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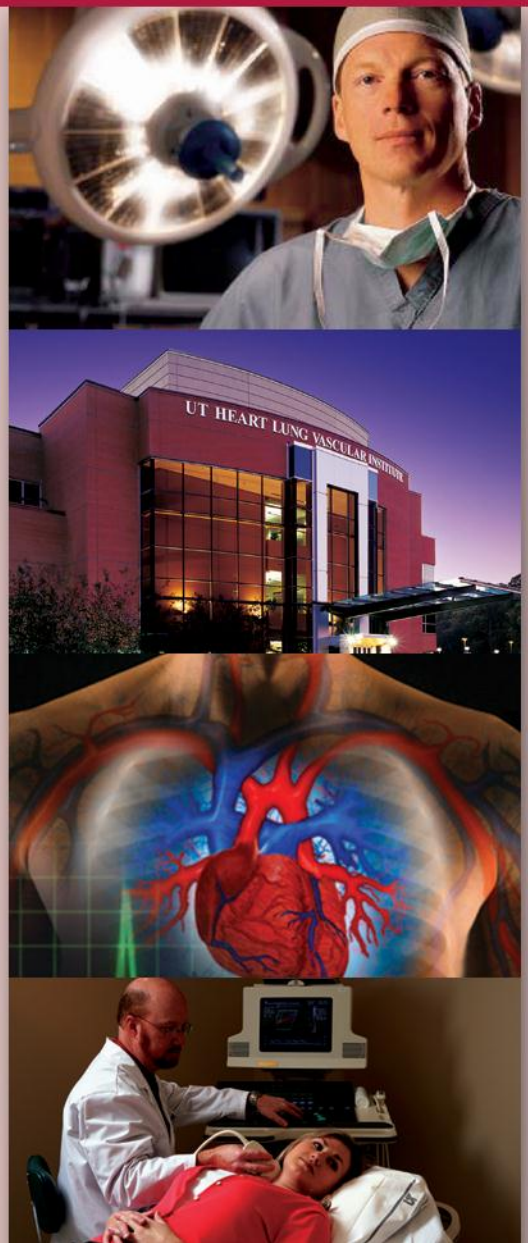

Sepsis and Septic Shock

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Outline

- Define and understand shock – the foundation
- Define sepsis and severe sepsis
- Pathophysiology
- Epidemiology
- Initial treatment / resuscitation
- General concepts of subsequent inpatient treatment
- Case studies throughout
- Recognize specific sepsis syndromes
- Learn some general critical care concepts

CASE

- 40 year old male with three days of cough and low grade fever.
- His spouse works night shift at the hospital. When she comes home she finds him confused with high fever.
- EMS called. Initial vital signs: Pulse 145, BP 85/40. Respiratory Rate 26. Temp 102. O2SAT 88%.

IS HE IN SHOCK?

Shock

- Syndrome of impaired tissue oxygenation and perfusion
- One or a combination of three mechanisms
  - Impaired oxygen delivery — Cardiac Output
  - Impaired tissue perfusion — SVR
  - Impaired oxygen utilization at the level of the tissue

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Clinical Indications of Shock
(Imbalance Between Supply and Demand)

- Hypotension
- Altered mental status
- Oliguria / Acute renal failure
- Lactic Acidosis
- Abnormal liver function
- Cool clammy skin

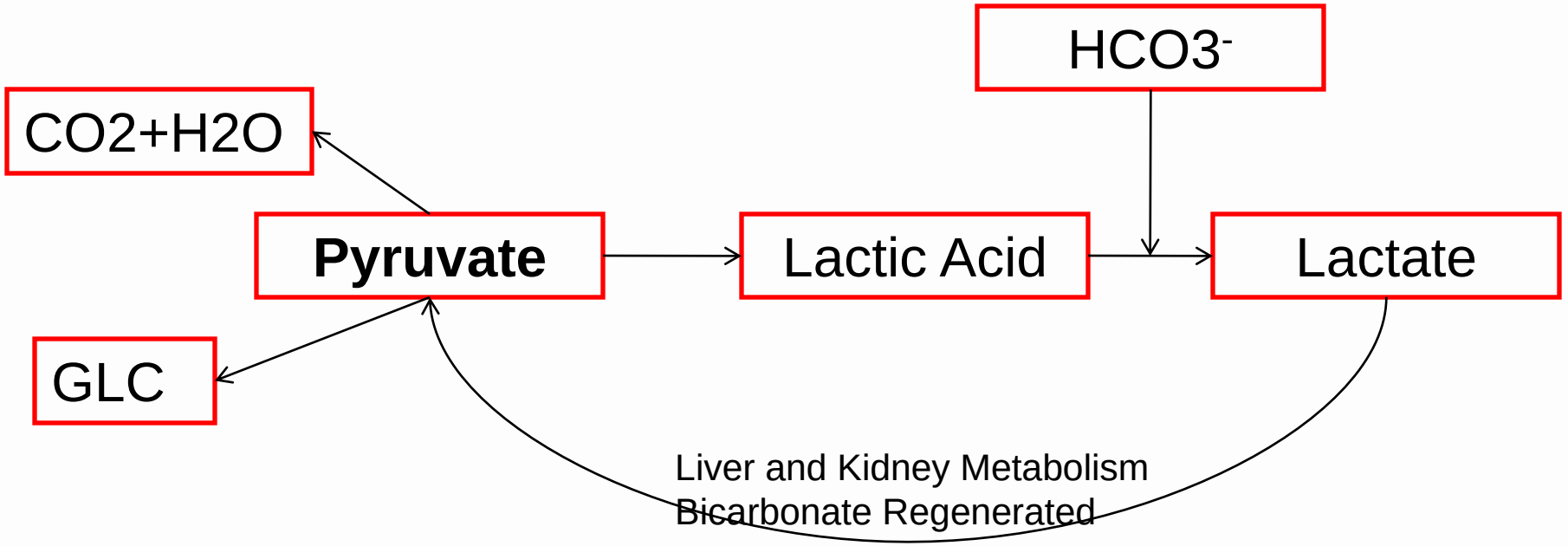
The Magic of Lactate

- Type A Lactic Acidosis – Marked tissue hypoperfusion in shock or after cardiopulmonary arrest
- Type B Lactic Acidosis – Findings of systemic hypoperfusion not evident
  - Malignancy
  - Metformin induced lactic acidosis

WE ARE INTERESTED IN TYPE A LACTIC ACIDOSIS

The Magic of Lactate

- Accumulation of Lactic Acid
  - Overproduction
  - Underuse



Determinants of Oxygen Delivery

- Cardiac output

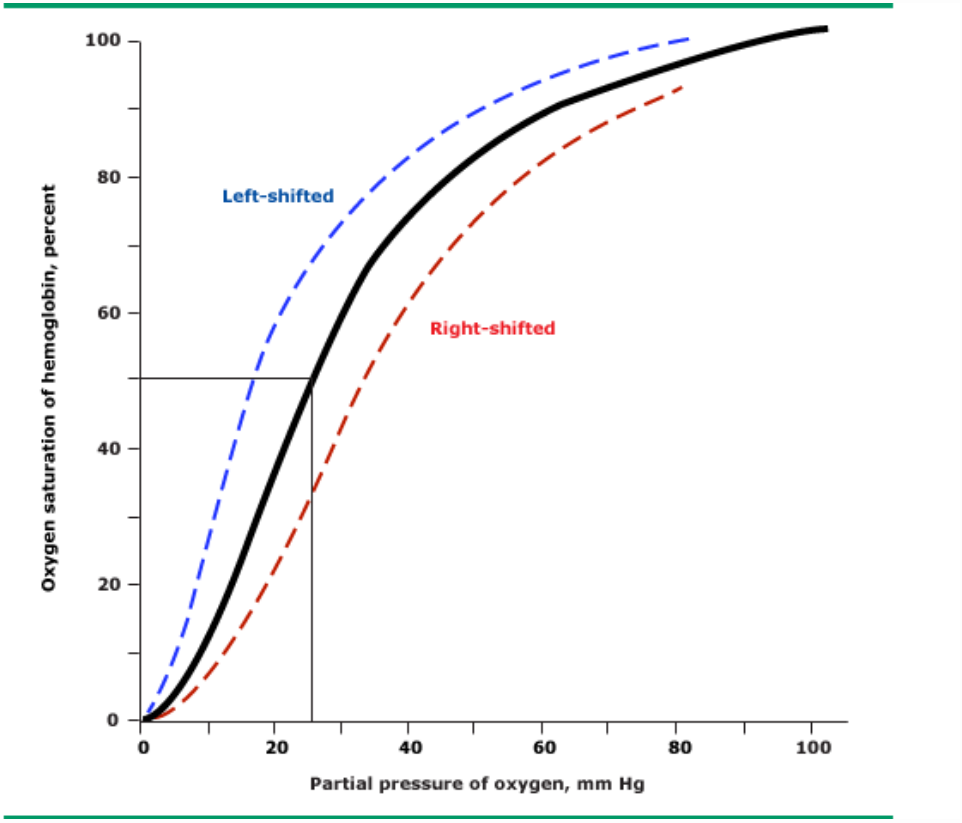
Stroke volume x heart rate

- Oxygen content of blood

disregard

$$([Hb] \times (So_2/100) \times 1.39) + (Po_2 \times 0.00003)$$

Oxyhemoglobin Dissociation Curve



UptoDate

Compensatory Mechanisms

- Tachycardia
- Vasoconstriction

CASE

- 40 year old diabetic male with three days of nausea, vomiting, but no fever.
- His spouse works night shift at the hospital. When she comes home she finds him confused.
- EMS called. Initial vital signs: Pulse 145, BP 85/40. Respiratory Rate 40. Temp 98. O2SAT 99% Glucose >450.

