

Sepsis: The Silent Killer

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Objectives



- Understand the continuum of sepsis
 - Identify patients with sepsis
- Current treatments for sepsis
- Understand basic principles of shock
 - What is "occult shock"
- Why do I need to know this (pre-hospital care)
- # Future trends for screening, triage, and treatment





- - Construction of new ICU hospital
 - Opened in fall 2008
 - Over 120 ICU beds

- Only level 1 TraumaCenter in Central Virginia
- ED 70,000 visits/yr



Who and What is VCURES



www.vcures.com

- Multidisciplinary Center of Excellence
- •Focus: Acute Care Research, and Education
- •8 Colleges, 30 Departments, 50 Investigators
- Nontraditional Partnerships: Engineering, Physics, Chemistry, Computer Science
- •Taking the Cancer Center Approach to Acute Injury and Illness

Restoring life through innovation and collaboration

Turning the Golden Hour into the Silver Day



Current Trends in Emergency Medicine Critical Care

Trends in ED Visits

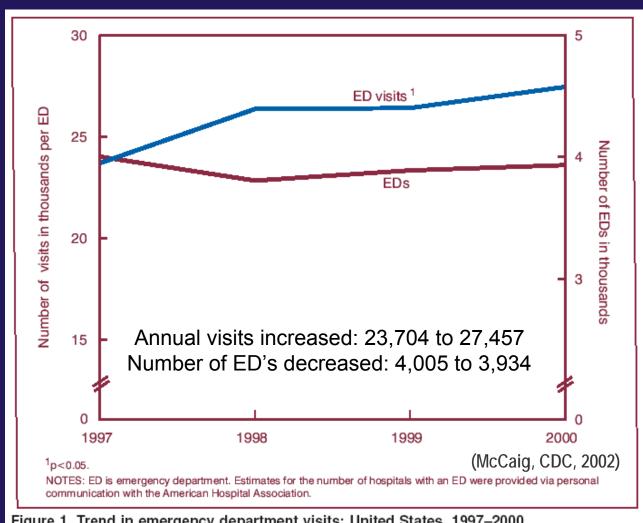


Figure 1. Trend in emergency department visits: United States, 1997-2000



Patient Demographics - Age/Race

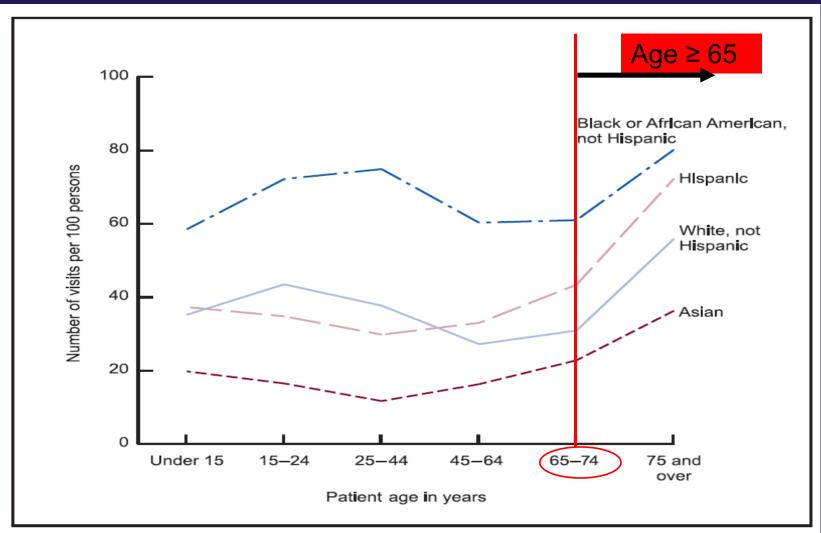


Figure 2. Annual rate of emergency department visits by patient age, race, and ethnicity: United States, 2004 McCaig 2006

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ED LOS Times (mean)

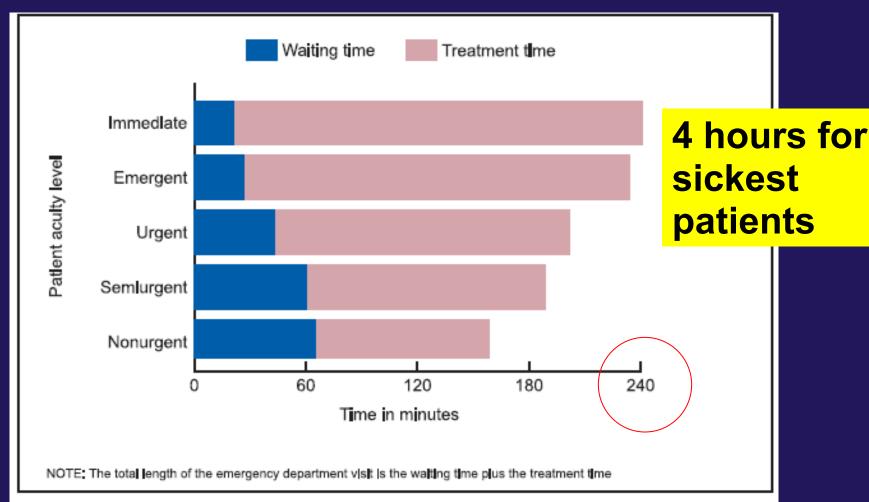


Figure 8. Mean waiting time and treatment time in emergency departments, by patient acuity level: United States, 2004

McCaig 2006

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Levels of Acuity

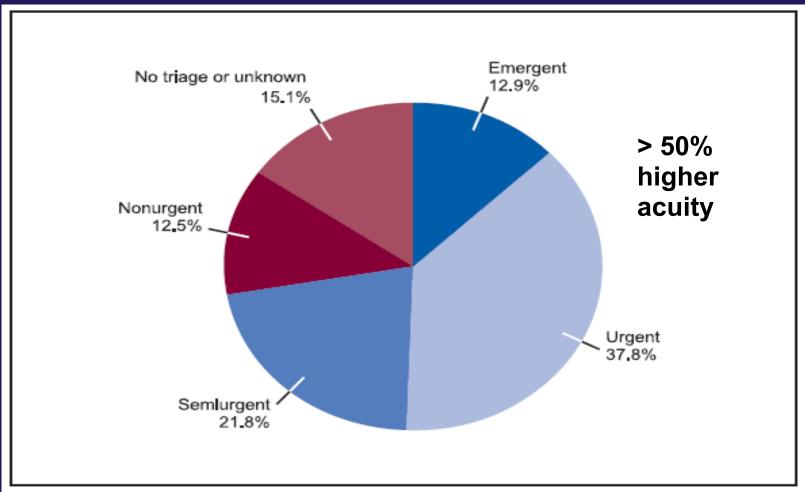
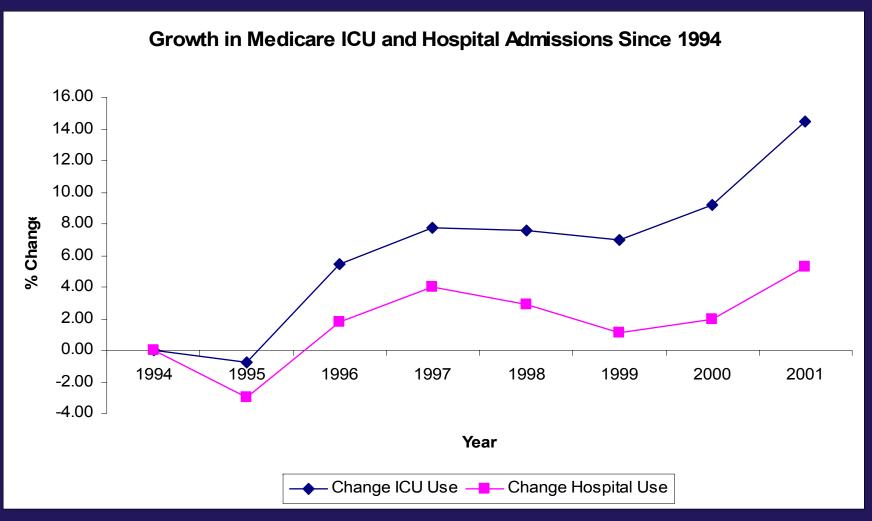


Figure 5. Percent distribution of emergency department visits, by immediacy with which the patient should be seen: United States, 2004

McCaig 2006



Hospital and ICU Admissions



Milbrandt, E.B. and Angus, D.C. Unpublished data from CRISMA laboratories, Pittsburgh, PA

EMS Data



- Number of annual ED Visits 114 million
 - 26% increase since 1993
 - Avg. 2% increase/year
 - Number of ED decreased 12.3% over same time
- Number arrived via EMS16 million (14%)
 - ♦ > 1/3 are older than 65
 - This number WILL increase over the next 20 years
- **\$ 58% of EDs were urban**
 - Representing 82% of all visits



So what are all of us faced with?

- Older population
- Increasing number of ED visits
- Decreasing number of EDs ?increased diversion
- More EMS transports (older)
- # Higher acuity
- Longer ED length of stay for the sickest
- More patients being admitted to ICU

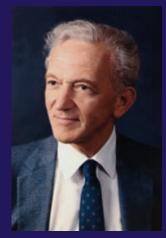
Can we make a difference?



Do we already?

- * STEMI Cath lab 90 min
- Stroke TPA within 3 hours
- Trauma system
- Sepsis?





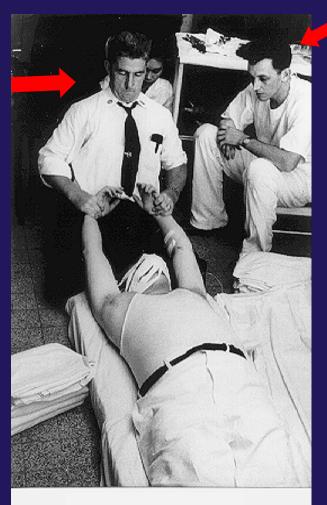
"Critical care is a continuum that begins with out-of-hospital care, continues with ED intervention, and culminates in ICU admission and management."

- Peter Safar, MD 1924-2003 Father of CPR

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Peter Safar, MD 1924-2003

Capt
McMahon,
Chief
Baltimore
Fire and
Ambulance
Service,
1957



BALTIMORE CITY HOSPITAL RESUS CITATION EXPERIMENT, JULY 13, 1957 CHEST PRESSURE ARM-LIFT METHOD

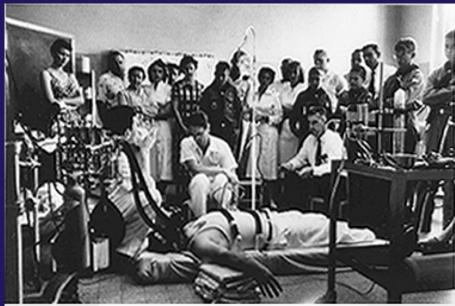


BALTIMORE CITY HOSPITAL RESUS CITATION EXPERIMENT, JULY 13, 1957 CHEST PRESSURE ARM-LIFT METHOD

Peter Safar, MD 1924-2003

"the most sophisticated intensive care often becomes unnecessarily expensive terminal care when the pre-ICU system fails." – Peter Safar, MD





BALTIMORE CITY HOSPITAL DEPARTMENT OF ANESTHESIOLOGY RESUSCITATION EXPERIMENT, JULY 13, 1957 VOLUNTEER: FELIX STEICHEN, M.D. RESIDENT IN SURGERY



What do you think of when you hear "sepsis"?

