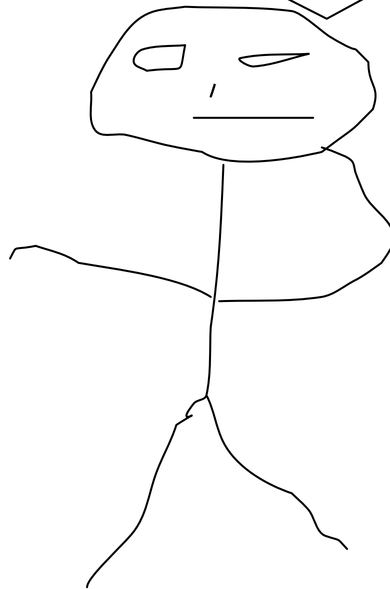
Hmmm,
Dry mucous
membranes

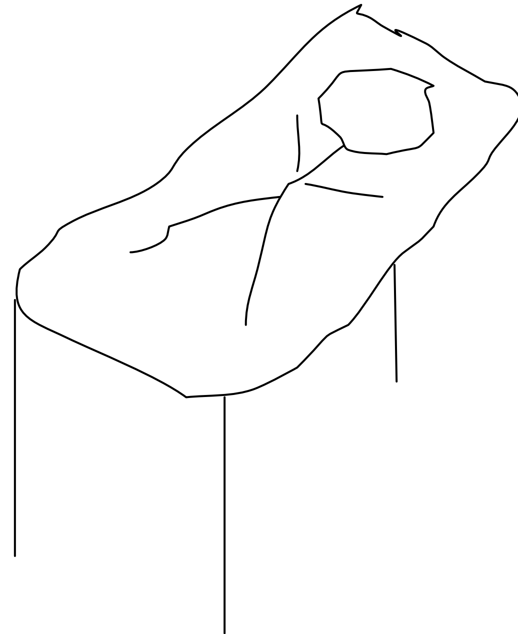




Determination of Volume Status

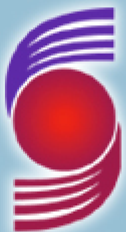
Hmmm,
patient
“looks” dry.





Determination of Volume Status

- History
- Orthostatics: increase in pulse > 20
- Neck vein distension/pulsation
- Measurement of CVP
- Urine output
- BUN/Cr
- Chest x-ray



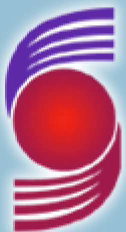
Fluid Requirements in Sepsis

Isotonic saline
Hydroxyethyl starch
5% Albumin

Cumulative Volume (liters)
0
2
4
6
8
10

0
6
12
18
24
Time (hours)

Rackow EC, et al. *Crit Care Med* 1983;11:839-50.



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

N Engl J Med
Volume 354;24:2564-2575
June 15, 2006

Study Overview

- One of the characteristics of acute lung injury is noncardiogenic pulmonary edema
- Arguments have been made for the management of acute lung injury with either a liberal or conservative approach to fluid administration
  - Liberal: preserve organ blood flow
  - Conservative: decrease oxygen requirements
- Subjects randomized to two fluid strategies
  - Conservative: CVP < 4 or PAOP < 8
  - Liberal: CVP = 10 – 14 or PAOP = 14 - 18

Probability of Survival to Hospital Discharge and of Breathing without Assistance during the First 60 Days after Randomization

Alive, liberal strategy

Alive, conservative strategy

Breathing without assistance, conservative strategy

Breathing without assistance, liberal strategy

Proportion of Patients

1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0

0 10 20 30 40 50 60

Days

Conclusion

- There was no significant difference in the primary outcome of 60-day mortality
- The conservative strategy of fluid management
  - shortened the duration of mechanical ventilation without increasing nonpulmonary-organ failures
- In this trial, neither approach offered a mortality benefit
- There were clinical and physiological benefits to conservative fluid management

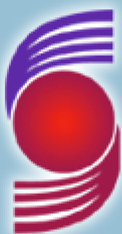
What is the "Best" Fluid:
Crystalloids vs Colloids?