Why is he breathing 40 times a minute?

Acidosis in Severe Illness
A Quick Detour

- Lactic Acidosis
- Diabetic Ketoacidosis (the stress of the severe underlying illness can cause diabetes to decompensate leading to ketoacidosis)
- Acute Kidney Injury
- Respiratory Acidosis

Blood Gas Review
Define the Acid-Base Disorder

- Technically speaking need measured electrolytes as well
- pH/pCO2/pO2
- 7.25/30/85
- 7.25/50/70
- 7.15/50/70
- 6.9/15/115
- 6.9/110/55

- Respiratory Acidosis
- Respiratory Alkalosis
- Metabolic Acidosis
- Metabolic Alkalosis

The Final Common Pathway

"The final common pathway of all severe illness is shortness of breath"

James E. Shamiyeh MD
January 8, 2013

Causes of Shortness of Breath in Severe Illness

- Hypoxemia
- Problems with respiratory mechanics
- Metabolic acidosis
- Sepsis itself
- Severe anemia

CASE

- 40 year old male generally healthy. He just got home last night from a business trip in Japan. He has had a nonproductive cough during the past two days.
- His spouse works night shift at the hospital. When she comes home she has breakfast with him. He develops abrupt shortness of breath and dizziness.
- EMS called. Initial vital signs: Pulse 145, BP 85/40. Respiratory Rate 26. Temp 99. O2SAT 88%.

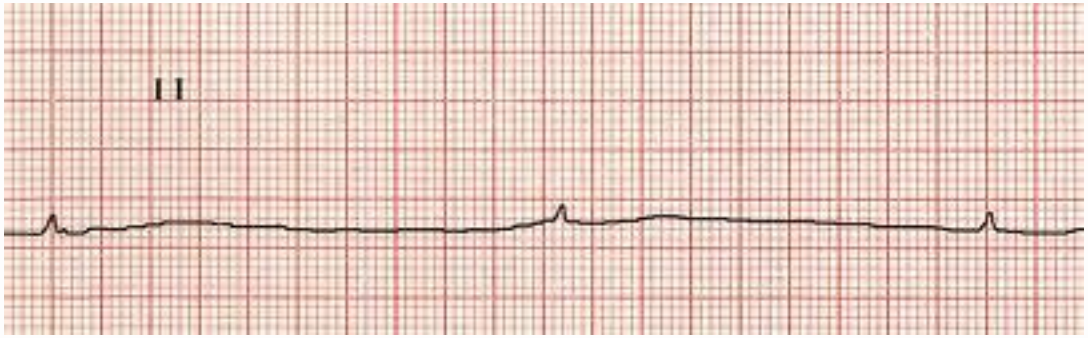
IS HE SEPTIC?

Types of Shock

- Cardiogenic shock
- Hypovolemic shock
- Distributive shock
- Obstructive shock

Causes of Cardiogenic Shock

- Pump failure (ischemia)
- Arrhythmia (bradycardia)
- Mechanical (acute valve rupture causing acute valvular regurgitation)



http://www.google.com/imgres?q=bradycardia+ecg&hl=en&tbo=d&biw=1396&bih=726&tbm=isch&tbnid=EzaYmixgSAzuwM:&imgrefurl=http://lifeinthefastlane.com/ecg-library/basics/hyperkalaemia/&docid=gEObt-BoW2Gh_M&imgurl=http://lifeinthefastlane.com

Causes of Hypovolemic Shock

- Hemorrhagic
- Non-hemorrhagic

Causes of Distributive (Vasodilatory) Shock

- Sepsis
- Neurogenic
- Adrenal Crisis
- Anaphylaxis

Causes of Obstructive Shock

CASE

- 40 year old male who is a heavy drinker develops severe midepigstric pain as well as nausea and vomiting over the past two days. This has happened to him once in the past.
- Spouse finds him in severe pain and confused
- EMS called. Initial vital signs: Pulse 145, BP 85/40. Respiratory Rate 26. Temp 100.5. O2SAT 94%

IS HE SEPTIC?

Sepsis Definitions

- Sepsis – Infection plus systemic manifestations of infection
- Severe sepsis – sepsis plus sepsis-induced organ dysfunction or tissue hypoperfusion
- Septic shock – sepsis induced hypotension persisting despite adequate fluid resuscitation
  - Sepsis induced hypotension – SBP<90, MAP<70, or decrease >40mm

SIRS

- Presence of two or more of the following
  - Temperature > 38.6 C or < 36 C
  - Heart rate > 90 beats / minute
  - Respiratory rate > 20 breaths/min or PaCO2<32mm Hg
  - WBC > 12,000, < 4000, or > 10 percent immature band forms

Sepsis Definition

- Infection + SIRS

Sepsis

- There are few people in the audience that may currently meet criteria for sepsis
- Unfortunately, a few others may by now be comatose

Severe Sepsis Definition

- Sepsis plus at least one of the following signs of organ hypoperfusion or dysfunction
  - Areas of mottled skin
  - Capillary refill longer than 3 seconds
  - Urine output < 0.5 mL/kg for at least 1 hour
  - Lactate > 2 mmol/L
  - Abrupt change in mental status
  - Abnormal EEG findings
  - Plts < 100,000
  - DIC
  - Acute Lung Injury
  - Cardiac Dysfunction

Septic Shock Definition

- MAP < 60 (<80 if baseline hypertension) despite adequate fluid resuscitation
- Norepinephrine, dopamine, or epinephrine requirement
- Adequate fluid resuscitation = 40-60 mL/kg normal saline
  - Think 3-4 liters

Multiorgan Failure

- PO2/FiO2 ratio
- Creatinine
- Platelet count
- Glasgow coma score
- Serum bilirubin

SIRS without Infection

- Pancreatitis
- Burns

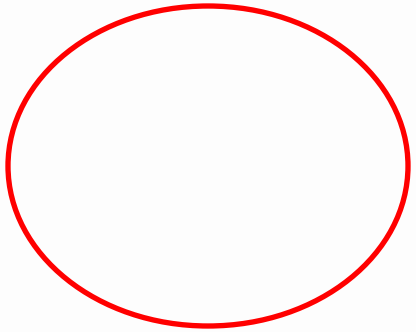
Pathophysiology

- Process of **malignant intravascular inflammation**
- **Malignant** – uncontrolled, unregulated, and self-sustaining
- **Intravascular** – blood-borne spread of what is usually a cell-to-cell interaction in the interstitial space
- **Inflammation** – all characteristics of septic response are exaggerations of the normal inflammatory response

Normal Inflammation

- At site of injury, endothelium expresses adherence molecules to attract leukocytes
- PMNs are activated, express adhesion molecules that cause their aggregation and margination to the vascular endothelium
- PMNs then migrate to site of injury
- Release of mediators by PMNs at the site of injury produces cardinal signs of local inflammation
  - Local vasodilation and hyperemia
  - Increased microvascular permeability, resulting in protein-rich edema
- Many cytokines released locally
- **In some cases, mediator release exceeds the boundaries of the local environment → SIRS**

Inflammatory Response to Sepsis



Russell J. NEJM 2006; 355: 1699-713

Procoagulant Response to Sepsis

Cellular Injury in Sepsis

- Ischemia
- Cytopathic Injury
- Increased rate of cell death

Epidemiology

- Over 750,000 cases of sepsis
- Over 200,000 fatalities
- Mortality exceeds 40%

Where in the Hospital Do Severe Sepsis Patients Originate?

Severe Sepsis is Deadly

11th leading cause of death overall (U.S.)