What is sepsis? Greek origin = putrefaction







Clinically, Confusion Reigns

- Wide range of mortality and morbidity\$35% 75% mortality
- #Unclear terminology commonly used
- *No clear consensus on what "Sepsis" meant
- **Bacteremia = septicemia = sepsis = sepsis syndrome = septic shock

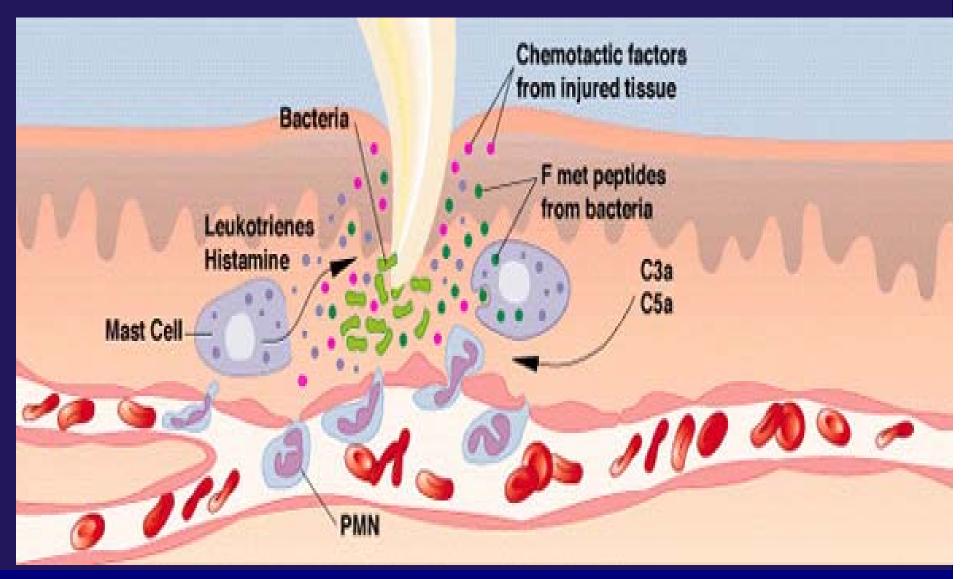


Body's response to an "attack"

The inflammatory response



Inflammatory Response - Local





The Endothelial System



Pan-endothelial Disruption

SIRS



(Systemic Inflammatory Response Syndrome)

- SIRS Definition (at least 2)
 - Fever or hypothermia (T > 38°C or < 36°C)</p>
 - Tachypnea (RR > 20 bpm or PaCO2 < 32 mmHg)</p>
 - Tachycardia (HR > 90 bpm)
 - Immune response (WBC > 12,000, or < 4,000 or > 10% immature (band) forms

ACCP/SCCM Consensus Conference, Critical Care Medicine 1992; 20:864-74



Sepsis

* At least 2 SIRS criteria PLUS a suspected infection

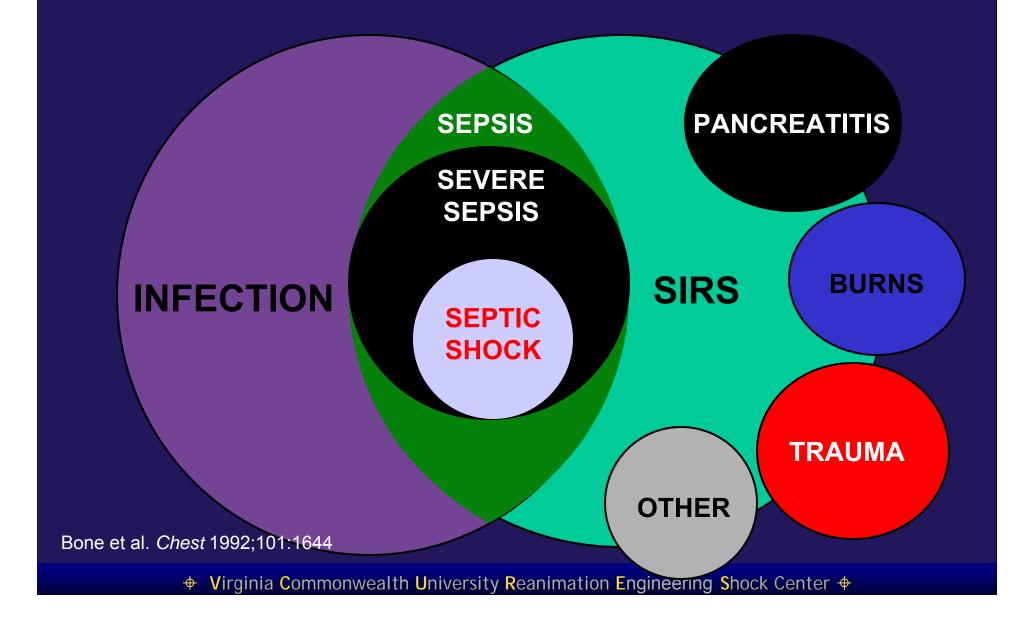
Up to 30 - 60% may be "culture negative"

Culture "positive" or "negative" have similar mortalities

ACCP/SCCM Consensus Conference, Critical Care Medicine 1992; 20:864-74

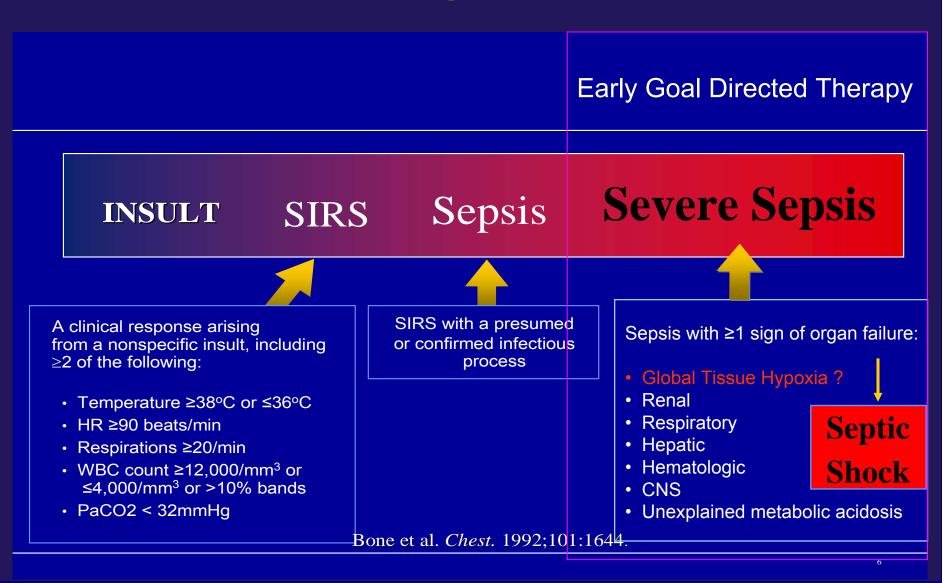
Relationship Of Infection, SIRS, Sepsis Severe Sepsis and Septic Shock







The continuum of sepsis





Some Clinical Signs of Severe Sepsis

Identifying Acute Organ Dysfunction as a Marker of Severe Sepsis



Altered Consciousness Confusion Psychosis

Tachypnea $PaO_2 < 70 \text{ mm Hg}$ $SaO_2 < 90\%$ $PaO_2/FiO_2 \le 300$

Jaundice

↑ Enzymes

↓ Albumin

↑ PT



Tachycardia
Hypotension
Altered CVP
Altered PAOP

Oliguria Anuria ↑ Creatinine

↓ Platelets↑ PT/APTT↓ Protein C↑ D-dimer

Balk RA. Crit Care Clin 2000;16:337-52



How big of a problem is Sepsis?

Severe Sepsis: A Significant Healthcare Challenge



Major cause of morbidity and mortality worldwide

- Leading cause of death in noncoronary ICU (US)*
- 11th leading cause of death overall (US) †§

More than 750,000 cases of severe sepsis in US annually with 215,000 deaths annually

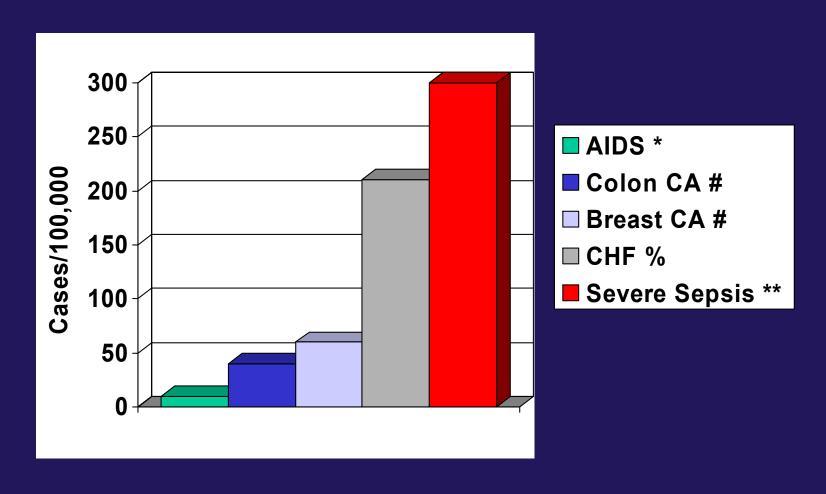
Costs \$16.7 Billion[‡]

In the US, more than 500 patients die of severe sepsis daily.[‡]

*Sands KE et al. *JAMA*. 1997;278:234-40; †Based on data for septicemia. §Murphy SL. National Vital Statistics Reports. ‡Angus DC et al. *Crit Care Med*. 2001;29:1303-1310; reflects hospital-wide cases of severe sepsis as defined by infection in the presence of organ failure.

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Incidence of Severe Sepsis



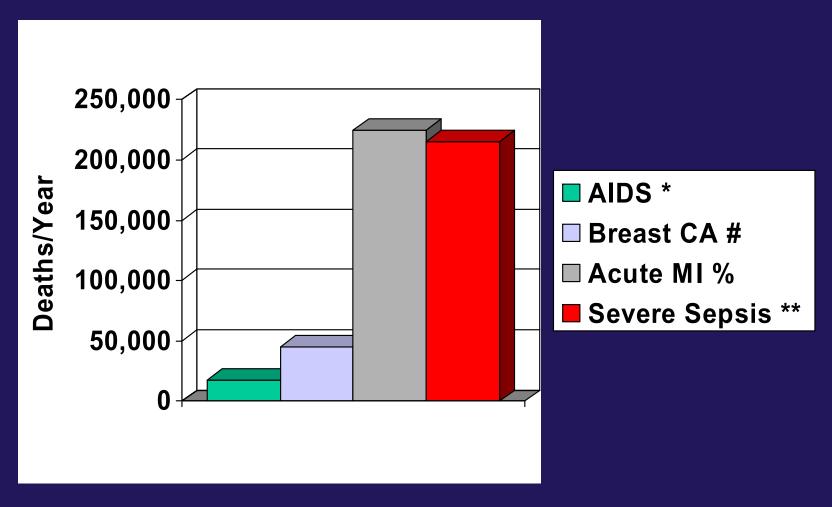
^{*} Karon JM et al. Am J Public Health. 2001;91:1060-8 # American Cancer Society, 2001

% American Heart Association, 2001

** Angus et al. Crit Care Med. 2001;29:71303-10

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Comparative Mortality



^{*} Karon JM et al. Am J Public Health. 2001;91:1060-8

American Cancer Society, 2001

[%] American Heart Association, 2001

^{**} Angus et al. Crit Care Med. 2001;29:71303-10



Is there a treatment?



