

# Critical Care Review:What the Anesthesiologist Needs to Know



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## Case Study



☹ It's now 3 pm and you get the dreaded call there is an emergency case for an exploratory lap that needs to go now !

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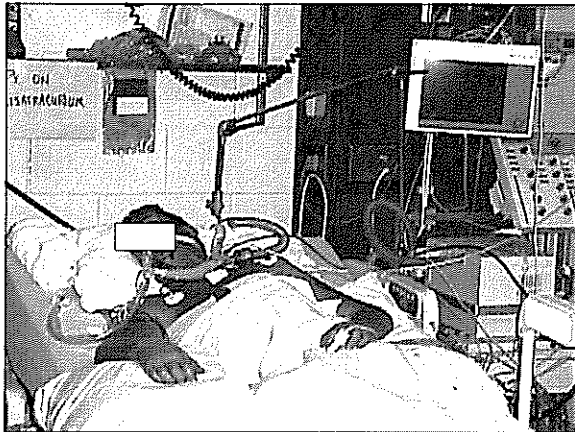
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 **Case Study** 

- ✘ 58 y.o. male with firm, distended abdomen and severe metabolic acidosis (lactate- 5.0) coming to OR for exploratory laparotomy
- ✘ Vent Settings: Pressure Control - 34 Peep- 12 R- 24, FiO<sub>2</sub>= 100%, PIP- 46
- ✘ ABG: 7.20 / pCO<sub>2</sub> - 50 / pO<sub>2</sub> - 65
- ✘ CXR- reveals 3 quadrant infiltrates
- ✘ HR 110, BP 75/40, C.I. - 4.0 SVR- 458
- ✘ Drips: vasopressin and insulin
- ✘ U/O - 5 cc last hour
- ✘ SV02 - 45%

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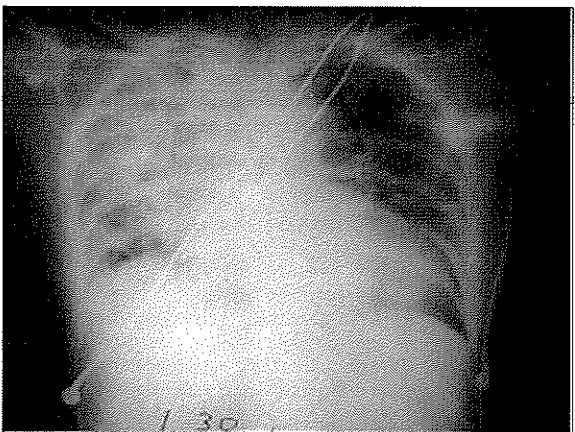
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What can we do to save this patient today... that perhaps we could not have a few years ago ??

But first... is he "critically ill" ?

What makes for a "critically ill" patient ?

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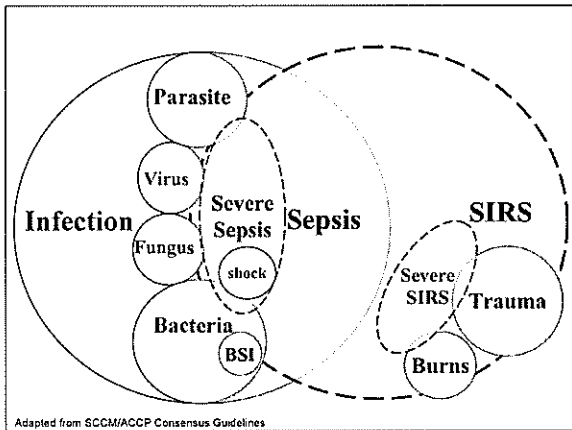
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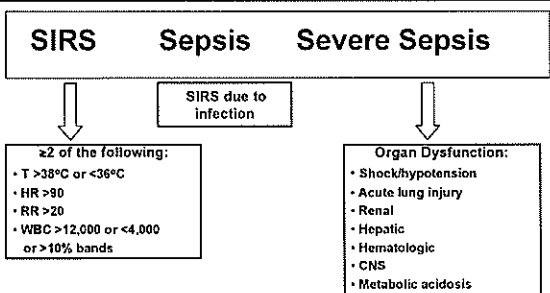
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### The Sepsis Continuum



Bone RC, et al. Chest 1992;101:1644-55.