Management of Severe Sepsis

- **EARLY RECOGNITION**
- Initial Resuscitation – FOCUS
- Antibiotic Therapy
- Source Control
- Vasopressors
- Inotropic Support
- Corticosteroids

CASE

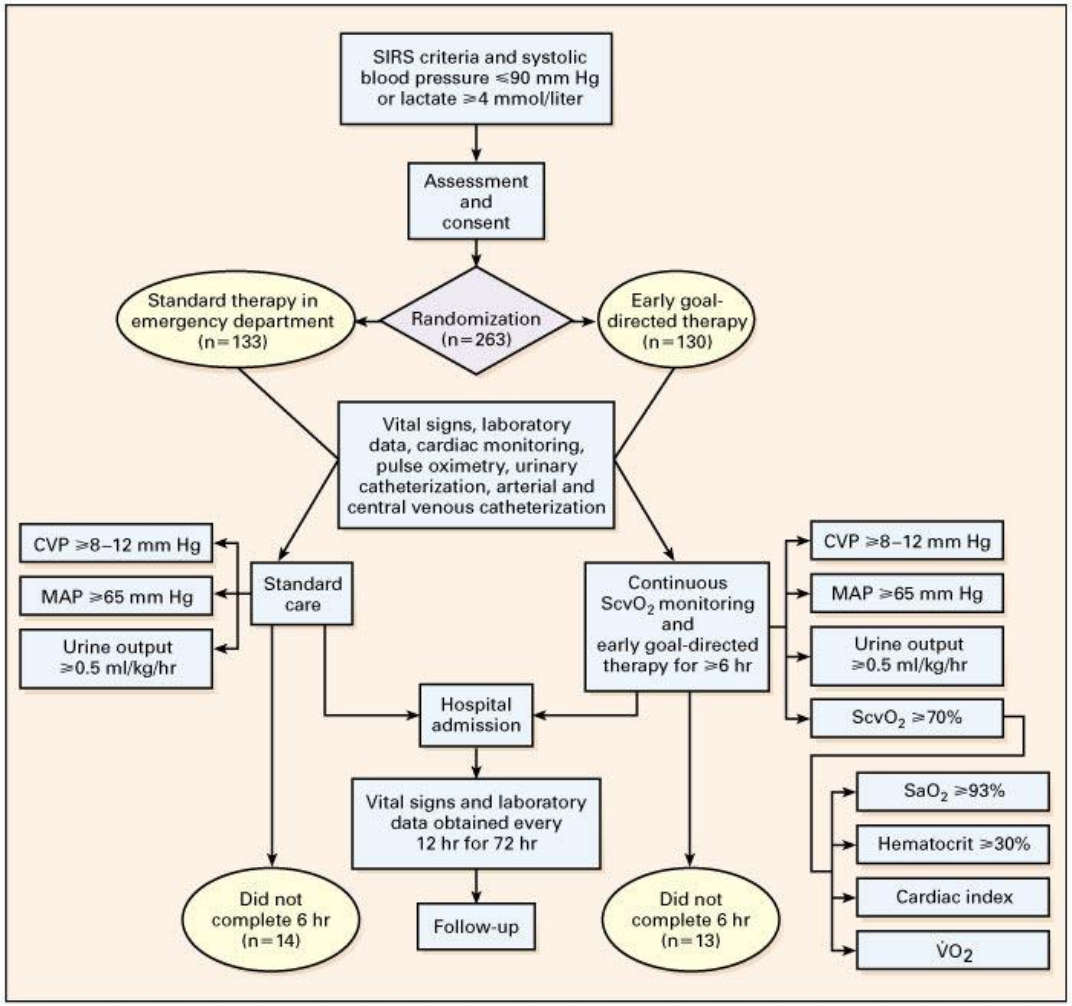
- 40 year old male with three days of cough and fever.
- His spouse works night shift at the hospital. When she comes home she finds him confused with high fever.
- EMS called. Initial vital signs: Pulse 145, BP 85/40. Respiratory Rate 26. Temp 102. O2SAT 88%.

WHAT IS OUR FIRST PRIORITY IN TREATMENT?

Initial Resuscitation

- Critical hypoperfusion can occur in absence of hypotension, especially during early sepsis
  - Cool, vasoconstricted skin (however can be warm and vasodilated in early sepsis)
  - Obtundation or restlessness
  - Oliguria
  - Lactic acidosis
- May be modified by preexisting factors
  - Elderly and patients on beta-blockers may not have tachycardia
  - Patients with chronic hypertension may exhibit signs of end organ damage at a relatively “normal” blood pressure

Initial Resuscitation – NEJM 2001



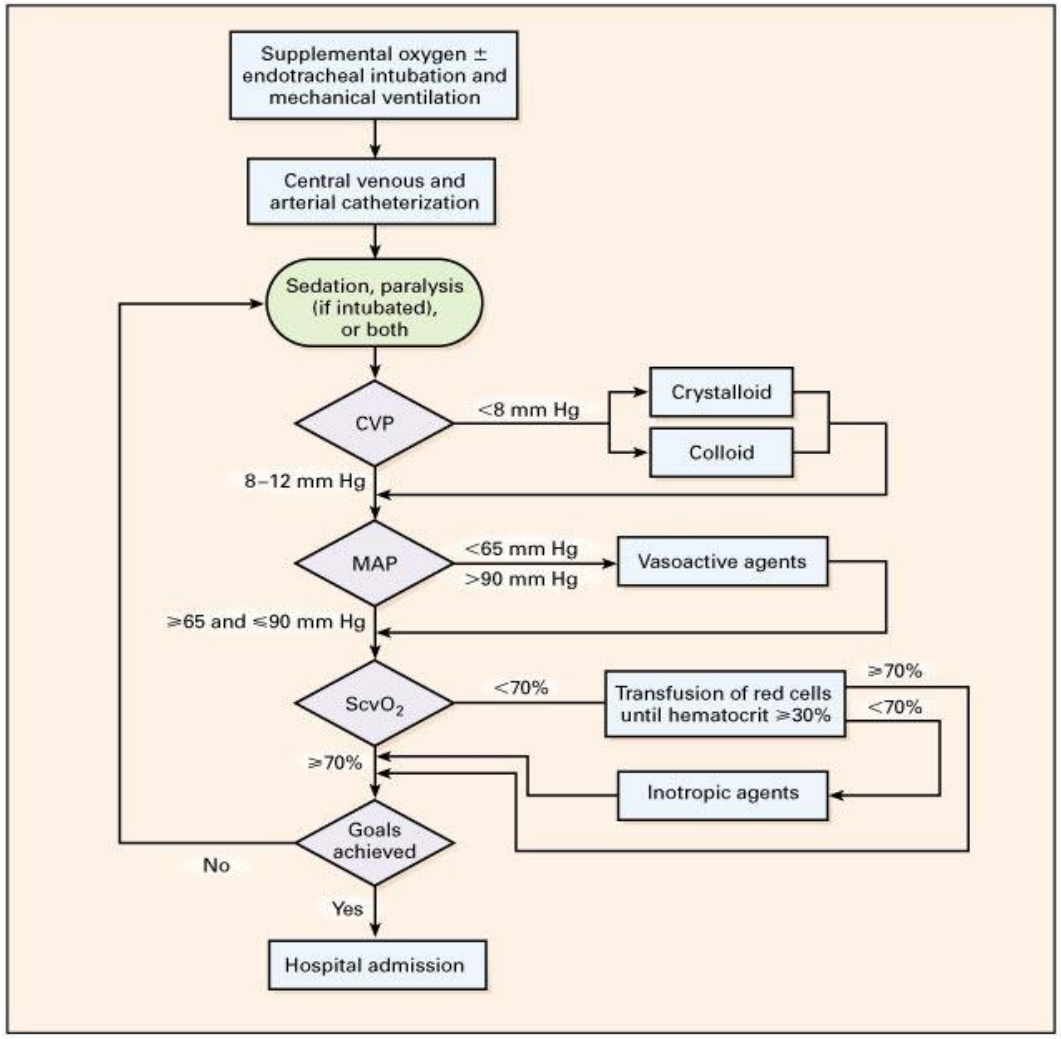
CVP
ScvO2

Rivers et al. NEJM 2001; 345: 1368-1377.

ScvO2

- Oxygen content in the central venous circulation is a surrogate of oxygen delivery
- If oxygen delivery is inadequate, we expect this percentage to be low

Initial Resuscitation – NEJM 2001



Rivers et al. NEJM 2001; 345: 1368-1377.

Initial Resuscitation – NEJM

TABLE 3. KAPLAN–MEIER ESTIMATES OF MORTALITY AND CAUSES OF IN-HOSPITAL DEATH.*

VARIABLE	STANDARD THERAPY (N=133)	EARLY GOAL-DIRECTED THERAPY (N=130)	RELATIVE RISK (95% CI)	P VALUE
	no. (%)			
In-hospital mortality†				
All patients	59 (46.5)	38 (30.5)	0.58 (0.38–0.87)	0.009
Patients with severe sepsis	19 (30.0)	9 (14.9)	0.46 (0.21–1.03)	0.06
Patients with septic shock	40 (56.8)	29 (42.3)	0.60 (0.36–0.98)	0.04
Patients with sepsis syndrome	44 (45.4)	35 (35.1)	0.66 (0.42–1.04)	0.07
28-Day mortality†	61 (49.2)	40 (33.3)	0.58 (0.39–0.87)	0.01
60-Day mortality†	70 (56.9)	50 (44.3)	0.67 (0.46–0.96)	0.03
Causes of in-hospital death‡				
Sudden cardiovascular collapse	25/119 (21.0)	12/117 (10.3)	—	0.02
Multiorgan failure	26/119 (21.8)	19/117 (16.2)	—	0.27

*CI denotes confidence interval. Dashes indicate that the relative risk is not applicable.

