Sepsis and Septic Shock

James Allen, M.D.

Division of Pulmonary & Critical Care Medicine
The Ohio State University

Clinical Case

- **55 yr old woman with nausea, vomiting, diarrhea for 3 days and progressive dyspnea for 2 days.**
- **PMH: diabetes, schizophrenia, hypertension**
- **Initial exam: PB 152/76, HR 120, RR 28, O2% 98%. Moderate respiratory distress.**

Does She Have Shock?

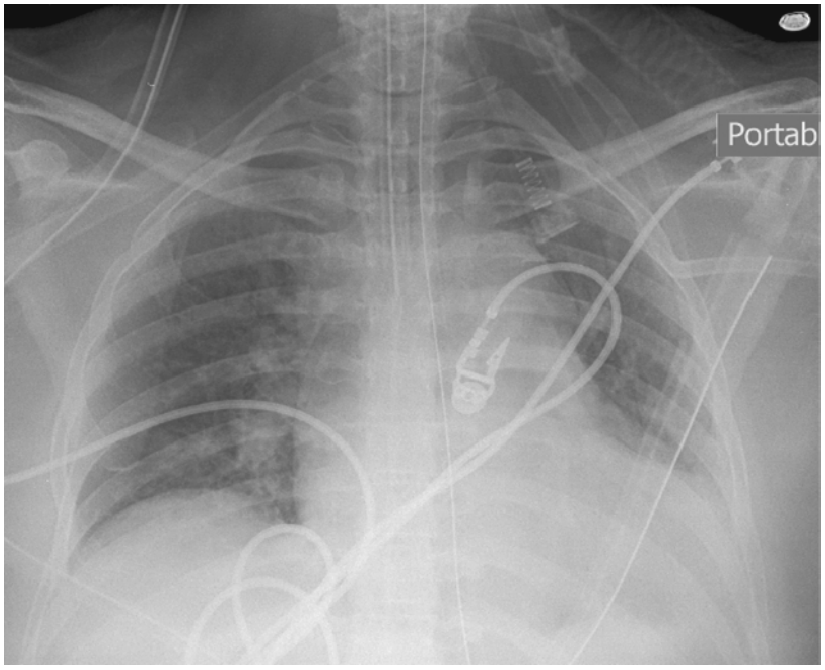
A. Yes

B. No

C. Maybe

Labs

• pH	6.81	• WBC	31,000
• PO2	168	• Hgb	11.3
• PCO2	42	• Glucose	131
• HCO3	5.2	• BUN	72
• O2%	97%	• Creatinine	14.7
		• Calcium	8.6
		• Lactate	17



Hospital Course

- **Intubated for respiratory distress and acidosis**
- **Became progressively more hypotensive**
- **Started on levarterenol drip, empiric antibiotics, IV fluids, CVVHD**
- **Lactate rose to 42 over the next 15 hours**
- **Blood cultures = *Salmonella enteritidis***

What is shock?

- Syndrome of impaired tissue oxygenation and perfusion
- Mechanisms:
  - Absolute/relative decrease in oxygen delivery
  - Ineffective tissue perfusion
  - Ineffective utilization of delivered oxygen

The Major Classes of Shock

- Cardiogenic
- Extracardiac Obstructive
- Oligemic
- Distributive

Clinical Features

	PCWP	CO	SVR
Cardiogenic	High	Low	High
Extra-cardiac obstructive	(Low)	Low	High
Oligemia	Low	Low	High
Sepsis	Variable	Variable	Low
Toxic Shock	(Low)	(High)	Low
Anaphylaxis	Low	High	Low

Cardiogenic vs. Septic Shock

	Cardiogenic	Septic
Pulse Pressure	Decreased	Increased
Diastolic BP	Slightly low	Very low
Extremities	Cool & pale	Warm & pink
Capillary refill	Slow	Rapid

Approach To All Patients

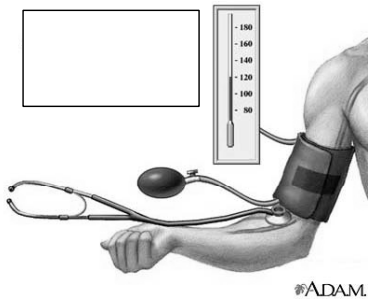
- A - airway
- B - breathing
- C - circulation
- D - disposition (ICU)
- E - electrical cardioversion
- F - fluids

Hemodynamic Monitoring

- Heart rhythm
- Arterial blood pressure
- Intravascular volume assessment:
  - ✓ Central venous pressure
    - Usually
  - ✓ Pulmonary capillary wedge pressure
    - Rarely

Shock ≠ Hypotension

- Patients with early shock can have ***normal*** blood pressure



Indices of Inadequate Perfusion:

- Systemic:
  - ✓ Increased lactate
  - ✓ Mixed venous oxygen saturation < 70%
- Regional:
  - ✓ Liver enzymes
  - ✓ Urine output < 0.5 ml/kg/hr
  - ✓ Sensorium
  - ✓ Clotting factors

* Indicators of inadequate perfusion trump blood pressure!