Favors Crystalloids — Favors Colloids

Study	Year	#Pts	Relative Risk	(95%CI)
Lowe	1977	141	0.68	0.14-3.24
Lucas	1978	52	0.07	0.00-1.20
Butros	1979	24	2.22	0.12-41.20
Virgilio	1979	29	1.07	0.07-15.54
Moss	1981	36	2.43	0.11-55.89
Goodwin	1983	50	0.27	0.09-0.86
Modig	1983	23	1.08	0.02-50.43
Rackow	1983	26	1.23	0.71-2.11
Shires	1983	16	1.00	0.02-45.63
Metildi	1984	32	0.82	0.52-1.29
Sade	1985	83	1.83	0.04-90.08
Karanko	1987	32	2.37	010-54.08
Dawidson	1991	20	1.00	0.07-13.87
London	1992	90	0.22	0.01-3.93
Pockaj	1994	76	0.90	0.02-4.34
Overall		732	0.66	0.63-1.17

Forest plot axis: 0.01 0.05 0.1 0.2 0.5 1 2 5 10 20 50 100

Choi PTL, et al. *Crit Care Med* 1999;27:200-10; Cook D, et al. *Ann Intern Med* 2001;135:205-8; Schierhout G, et al. *BMJ* 1998 28;316:961-4; Wilkes MM, et al. *Ann Intern Med* 2001;135:149-64.



Balancing the Risks of Pulmonary Artery Catheter Monitoring

Insertion Risks

- **Arrhythmia**
- **Pneumothorax**
- **Arterial puncture**

Indwelling Risks

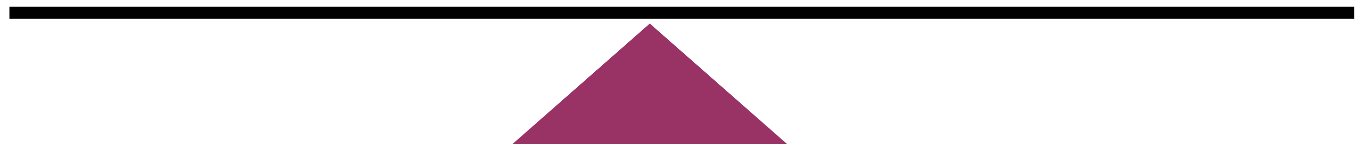
- **Infection**
- **Pulmonary infarct**
- **PA rupture**

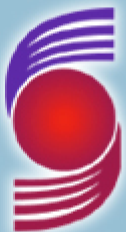
Data Problems

- **Poor quality**
- **Misinterpretation**

Unexpected Treatable Diagnosis

Optimal Hemodynamic Management





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

N Engl J Med
Volume 354;21:2213-2224
May 25, 2006

Kaplan-Meier Estimates of the Probability of Survival and of Survival without the Need for Assisted Ventilation during the First 60 Days after Randomization

Proportion of Patients

1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0

0 10 20 30 40 50 60

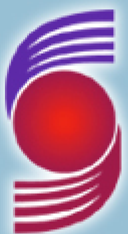
Days

Alive, CVC group

Alive, PAC group

Unassisted breathing, CVC group

Unassisted breathing, PAC group

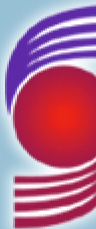


Catheter-Related Complications

Table 2. Catheter-Related Complications.

Complication	PAC Group				CVC Group		
	Sheath	PAC	CVC	Total	Sheath	CVC	Total
	number of patients						
Technical and mechanical complications							
Difficult placement	1	8	1	10	0	2	2
Catheter malfunction	0	4	0	4	0	0	0
Pneumothorax	3	2	1	6	0	6	6
Air embolism	1	1	1	3	0	0	0
Arterial puncture	1	0	2	3	0	0	0
Arrhythmia							
Atrial	3	15	0	18	0	0	0
Ventricular	4	15	0	19	1	5	6
Conduction defect	1	4	0	5	1	0	1
Bleeding and clotting							
Hemothorax	2	1	0	3	1	0	1
Insertion-site bleeding	2	1	3	6	1	2	3
Thromboembolism	0	0	0	0	1	0	1
Local thrombosis	1	1	1	3	0	6	6
Infection							
Local	3	2	7	12	1	8	9
Bloodstream*	1	3	1	5	0	3	3
Other	0	2	1	3	0	3	3
Total	23	59	18	100	6	35	41

* Positive blood cultures were believed to be related to the presence of the catheter. Overall, 19 percent of patients in the PAC group and 18 percent of patients in the CVC group had one or more positive blood cultures (P=0.43).