†Percentages were calculated by the Kaplan–Meier product-limit method.

‡The denominators indicate the numbers of patients in each group who completed the initial six-hour study period.

Key difference was in sudden cardiovascular collapse, not MSOF

Rivers et al. NEJM 2001; 345: 1368-1377.

Initial Resuscitation – NEJM

TABLE 4. TREATMENTS ADMINISTERED.*

TREATMENT	HOURS AFTER THE START OF THERAPY		
	0–6	7–72	0–72
Total fluids (ml)			
Standard therapy	3499±2438	10,602±6,216	13,358±7,729
EGDT	4981±2984	8,625±5,162	13,443±6,390
P value	<0.001	0.01	0.73
Red-cell transfusion (%)			
Standard therapy	18.5	32.8	44.5
EGDT	64.1	11.1	68.4
P value	<0.001	<0.001	<0.001
Any vasopressor (%)†			
Standard therapy	30.3	42.9	51.3
EGDT	27.4	29.1	36.8
P value	0.62	0.03	0.02
Inotropic agent (dobutamine) (%)			
Standard therapy	0.8	8.4	9.2
EGDT	13.7	14.5	15.4
P value	<0.001	0.14	0.15
Mechanical ventilation (%)			
Standard therapy	53.8	16.8	70.6
EGDT	53.0	2.6	55.6
P value	0.90	<0.001	0.02
Pulmonary-artery catheterization (%)‡			
Standard therapy	3.4	28.6	31.9
EGDT	0	18.0	18.0
P value	0.12	0.04	0.01

*Plus–minus values are means ±SD. Because some patients received a specific treatment both during the period from 0 to 6 hours and during the period from 7 to 72 hours, the cumulative totals for those two periods do not necessarily equal the values for the period from 0 to 72 hours. EGDT denotes early goal-directed therapy.

†Administered vasopressors included norepinephrine, epinephrine, dopamine, and phenylephrine hydrochloride.

‡All pulmonary-artery catheters were inserted while patients were in the intensive care unit.

Rivers et al. NEJM 2001; 345: 1368-1377.

Initial Resuscitation

- Protocolized resuscitation
- Target CVP of 8 (12 in ventilated patients)
- Continue “challenge” approach until CVP at goal and still seeing improvement in BP, HR, and urine output
- Start with >1000 mL crystalloid or >300-500 mL colloid
- Reduce rate substantially when cardiac filling pressures increase without concurrent hemodynamic improvement
- Vasopressors
- ScvO2 monitoring
- PRBC administration
- Inotrope administration

Rivers et al. NEJM 2001; 345: 1368-1377.

Subsequent Hospital Care of Sepsis

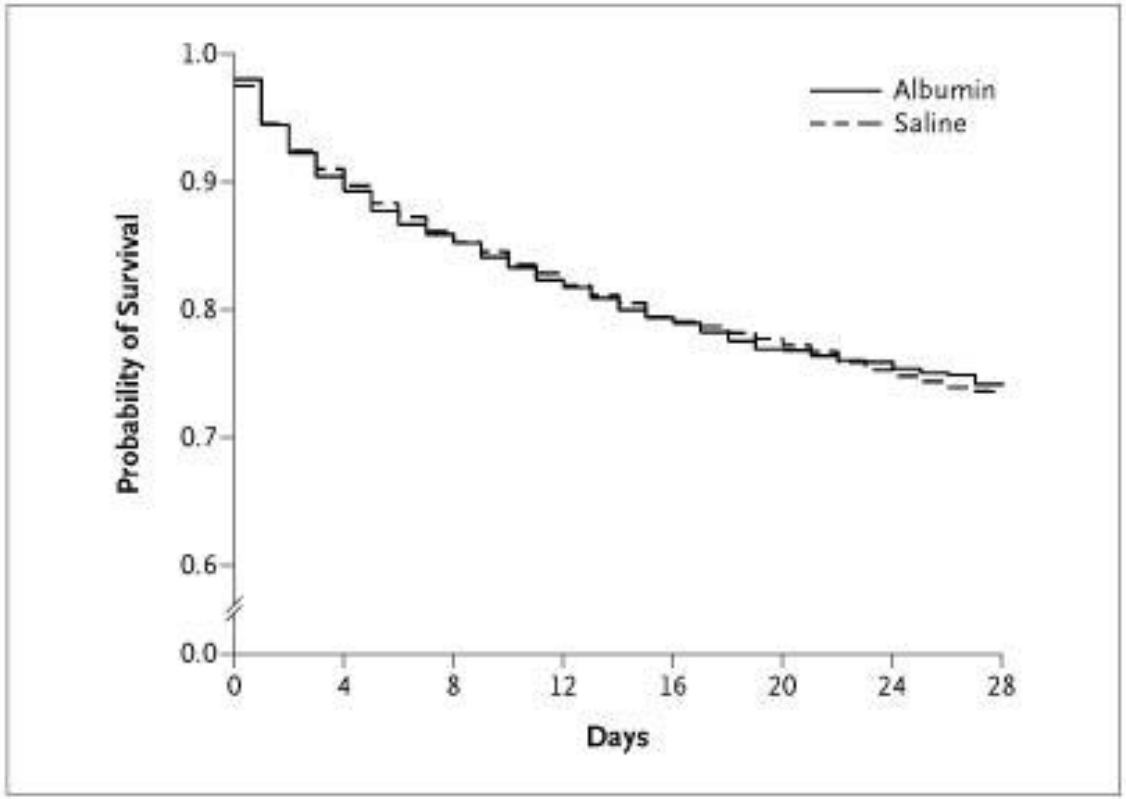
Antibiotic Therapy

- Recently used antibiotics should generally be avoided
- MRSA in the community?
- Risk factors for candidemia?
- Combination therapy for pseudomonas
- Combination therapy for neutropenic patients
- After 3-5 days, deescalate to most appropriate single therapy
- 7-10 days of therapy, but depends on the clinical course

Source Control

- Remove even possibly infected vascular access
- Intraabdominal abscess
- Cholangitis
- Pyelonephritis
- Empyema
- Septic arthritis
- Necrotizing fasciitis
- Infected peripancreatic necrosis – only localized “source” that may benefit from delayed intervention

Fluid Therapy – SAFE study Crystalloid vs. Colloid



SAFE study investigators. NEJM 2004; 350: 2247-56.

Fluid Therapy – SAFE study, NEJM, 2004 – Sepsis Subset

Table 3. Primary and Secondary Outcomes.*

Outcome	Albumin Group	Saline Group	Relative Risk (95% CI)	Absolute Difference (95% CI)	P Value
Status at 28 days — no./total no. (%)					
Dead	726/3473 (20.9)	729/3460 (21.1)	0.99 (0.91 to 1.09)		0.87
Alive in ICU	111/3473 (3.2)	87/3460 (2.5)	1.27 (0.96 to 1.68)		0.09
Alive in hospital†	793/3473 (22.8)	848/3460 (24.5)	0.93 (0.86 to 1.01)		0.10
Length of stay in ICU — days	6.5±6.6	6.2±6.2		0.24 (–0.06 to 0.54)	0.44
Length of stay in hospital — days†	15.3±9.6	15.6±9.6		–0.24 (–0.70 to 0.21)	0.30
Duration of mechanical ventilation — days	4.5±6.1	4.3±5.7		0.19 (–0.08 to 0.47)	0.74
Duration of renal-replacement therapy — days	0.48±2.28	0.39±2.0		0.09 (–0.0 to 0.19)	0.41
New organ failure — no. (%)‡					0.85§
No failure	1397 (52.7)	1424 (53.3)			
1 organ	795 (30.0)	796 (29.8)			
2 organs	369 (13.9)	361 (13.5)			
3 organs	68 (2.6)	75 (2.8)			
4 organs	18 (0.7)	17 (0.6)			
5 organs	2 (0.1)	0			
Death within 28 days according to subgroup — no./total no. (%)					
Patients with trauma	81/596 (13.6)	59/590 (10.0)	1.36 (0.99 to 1.86)		0.06
Patients with severe sepsis	185/603 (30.7)	217/615 (35.3)	0.87 (0.74 to 1.02)		0.09
Patients with acute respiratory distress syndrome	24/61 (39.3)	28/66 (42.4)	0.93 (0.61 to 1.41)		0.72

* Plus–minus values are means ±SD. CI denotes confidence interval, and ICU intensive care unit.
† The data include the numbers of patients in the ICU or the length of stay in the ICU.
‡ Data were available for 2649 patients in the albumin group and 2673 patients in the saline group. New organ failure was defined as a Sequential Organ-Failure Assessment score[13] of 0, 1, or 2 in any individual organ system at baseline, followed by an increase in the score to 3 or 4 in the same system.
§ The P value pertains to the comparison between the albumin and saline groups in the numbers of patients who had no new organ failure or new failure of one, two, three, four, or five organs.

SAFE study investigators. NEJM 2004; 350: 2247-56.