New therapies for Sepsis

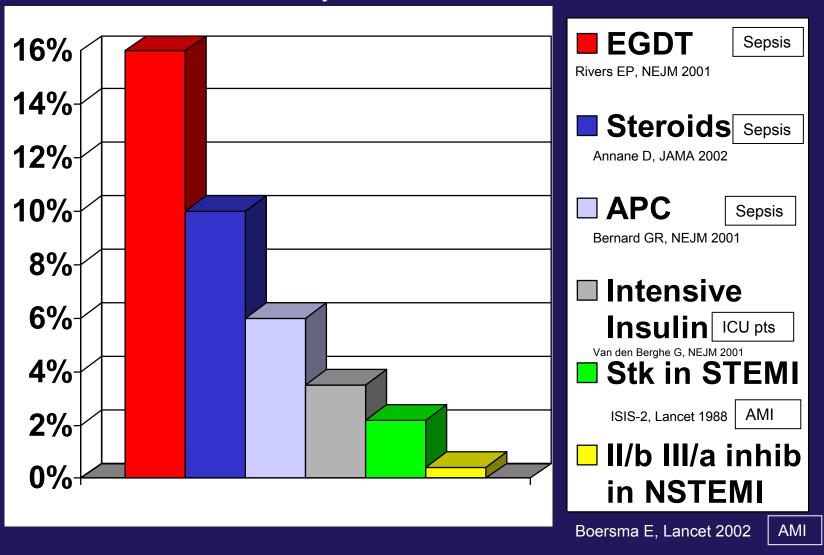
- **Early antibiotic administration**
- Low volume ventilation ARDS
- Drotrecogin alpha (activated) Xigris®
- ****Corticosteroids**
- Strict glycemic control
- ***Early goal-directed therapy**



Common treatments for critically ill



Absolute Mortality Reductions





Early Goal Directed Therapy

- Based on recognizing EARLY Shock States
- Reverses oxygen debt
- * Therapy aimed at improving delivery of oxygen to the tissues
- Works along with
 - Antibiotics
 - Steroids
 - Xigris®
 - Glucose control
 - Source control (abscess drainage, etc...)



SHOCK



What is Shock?







SHOCK

Inability to supply (or utilize) enough oxygen to meet the metabolic needs of the tissue.

Tissue Hypoperfusion!

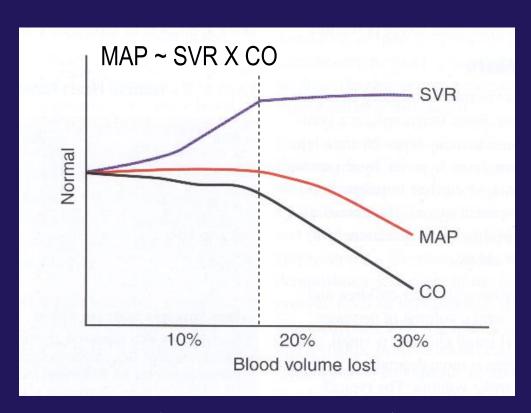
Shock: An Outdated Definition

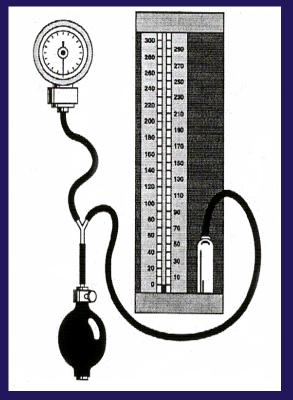
Global Tissue Traditional Normal Hypoxia and O2 Debt perfusion Shock HYPOPERFUSION **Abnormal Vitals** Normal Vitals \rightarrow Normal Vitals \rightarrow (Hypotension)

Blood pressure fails to detect global tissue hypoxia



Adequate pressure does not always mean adequate flow to tissues



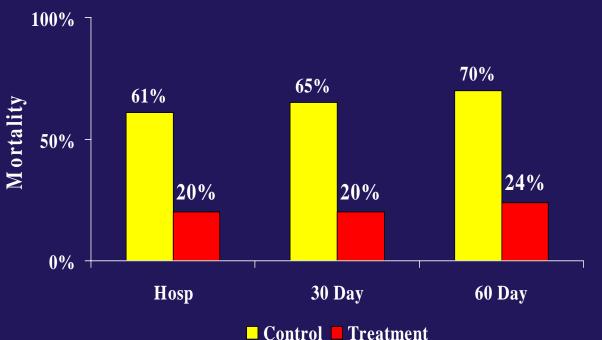


Cryptic Shock



Patients with a Baseline MAP > 100

Lactate > 4 mM/L Control n = 25 EGDT n = 23



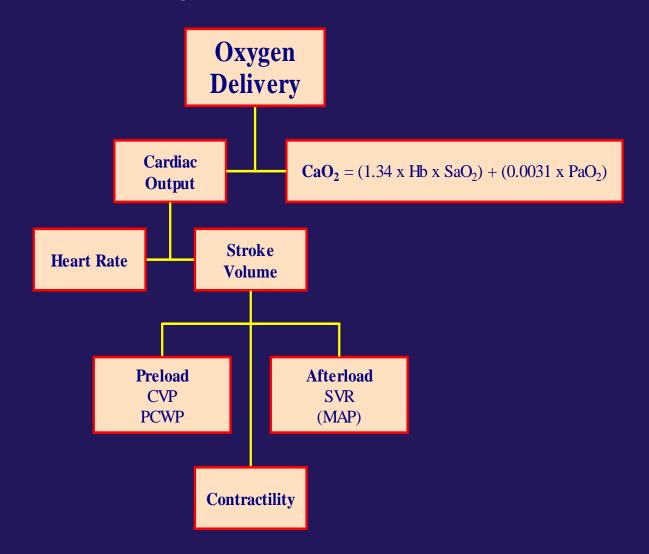
- A significant co-morbid variable:
 - 2-fold increase in <u>sudden</u> <u>cardiovascular collapse</u>, cause of early death.
 - 56.5% in <u>early hospital</u> mortality.
 - Natural selection process between the onset of severe illness and ICU arrival.

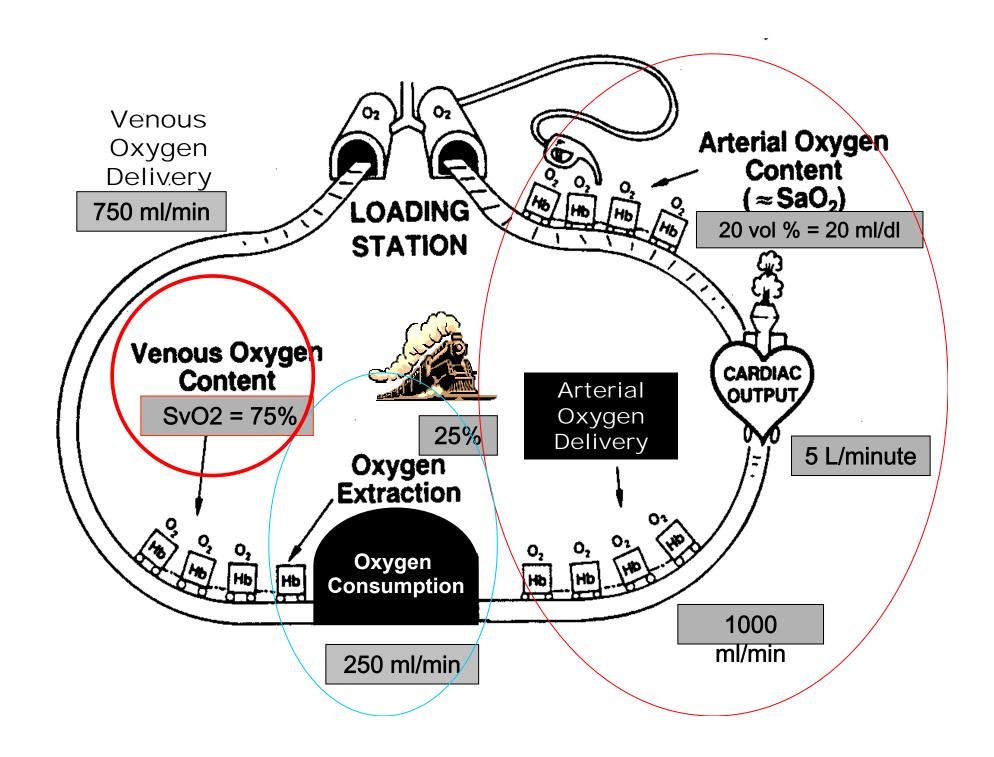


What's really going on?



Oxygen Delivery



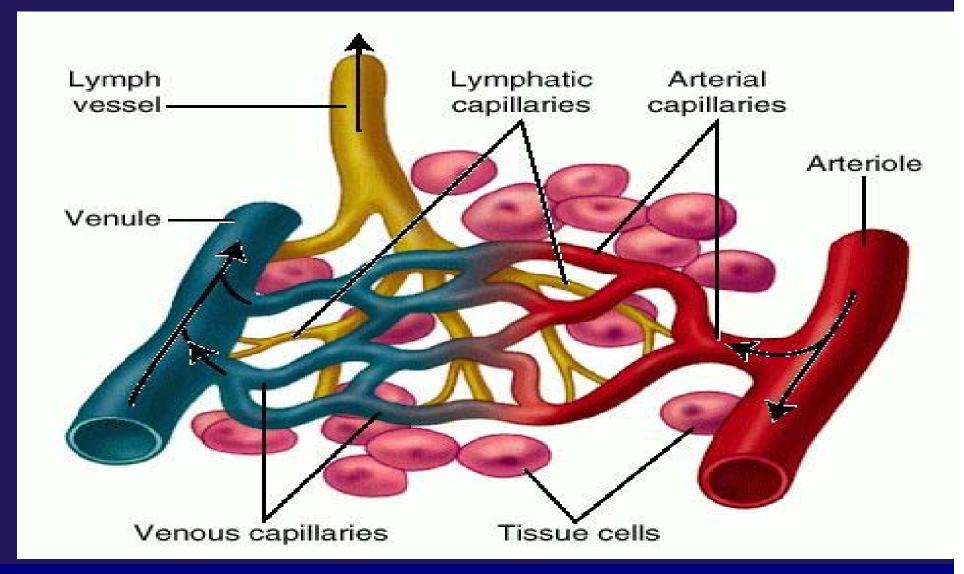


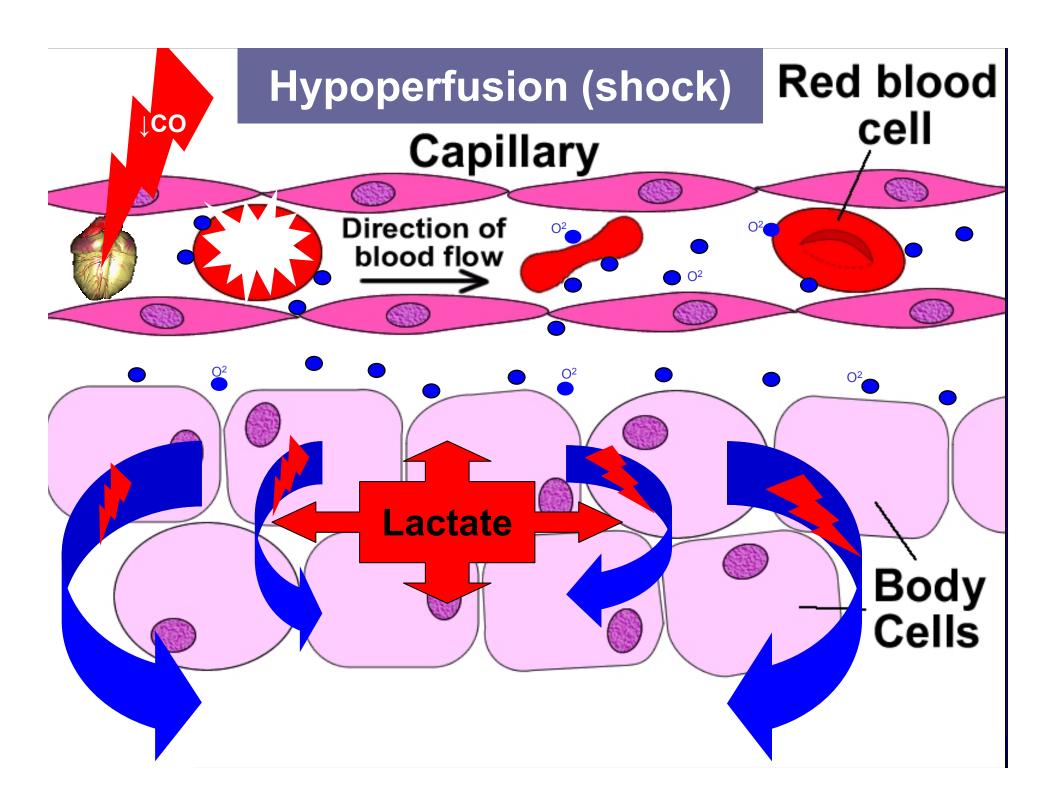


What is going on at the tissue level?