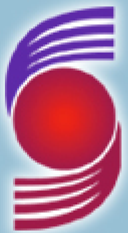


Conclusions

- There was no significant difference in 60-day mortality whether monitoring was performed with a pulmonary-artery catheter or a central venous catheter
- PAC-guided therapy was associated with more complications than CVC-guided therapy
- These results, when considered with those of previous studies, suggest that the PAC should not be routinely used for the management of acute lung injury

Vasoactive Drugs

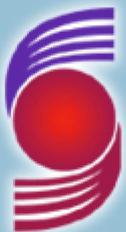
What is the best pressor?



Vasoactive Drugs:
Dopamine

- Does not enhance renal perfusion[1]
- Does not prevent renal dysfunction[2]
- May impair splanchnic blood flow[3]
- Tachycardia is more common than with norepinephrine

[1]Hanneman L, et al. *Crit Care Med* 1995;23:1962-70.
[2]Bellomo R, et al. *Lancet* 2000;356:2139-43.
[3]Marik PE, et al. *JAMA* 1994;272:1354-7.



Vasoactive Drugs:
Dopamine (cont)

- Dopamine for renal dysfunction
  - Randomized, blinded, placebo-controlled, multicenter trial
  - N=328
  - Inclusion criteria
    - ≥2 SIRS criteria + oliguria, or
    - Creatinine ≥1.7 mg/dL, or
    - 24-hour rise in creatinine ≥0.9 mg/dL
  - Dosing
    - Dopamine 2 μg/kg/min via CVC

Bellomo R, et al. *Lancet* 2000;356:2139-43.

Vasoactive Drugs:
Dopamine (cont)

120
100
80
60
40
20
0

UOP (mL/hr)

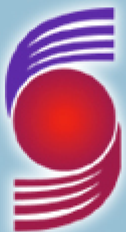
Dopamine
Placebo

Baseline
1 hour
24 hours
48 hours

Bellomo R, et al. *Lancet* 2000;356:2139-43.

Vasoactive Drugs: Dopamine (cont)

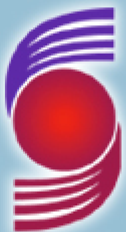
- **Treatment with dopamine produced no difference in the following:**
  - Peak serum creatinine
  - Percent requiring renal replacement therapy
  - Time to recovery of renal function
  - Dose of furosemide
  - ICU or hospital LOS
  - Survival



Bellomo R, et al. *Lancet* 2000;356:2139-43.

Vasoactive Drugs: Norepinephrine vs Dopamine in Septic Shock

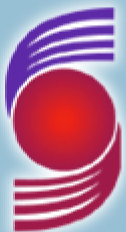
- No evidence that norepinephrine harms renal function[1]
- Norepinephrine produces more reliable, rapid and effective BP control than dopamine[2]
- Norepinephrine may increase splanchnic perfusion
- Norepinephrine produces less tachycardia than dopamine



[1]Desjars P, et al. *Crit Care Med* 1989;17:426-9.
[2]Martin C, et al. *Chest* 1993;103:1826-31.

What is the "Best" Pressor: Norepinephrine?

- Effect of norepinephrine compared with high-dose dopamine and/or epinephrine on the outcome of septic shock
  - Prospective, observational cohort
  - N=97
  - Norepinephrine ↓ mortality
    - 62% vs 82%
    - $P<0.001$



Martin C, et al. *Crit Care Med* 2000;28:2758-65.

What is the "Best" Pressor: Norepinephrine?