Vasopressors

- MAP $\geq$ 65
  - Consider higher if previously hypertensive
  - Follow lactate and urine output to ensure goal BP is adequate
- No high quality evidence to recommend one catecholamine over another
- Clinical and animal data suggest some advantages of norepinephrine or dopamine over epinephrine (tachycardia and effects on splanchnic circulation) and phenylephrine (decrease in stroke volume)
  - Even so, guidelines recommend epinephrine be “the first chosen alternative agent in septic shock that is poorly responsive to norepinephrine or dopamine” - ? Disagree
- Norepinephrine – increases MAP due to vasoconstrictive effects, with little change on heart rate and less effect on stroke volume
  - More potent than dopamine, may be more effective at reversing septic shock
- Dopamine – increases mean arterial pressure and cardiac output, primarily due to an increase in stroke volume and heart rate

Vasopressors - Vasopressin

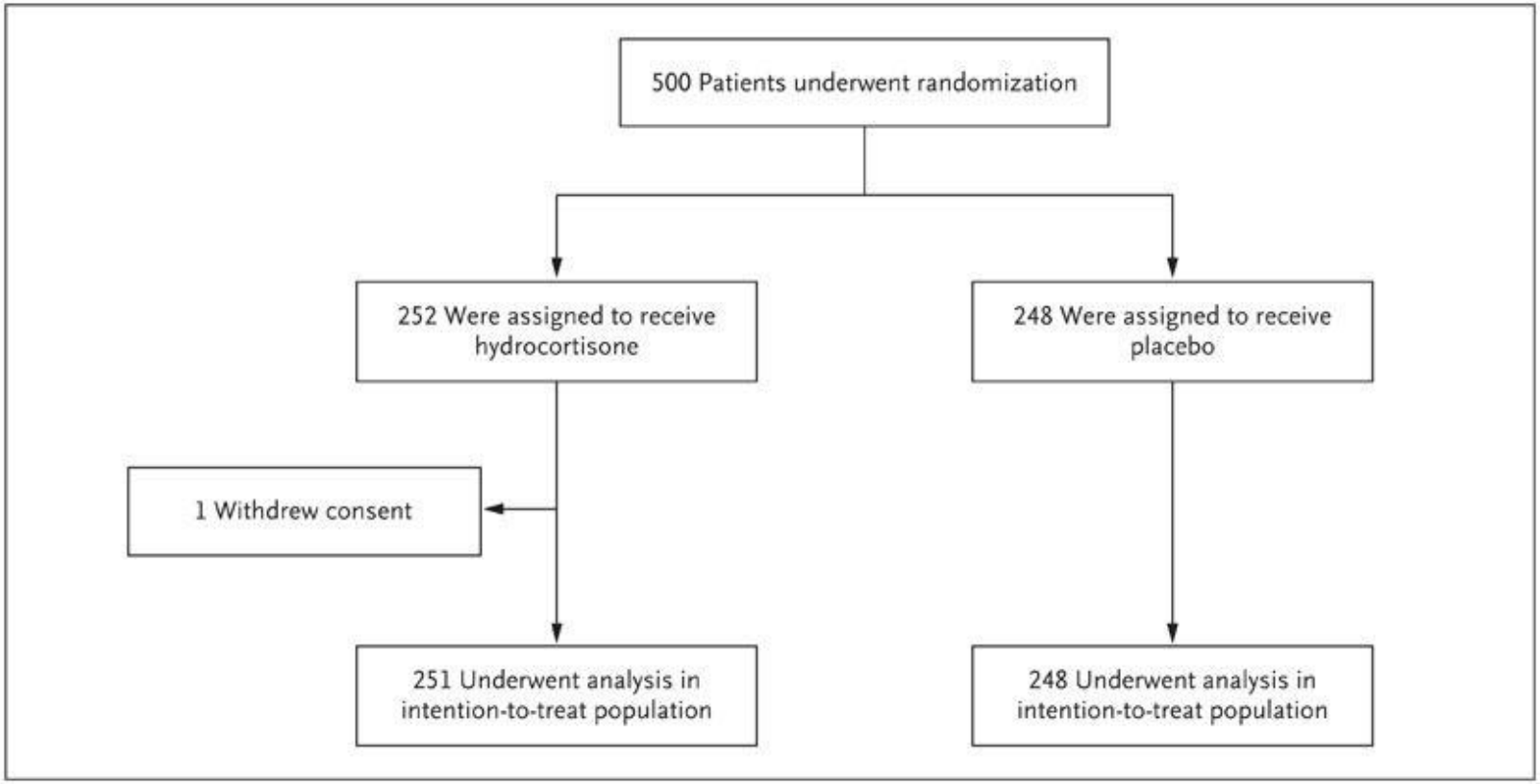
- Vasopressin levels are elevated in early sepsis but normalize in later sepsis – i.e. *relative vasopressin deficiency*
- VASST (NEJM 2008)– vasopressin in septic shock trial
  - Patients on at least 5 micrograms/minute of norepinephrine
  - Received either vasopressin 0.03 units/min or norepinephrine 5-15 micrograms/kg/min
  - No survival difference overall
  - Patients with lower norepinephrine requirement had improved survival with vasopressin
- Higher doses of vasopressin have been associated with cardiac, digital, and splanchnic ischemia
- "Vasopressin 0.03 units/minute may be added to norepinephrine subsequently with anticipation of an effect equivalent to that of norepinephrine alone."

Russell et al. NEJM 2008; 358: 877-887.

Inotropic Support

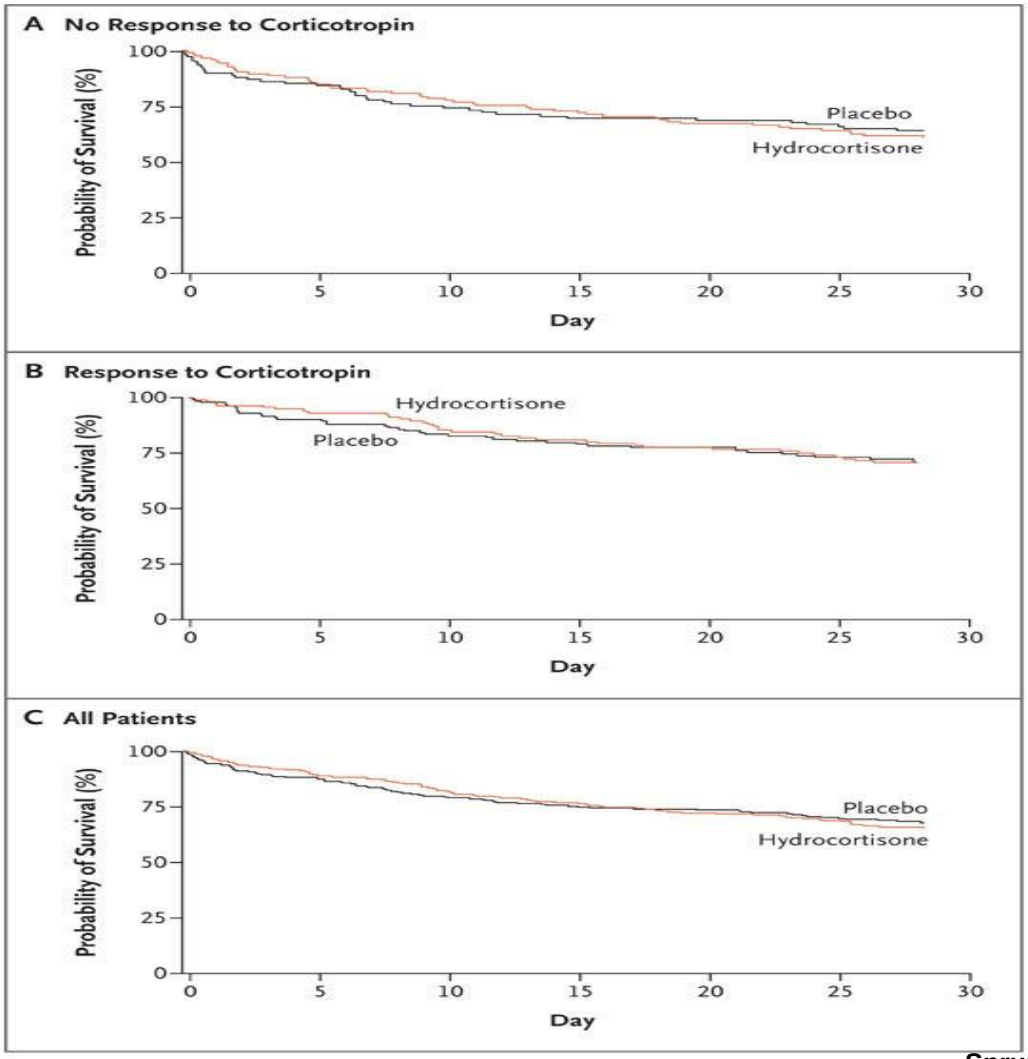
- Septic patients with who remain hypotensive after fluid resuscitation may have low, normal, or increased cardiac outputs
  - Treatment with combined inotrope/vasopressor recommended (like norepinephrine or dopamine)
- Two large studies that included critically ill ICU patients with severe sepsis failed to demonstrate benefit from increasing oxygen delivery to supranormal levels by use of dobutamine
  - Did not apply to early resuscitation