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## DEFINITIONS

- **MOFS: multiple organ failure syndrome**
  - Progressive, persistent, hyperdynamic, hypermetabolic state associated with gradual deterioration of multiple organs, lungs usually being the first
- **MODS: multiple organ dysfunction syndrome**
  - Organs rarely fail abruptly

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## PATHOPHYSIOLOGY

- The (abnormal?) host response to insult
- **Prolonged shock state**
  - Can be from any form of shock (hypovolemic, cardiogenic, distributive/vasodilatory, or obstructive)
- Cellular level: mitochondrial dysfunction and "cytopathic hypoxia"
  - Mitochondria "leak" free radicals, and activate nuclear factor kappa B (NF- $\kappa$ B), a transcription factor for many pro-inflammatory mediators
  - Mediators may stimulate cytokines (TNF, interleukins), complement system, coagulation and fibrinolytic system, and cellular system (macrophages, neutrophils, endothelial cells, and platelets)

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## PATHOPHYSIOLOGY

- "2<sup>nd</sup> hit" phenomenon
  - The initial insult "primes" inflammatory system, and a second insult amplifies the response
- "Gut" hypothesis
  - GI tract is the "undrained abscess" causing MODS. The gut leaks bacteria/products
  - Possibly via lymphatics (ALI/ARDS)
  - GI tract is largest immune organ (GALT)

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**Who believes bacteria translocate from the gut to blood and cause infection ?**

Yes

No

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**Bacteria DO NOT translocate from the gut to the blood !**

The data are relatively clear for this...but gut failure is VITAL to prevent !

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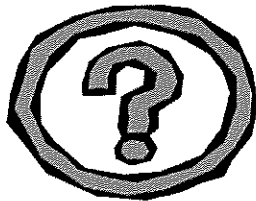
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**WHY ???**



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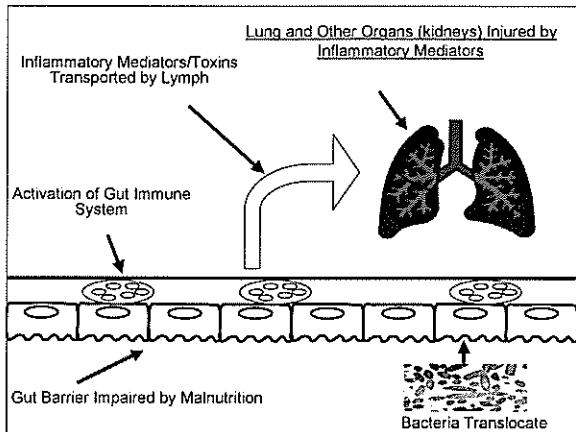
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**Animals Undergoing Trauma**

- If lymph duct is not ligated all animals get ARDS and die
- If lymph duct is ligated, no ARDS, all animals live !
- Lymph from traumatized animals is toxic to cells

Deitch E et al.

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**CLINICAL MANIFESTATIONS of MOFS**

- Patients appear to stabilize after resuscitation to a "hypermetabolic" state
- Lungs usually the first (ALI/ARDS) to injure
- Sequence of other organs influenced by co-morbidities
- Renal dysfunction usually follows second
- Liver failure late
- Usually die from hypotension unresponsive to pressors

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## TREATMENT

- **THERE IS NO KNOWN TREATMENT!!!!**

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## PREVENTION

- Best defined by literature that shows improved outcomes or survival in patients typically at risk for MODS
- Prospective, randomized, placebo controlled trials (PRCT's)

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**Once we have a critically ill patient... What does the latest literature say...**

1) Does Not Work

2) May Work

3) Does Work

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## What Doesn't Work

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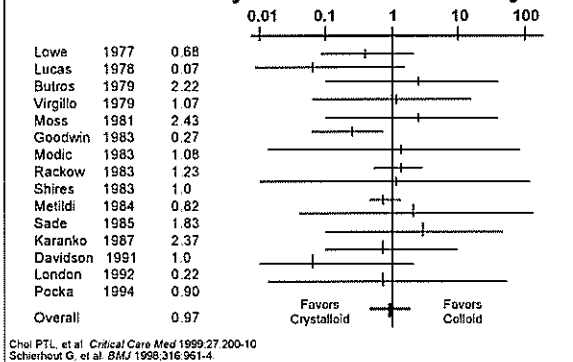
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## Colloid vs Crystalloid Controversy




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## Dopamine for Renal Dysfunction

- RCT, 328 patients
- Included: 2 SIRS criteria *plus* oliguria or creatinine >1.7 or 24-hour rise in creatinine >0.9
- Dosing: Dopamine 2 µg/kg/min via CVC
- No differences found in
  - Peak creatinine, fraction with creatinine >3.4
  - Percent requiring renal replacement therapy
  - Time to recover renal function
  - Furosemide dose, ICU LOS, hospital LOS
  - Time on ventilator, survival

