

Update on Surviving Sepsis 2008

Objectives

- Epidemiology of Sepsis
- Definition of Sepsis and Septic Shock
- Review Guidelines for Resuscitation
 - Dx: Lactate, cultures, SVO₂
 - Tx: EGDT, timing/choice of abx, activated protein C

Epidemiology

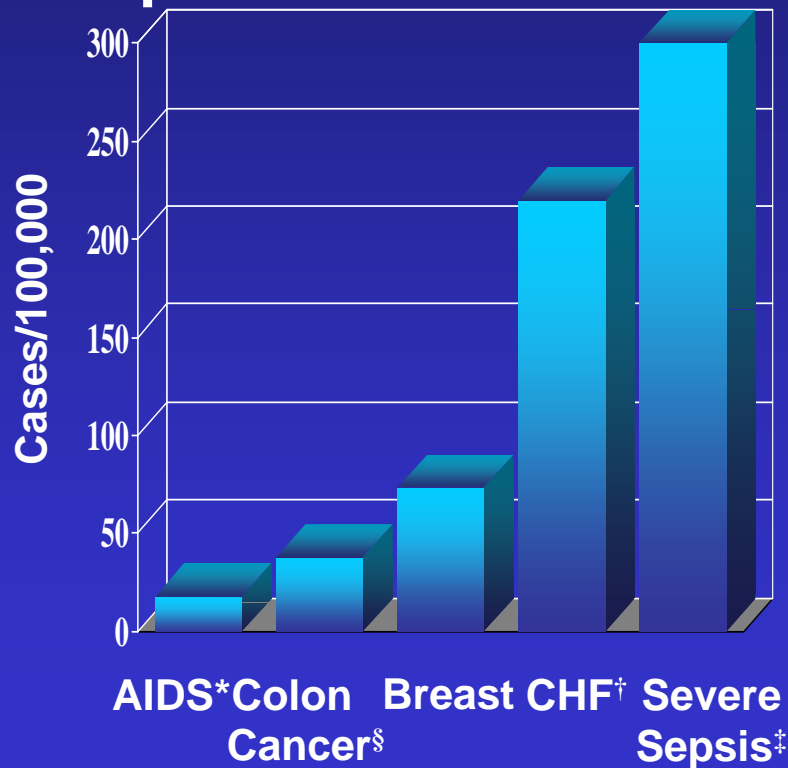
- In the U.S. Annually:
 - Incidence of Sepsis 750,000
 - 160,000 (~20%) are surgical patients
 - 30-40% mortality despite abx and source control
 - ~250,000 deaths per year
 - Cost \$17 Billion

Epidemiology

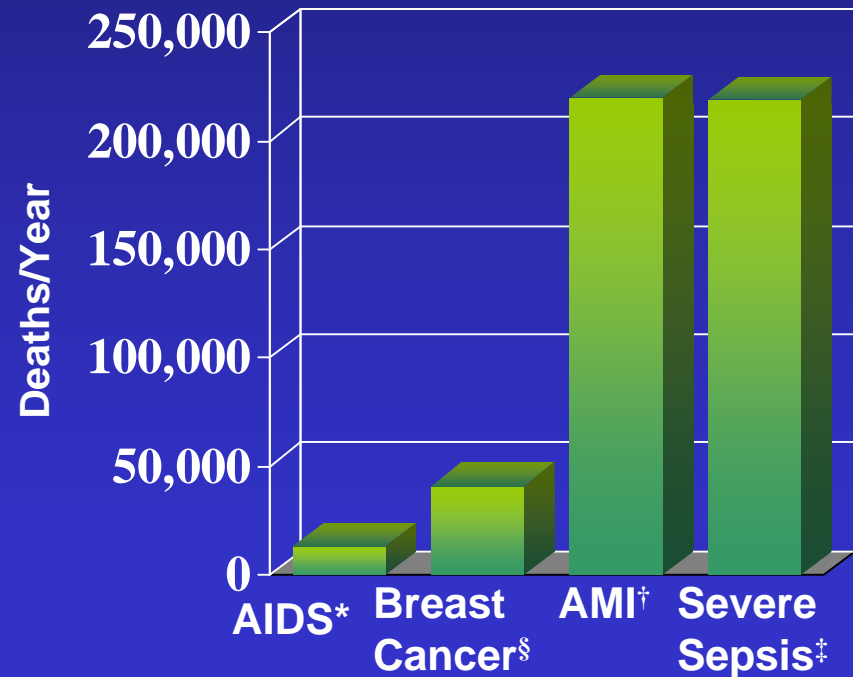
- Compared to medical septic pts, surgical pts:
 - LOS + 7 days
 - Cost +\$10,000
- Compared to non-septic surgical pts:
 - Cost 5x higher