Norepinephrine after Dopamine

MAP (mm Hg) or UOP (mL/hr)

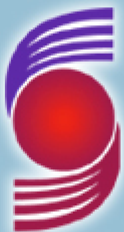
100
80
60
40
20
0

Dopamine

Dopamine + Norepinephrine

MAP

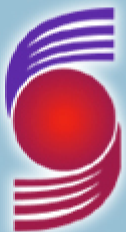
Urine Output



Meadows D, et al. *Crit Care Med* 1988;16:663-6.

What is the "Best" Pressor: Epinephrine?

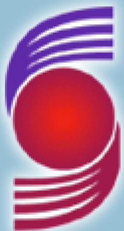
- Prospective, randomized study of adults with septic shock
- N=30
- Epinephrine vs norepinephrine *plus* dobutamine
- Results
  - Similar effect on global hemodynamics
  - Epinephrine associated with higher lactate and lower gastric pHi
- Conclusion: Norepi + dobutamine > epi



Levy B, et al. *Intensive Care Med* 1997;23:282-7.

What is the "Best" Pressor: Phenylephrine?

- Prospective, observational study of adults with septic shock (N=13)
- Effect of adding phenylephrine to low-dose dopamine or dobutamine after fluids
- Results with phenylephrine
  - Increased MAP, SVR, CI
  - No change in HR
  - Increased oxygen delivery and consumption
  - Increased UOP
- Animal Studies: concern with decreased splanchnic perfusion



Gregory JS, et al. *Crit Care Med* 1991;19:1395-400.

Soooo!!!!
What is the “Best” Pressor?:

- Dopamine
- Epinephrine
- Norepinephrine
- Phenylephrine

Vasopressin in Vasodilatory Shock

Sepsis or Tissue Hypoxia with Lactic Acidosis

↑ Nitric oxide synthase

↓ ATP, ↑ H^+, ↑ lactate in vascular smooth muscle

↑ Vasopressin secretion

↑ Nitric oxide

Open K_{Ca}

Open K_{ATP}

↓ Vasopressin stores

↑ cGMP

↓ Cytoplasmic Ca^{2+}

↓ Phosphorylated myosin

↓ Plasma vasopressin

Vasodilatation

Landry DW, et al. *N Engl J Med* 2001;345:588-95.

Vasopressin in Vasodilatory Shock (cont)