Corticosteroids – NEJM 2008 CORTICUS Study Group



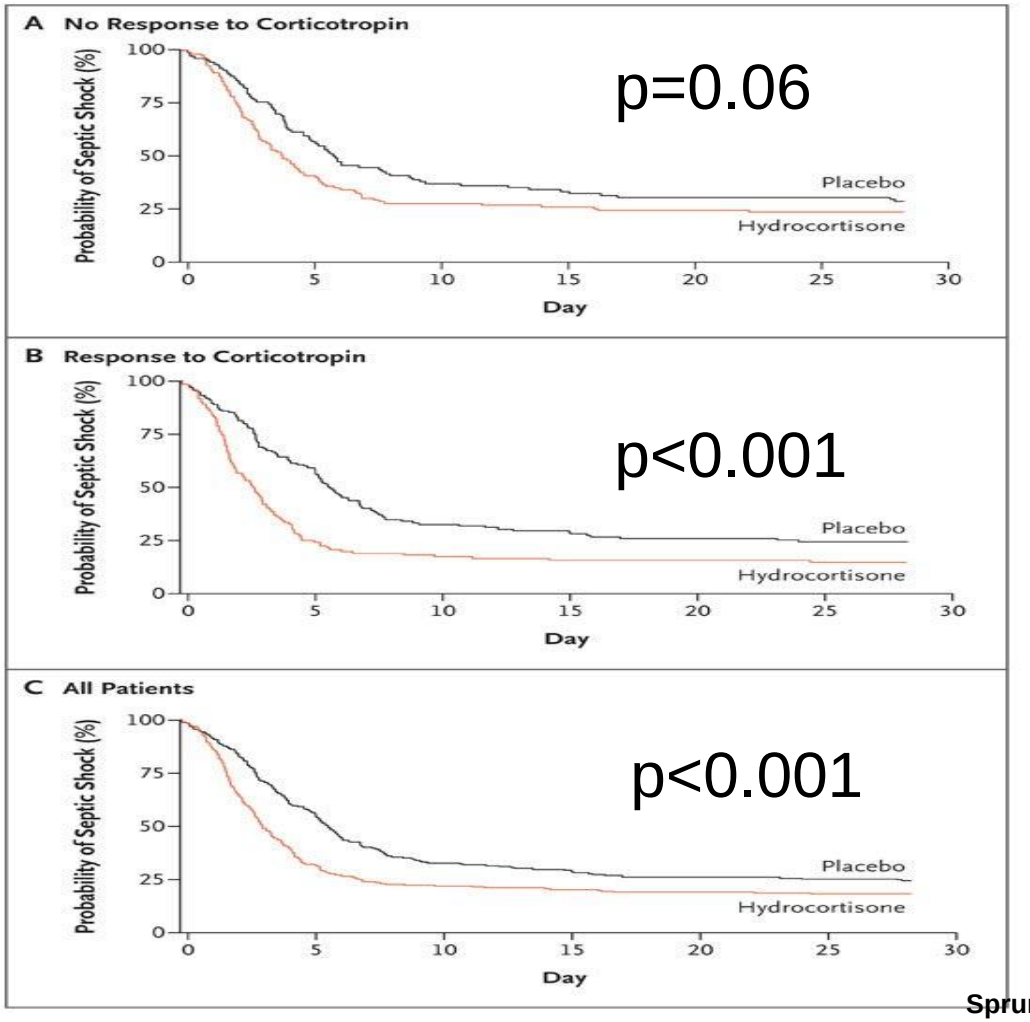
Sprung et al. NEJM 2008; 358: 111-124.

Corticosteroids – Survival – NEJM 2008



Sprung et al. NEJM 2008; 358: 111-124.

Corticosteroids – Time to Reversal of Shock – NEJM 2008



Sprung et al. NEJM 2008; 358: 111-124.

Adverse Outcomes – NEJM 2008

Table 4. Adverse Events (Per-Protocol Population).*

Event	Hydrocortisone (N=234)	Placebo (N=232)	Relative Risk (95% CI)
	no. of patients (%)		
Superinfection	78 (33)	61 (26)	1.27 (0.96–1.68)
Catheter-related	3 (1)	3 (1)	0.99 (0.20–4.86)
Lung	34 (15)	30 (13)	1.12 (0.71–1.77)
Gastrointestinal	22 (9)	19 (8)	1.15 (0.64–2.06)
Urinary tract	11 (5)	10 (4)	1.09 (0.47–2.52)
Wound	9 (4)	7 (3)	1.27 (0.48–3.37)
Other	16 (7)	8 (3)	1.98 (0.87–4.54)
New sepsis	6 (3)	2 (1)	2.97 (0.61–14.59)
New septic shock	14 (6)	5 (2)	2.78 (1.02–7.58)
Other adverse event			
Anastomotic leak	4 (2)	4 (2)	0.99 (0.25–3.92)
Wound dehiscence	2 (1)	2 (1)	0.99 (0.14–6.98)
Repeat shock	72 (31)	57 (25)	1.25 (0.93–1.68)
Bleeding			
Any	21 (9)	16 (7)	1.30 (0.70–2.43)
Gastrointestinal	15 (6)	13 (6)	1.14 (0.56–2.35)
Polyneuropathy	2 (1)	4 (2)	0.50 (0.09–2.68)
Multiple organ system failure	34 (15)	33 (14)	1.02 (0.66–1.59)
Refractory shock	20 (9)	25 (11)	0.79 (0.45–1.39)
Pulmonary	8 (3)	13 (6)	0.61 (0.26–1.44)
Renal	7 (3)	6 (3)	1.16 (0.39–3.39)
Neurologic	1 (<1)	1 (<1)	0.99 (0.06–15.76)
Hyperglycemia (glucose ≥150 mg/dl on any day from day 1 to day 7)†	186 (85)	161 (72)	1.18 (1.07–1.31)
Hypernatremia (sodium ≥150 mmol/liter on any day from day 1 to day 7)‡	67 (29)	42 (18)	1.58 (1.13–2.22)
Possibly related to shock			
Stroke	3 (1)	1 (<1)	2.97 (0.31–28.39)
Acute myocardial infarction	14 (6)	13 (6)	1.24 (0.34–4.56)
Peripheral limb ischemia	0	1 (<1)	

* Some patients had more than one adverse event. Relative risks are for the comparison between the hydrocortisone group and the placebo group. To convert values for glucose to millimoles per liter, multiply by 0.05551.
† For the diagnosis of hyperglycemia, 220 patients were evaluated in the hydrocortisone group and 225 patients in the placebo group.
‡ For the diagnosis of hypernatremia, 231 patients were evaluated in the hydrocortisone group and 229 patients in the placebo group.

Sprung et al. NEJM 2008; 358: 111-124.

Corticosteroids – NEJM 2008

- "In an unexpected finding, the earlier rate of reversal of shock was greater in patients who had a response to corticotropin but was not associated with a survival benefit or a reduction in length of stay either in the ICU or the hospital"
- "Hydrocortisone may have a role among patients who are treated early after the onset of septic shock who remain hypotensive despite the administration of high dose vasopressors (vasopressor unresponsive)"

Sprung et al. NEJM 2008; 358: 111-124.