Importance of Severe Sepsis: Comparison With Other Major Diseases

Incidence of Severe Sepsis



Mortality of Severe Sepsis



†National Center for Health Statistics, 2001. §American Cancer Society, 2001. *American Heart Association, 2000. ‡Angus DC et al. *Crit Care Med.* 2001 (In Press).

Determinants of Mortality

- Source control is most vital factor
- Resuscitation/re-establish perfusion in 6 hrs
- Appropriate IV abx in 1 hr

Definitions

SIRS

MODS

septicemia

severe sepsis

sepsis

septic shock

Systemic Inflammatory Response Syndrome (SIRS)

- Inflammatory response that includes 2 or more of the following:
 - Temp $> 38^{\circ}\text{C}$ or $< 36^{\circ}\text{C}$
 - HR $> 90/\text{min}$
 - RR $> 20/\text{min}$ or PaCO₂ < 32 mmHg
 - WBC $> 12\text{K}$, $< 4\text{K}$, or $> 10\%$ bands
- Sepsis : SIRS + Infection

Severe Sepsis

- Sepsis with end-organ dysfunction
 - Oliguria
 - Increase Creatinine
 - Altered mental status
 - Elevated Lactate

Septic Shock

- Sepsis with hypotension despite adequate fluid resuscitation (20 ml/kg)
 - SBP < 90 or MAP < 70
 - In hypertensive pts, SBP decrease > 40mm Hg from baseline

Definition Summary

- SIRS: $HR > 90$, $RR > 20$, $12 < WBC < 4$,
 $38 < temp < 36$
- Sepsis: SIRS + Infection
- Severe Sepsis: Sepsis + organ dysfunction
- Septic Shock: Sepsis + hypotension

Pathophysiology

- Distributive shock state
 - Vasodilation of arterioles – low SVR, low BP
 - Compensate with tachycardia and elevated CO/CI
 - Pre-capillary A-V shunts
 - Low BP – bypass capillary resistance beds
 - Elevated SVO₂
 - Elevated lactate

Pathophysiology

- Classic physiologic derangements most associated with LPS
- Can be associated with exotoxin from gram positive bacteria or large gram positive load
- Least associated with fungemia (atypical symptoms)

Diagnosing the Septic Pt

- Combine clinical exam and labs/imaging
 - Elderly
 - Can't mount a fever or leukocytosis
 - Ability to develop bandemia preserved
 - Immunosuppressed/steroids