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

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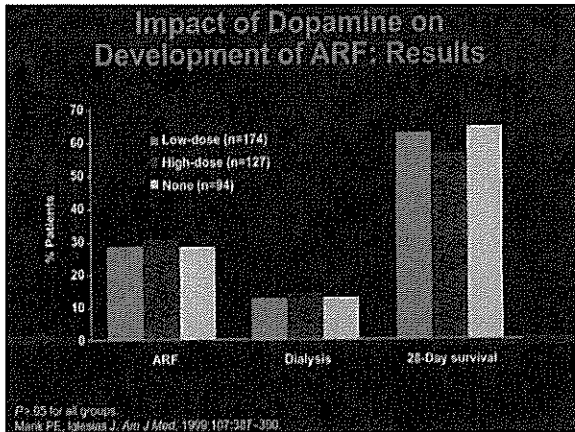
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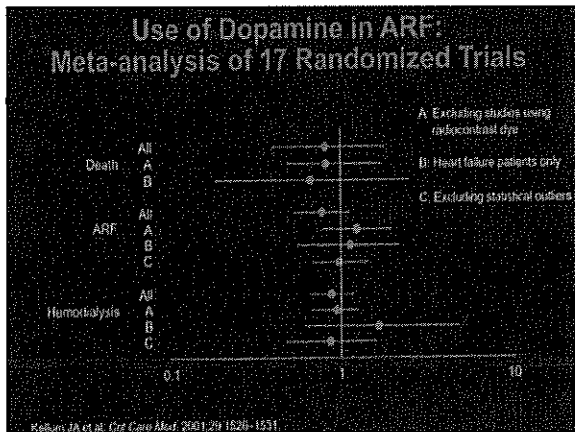
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## What Might Work

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## Initial Resuscitation

### Goals during first 6 hours:

- Central venous or mixed venous  $O_2$  sat < 70% after CVP of 8–12 mm Hg
  - Packed RBCs to Hct 30%
  - Dobutamine to max 20  $\mu$ g/kg/min

Grade B

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### Mixed Venous Oxygen Saturation > 70% MOST IMPORTANT POINT OF LECTURE !!!

- $SVO_2$  is the most important number in critical care !
- It measures oxygen delivery to tissues better than any other number
- Is effected primarily by cardiac output, hemoglobin, oxygen saturation
- Should be > 70%
- **YOU MUST LEARN TO FOLLOW THIS NUMBER IN THE OPERATING ROOM WHILE CARING FOR SICK PATIENTS !**

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### Case Study MOST IMPORTANT POINT OF LECTURE !!!

- 50 yo AA male presents to ER with apparent cholangitis
- BP 140/70, HR 105, Sat 95% on 2 L NC  $O_2$
- He is talking to you and complains of RUQ pain
- What is his mixed venous sat ?

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**Case Study**  
MOST IMPORTANT POINT OF LECTURE !!!

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- *What is his mixed venous sat ?*
  - A. 29%
  - B. 45%
  - C. 60%
  - D. 74%

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**Case Study**  
MOST IMPORTANT POINT OF LECTURE !!!

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- *What is his mixed venous sat ?*
  - A. 29%

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**Case Study**  
MOST IMPORTANT POINT OF LECTURE !!!

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- *Patient receives 3 L lactated ringers and 5 ug/kg/min of dobutamine...*
- *BP 140/70, HR 105, Sat 95% on 2 L NC O<sub>2</sub>*
- *He is talking to you and complains of RUQ pain*
  
- *What is his mixed venous sat ?*
  
- *74%*

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**Case Study**  
**MOST IMPORTANT POINT OF LECTURE !!!**

- *So the next time you are in the OR and...*
- *You have a large abdominal case you have given 5 L of crystalloid to and your urine is marginal....*
- *How can you tell if your patient is resuscitated?*
  
- *Get a mixed venous gas from your triple lumen !*

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**Mixed Venous Oxygen Saturation > 70%**  
**MOST IMPORTANT POINT OF LECTURE !!!**

- *How do we measure:*
- 1) *Draw venous gas from distal port of central venous catheter*
- 2) *Use SVO2 central venous catheter to continuously monitor*
- 3) *Use Swan-Ganz catheter*

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**Early Goal-directed Therapy  
for Septic Shock**

- RCT , n = 263
- Septic shock unresp to 20 ml/kg crystalloid or lactate > 4
- Rx (all patients receive CVP and SvO2 monitor
  - Traditional: CVP 8-12, Vasopressor for SBP < 90 mm Hg, keep UOP > 0.5 ml/kg/hr
  - Investigation: As above + RBCs for hct < 30 AND SvO2 < 70, if fails add dobutamine to dose 20 ug/kg/min

Rivers et al NEJM 345:1368 2001

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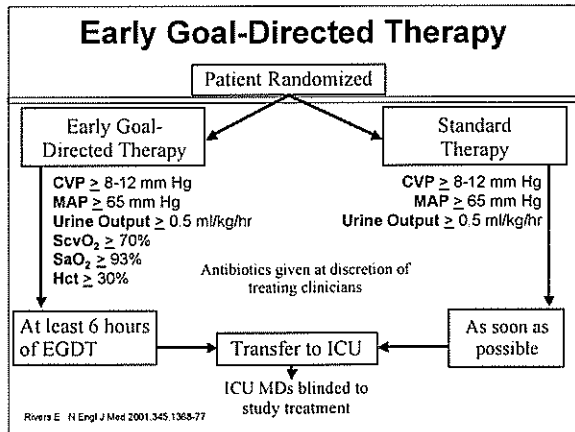
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### EGDT in Septic Shock: Treatments actually received (0-6 hrs)