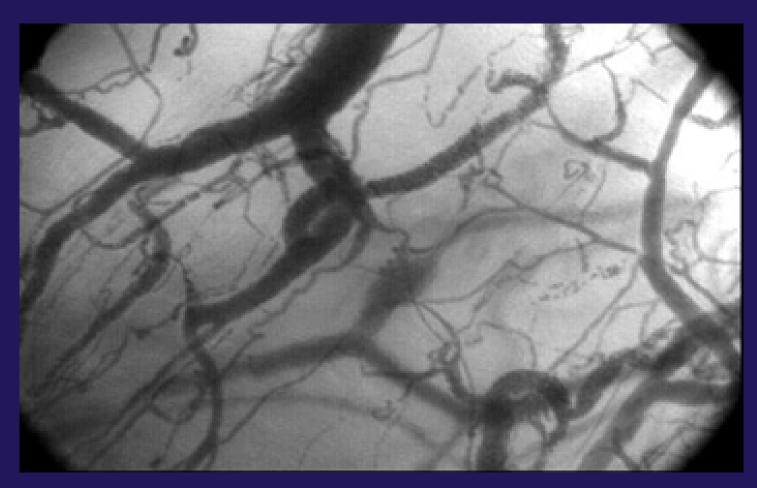
Capillary system







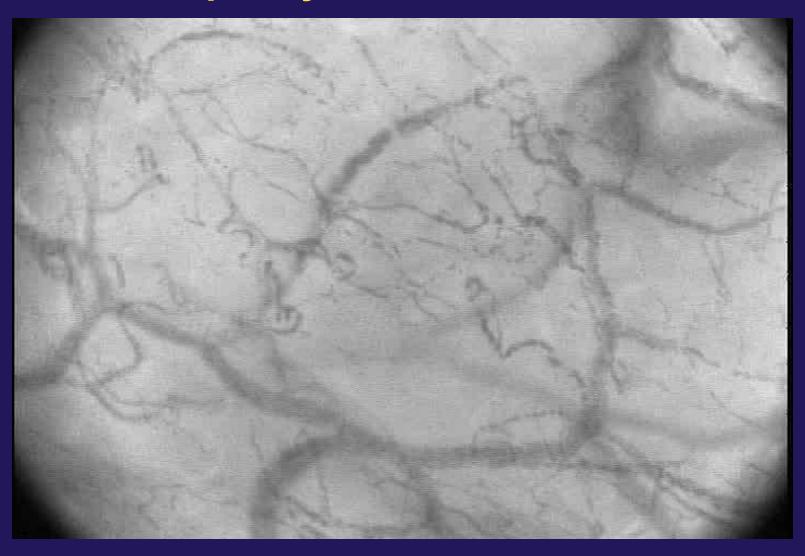




Normal Sublingual Circulation

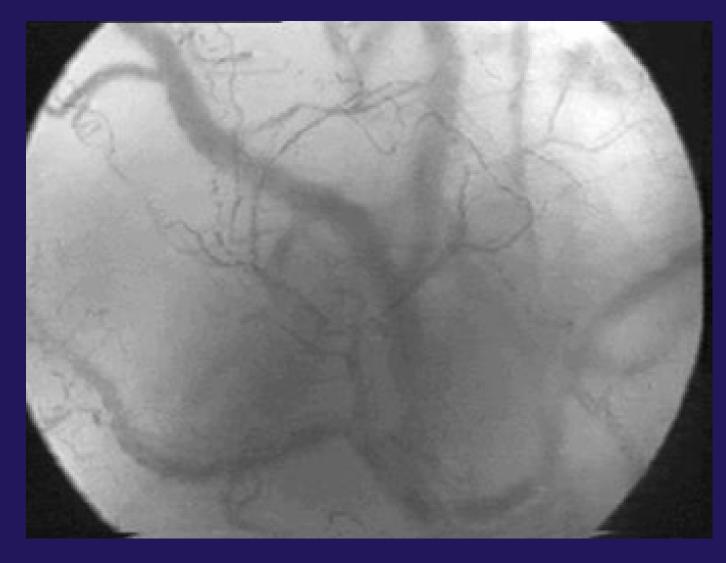


Normal Capillary Bed



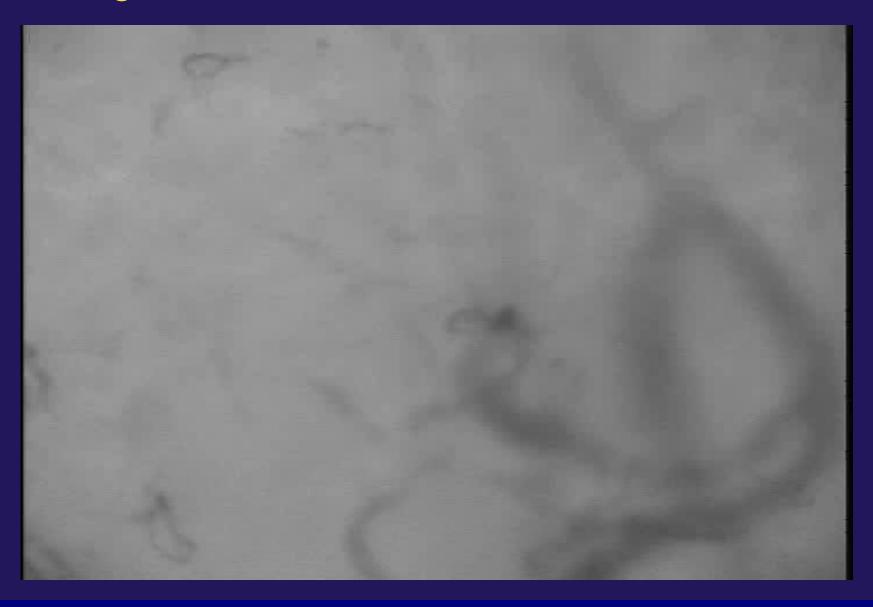
Sublingual Circulation in Shock







Sublingual Circulation in Shock





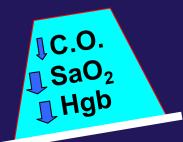
The Balance of Life

Oxygen Extraction

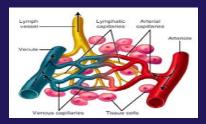
(Metabolic needs of the tissues)



Oxygen Delivery



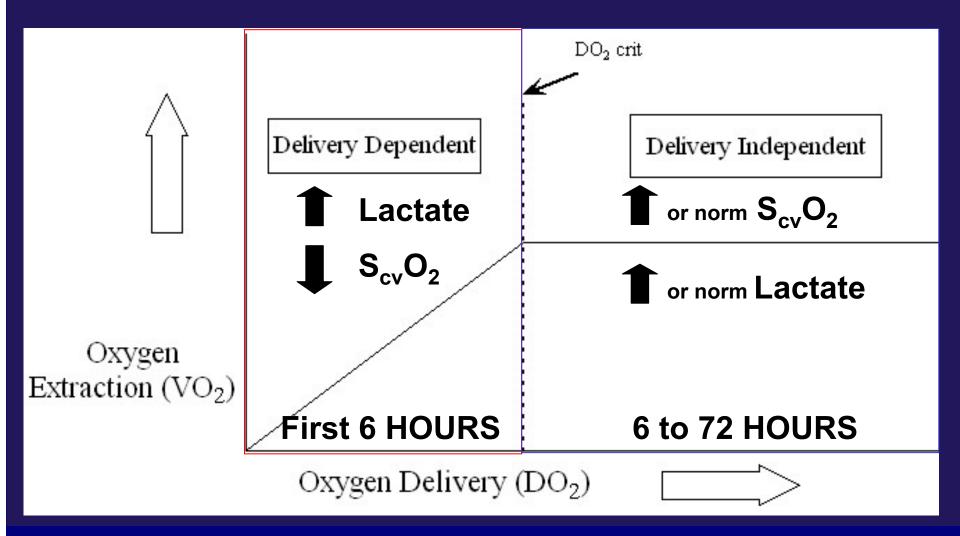
Microvascular Alterations



Oxygen Utilization



Oxygen Delivery Basics



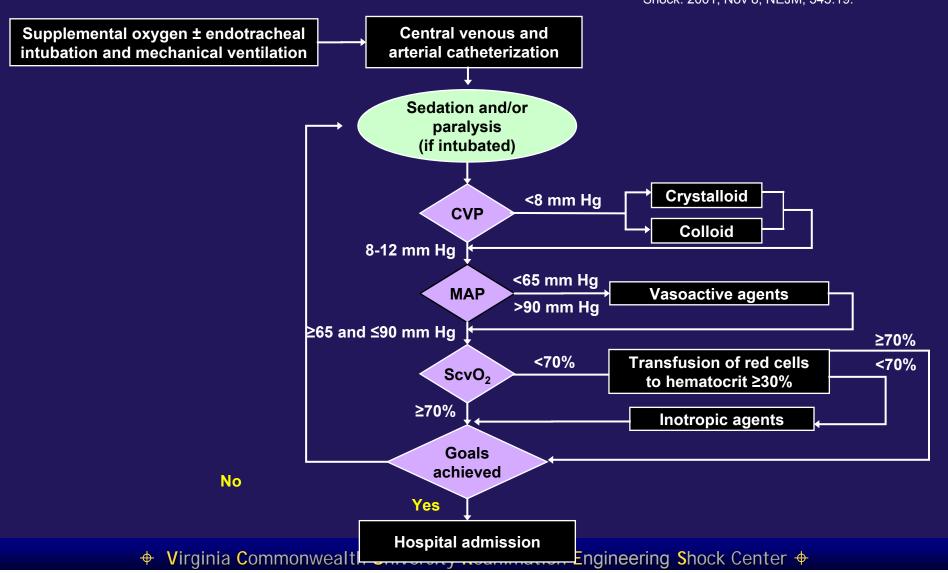


How do we bring our septic shock patient back into "balance"?