Diagnosing Sepsis

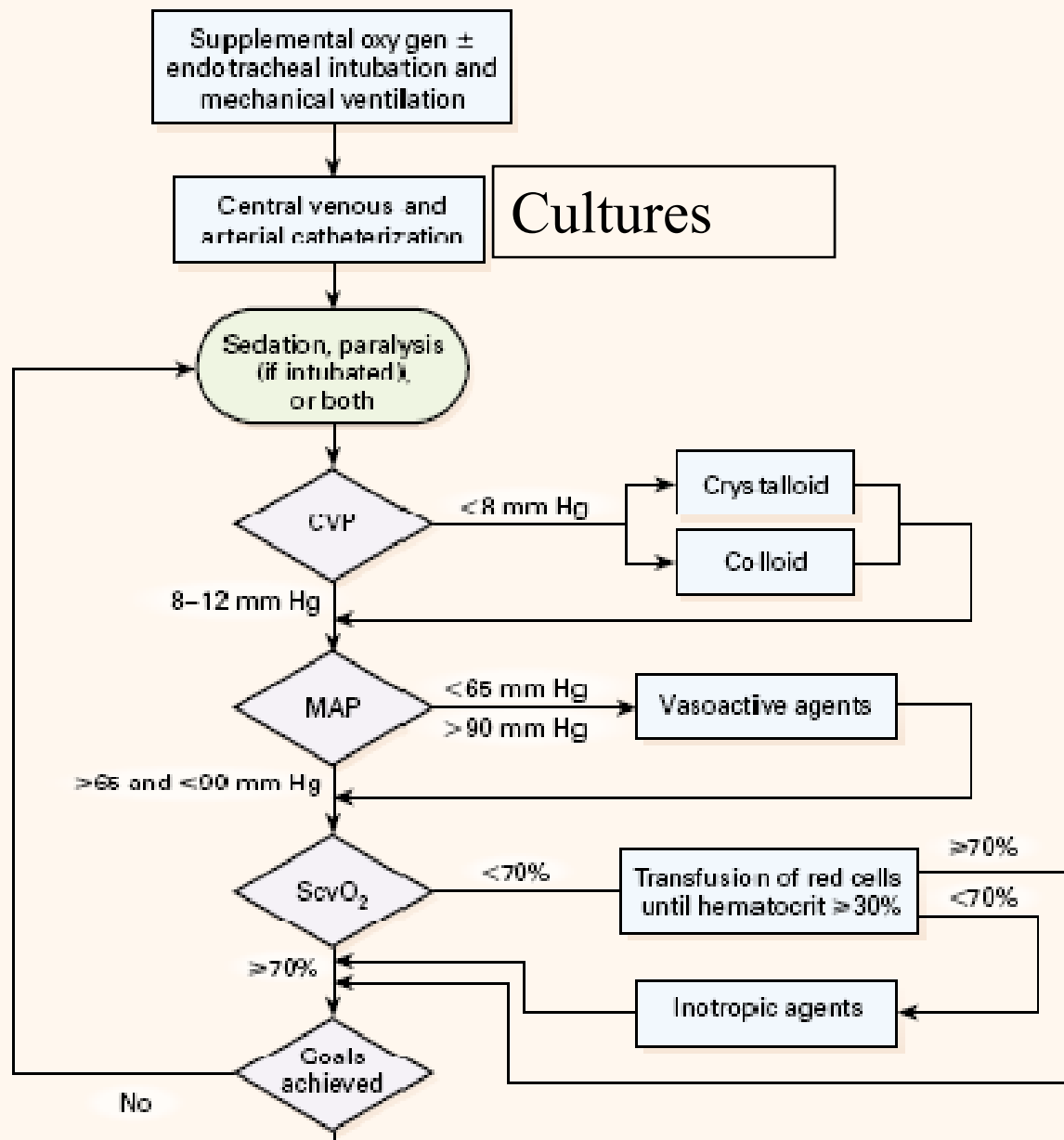
- Lab tests: CBC, Chem, CULTURES, lactate, SVO₂
 - SVO₂ is a measure of O₂ extraction (NL 70%)
 - **UNDER-RESUSCITATED** septic pts have a **LOW** SVO₂
 - **RESUSCITATED** septic pts have a **HIGH** SVO₂
 - Lactate is a measure of the severity of sepsis
 - Lactate > 4 that does not correct in 6 hrs is bad

Treatment

- Based on Early Goal Directed Therapy
- Very broad, high dose, rapid administration of iv abx
- Consider Activated Protein C
- Minimal role for steroids

Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock, 2008. Critical Care Med