	Traditional	EGDT
• Fluids (mL)	3500	5000
• RBCs (%patients)	19	64
• Vasopressor (%pts)	30	27
• Dobutamine (%pts)	1	14

Rivers et al NEJM 345:1368 2001

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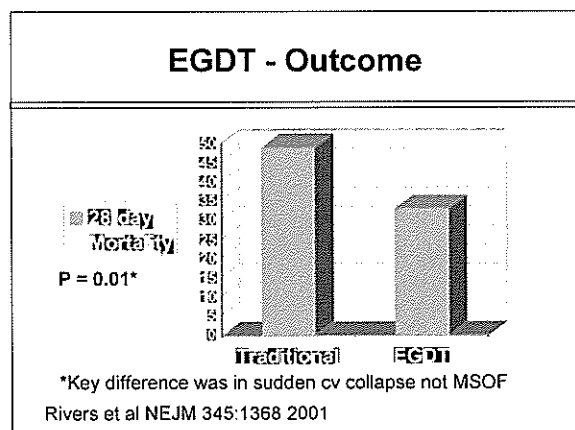
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**Vasopressin... Why Vasopressin ??**

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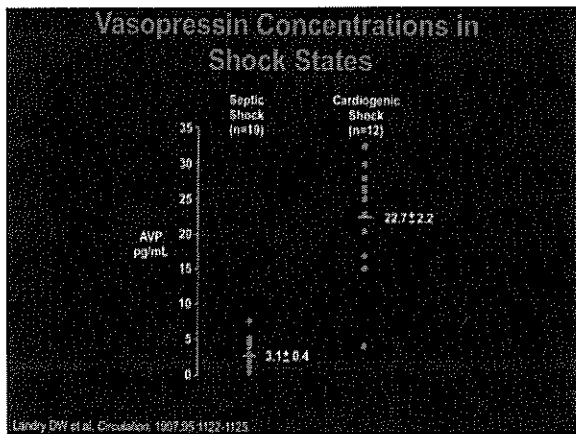
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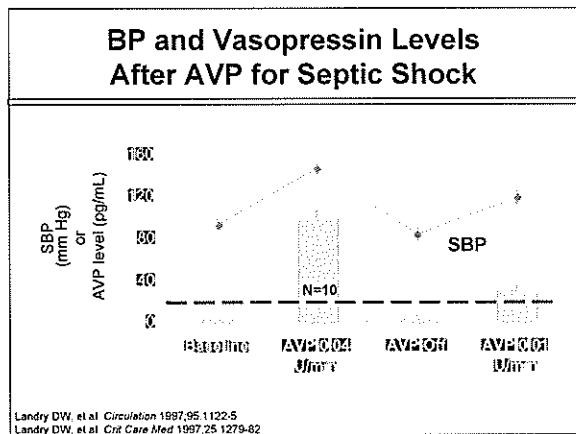
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### Shock States: Dosing Vasopressin

Physiologic	Pharmacologic
• 0.01—0.04 U/min	• >0.04 U/min
• Plasma levels 20—30 pg/mL	• Plasma levels >100 pg/mL
• Synergistic activity with catecholamines	• Potential for renal, mesenteric, coronary, pulmonary vascular constriction
• No hypoperfusion	
• Some selective vasodilation	

Reames CL et al. Chest. 2011;139:999-1002.

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### Vasopressin Summary

- VASS trial has just finished (Norepi versus Vasopressin in Septic Shock)
- Vasopressin was not better than norepinephrine in improving outcome from septic shock
- In severe sepsis, vasopressin led to increased digital necrosis versus norepi.
- Bottom Line: Levophed (Norepi) should be our first line therapy in sepsis for now

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### Vasopressors Vasopressin

- Not a replacement for norepinephrine or dopamine as a first-line agent
- Consider in refractory shock despite high-dose conventional vasopressors
- If used, administer at 0.01-0.04 units/minute in adults

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**Surviving Sepsis Campaign**

## Vasopressors

- **Either norepinephrine or dopamine administered through a central catheter is the initial vasopressor of choice.**
  - Failure of fluid resuscitation
  - During fluid resuscitation