ADH

Non-shock

Hyperosmolality
or
Hypotension

V1 receptors

V2 receptors

Phospholipase C

Reduced Ca++

NO

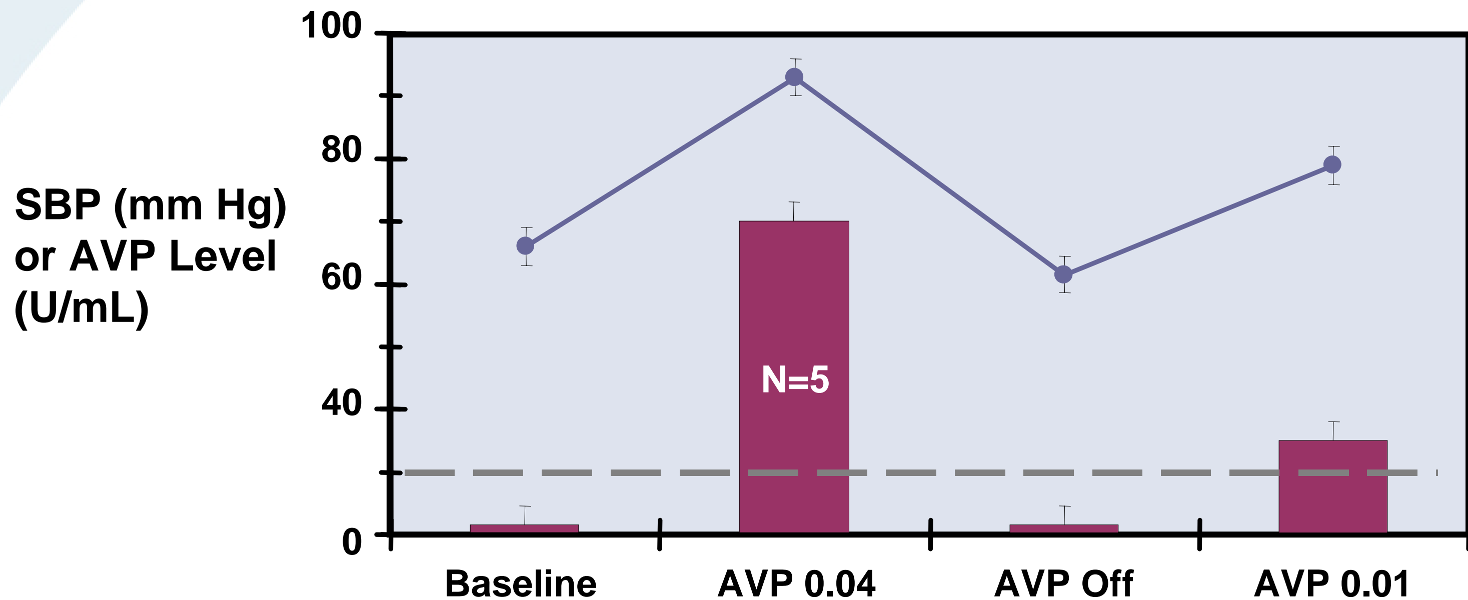
Ca++

cAMP

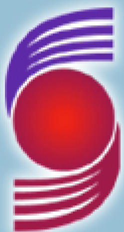
Water retention

Vasodilatory Shock

BP and Vasopressin Levels After AVP for Septic Shock

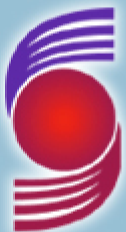


Landry DW, et al. *Circulation* 1997;95:1122-5.



Vasopressin in Septic Shock

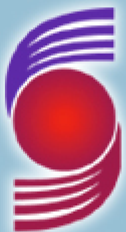
- Retrospective review
- N=45
- Results
  - MAP increased 58 to 71 mm Hg
  - Non-significant decline in CI and creatinine
  - Significant increase in UOP
  - 50% reduction in vasopressor dose



Holmes CL, et al. *Am J Respir Crit Care Med* 2000;161:A879.

Vasopressin Summary

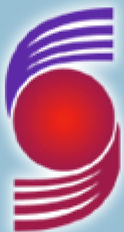
- No large, randomized, controlled trials
- Raises MAP by increasing SVR in "vasodilatory shock"
- If effective, acts rapidly and at low doses
- Synergistic with catecholamines
- High dose: coronary vasoconstriction
- Inexpensive



Landry DW, et al. *N Engl J Med* 2001;345:588-95.

Changing pH Has Limited Value

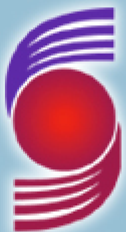
Treatment	Before	After
$NaHCO_3$ (2 mEq/kg)		
pH	7.22	7.36
PAOP	15	17
Cardiac output	6.7	7.5
0.9% NaCl		
pH	7.24	7.23
PAOP	14	17
Cardiac output	6.6	7.3



Cooper DJ, et al. *Ann Intern Med* 1990;112:492-8.

Summary: Hemodynamic Management

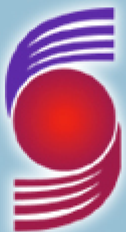
- Septic patients initially present with inadequate circulating volume
- Early goal-directed therapy may be beneficial
- Crystalloids are the preferred fluid
- There is no role of the PAC in patients with acute lung injury
- Norepinephrine is the preferred vasoactive agent
- "Renal-dose" dopamine does not work



Bellomo R, et al. *Lancet* 2000;356:2139-43; Connors A, et al. *JAMA* 1996;276:889-97; Price BJ, et al. *Crit Care Nursing Clin North Am* 1998;10:75-85; Rivers E, et al. *N Engl J Med* 2001;345:1368-77; Schierhout G, et al. *BMJ* 1998 28;316:961-4.

Summary:
Hemodynamic Management (cont)

- Vasopressin may raise BP in patients with refractory septic shock
- Raising an acidemic pH has no proven benefit
- Supranormal oxygen delivery is not beneficial



Price BJ, et al. *Crit Care Nursing Clin North Am* 1998;10:75-85.