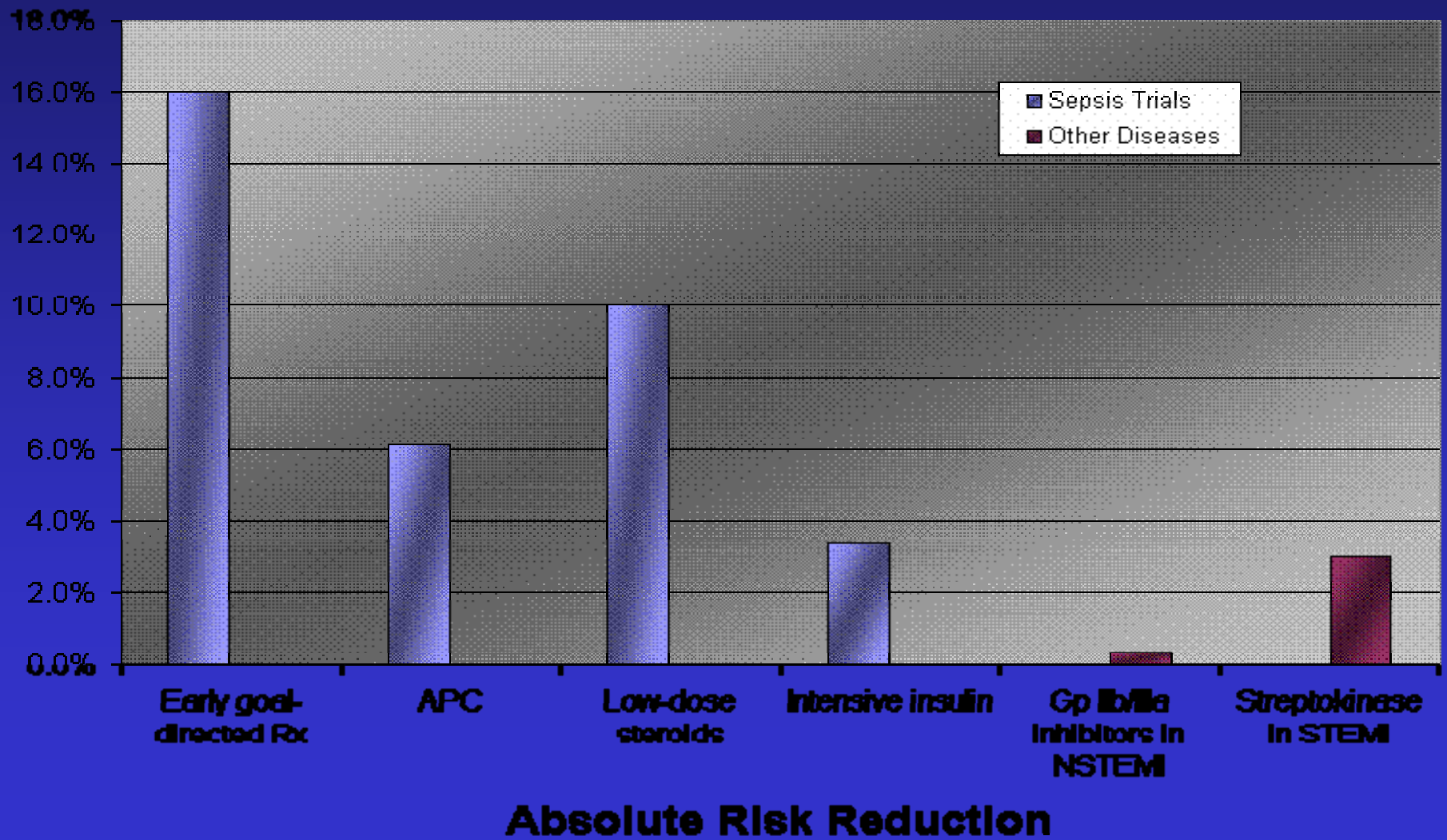
N=230
9% Surgical



Rivers, NEJM
2001; 345:1368

Treatment

Comparative Mortality Reductions



Treatment

Start with 1-4 liter bolus of saline or LR

- Elevated lactate is not a contraindication to LR
- Pressor if needed to temporize while fluids are running or if unresponsive to fluids alone

Treatment – Fluid Choice

- Colloid (Hespan)
 - Starch polymer that cannot cross cap endothelium in non-inflamed state
 - Mild anti-platelet effects after 1.5-2 liters/day
 - Possible adverse effect on renal function
- Albumin (SAFE Trial)*
 - No difference between Albumin and saline
 - Possibly worse in trauma, esp TBI
 - Excluded liver and burn pts