Rivers, EP et. al. Early Goal Directed Therapy In The Treatment Of Severe Sepsis And Septic Shock. 2001, Nov 8, NEJM, 345:19.





Mortality

	Control	EGDT	RR (95% C.I.)	P-value
In-hospital	46.5	30.5	0.58 (0.38-0.87)	0.009
28-day	49.2	33.3	0.58 (0.39 – 0.87)	0.01
60-day	56.9	44.3	0.67 (0.46-0.96)	0.03

EGDT Therapy Comparison – Timing is Everything!



	0 – 6 hr	7 – 72 hr	0 – 72 hr
Total Fluid (cc)			
EGDT	4,981*	8,625	13,443
Control	3,499	10,602*	13,358
Fransfusion			
EGDT	64%*	11%	68%*
Control	19%	33%*	45%
Vasopressor			
EGDT	27%	29%	37%
Control	31%	43%*	51%*
notrope use			
EGDT	14%*	15%	15%
Control	1%	8%	9%
Ventilator use			
EGDT	53%	3%	56%
Control	54%	17%*	71%*



Is this practical?

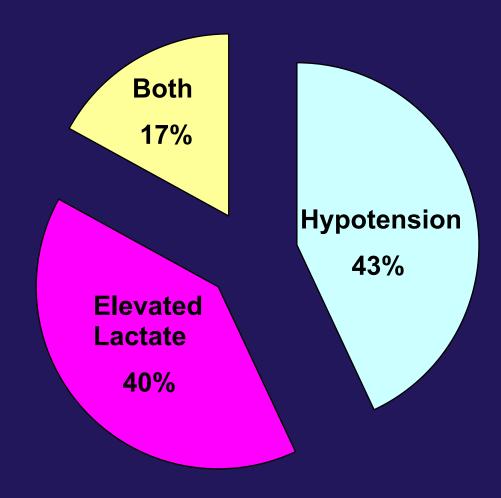
EGDT Experiences at Two Hospitals



- Brown University
 - Primarily ED identifies and EGDT team does the resuscitation
- Beth Israel Deaconess Medical Center
 - ED identifies and ICU team does the resuscitation

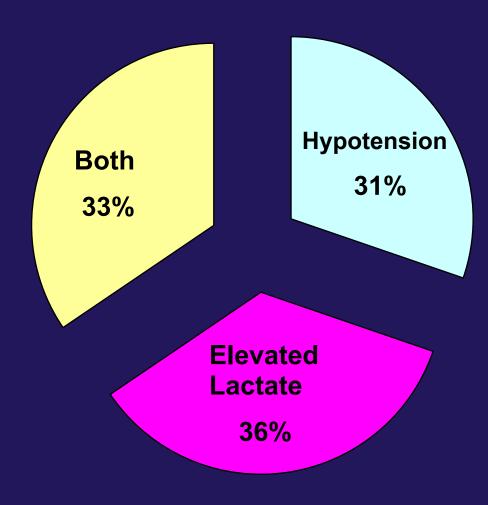
Brown University ED Trigger to Start EGDT





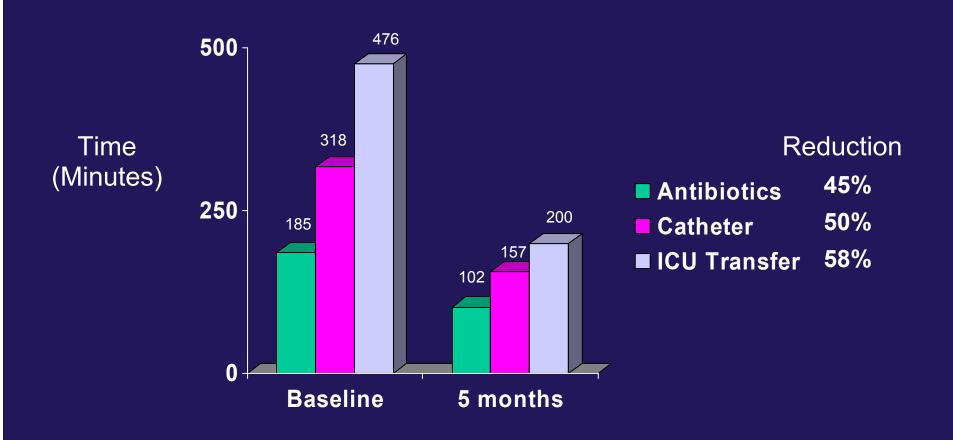
BIDMC ED Trigger to Start EGDT





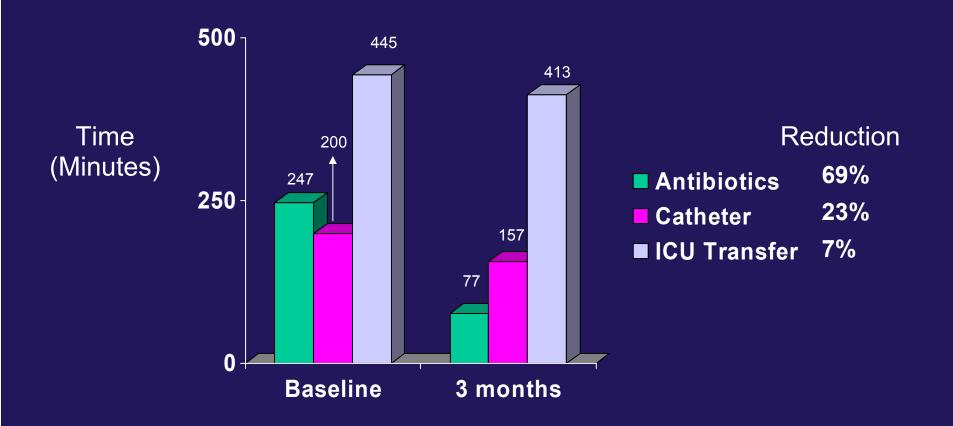
Time for Sepsis Therapies in ED – Brown University





Time for Sepsis Therapies in ED – BIDM







Time to Catheter Insertion (EGDT starting)

- ** Both centers combined and mean times used
 - Before teams formed
 - 254 minutes (4.2 hours)
 - After teams formed
 - 157 minutes (2.6 hours)



Common Findings

- Both institutions had difficulties
 - Most common
 - Patient identification
 - Line insertion
- Lactate used as a trigger = 73% of the cases!
 - Lactate alone up to 40%
 - Lactate with hypotension up to 33%
- TIME is TISSUE
 - Early detection of tissue hypoxia is ESSENTIAL



EGDT Pitfalls - Survey

- **ED Physicians unfamiliarity with continuum of Sepsis**
- Unfamiliarity with cryptic shock, only follow vital signs
- Screening in triage not sensitive enough to identify cryptic shock
- ED Physicians may have limited resources
- Many hospitals don't routinely test for Lactate or it is delayed several hours
- Possibly patients with cryptic shock are admitted to floor or even discharged home without addressing oxygen debt
- Even in prestigious medical centers with an EGDT system in place, a delay of over 2^{1/2} hours occurs before EGDT can be started



Can we do better?

Can we detect hypoperfusion in the field?



Lactate = the biochemical vital sign for hypoperfusion

Lactate = First biochemical vital sign!!



- Lactate is a familiar marker
 - Weil shown lactate predicts mortality in 60's
 - Compare to BNP or Troponin where clinicians are still getting used to interpreting the results and various assays
 - Mortality outcome prediction has held the test of time
 - Does not matter what causes elevated lactate (topic of debate)
 - Smaller studies validate usage in several disease states
 - Cardiac
 - Infectious
 - Trauma
 - Abdominal pain



Lactate is not a new marker

- Margaria R, Edwards R, Dill D. The possible mechanisms of contracting and paying the oxygen debt and the role of lactic acid in muscular contraction. Am J Physiol 1933, 106:689-715.
- Broder, G and Weil, M. H. Excess lactate: an index of reversibility of shock in human patients. Science 1964, 143:1457.
- Schweizer O, Howland WS. Prognostic significance of high lactate levels. Anesth Analg 1968, 47:383-388.
- Cowley RA, Attar S, LaBrosse E, McLaughlin J, Scanlan E, Wheeler S et al. Some significant biochemical parameters found in 300 shock patients. *J Trauma* 1969, 9:926-938.
- Weil MH, Afifi AA. Experimental and clinical studies on lactate and pyruvate as indicators of the severity of acute circulatory failure (shock). Circulation 1970, 41:989-1001.

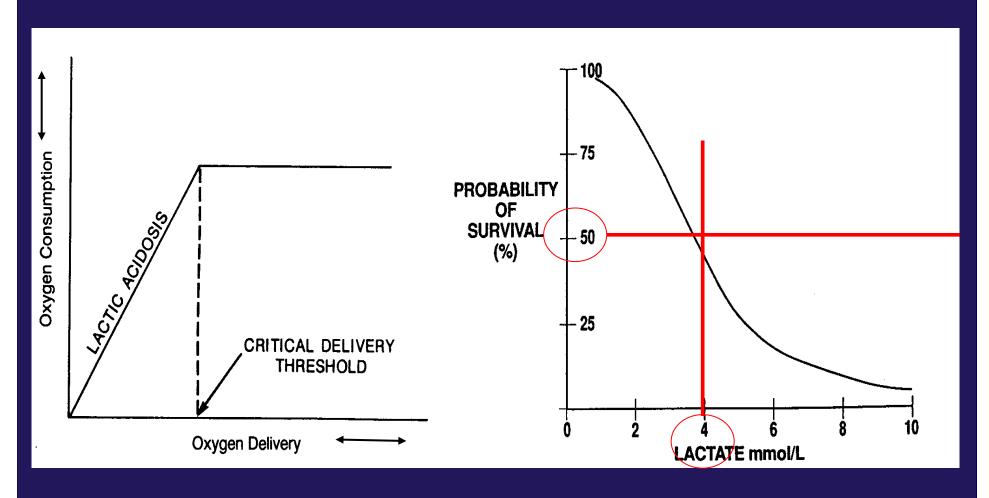
Lactate still correlates with severity of illness



- Bakker J, Coffernils M, Leon M, Gris P, Vincent JL. Blood lactate levels are superior to oxygen-derived variables in predicting outcome in human septic shock. Chest 1991, 99:956-962.
- Abramson D, Scalea TM, Hitchcock R, Trooskin SZ, Henry SM, Greenspan J. Lactate clearance and survival following injury. J Trauma 1993, 35:584-588.
- Bakker J, Gris P, Coffernils M, Kahn RJ, Vincent JL. Serial blood lactate levels can predict the development of multiple organ failure following septic shock. Am J Surg 1996, 171:221-226.
- Nguyen HB, Rivers EP, Knoblich BP, Jacobsen G, Muzzin A, Ressler JA et al. Early lactate clearance is associated with improved outcome in severe sepsis and septic shock. Crit Care Med 2004, 32:1637-1642.