Clinical Features

	PCWP	CO	SVR
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Sepsis	Variable	Variable	Low
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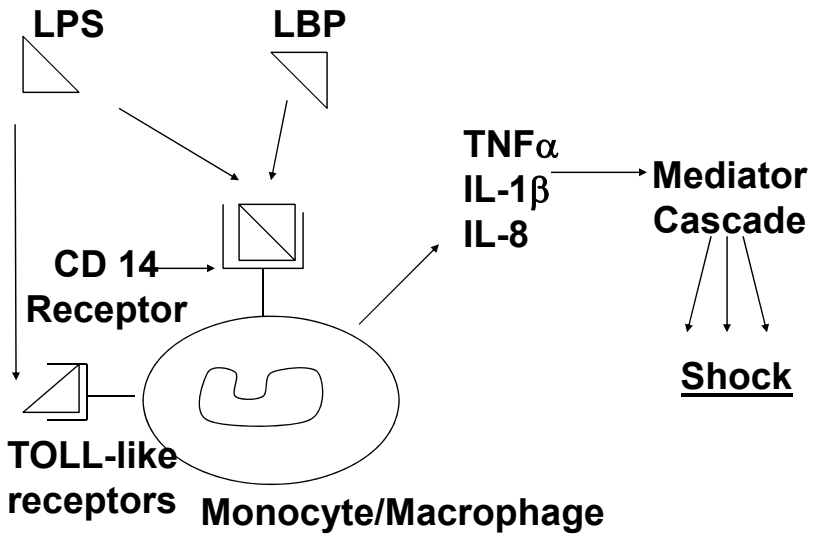
Anaphylaxis	Low	High	Low

	Pre-Shock	**Early Shock**	**Late Shock**
Blood Pressure	Normal	Low	Very Low
SVR	Low	Very Low	Low to Normal
Cardiac Output	High	High	Low
ABG	Respiratory Alkalosis	Resp. Alk. Met. Acid.	Metabolic Acidosis

Mechanism Of Shock In Sepsis



Septic shock commonly results in multiple organ system failure

Common Effects Of Sepsis

Organ	Effect
Kidney	Acute tubular necrosis
Lungs	Acute respiratory distress syndrome
Heart	Myocardial depression
Liver	Cholestasis or liver failure
GI	Stress erosions
Brain	Stupor
Blood	Neutrophil vacuolization
Metabolic	Hypocalcemia, hypo/hyperglycemia

Treatment goals in managing septic shock

- Restore tissue perfusion and oxygenation
- Treat specific etiology
- Monitor
- Treat organ-specific failure
- Prevent complications

The ultimate goal of septic shock management is to improve tissue oxygen delivery!

- **Determinants:**
  - ✓ Blood pressure
  - ✓ Cardiac output
  - ✓ Oxygen content
- **Interventions:**
  - ✓ Fluids
  - ✓ Vasoactive drugs
  - ✓ Blood transfusion
  - ✓ Supplemental oxygen

Early resuscitation is key:

- Goal-directed protocols
  - ✓ Central venous catheter
  - ✓ Hydration to CVP (or PCWP) = 8-12
  - ✓ Vasopressors if MAP < 65
- Target SvO2 > 70%
- Early involvement of intensivists
- Early transfer to an ICU facility

Rivers, et al. N Engl J Med 2001; 345:1386-77
Sebat, et al. Chest 2005; 127:1729-43