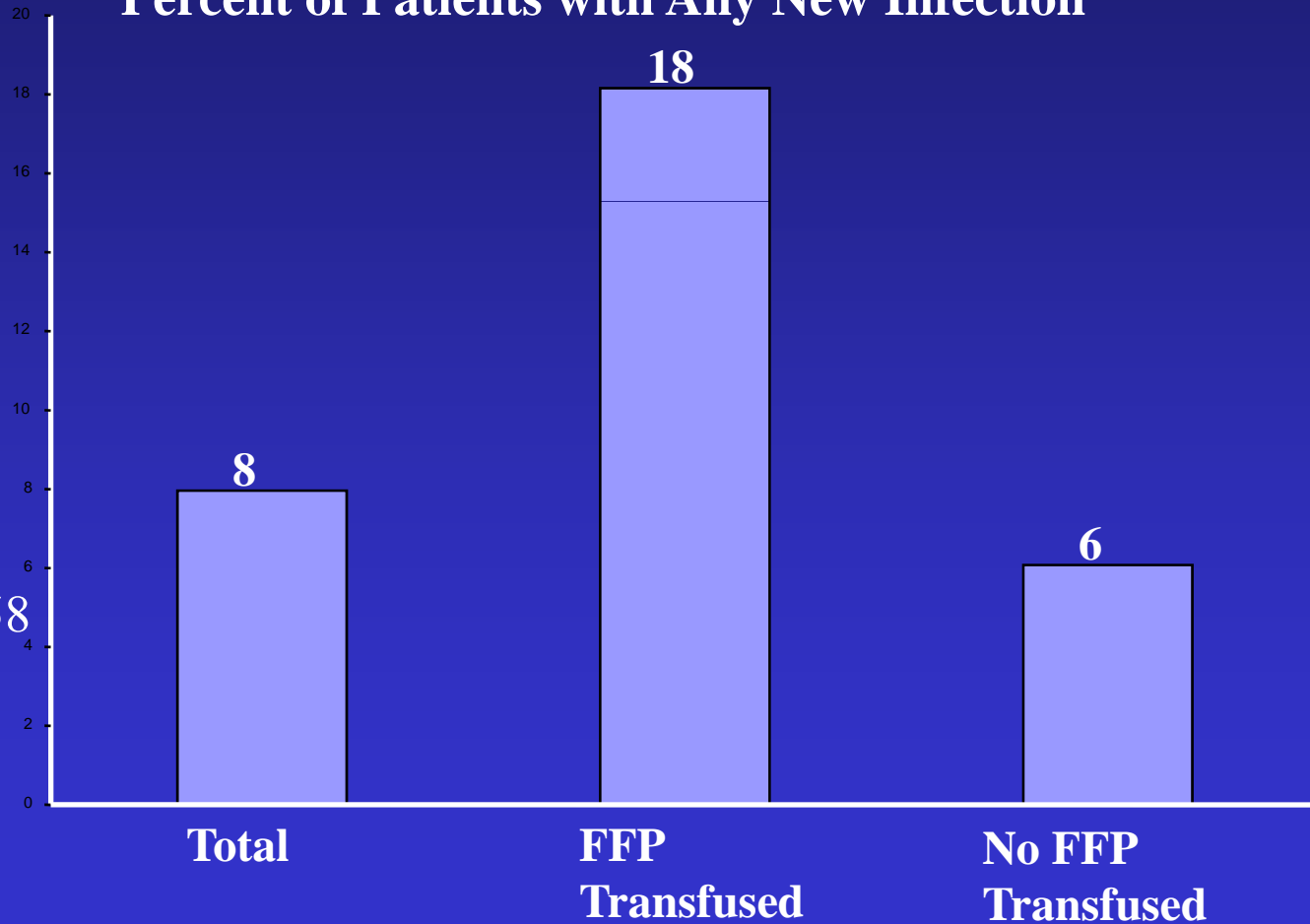
*NEJM 2004; 350:2247

Treatment – Choice of Fluids

- FFP – “We recommend FFP *not* be used to correct laboratory clotting abnormalities in the absence of bleeding or planned operation”*