Grade D

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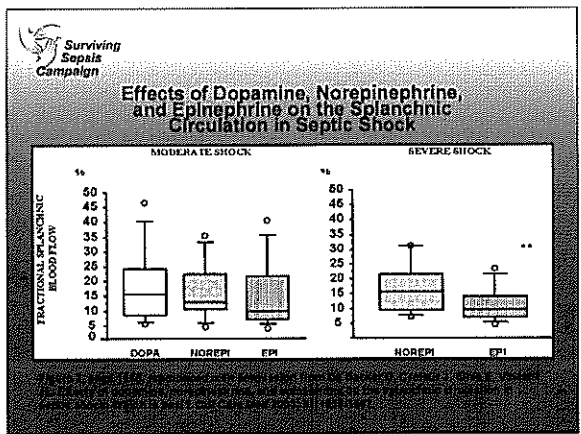
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## Intensive Insulin Therapy in Critically Ill Patients

The New England Journal of Medicine

Copyright © 2001 by the Massachusetts Medical Society

VOLUME 345      NOVEMBER 8, 2001      NUMBER 18

INTENSIVE INSULIN THERAPY IN CRITICALLY ILL PATIENTS

GREET VAN DEN BERGHE, M.D., Ph.D., PETER WOLFFENBUTEL, M.D., FRANK WILHELM, M.D., GHAELI STRARBELLI, M.D., FRANCESCO BONOMO, M.D., MICHAEL SUTZ, M.D., Ph.D., DON VANSLAERE, M.D., PATRICK FEINIKER, M.D., Ph.D., PETER LAURYS, M.D., AND ROGER BOUillon, M.D., Ph.D.

Van den Berghe G. et al. N Eng J Med 2001;345:1359-1367

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### Intensive Glucose Control in the Critically ILL

- RCT, n = 1548
- Mechanically ventilated SICU patients
- Treatments
  - Titrate blood glucose 80-110
    - VS
  - Titrate blood glucose 180-200
- All patients received 200-300 gms glucose/d on day - 1 (?D<sub>10</sub>W)
- TPN w/in 24 h of adm (60-80% as glucose calcs)

Berghe et al NEJM 345:1359 2001

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### Intensive Glucose Control Treatments received

	Conventional	Intensive
• Patients on insulin	39%	99%
• Insulin (median u/d)	33	71
• Duration (%ICU days)	67	100
• AM glucose (all pts)	153	103
• AM glucose (insulin pts)	173	103

Van Den Berghe et al NEJM 345:1359 2001

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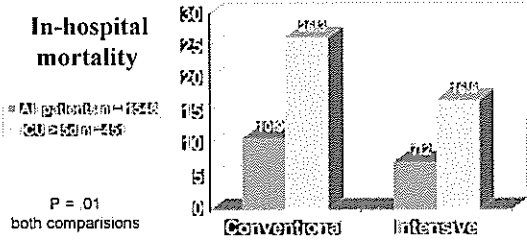
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### Intensive Glucose Control Outcome



Berghe et al NEJM 345:1359 2001

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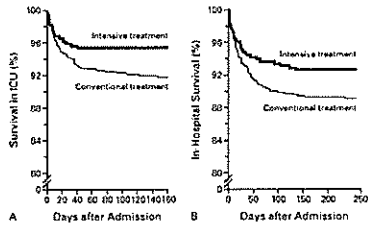
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### Intensive Insulin Therapy in Critically Ill Patients: Kaplan-Meier Curves



Van den Berghe G, et al. N Eng J Med 2001;345:1363

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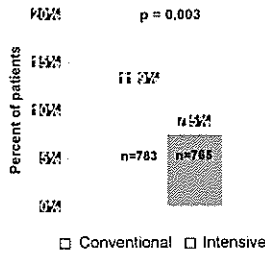
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### Intensive Insulin Therapy in Critically Ill Patients: Morbidity

#### Percent of Patients Requiring >14 Days of Ventilatory Support



Van den Berghe G, et al. N Eng J Med 2001;345:1365

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### Intensive Insulin Therapy in Critically Ill Patients: Morbidity

#### Percent of Patients with Renal Impairment

	Conventional n=783	Intensive n=765	P-value
Peak plasma creatinine >2.5 mg/dL	12.3%	9.0%	0.04
Peak plasma urea nitrogen >54 mg/dL	11.2%	7.7%	0.02
Dialysis or CVVH	8.2%	4.8%	0.007

Van den Berghe G, et al. N Eng J Med 2001;345:1359-1367

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## Intensive Insulin Therapy in Critically Ill Patients: Morbidity

- Percent of Patients with Bloodstream Infections

	Conventional n=783	Intensive n=765	P-value
Septicemia during intensive care	7.8%	4.2%	0.003
Treatment with antibiotics > 10 days	17.1%	11.2%	<0.001

Van den Berghe G, et al. N Engl J Med 2001;345:1365

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## Intensive Insulin Therapy in Medical Intensive Care Patients

- Decreased weaning time on ventilator
- Increased number of patients discharged from ICU and Hospital alive
- Reduced mortality in patients in ICU longer then 3 days
- No effect on mortality in intention to treat group

Van den Berghe G, et al. N Engl J Med, 2006 Feb 2;354(5):449-61.