Hemodynamic Treatment Of Septic Shock

- IV fluids
- IV fluids
- IV fluids

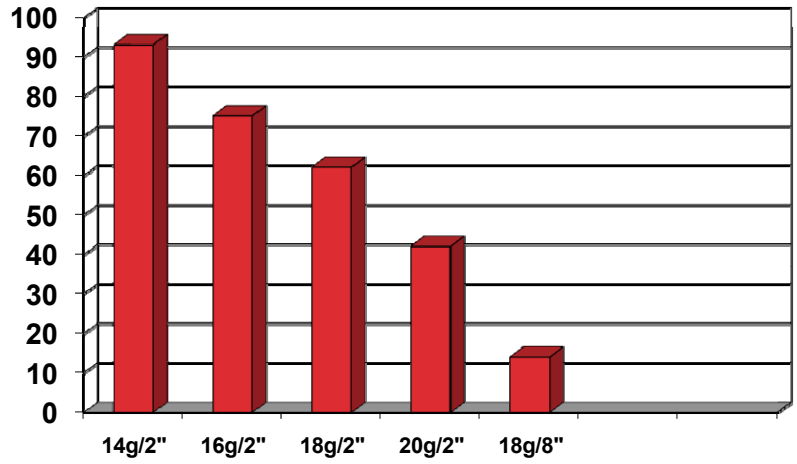
- Vasopressors

Fluid Selection

Distribution	% Intravascular
0.9% NaCl	Extracellular space 20%
Lactated Ringer's	Extracellular space 20%
D5W	Total body water space 8%
RBCs*	Intravascular space 100%

* Use 2:3 plasma:PRBC transfusion ratio

IV Catheter Flow Rates (ml/min)



Treat the underlying infection:

- Antibiotics – broad spectrum; give early
- Remove potentially infected devices
- Drain pus
- Debride/remove dead tissue

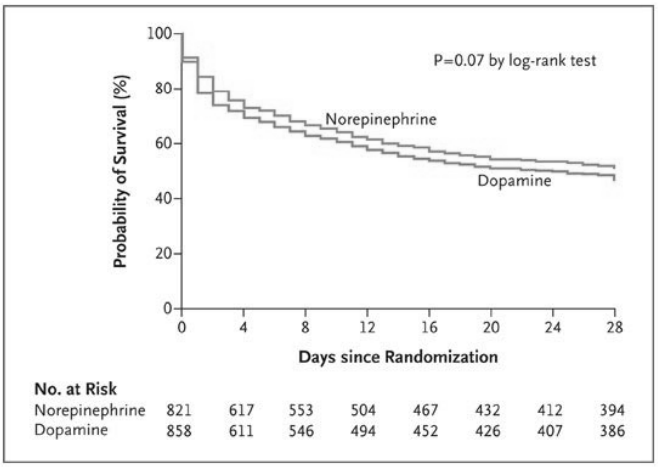
What Else Can You Do?

- **Definitely:**
  - ✓ Vasopressors
  - ✓ Activated protein C
  - ✓ Intensivists
  - ✓ Closed ICUs
- **Maybe:**
  - ✓ Low dose steroids
  - ✓ Glycemic control
  - ✓ Vasopressin
  - ✓ Avoid etomidate

What Vasopressor Do You Most Commonly Use In Septic Shock?

A. Dopamine
B. Levarterenol (Levophed)
C. Phenylephrine (Neosynephrine)
D. Dobutamine
E. Epinephrine

Kaplan-Meier Curves for 28-Day Survival in the Intention-to-Treat Population



***There were fewer adverse events with norepinephrine**

De Backer D et al. N Engl J Med 2010;362:779-789

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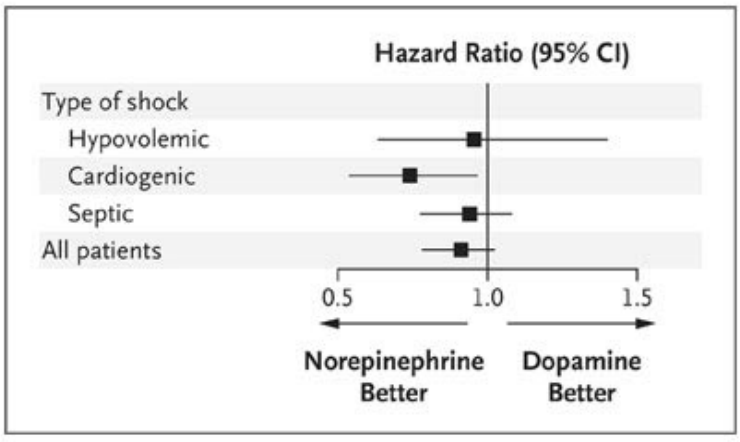
Forest Plot for Predefined Subgroup Analysis According to Type of Shock



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Vasopressors In Septic Shock