FFP Study (HUP)

Percent of Patients with Any New Infection



FFP N=380

No FFP N=2058

FFP Study (HUP)

	OR	95% CI	P value
Age	0.994	0.98-1.005	0.27
FFP	1.039	1.013-1.067	<0.01
RBC	1.074	1.043-1.107	<0.01
APACHE II	1.126	1.102-1.152	<0.01

Treatment - Fluids

- Endpoints of therapy
 - MAP > 65 mm Hg, HR < 100 bpm
 - UOP > 0.5 cc/kg/hr
 - SVO₂ 70% or more
 - CVP > 10-15
 - Higher if known cardiomegaly or intubated
 - TTE showing cardiac filling
 - Until you no longer see improvement in hemodynamics following boluses (concept of volume-responsiveness)

Treatment - Vasopressors

	DA-R (↑UOP)	B ₁ (↑ HR)	B ₂ (↓BP)	α ₁ (↑ BP)
Dopamine 1-15 mcg/kg/min	1-5 mcg/kg/min	6-10 mcg/kg/min		>10 mcg/kg/min
Phenylephrine (Neosynephrine) 1-300mcg/min				+++
Norepinephrine (Levophed) 1-20 mcg/min		+		++++
Epinephrine (God's Pressor) 1-10 mcg/min		++++	+++	++++
Dobutamine (1-10 mcg/kg/min)		+++	++	
Milrinone (0.125- 0.5 mcg/kg/min)		+++	+++	

Potency + scale is from 1-4

Treatment

- Blood Transfusion
 - Rivers' trial transfused for Hg < 10 if SVO₂ remained low after IVF and after MAP > 65
 - Role for pre-emptive transfusion?
 - e.g. Hg 10-11 with elevated lactate/shock
 - Time to replete 2,3 DPG, good colloid resuscitant
 - Immunosuppressive

O2 Delivery in Sepsis

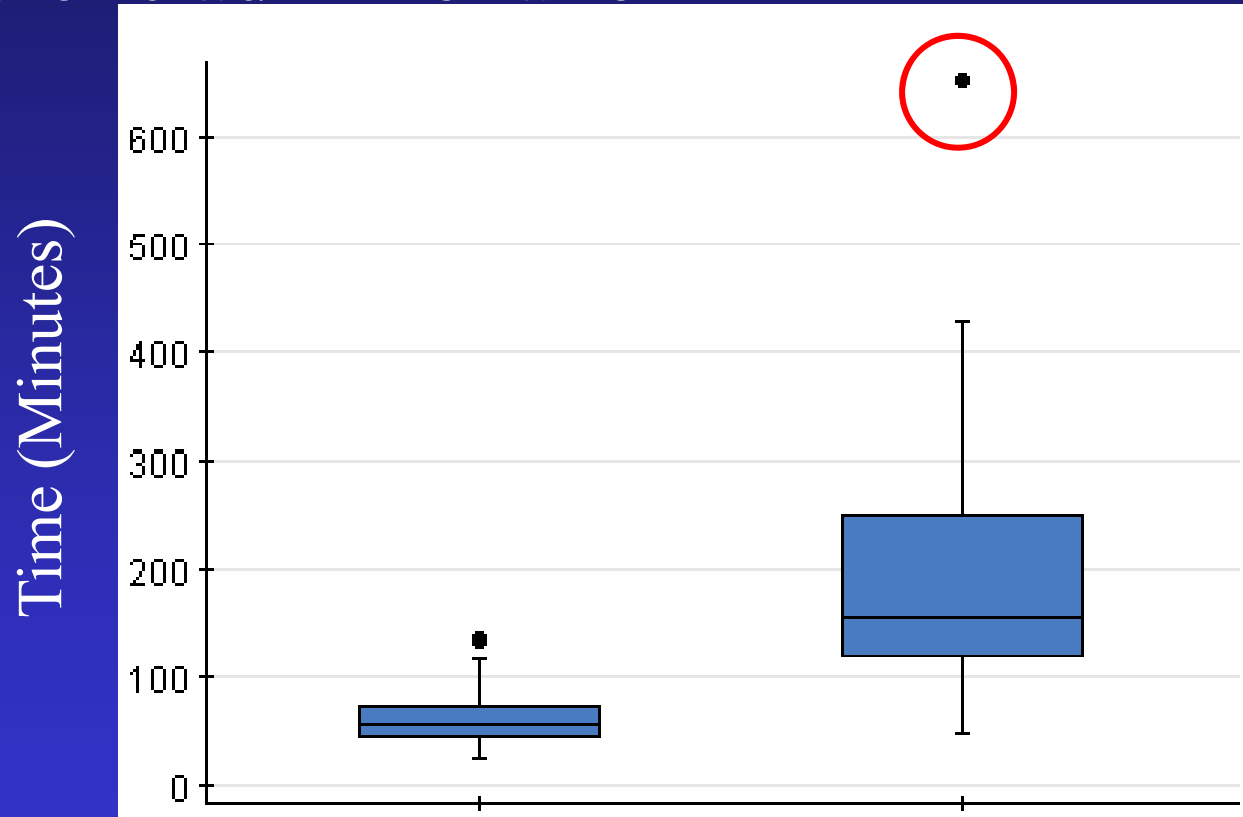
Author, Year, Journal	Population	Findings
Dietrich 1990 Crit Care Med	N= 32, MICU, septic, RCT	Hg 8→10.5, no change in PAOP, CI, lactate, SVO2
Lorente 1993 Crit Care Med	N=16, MICU, septic, RCT	Dobutamine increases SVO2 but RBC does not
Fernandes 2001 Crit Care	N=15, MICU, septic, RCT	RBC does not change gastric tonometry or lactate