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## New Data: The end of Intensive Insulin Therapy ???

- New data to be presented at ESICM and SCCM will reveal that the risk of hypoglycemia (<40) with a goal of 80-110, is GREATER then the benefit
- The data revealed in patients who became hypoglycemic, their mortality rate doubled
- This data is from a large trial of more then 800 patients
- This data reveals that 120-180 may be equally as beneficial as 80-110
- ICU nurses rejoice !!!!!

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# What Works

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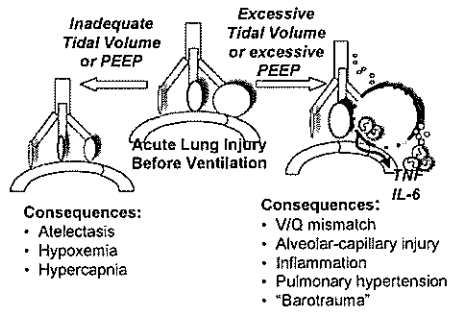
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## Balancing Ventilation Priorities




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## Ventilator Management

- Assist control mode
- Reduce TV to 6 mL/kg predicted body weight
- Keep plateau airway pressure <30 cm H<sub>2</sub>O
- Maintain SaO<sub>2</sub> / SpO<sub>2</sub> 88%-95% using this scale:

FiO <sub>2</sub>	.3	.4	.4	.5	.5	.6	.7	.7	.8	.9	.9	.9	1.0
PEEP	5	5	8	8	10	10	10	12	14	14	14	16	18 20-24

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The Acute Respiratory Distress Syndrome Network. *N Engl J Med* 2000;342:1301-8

## Ventilator Management

- Accept mild respiratory acidosis
  - If pH <7.30 increase rate (max 35)
  - If acidosis persists and rate = 35, consider NaHCO<sub>3</sub>
  - If acidosis refractory/unresponsive, may raise TV to achieve pH >7.15
- Perform a spontaneous breathing trial daily if
  - Shock absent
  - Spontaneous efforts present
  - FiO<sub>2</sub> ≤0.4 and PEEP = 8

The Acute Respiratory Distress Syndrome Network. *N Engl J Med* 2000;342:1301-8.

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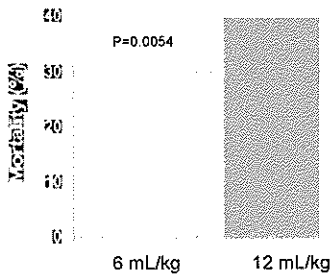
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## Mortality Prior to Discharge



The Acute Respiratory Distress Syndrome Network. *N Engl J Med* 2000;342:1301-8.

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## Sepsis Specific Therapy

At Last a Reality

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### The PROWESS Trial: Drotrecogin Alfa (Activated) in Patients with Severe Sepsis

- Anticoagulant
  - Inactivates coagulation factors Va, VIIIa
  - Inhibits formation of thrombin
- Pro-fibrinolytic
  - Allows activity of tissue plasminogen activator (endogenous TPA)
- Antiinflammatory
  - Reduces IL-6 and proinflammatory cytokines

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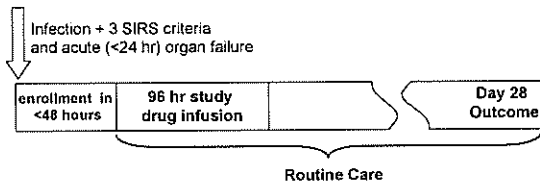
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### Drotrecogin Alfa (Activated) in Severe Sepsis: Phase III Study

- Randomized 1:1
- Blinded
- Large N=1690
- Placebo-controlled
- 164 centers
- 11 countries
- Severe sepsis



Bernard GR, et al. *N Engl J Med* 2001;344:699-709

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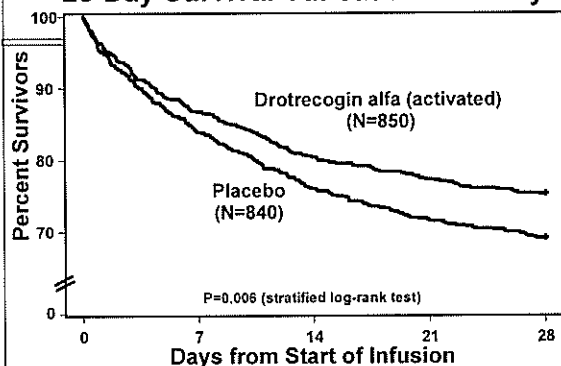
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### 28-Day Survival All-cause Mortality