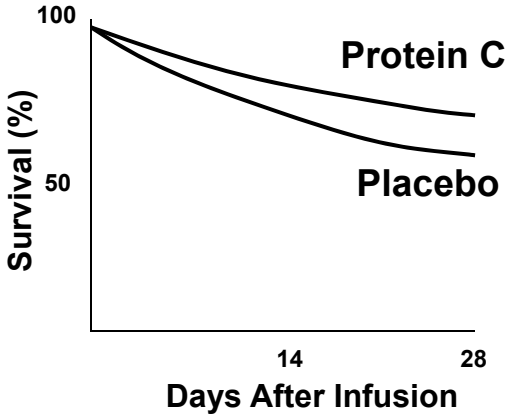
	Heart Rate	Contractility	Vasoconstriction
Dopamine			
2-10 mcg/kg/min	2+	2+	0
>10 mcg/kg/min	2+	2+	3+
Dobutamine	1+	4+	1-
Levarterenol	2+	2+	4+
Phenylephrine	2-	0	4+
Epinephrine	4+	4+	4+

What about dobutamine?

- Dobutamine is a ***vasodilating*** inotrope
- Main role is in patients with combined septic plus cardiogenic shock
  - ✓ Should be combined with an alpha adrenergic agent
  - ✓ However, use of dobutamine to "drive" up already high cardiac output is not effective

Effect Of Activated Protein C In Sepsis

- Randomized, double blinded, controlled
- 1,690 patients
- Serious bleeding:
  - ✓ 2% control
  - ✓ 3.5% protein C



Bernard, N. Engl. J. Med. 2001; 344:699-709

Indications For Drotrecogin (activated protein C)

- Known or suspected infection AND
- SIRS (3 of 4):
  - ✓ Fever or hypothermia
  - ✓ Tachycardia
  - ✓ Tachypnea
  - ✓ Leukocytosis or leukopenia
- APACHE II ≥ 25 OR
- At least 2 *acute* organ failures:
  - ✓ Cardiovascular
  - ✓ Renal
  - ✓ Respiratory
  - ✓ Hematologic (platelets)
  - ✓ Metabolic acidosis

Drotrecogin Contraindications

- **Absolute:**
  - ✓ Active bleeding
  - ✓ Recent surgery/trauma
  - ✓ Recent GI bleeding
  - ✓ CVA, head trauma, brain surgery in past 2 months
  - ✓ Brain tumor/aneurysm
  - ✓ Recent epidural
- **Relative:**
  - ✓ Platelets < 30,000
  - ✓ INR > 3
  - ✓ Anticoagulation
  - ✓ Cirrhosis
  - ✓ Bleeding disorder
  - ✓ Pregnancy

Drotrecogin Dosing:

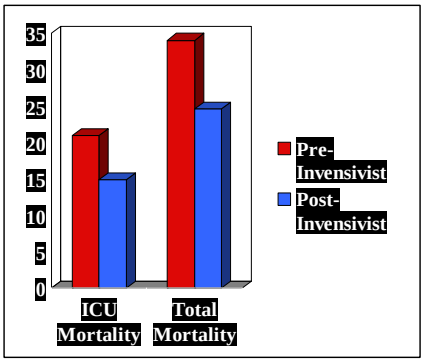
- 24 mg/kg/hr x 4 days
  - ✓ Maximum dose = 3,200 mg/hr
- Turn infusion off 2 hours before procedures
- No adjustment necessary for renal failure
- Average cost /patient = $$$$$

Intensivists Improve Outcomes

Effect of a surgical intensivist:

- ✓ 3-fold mortality reduction
- ✓ Decreased sepsis
- ✓ Decreased renal failure
- ✓ Decreased reintubation

Effect of a medical Intensivist:

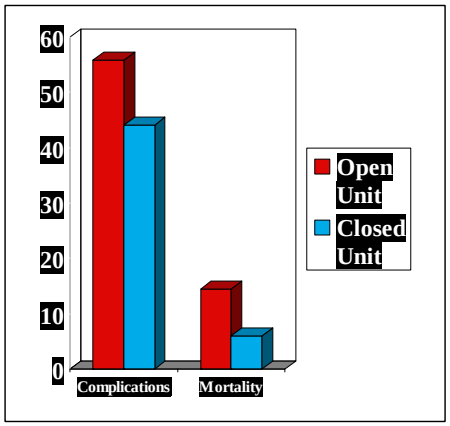


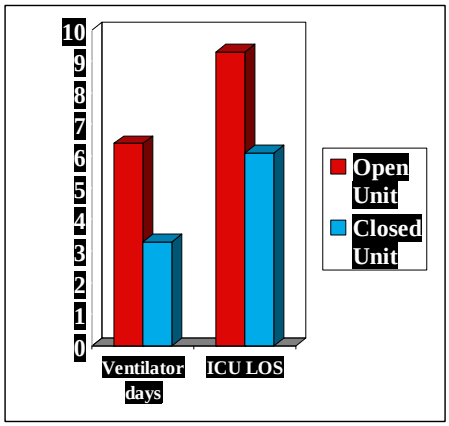
Pronovost, et al. JAMA 1999; 281:1310

Manthous, et al. Mayo Clin Proc 1997; 72:391

Closed ICUs Improve Outcomes

Rhode Island Hospital SICU





Ghora. Ann Surg 1999; 229:163

Multz. Am J Resp Crit Care Med 1998; 57:1468

…and some of the more controversial management issues

When Do You Use Corticosteroids In Septic Shock?

A. Always
B. Never
C. Only if a random cortisol is low
D. Only if an ACTH stim test is abnormal

Corticosteroid Insufficiency In Septic Shock

- 25-75% of patients with septic shock are corticosteroid insufficient
- Definition: cortisol level < 10 mcg/dL or increase < 9 mcg/dL after ACTH stimulation test
- Corticosteroid replacement ***may*** improve outcomes in adrenal insufficiency
- Beware of patients receiving etomidate!!

Do Steroids Work In Septic Shock?

- YES: 300 septic patients (JAMA 2002)
- YES: Cochrane database analysis (2004)
- NO: 499 patients with septic shock (N Engl J Med 2008)
- YES: Meta-analysis of 20 studies (JAMA 2009)

Surviving Sepsis Guideline 2008

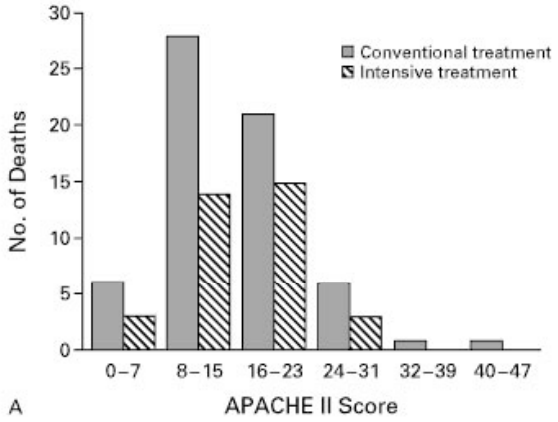
- Consider steroids when patients do not respond to fluids and vasopressors
- ACTH stimulation test is not recommended
- Hydrocortisone preferred:
  - ✓ Dose should be < 300 mg/day

How Do You Use Glycemic Control In Your Patients With Septic Shock?

A. Target glucose 80-110
B. Target glucose 110-140
C. Target glucose 140-180
D. Only treat if glucose > 200

Insulin in Critically Ill

Target glucose:
80-110 mg/dl



van den Berghe, et al. N Engl J Med 2001; 345:1359-1367

Tight glycemic control: 2010 meta-analysis

- 7 randomized-controlled studies reviewed
- 11,425 patients
- Tight glycemic control did NOT:
  - ✓ Reduce 28-day mortality
  - ✓ Reduce requirement for renal replacement therapy
- Tight glycemic control was associated with significantly increased hypoglycemia

Chest 2010; 137: 544-51

The AACE/ADA recommendations for Hospitalized Patients*

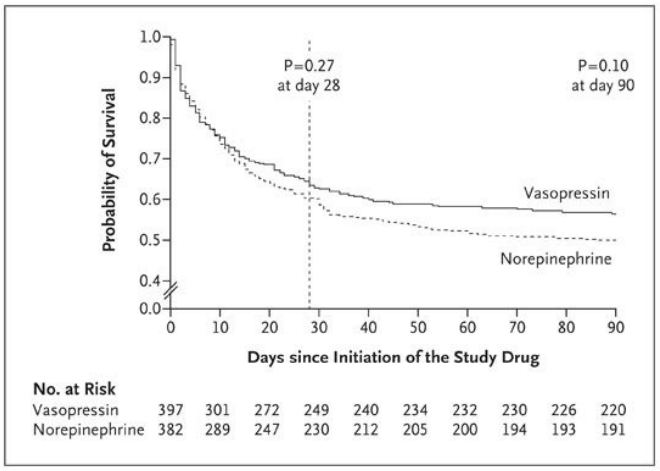
- A target of 140-180 mg/dl is preferable for MOST patients.
- A target of 110-140 mg/dl may be appropriate in SELECTED patients (patients treated in sites with extensive experience and appropriate support:
  - ✓ perhaps CABG surgical patients
  - ✓ sites with low rates of hypoglycemia
  - ✓ patients on TPN etc).
- A target > 180 mg/d/ or < 110 mg/dl is <u>NOT</u> recommended.