Guidelines - Corticosteroids

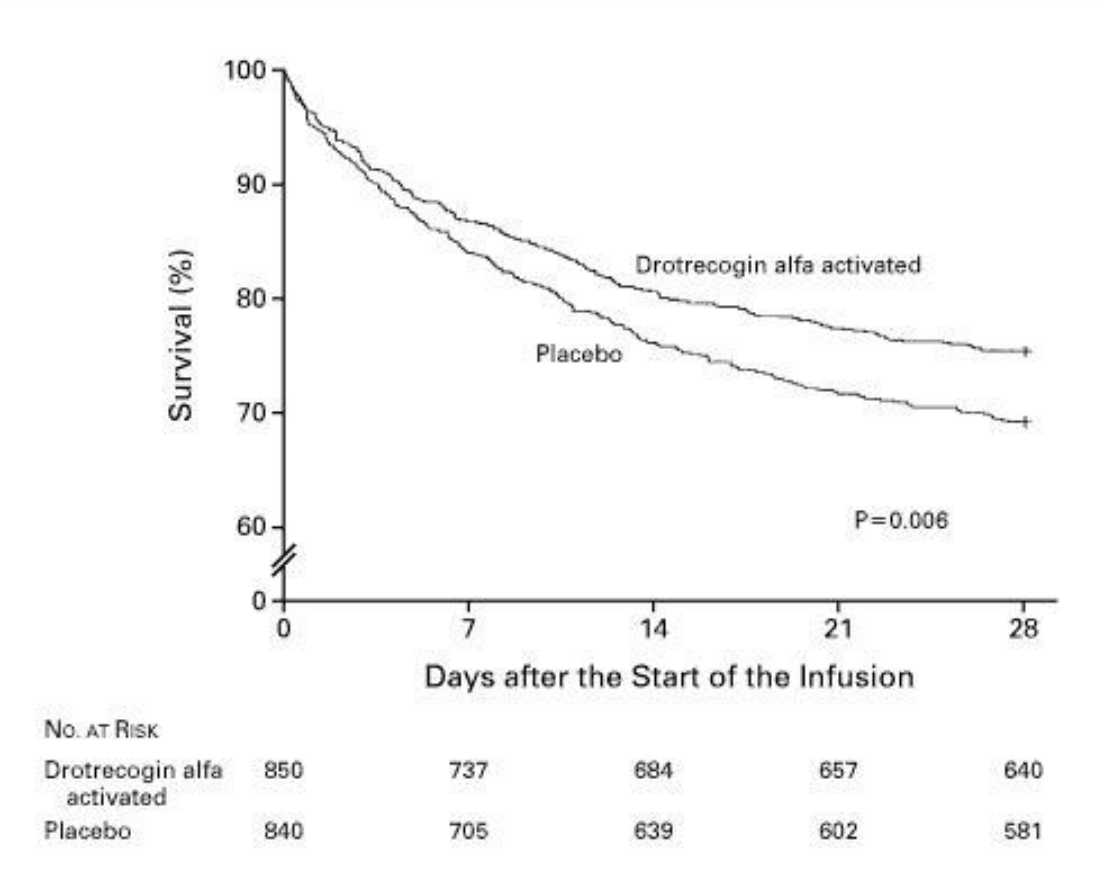
- IV hydrocortisone be given only to adult septic shock patients after it has been confirmed that their blood pressure was poorly responsive to fluid resuscitation and vasopressor therapy
- ACTH stimulation test not used
- Should not receive dexamethasone
- Only add fludrocortisone if available steroid does not have significant mineralocorticoid activity
- Wean steroids when vasopressors no longer required

Etomidate

- Etomidate known to inhibit adrenal mitochondrial hydroxylase activity, with resultant reduction in steroidogenesis after single dose
- JAMA 2002 – 21 months after starting trial, entry criteria were changed to exclude patients who had received etomidate
  - Of the 72 ptaitents who had received etomidate, 69 did not respond to a high dose cosyntropin stimulation test
  - Subgroup analysis revealed that of these etomidate nonresponders, administration of steroids vs. placebo resulted in statistically significant difference in death (54% vs. 76%)
    - Mortality difference in etomidate-free nonresponders was 52% vs. 58%

Annane et al. JAMA 2008; 288: 862-871.

Recombinant Human Activated Protein C



No. at Risk					
Drotrecogin alfa activated	850	737	684	657	640
Placebo	840	705	639	602	581

19.4% reduction in relative risk of death, 6.1% reduction in absolute risk of death, and NNT=16

Bernard et al. NEJM 2001; 344: 699.

PROWESS-SHOCK Trial

- Did not reproduce mortality benefit found in other study
- Recombinant activated protein C abruptly pulled in October 2011

Ranieri et al. NEJM 2012; 366: 2055-2064.

Supportive Therapy of Severe Sepsis

- Mechanical Ventilation of sepsis-induced Acute-Lung Injury
- Glucose Control
- Renal Replacement
- Bicarbonate Therapy
- Deep Vein Thrombosis Prophylaxis
- Stress Ulcer Prophylaxis

Mechanical Ventilation

- ARDS
  - 6mL/kg tidal volume
  - Plateau pressure $\leq$ 30 (take chest wall compliance into account)
  - Permissive hypercapnia
  - PEEP to avoid extensive lung collapse
  - Conservative Fluid Strategy

Glucose Control

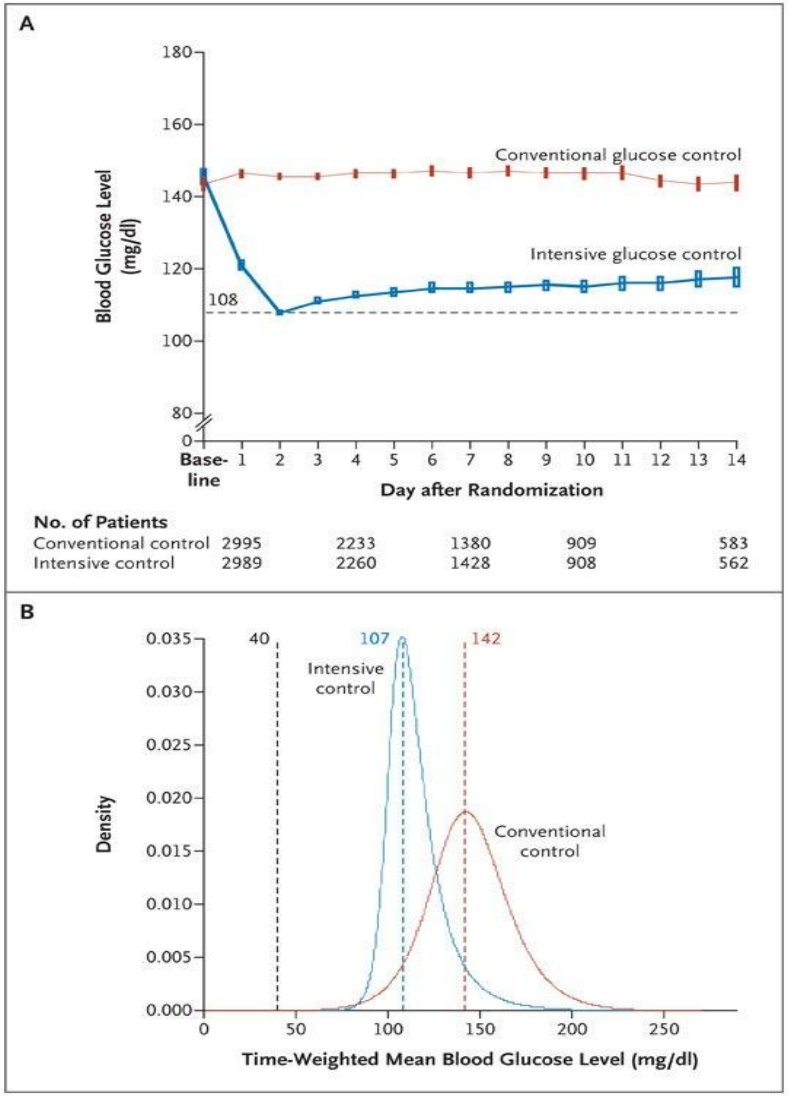
- Consider initiating insulin therapy when blood glucose levels exceed 180 mg/dl with goal approximately 150
- All patients receiving IV insulin receive a glucose calorie source
- Monitor levels every 1-2 hours until values stable, then every 4 hours thereafter
- Low glucose levels with capillary blood may overestimate arterial blood or plasma glucose levels, particularly when glucose low

NICE-SUGAR

- Within 24 hours of admission to ICU, patients who were expected to spend 3 or more consecutive days in ICU were randomized
  - Intensive glucose control- 81-108
  - Conventional glucose control- 180 or less
- Primary end point death from any cause within 90 days after randomization

The Nice Sugar Study Investigators. NEJM 2009; 360: 1283-1297.

NICE-SUGAR



The Nice Sugar Study Investigators. NEJM 2009; 360: 1283-1297.