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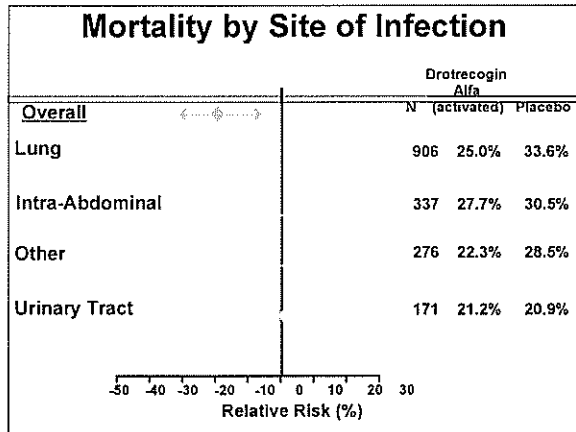
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### Other Important New Data You Should Be Aware Of !!

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### “Appropriate” antibiotics Kollef, Chest 1999

- ✓ Inadequate antimicrobial treatment of infection
- ✓ Defined as microbiologic documentation of infection (*ie*, positive culture result) not being effectively treated at time of identification
- ✓ Absence of antimicrobial agents directed at specific class of microorganisms (absence of tx for fungemia due to *Candida*) and administration of agent to which microorganism responsible for infection were resistant (eg, empiric tx with methacillen for pneumonia subsequently attributed to methacillen-resistant *Staphylococcus aureus* [MRSA] based on culture results).

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**“Appropriate” antibiotics  
Kollef, Chest 1999**

⊗ 169 patients out of 2000 surveyed were “inappropriately treated” at diagnosis of infection

⊗ Mortality rate in this group was 52.1 %

⊗ 12.2% mortality in appropriately treated group versus 52.1% (NNT = 2.5)

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**“Invasive” strategy for VAP diagnosis  
Fagon, Ann Int Med 2000**

▲▲ Examined diagnosis of ventilator associated pneumonia via bronchoscopic BAL samples and their quantitative cultures

▲▲ Versus noninvasive isolation of microorganisms by nonquantitative analysis of endotracheal aspirates, and clinical practice guidelines.

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**“Invasive” strategy for VAP diagnosis  
Fagon, Ann Int Med 2000**

Patients who recv'd invasive diagnosis had:

▲▲ Reduced mortality at day 14 (16.2% vs. 25.8%; p < 0.02)

▲▲ Decreased Sepsis-related Organ Failure Assessment scores at day 3 and day 7

▲▲ Decreased antibiotic use (mean number of antibiotic-free days, 5.0+/-5.1 and 2.2+/-3.5; P < 0.001).

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### Intensivist led multidisciplinary ICU team

- 📌 Young, Effective Clinical Practice 2000
- 📌 Concept of closed ICU service led by ICU physician
- 📌 Up to 60% reduction in mortality

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### Optimal Hemoglobin in the Critically Ill Patient !?!

- ? Clearly higher Hgb achieved via transfusion is not helpful and may be harmful
- ? Is there a lower threshold?

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### Transfusion Requirements in Critical Care

- 📌 Multicenter, RCT
- 📌 Subjects
  - Acutely ill in ICU, Hgb < 9.0
  - Excluded if: chronic anemia, ongoing bleeding, admission after CABG

Hebert et al. NEJM 1999; 340:409-17

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### Transfusion Requirements in Critical Care

- Randomized to 2 strategies
- Liberal strategy:
  - Maintain Hgb between 10-12
- Restrictive strategy:
  - Maintain Hgb between 7-9
- Endpoints
  - All cause mortality, MSOF
  - Predefined subgroups: age > 55, CAD, APACHE II > 20

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### Transfusion Requirements in Critical Care

	Restrictive (n=2118)	Liberal (n=2220)	P
ICU mortality	18.2%	18.9%	0.23
Death (30d)	18.7%	20.3%	0.11
ICU LOS	11.0	11.5	0.53
MODS	8.8	8.8	0.10
MI	0.7%	2.2%	0.02

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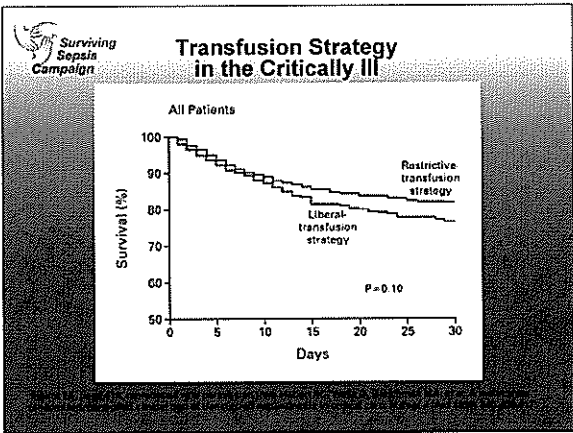
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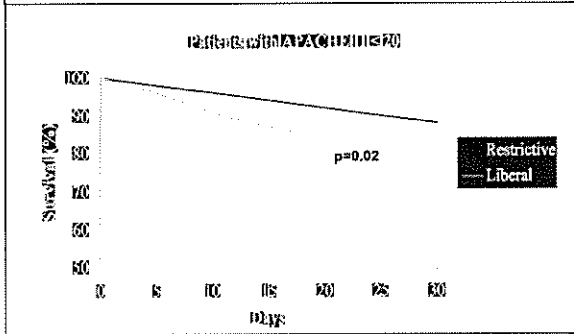
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### Transfusion Requirements in Critical Care