Treatment – Source Control

- Imaging
 - Consider U/S if too unstable to travel
 - Bedside percutaneous interventions/drains
- Conditions with 100% mortality if not operated on quickly
 - Nec fasciitis, non-sealed perforated viscus

Treatment – IV Abx

- Mortality increases 7% for every hour delay in antibiotic administration*



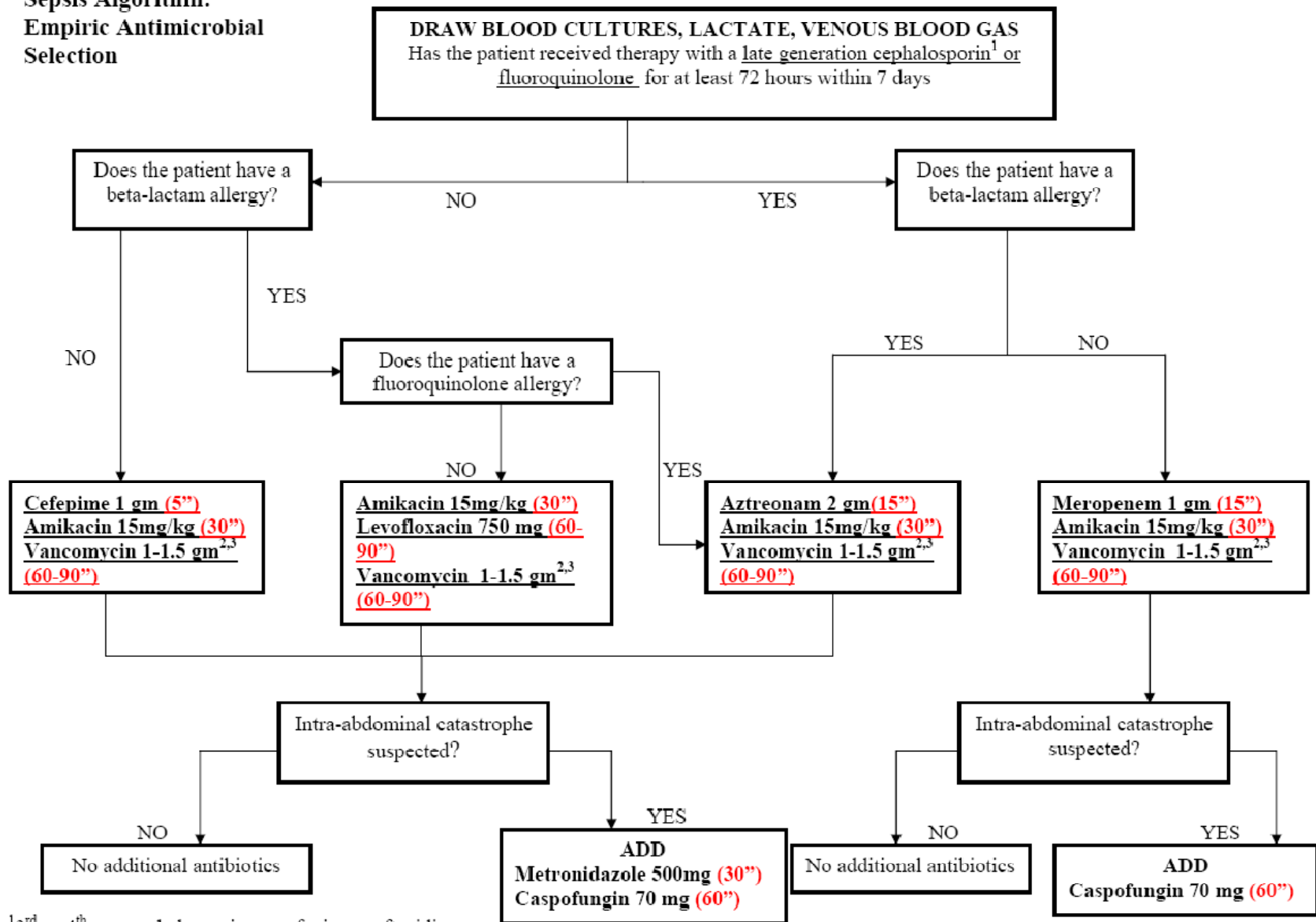
Sepsis

Sunrise

Bundle at
HUP

*Kumar A. Crit Care Med 2006; 34:
1589-96

**Sepsis Algorithm:
Empiric Antimicrobial
Selection**



¹3rd or 4th gen cephalosporins = cefepime, ceftazidime.

²Vancomycin dose: weight ≤ 70kg = 1 gm x 1, weight > 70kg = 1.5gm x 1

³Infuse vancomycin before caspofungin (if given), but after other antibiotics have

Treatment - Steroids

- Recommended only for shock refractory to pressors
- Annane – multicenter, European, RCT
 - Pts with vasopressor-resistant hypotension
 - Improved mortality if rise in cortisol following ACTH was $< 9\text{mcg/dL}$ and if baseline cortisol < 21
- CORTICUS – larger, European, RCT
 - All pts with septic shock (regardless of vasopressor response)
 - No difference in mortality but vasopressor sparing effect with steroids
 - ACTH stim could not predict who was steroid deficient

Annane 2002; 288:862

Insert CORTICUS Reference

Treatment - Xigris

- Activated protein C
 - Anticoagulant (inhibits Factors V and VIII)
 - Stop microthrombi formation and prevent end-organ loss?
 - Endothelial cell stabilizer (anti-inflammatory)
 - Stop excessive production of cytokines and apoptosis?

Treatment - Xigris

- PROWESS – RCT, 1690 pts, stopped early
 - 532 surgical pts
 - 6% decrease in mortality overall
 - Greatest decrease if APACHE II score > 25
 - Greater decrease in medical pts
 - Surgical pts 3% decrease mortality overall and 9% decrease if abdominal operation performed (better source control)
 - 1.5% increase in risk of bleeding
 - Equal between medical and surgical groups

PROWESS - Limitations

- Never replicated
- Entry criteria changed in the middle of the study
- Study terminated early
- Drug approved for use in a post-hoc derived subgroup (APACHE II > 25 or high risk of death as determined by intensivist)
- Higher APACHE II mortality in the control arm than anticipated