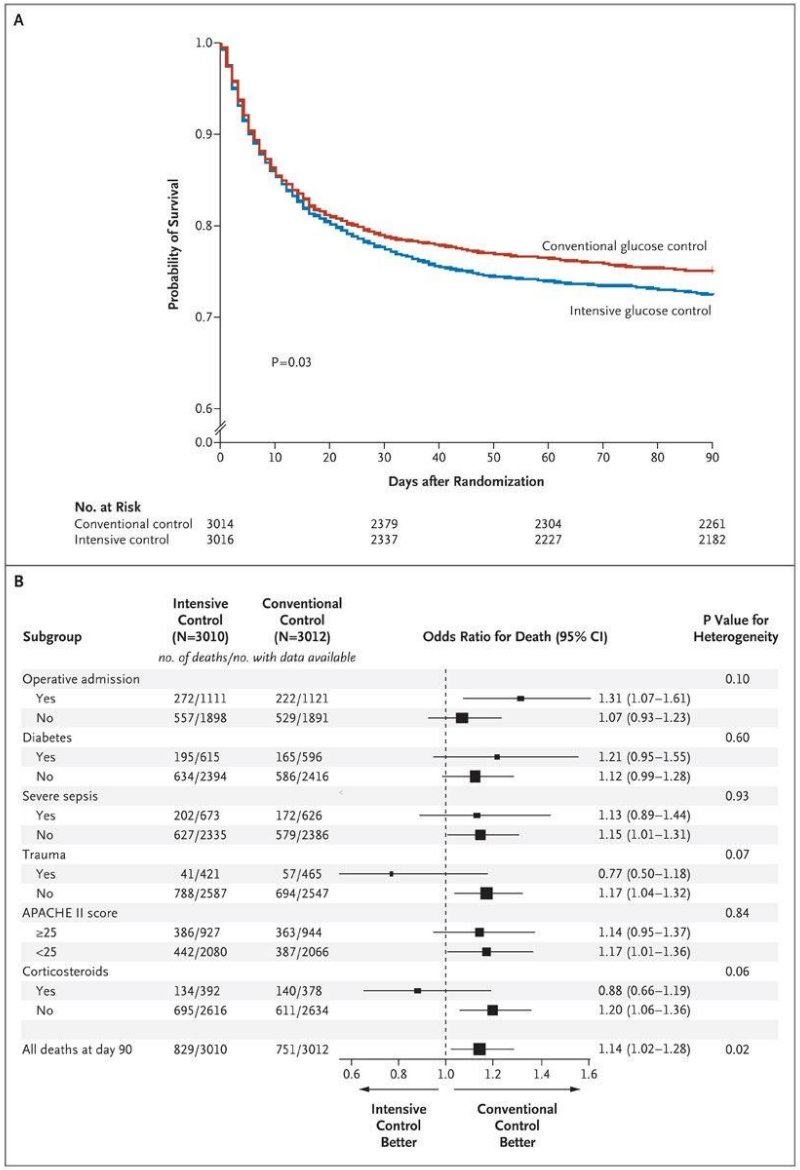
NICE-SUGAR

Table 3. Outcomes and Adverse Events.*

Outcome Measure	Intensive Glucose Control	Conventional Glucose Control	Odds Ratio or Absolute Difference (95% CI)†	Statistical Test	P Value
Death — no. of patients/total no. (%)				Logistic regression	
At day 90	829/3010 (27.5)	751/3012 (24.9)	1.14 (1.02 to 1.28)		0.02
At day 28	670/3010 (22.3)	627/3012 (20.8)	1.09 (0.96 to 1.23)		0.17
Potentially life-sustaining treatment limited or withheld before death — no. of patients/total no. (%)	746/816 (91.4)	669/741 (90.3)	1.13 (0.81 to 1.62)	Logistic regression	0.44
Limited because death was imminent	527/816 (64.6)	459/741 (61.9)	1.12 (0.91 to 1.38)		0.28
Withheld because not appropriate	219/816 (26.8)	210/741 (28.3)	0.93 (0.74 to 1.16)		0.51
CPR as terminal event — no. of patients/total no. (%)	70/816 (8.6)	72/741 (9.7)	0.87 (0.62 to 1.23)	Logistic regression	0.44
Days from randomization to limitation or withholding of potentially life-sustaining treatment — median (IQR)	6 (3 to 16)	6 (2 to 15)		t-test	0.42
Proximate cause of death — no. of patients/total no. (%)				Pearson's test	0.12
Cardiovascular-distributive shock	168/829 (20.3)	140/751 (18.6)			
Other cardiovascular	177/829 (21.4)	129/751 (17.2)			
Neurologic	180/829 (21.7)	194/751 (25.8)			
Respiratory	191/829 (23.0)	177/751 (23.6)			
Other	113/829 (13.6)	111/751 (14.8)			
Place of death — no. of patients/total no. (%)					
ICU	546/829 (65.9)	498/751 (66.3)			
Elsewhere in hospital	220/829 (26.5)	197/751 (26.2)			
Outside hospital, after discharge	63/829 (7.6)	56/751 (7.5)			
Severe hypoglycemia — no. of patients/total no. (%)	206/3016 (6.8)	15/3014 (0.5)	14.7 (9.0 to 25.9)	Logistic regression	<0.001
Days in ICU — median (IQR)	6 (2 to 11)	6 (2 to 11)	0	Log-rank test	0.84
Days in hospital — median (IQR)	17 (8 to 35)	17 (8 to 35)	0	Log-rank test	0.86
Mechanical ventilation — no. of patients/total no. (%)	2894/3014 (96.0)	2872/3014 (95.3)	0.7 (−0.3 to 1.76)	Pearson's test	0.17
Days of mechanical ventilation	6.6±6.6	6.6±6.5	0	Wilcoxon rank-sum test	0.56
Renal-replacement therapy — no. of patients/total no. (%)	465/3014 (15.4)	438/3014 (14.5)	0.9 (−0.9 to 2.7)	Pearson's test	0.34
Days of renal-replacement therapy	0.8±2.6	0.8±2.8	0	Wilcoxon rank-sum test	0.39
No. of new organ failures — no. of patients/total no. (%)‡				Pearson's test	0.11
0	1571/2682 (58.6)	1536/2679 (57.3)			
1	790/2682 (29.5)	837/2679 (31.2)			
2	263/2682 (9.8)	257/2679 (9.6)			
3	44/2682 (1.6)	46/2679 (1.7)			
4	11/2682 (0.4)	2/2679 (0.1)			
5	3/2682 (0.1)	1/2679 (<0.1)			
Temporary sequelae of severe hypoglycemia — no. of patients/total no. (%)					
Neurologic	1/206 (0.5)	1/15 (6.7)			
Cardiovascular	6/206 (2.9)	1/15 (6.7)			
Other	6/206 (2.9)	0			
Blood culture positive for pathogenic organisms — no. of patients/total no. (%)	387/3014 (12.8)	372/3011 (12.4)		Pearson's test	0.57
Transfusion of packed red cells — no. of patients/total no. (%)	1268/3013 (42.1)	1246/3014 (41.3)		Pearson's test	0.56
Volume of packed cells transfused — ml	122±144	126±193		Wilcoxon rank-sum test	0.82

The Nice Sugar Study Investigators. NEJM 2009; 360: 1283-1297.

NICE-SUGAR



The Nice Sugar Study Investigators. NEJM 2009; 360: 1283-1297.

NICE-SUGAR

- Conclusion – intensive glucose control increased mortality among adults in the ICU

Renal Replacement

- No current data proving that mortality is lower with continuous therapies
- No current data proving better hemodynamic tolerance of continuous methods
- 3 of 4 RCTs imply that in those receiving continuous therapy, higher dose of dialysis improves mortality (none of the trials looked specifically at sepsis)
  - 2 major studies looking at dose of renal replacement in 2008
- Guidelines did not address renal replacement therapy to reverse acidosis independent of renal dysfunction

Bicarbonate Therapy

- “Recommend against the use of sodium bicarbonate therapy for the purpose of improving hemodynamics or reducing vasopressor requirements in patients with hypoperfusion induced lactic acidemia”
- No evidence supports use of bicarbonate therapy in the treatment of hypoperfusion-induced lactic acidemia associated with sepsis
  - Few patients with pH<7.15
- Associated with increase in serum lactate and PCO2, decrease in serum ionized calcium

Additional Case Studies
Specific Sepsis Syndromes

The Majority

- Pneumonia
- Urinary tract infections
- Dialysis access infections
- Chronic central access infections

CASE

- 20 year old college student has lived in the dorm at UT for the past 3 months
- Over 8 hours, develops headache, high fever, rash, and confusion

MENINGOCOCCEMIA

UptoDate

CASE

- 55 year old diabetic patient with progressive soft tissue erythema and severe pain

NECROTIZING FASCIITIS

CASE

- 40 year old male who is a heavy drinker develops severe midepigstric pain as well as nausea and vomiting over the past two days. This has happened to him once in the past.
- Spouse finds him in severe pain and confused
- EMS called. Initial vital signs: Pulse 145, BP 85/40. Respiratory Rate 26. Temp 100.5. O2SAT 94%

CASE

- Nursing home resident with chronic foley catheter develops fever and is placed on antibiotics for presumed urinary tract infection
- Within 24 hours, the patient is hypotensive, fever to 104, altered mental status, rash
- Labs include platelet count 20,000 and INR 4 (not on warfarin)

DIC

“FOUND DOWN”

- Often sepsis is the primary diagnosis in this situation
- However, depending on how long the patient has been down and whether or not the patient aspirated, sepsis may have developed as a secondary issue
  - i.e. – stroke with aspiration, overdose with aspiration
  - In this situation, sometimes sepsis dominates management even if not the original issue

When in Doubt …

- Initial sepsis management is straightforward – support ABCs, resuscitate, and give appropriate antibiotics early
- If you are not sure that sepsis is present, ALWAYS ASSUME THAT IT IS
- THE FIRST 6-24 HOURS OF SEPSIS MANAGEMENT IS CRITICAL

CASE

- 67 year old male with history of diabetes, congestive heart failure
- Three days of cough, fever, progressive confusion
- Initial workup. Multilobar pneumonia on CXR. WBC 1.0. Lactic acid 20. Creatinine 5.0 (new). No urine output after 3 liters of IVF. Intubated for respiratory failure in ER. Presenting SBP 60/palp. pH 7.1
- Managed according to sepsis bundle
- After 6 hours, he is on FiO2 100%, on three vasopressors, SBP 75. He has received stress dose steroids and all appropriate antibiotics STAT. Lactate 19. Nephrology feels that he is too unstable to tolerate continuous dialysis

WHAT NEXT?

Questions?