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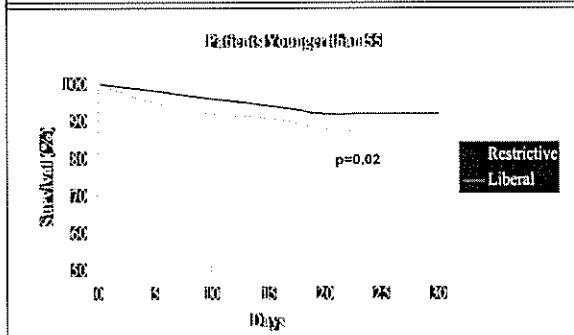
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### Transfusion Requirements in Critical Care




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### Transfusion Requirements in Critical Care

- **Conclusions**
  - ① - Lower transfusion threshold was as effective as higher trigger
  - ② - Lower threshold superior in some subgroups
  - ③ - Mechanism of worse outcomes with liberal strategy unclear (? promotes cytokine cascade, increased risk of ARDS)

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## Transfusion Requirements in Critical Care

🗨️ Editorial comment in NEJM

“This study has made it clear that a single threshold for transfusion in all patients is not appropriate..... With this knowledge, more physicians will be able to follow the dictum “first do no harm,” and we will have a surplus of blood rather than a shortage.”

Ely et al. NEJM 1999; 340: 466.

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## SUMMARY



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## NEW THERAPIES IN ICU PATIENTS (“Drivers” of Mortality)

🗨️ “Goal directed” early (ED) resuscitation  
📌 Rivers, NEJM 2001  
📌 30.5% mortality versus 46.5% (NNT = 6)

🗨️ Intensive insulin therapy  
📌 Van den Berghe, NEJM 2001  
📌 10.6% mortality versus 20.2% (NNT = 20)

🗨️ Low dose steroids in sepsis  
📌 Annane, JAMA 2002  
📌 53% mortality versus 63% (NNT = 10)

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 **NEW THERAPIES (cont)** 

- ✎ Low tidal volumes for ALI/ARDS
  - ✎ ARDS network, NEJM 2000
  - ✎ 31.0% mortality versus 39.8% (NNT = 11)
- ✎ “Appropriate” antibiotics
  - ✎ Kollef, Chest 1999
  - ✎ 12.2% mortality versus 52.1% (NNT = 2.5)
- ✎ “Invasive” strategy for VAP diagnosis
  - ✎ Fagon, Ann Int Med 2000
  - ✎ 16.2% mortality versus 25.8% (NNT = 10)

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 **NEW THERAPIES (cont)** 

- ✎ Activate protein C (Xigris®) for sepsis
  - ✎ Bernard, NEJM 2001
  - ✎ 24.7% mortality versus 30.8% (NNT = 16)
- ✎ Intensivist led multidisciplinary ICU team
  - ✎ Young, Effective Clinical Practice 2000
  - ✎ Up to 60% reduction in mortality

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 **LESS PROVEN THERAPIES**  
(no good placebo controls) 

- Transfusion practices
- Pulmonary artery catheters
  - Have not been shown to improve outcome
- Liberal versus conservative fluid strategy
- Prevent the “2<sup>nd</sup> hit” (DVT, VAP, GI bleeding)

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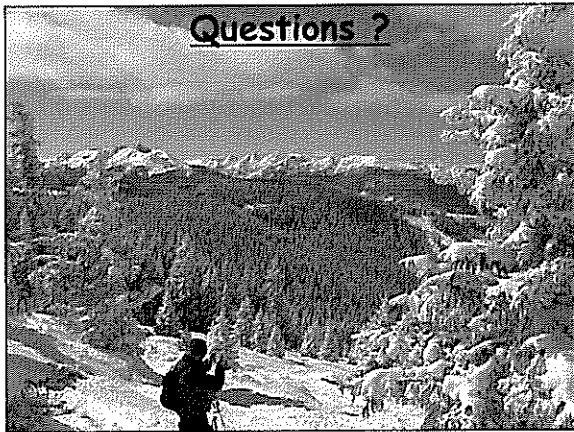
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