Lactate and Outcome



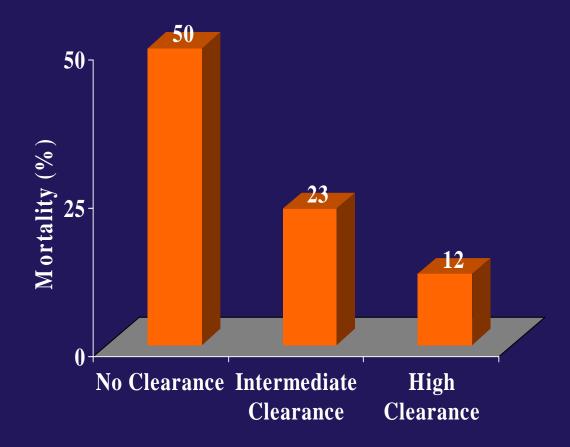
(Mizock, Dis Mon, 1989)

(Weil, Circulation, 1970)

♦ Virginia Commonwealth University Reanimation Engineering Shock Center ♦



Lactate Clearance and Mortality

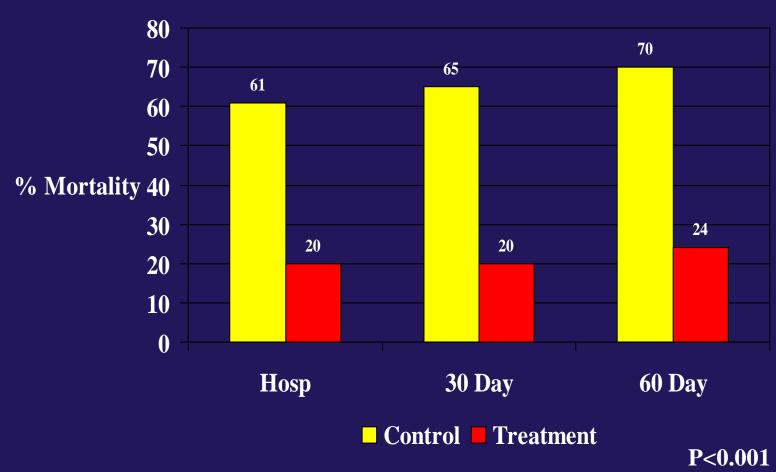


(Knoblich and Rivers, Acad Emerg Med, 1999)



Cryptic Shock

Outcomes of Patients with a Baseline MAP > 100, Lactate > 4 mM/L Control n = 33 and Treatment n = 30





Why should we detect hypoperfusion in the field

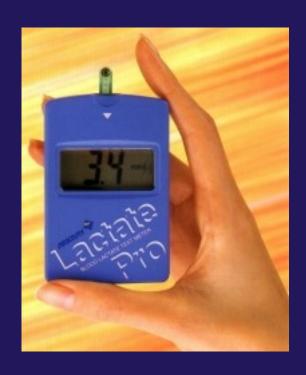
- Start therapy early (IV fluids)
- Triage to appropriate ED
- * Monitor resuscitation (lactate clearance)
- **Start definitive care in the ED earlier**
- Improve outcome?



How do you check lactate in the field?



Abbott i-Stat
CLIA Mod-complex



Roche Accutrend Lactate CLIA Mod-complex

Accutrend Lactate









Why is it so hard to get adequate resources to treat sepsis?

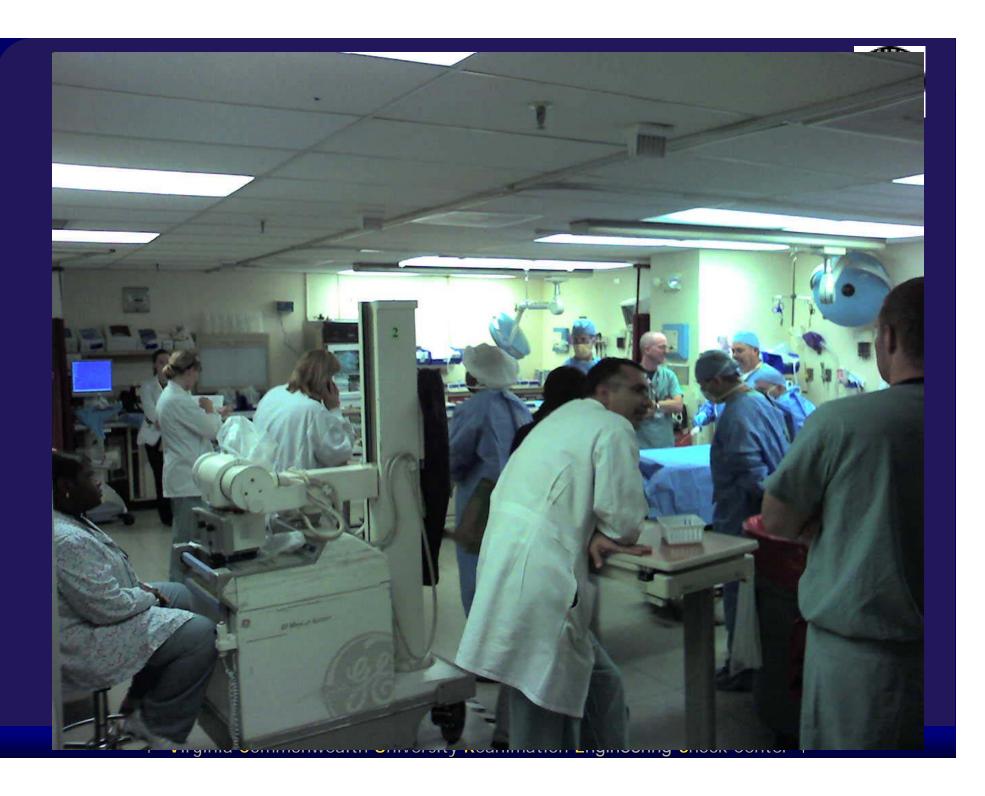




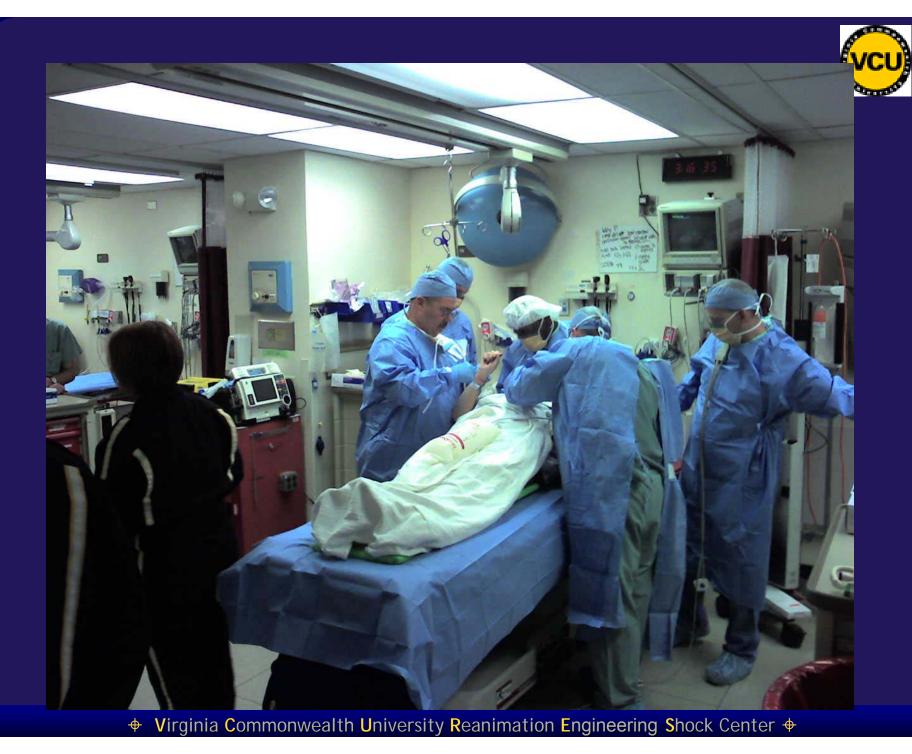
- # Heart Thrombolytics (< 6hr onset): 1.5% ARR</p>
 - PTCA "Door to balloon time" < 1 hr vs up to 90 min: 4% ARR</p>
- Brain rTPA: 90 min, 30% increase in functional neurologic outcome up to 90 days after. (Tissue plasminogen activator for acute ischemic stroke. N Engl J Med 1995)
 - 3X the rate of ICH vs control
- ** Trauma "Golden Hour" R Adams Cowley, MD coined this phrase in the 1970's
 - Trauma centers, trauma teams
- Severe Sepsis Early Goal Directed Therapy: 6 hours
 - ARR of 16% Best results of any sepsis trial to date
 - ????? How do you make Pus and Sepsis Sexy?!



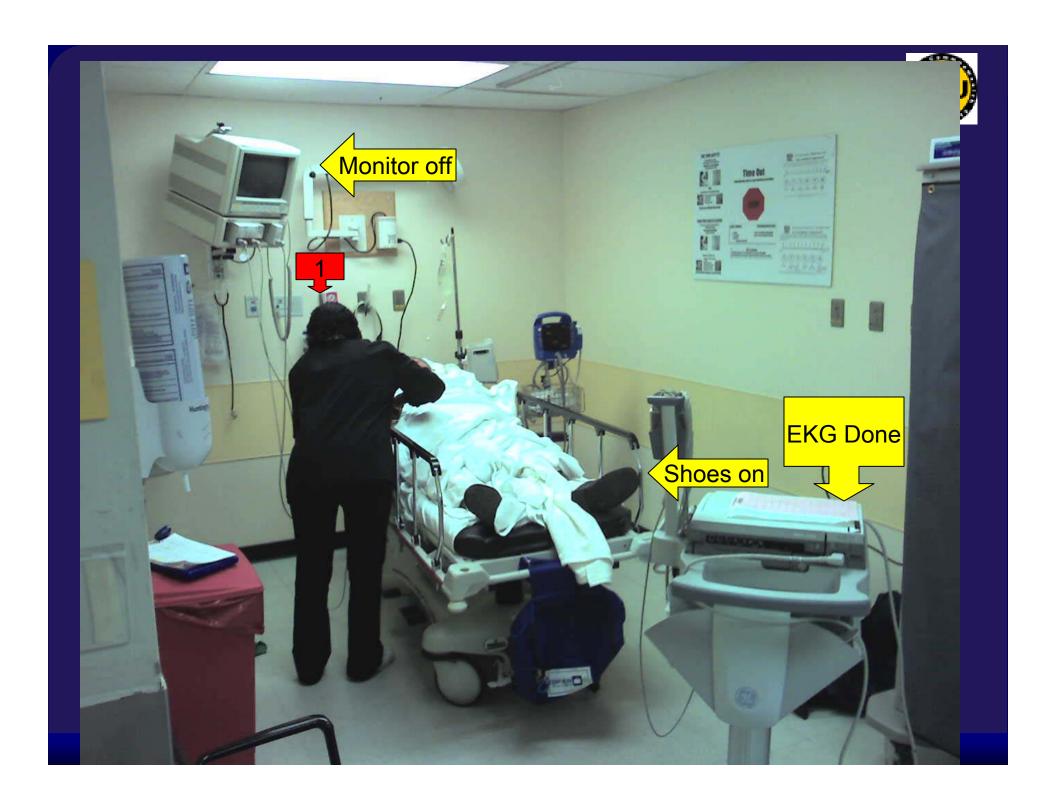












Time is Tissue!



- Need to identify hypoperfusion as early as possible
- Need to start treating the hypoperfusion
- * Transfer to definitive care center
 - Trauma Center
 - Cardiac Cath Center
 - Stroke Center
 - ?Sepsis Center?
 - ?Shock Center?



What's New? Possible Future Direction

EMS Lactate!





- Triage to appropriate ED
- * Treatment
 - Start therapy early (IV fluids)
- Monitor resuscitation (lactate clearance)
- Transport to the appropriate ED
- **** Start definitive care in the ED earlier**
- # Improve outcome?