*Diabetes Care, Volume 33, supplement 1: January 2010

Vasopressin In Septic Shock

- Vasopressin levels are low in septic shock
- Vasopressin replacement *may*:
  - ✓ Improve blood pressure
  - ✓ Diminish need for other vasopressors
- Do not use in <u>pediatric</u> septic shock!! (Am J Respir Crit Care Med 2009; 180:632-9)
- Dose = 0.04 units/min

Effect of Vasopressin On 28-Day Mortality



N = 778

Russell J et al. N Engl J Med 2008;358:877-887

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What about renal failure?

	Prerenal	ATN
BUN/creatinine ratio	>20	10-20
Urine specific gravity	>1.020	>1.010
Urine osmolality (mOsm/L)	>500	<350
Urine sodium (mmol/L)	<20	>40
Fractional excretion of Na (%)	<1	>2

Management of oliguria in septic shock:

- Volume challenge
- Loop diuretic for fluid management
- Monitor and maintain fluid balance
- Dose-adjust medications
- Avoid nephrotoxic drugs & dye
- Renal replacement therapy

Not all distributive shock is septic shock

Clinical Features

	PCWP	CO	SVR
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Anaphylaxis	Low	High	Low

Toxic Shock Syndrome

- TSST-1 produced by Staph aureus, group A Strep, & group G Strep
- Common sites of infection:
  - ✓ Vagina (menstrual-associated)
  - ✓ Surgical wounds
  - ✓ Foreign bodies
  - ✓ Mucous membrane injury

TSST-1

Toxic Shock Syndrome: Clinical Features

- Abrupt onset: fever, myalgias, headache
- Multiple organ failure
- Severe metabolic abnormalities
- Blood cultures usually negative
- Palmar skin exfoliation

Courtesy of the CDC

Toxic Shock Syndrome: Treatment

- IV fluids: often need 10-20 liters in first day
- Remove foreign bodies
- Anti-staphylococcal antibiotics
- IV immunoglobulin - *possibly* effective

Vasopressors For Toxic Shock Syndrome

	Heart Rate	Contractility	Vasoconstriction
Dopamine			
2-10 mcg/kg/min	2+	2+	0
>10 mcg/kg/min	2+	2+	3+
Dobutamine	1+	4+	1-
Levarterneol	2+	2+	4+
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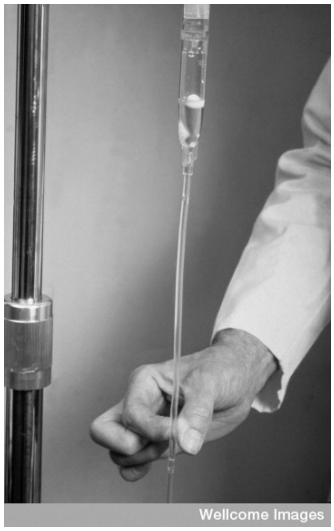
Anaphylactic Shock

- Offending agent can be difficult to identify
- Serum tryptase level useful when diagnosis uncertain

Courtesy Bartosz Kosiorek



Anaphylactic Shock: Initial Therapy

- Maintain airway
- Stop absorption!
- Epinephrine is the vasopressor of choice
  - ✓ 1:1,000 concentration (0.5 - 1.0 ml SQ)
  - ✓ 1:10,000 concentration (5 - 10 ml IV)
- Inhaled albuterol

Anaphylactic Shock: Secondary Treatment

- Antihistamines
- Corticosteroids
- 18 - 24 hour observation

Summary: Keys To Sepsis Survival

- Early recognition
- Early stratification
- Early resuscitation
- Early use of:
  - ✓ Central venous catheters
  - ✓ Intensive care units
  - ✓ Critical care specialists

Relative Effects of Different Vasopressors

	Heart Rate	Contractility	Vasoconstriction
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Phenylephrine	2-	0	4+
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Clinical Case Outcome

- Blood pressure improved over 48 hours
- Extubated hospital day #9
- Remained on dialysis
- Transferred to skilled nursing facility on hospital day #21