Abbott i-Stat
CLIA Mod-complex



Roche Accutrend Lactate CLIA Mod-complex

Accutrend Lactate



Lack of correlation between lactate and hemodynamics



Lactate Tiers

Hemodynamic Variables

	Total n = 857	Normal (< 2.5) n = 599	Intermediate (2.5 - 3.9) n = 140	High (≥ 4.0) n = 118
HR	r = 0.15	r = 0.09	r = -0.15	r = 0.13
(BPM)	(0.08 to 0.21)	(0.01 to 0.17)	(-0.31 to 0.01)	(-0.05 to 0.30)
SBP	r = -0.08	r = -0.01	r = -0.23	r = -0.01
(mmHg)	(-0.14 to -0.01)	(-0.09 to 0.07)	(-0.07 to -0.038)	(-0.19 to 0.18)
DBP	r = 0.14	r = -0.04	r = -0.26	r = -0.08
(mmHg)	(-0.21 to -0.07)	(-0.12 to 0.05)	(-0.41 to -0.09)	(-0.26 to 0.11)
MAP	r = -0.15	r = -0.03	r = -0.26	r = -0.10
(mmHg)	(-0.21 to -0.08)	(-0.10 to 0.06)	(-0.41 to -0.10)	(-0.28 to 0.08)
Shock Index	r = 0.20	r = 0.07	r = 0.09	r = 0.10
HR/SBP	(0.13 to 0.26)	(-0.01 to 0.15)	(-0.08 to 0.25)	(-0.08 to 0.28)

Gunnerson KJ, et al. Chest, Oct 1, 2008, 134:65003S

Cryptic Shock?



Lactate Tier	Systolic Blood Pressure (mm / Hg)		
(mmol / L)	≤ 90	> 90	
< 2.5 (n = 599)	14 (2.3%)	585 (97.7%)	
2.5 – 3.9 (n = 140)	11(7.9%)	129 (92.1%)	
≥ 4.0 (n = 118)	12 (10.2%)	106 (89.8%)	

Table 1. Number of patients in each lactate level tier and their association with hypotension (defined by a SBP \leq 90 mm/Hg). Total n = 857

Gunnerson KJ, et al. Chest, Oct 1, 2008, 134:65003S

^{*14%} of all transports had HIGH lactate levels (≥ 4)

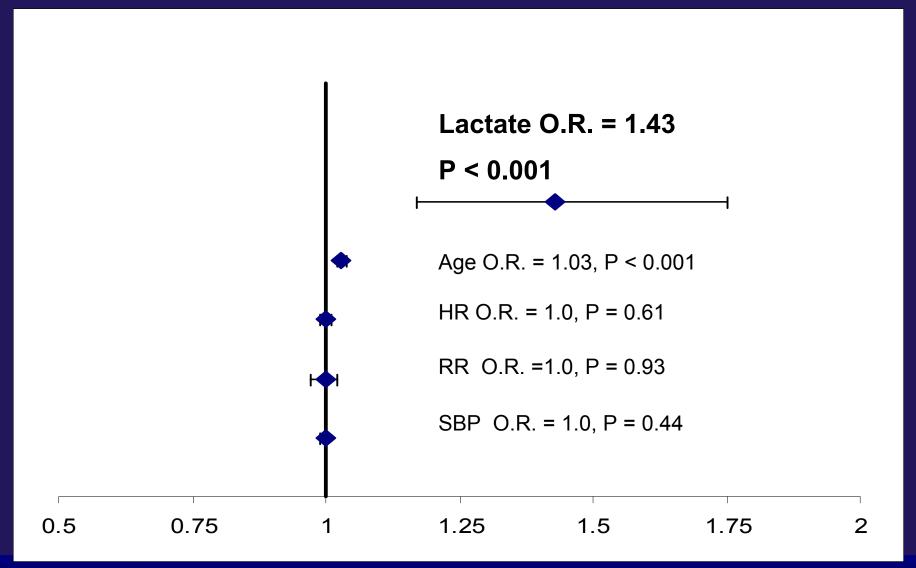
Lactate as a predictor of Admission and type of admission



- 2,034 patients transported to VCU Med Center or community hospitals in Richmond area
- RAA and Chesterfield Fire and EMS
- Common EMS vital signs used (HR, BP, GCS, RR, Glucose level, Age) and LACTATE
- Logistic regression model
- Only independent predictors of admission
 - Age
 - Lactate
- Lactate was better at predicting admission by more than 40% than all other variables

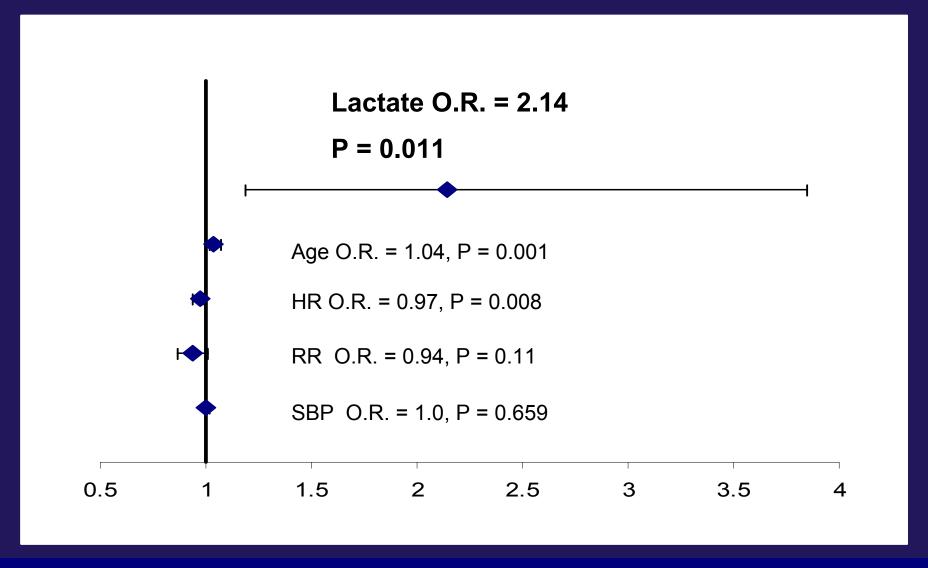
Pre-hospital Lactate as an independent predictor of admission





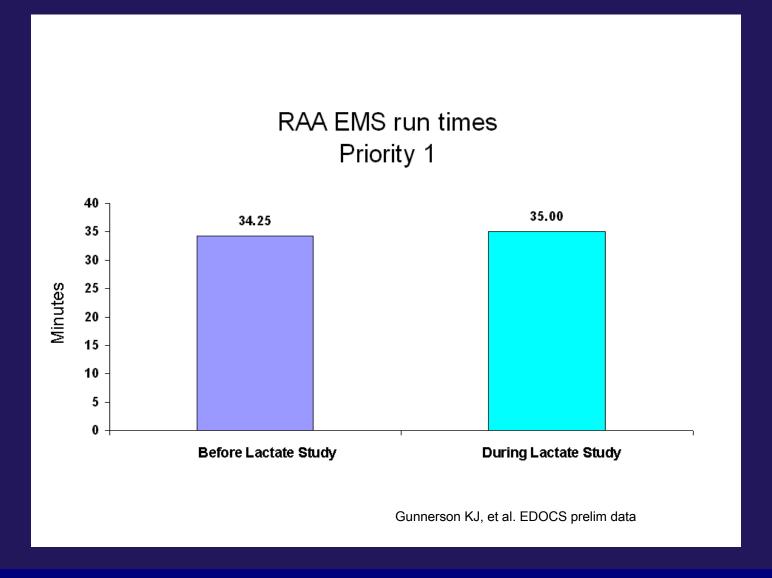
Pre-hospital lactate as an independent predictor of death





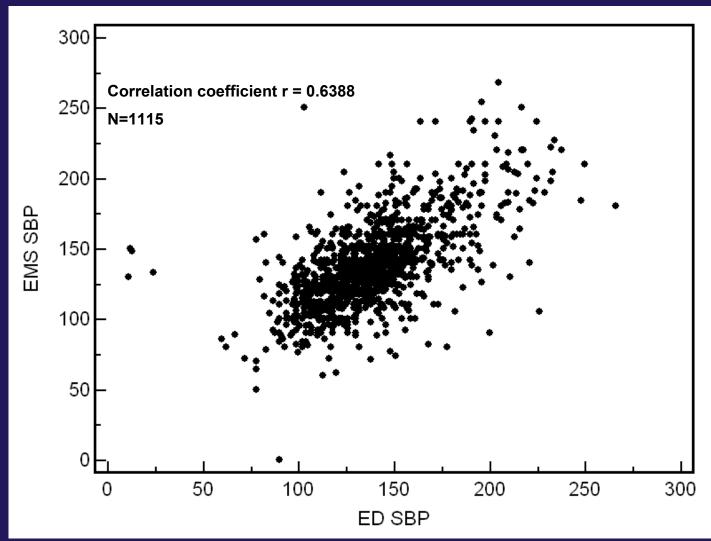
Does this slow down our paramedics?





EMS SBP overestimates ED SBP





Gunnerson KJ, et al. EDOCS prelim data



What do we do after you drop them off?







Surviving Sepsis Campaign



Launched in Fall 2002 as a collaborative effort of European Society of Intensive Care Medicine, the International Sepsis Forum, and the Society of Critical Care Medicine

- ***** Goal: reduce sepsis mortality by 25% in the next 5 years
- Guidelines revealed at SCCM in Feb 2004 and updated in 2008
 - * Critical Care Medicine March 2004 32(3):858-87.
 - Website: survivingsepsis.org



Background

- The Surviving Sepsis Campaign's mission is to increase awareness and improve outcome in severe sepsis
- Guidelines developed by a group of international experts representing 11 organizations
- Developed under unrestricted industry educational grants
- * Published in March 3, 2004 issue of Critical Care Medicine



Sponsoring Organizations

- American Association of Critical-Care Nurses
- American College of Chest Physicians
- American College of Emergency Physicians
- American Thoracic Society
- Australian and New Zealand Intensive Care Society
- European Society of Clinical Microbiology and Infectious Diseases
- European Society of Intensive Care Medicine
- European Respiratory Society
- International Sepsis Forum
- Society of Critical Care Medicine
- Surgical Infection Society

Key Components



- *** Fluid resuscitation**
- * Appropriate cultures prior to antibiotic administration
- *** Early targeted antibiotics and source control**
- * Use of vasopressors/inotropes when fluid resuscitation optimized



Cases

VCU

Case 1

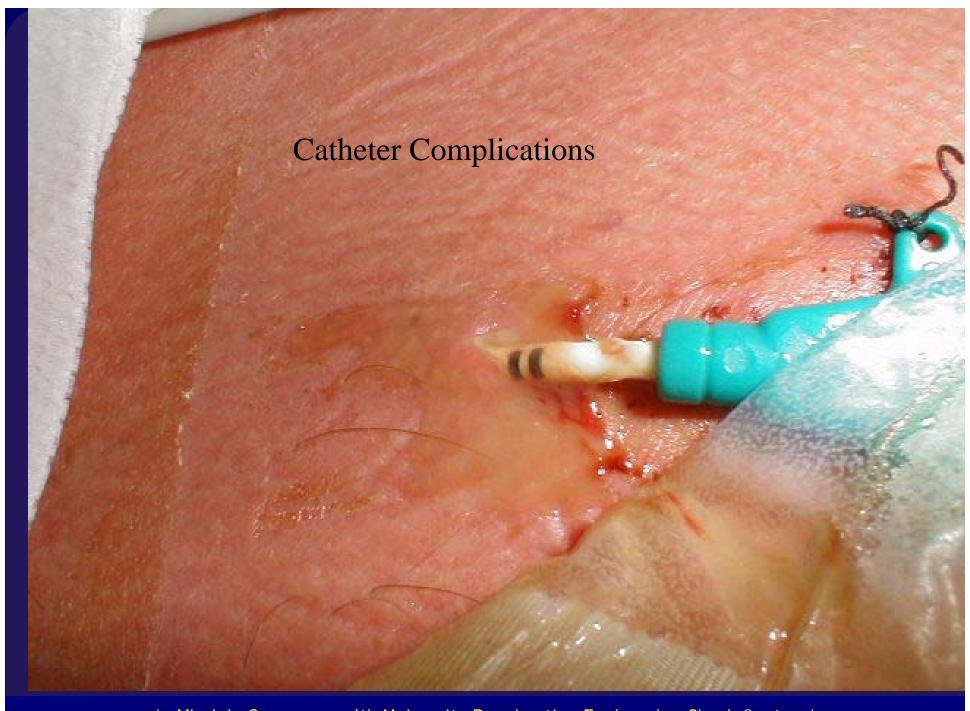
- ** 80 y/o Nursing home transfer with mental status changes and decreased urine output
- **# HR 110**
- ***** RR 28
- *** Temp 102**
- **#** BP 110/50
- Pulse ox 95% 21

Central line





♦ Virginia Commonwealth University Reanimation Engineering Shock Center ♦





What is the problem?

- Is your patient septic?
- # Hypoperfusion? Does BP matter?
 - Lactate in ER 9.5 mmol/L
- * What are you going to do?

Case 2



- ** 28 y/o male recently discharged from the hospital for an abscess in upper arm
- # He is in severe pain and wants you to take him to the ER for pain meds
- **# HR 130**
- **#** BP 100/40
- ***** RR 22
- ***** Temp 96
- Pulse ox 92% on RA

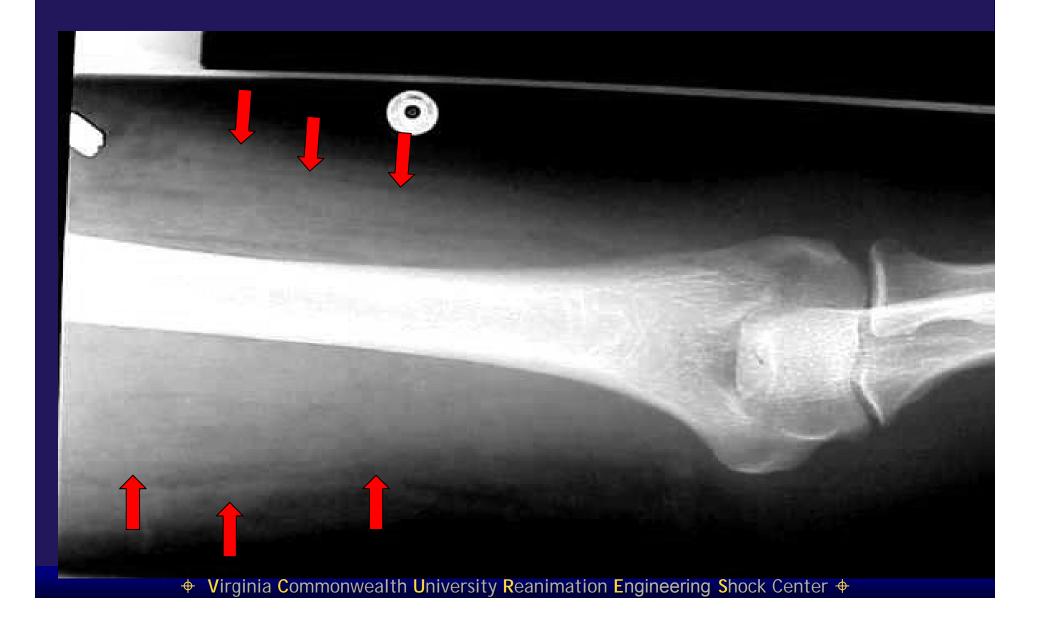
Clostridium septicum of upper arm after IV injection of cocaine





Sub-Cutaneous emphysema of soft tissue





Sub-Cutaneous emphysema of soft tissue in chest wall

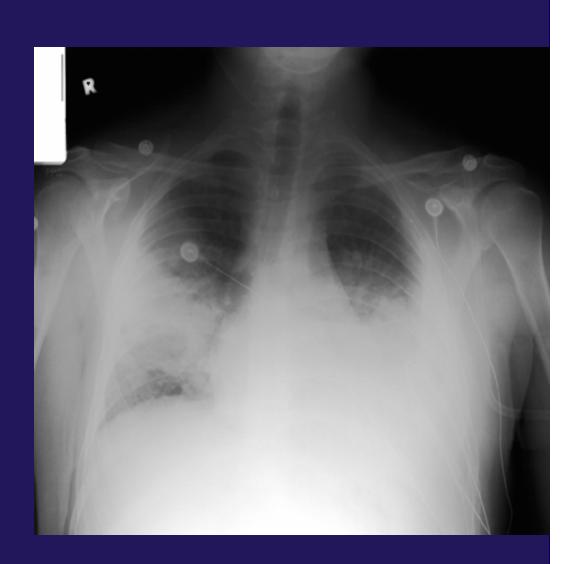






Case 3

- 60 yo female with family, c/o SOB, fever. Family: pt confused
- HR 130, T=39.8, RR 26,BP=80/30, MAP 55
- PE: No retractions, no ST infections, Lungs: decreased BS, ABD: s/nt/nd, Ext: no edema, Neck: no JVD







Medscape® www.medscape.com

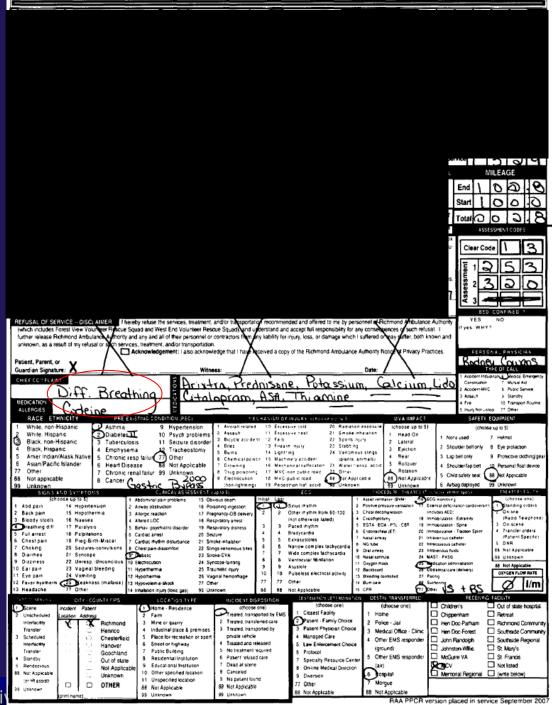
Petechiae

Ecchymoses / Purpurae

Typical EMS Encounter

32 F with hx of asthma

CC: Difficulty Breathing



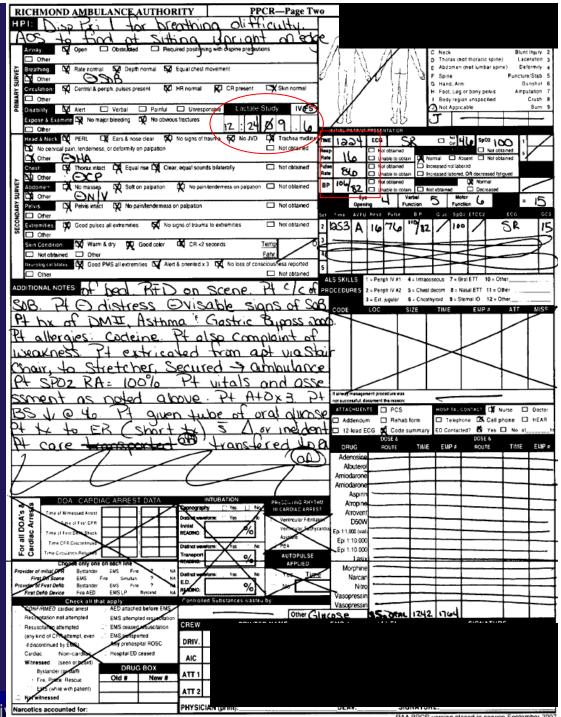
Typical EMS **Encounter**

HR = 86

RR = 16

BP = 106/82

LACTATE = 9.6



Hospital Course



- * Admitted for "Asthma"
- Condition worsened and moved to stepdown severe sepsis
- **E.** Coli grew out in the urine
- Pseudomonas grew out of old chest tube sites
- **# Enterococcus grew out in blood cultures**
- * Hospitalized for 7 days 3 in step-down.
- Discharged home on home IV antibiotics

32 male with hx of paraplegia, wheelchair bound,

PICC line for long term antibiotics for decubitus ulcer,

Suprapubic catheter in place.

C/O of fever and "feeling cold" to visiting nurse.

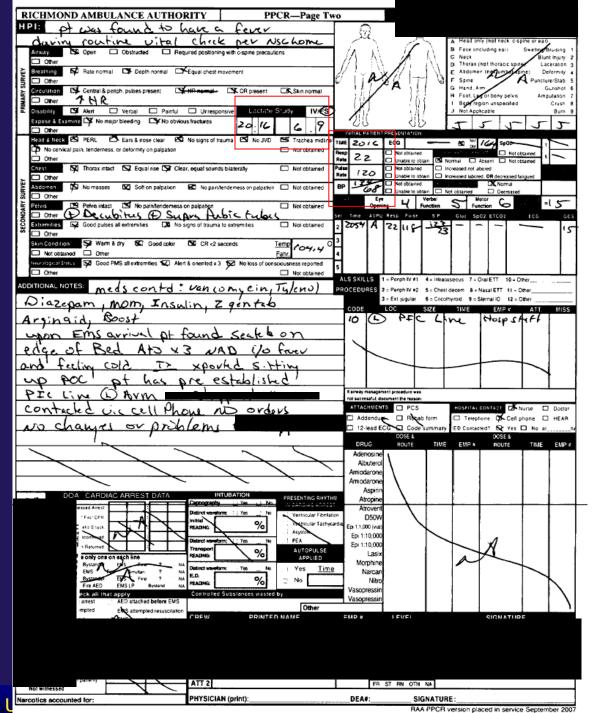
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HR 120, RR 22, BP 134/68, Temp 100.8 (ER) WBC 12.2

Lactate 6.9
SIRS Criteria?
Potential
infectious source

PICC Line Decubitus ulcer Suprapubic Catheter

- Only on vancomycin





Hospital Course

- Taken to community hospital
- "Vital signs" not much different than EMS
- * Rapid Urine Screen (+) for UTI
- **# Final culture Candida albicans**
- Discharged back home
- No lactate available for follow-up

VCU

Sepsis conclusions

- Does my patient have sepsis?
 - 2 of 4 SIRS Criteria (HR, Temp, WBC, Resp Rate)
 - Infection causing this?
- Is there hypoperfusion (organ dysfunction)
 - Altered mental status
 - Jaundice
 - Petechiae
 - Elevated Lactate, > 4 mmol/l?
- Start treating the hypoperfused state
 - IVF
 - Tell the ED doc
- Definitive care
 - Sepsis Teams
 - Shock Centers



Thank you for your attention

Questions?

Email: kgunnerson@vcu.edu