

Disclosure

I have no real or potential conflicts of interest to report.

Management of Septic Shock

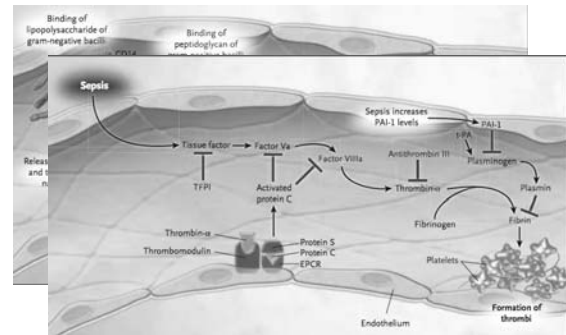
Rational Steps Forward In the Face of Disappointment

Jamie Falk, BScPharm, PharmD
CSHP BC Annual General Meeting

Session Objectives

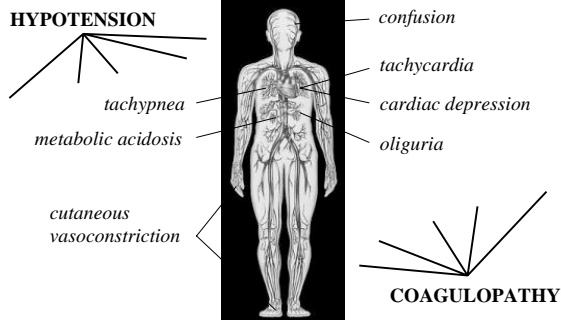
- Understand the basic pathophysiology of septic shock
- Appreciate the time-sensitive nature of antibiotic delivery in severe sepsis/septic shock
- Identify major principles of hemodynamic support and understand how vasopressors/inotropes fit into this framework
- Contrast clinical trial data and real life practice concerning the use of activated protein C
- Identify arguments for and against the use of corticosteroids in severe sepsis/septic shock
- Understand the potential benefits and risks with the use of intensive insulin therapy in the septic patient

Pathophysiology



Russell J. N Engl J Med 2006;355:1699-1713.

Presentation/Assessment



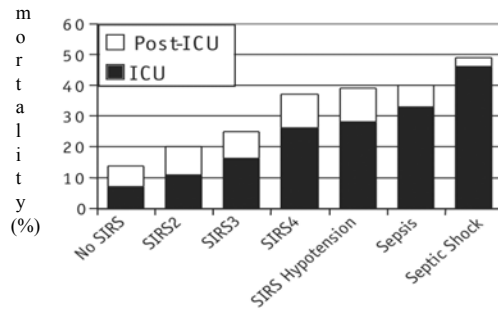
Definitions

- Systemic Inflammatory Response Syndrome (SIRS):
 - Inflammatory response from a non-specific insult, including ≥ 2 of the following:
 - Temperature > 38 or < 36 °C
 - Heart rate > 90 bpm
 - WBC > 12 or < 4 , or $> 10\%$ immature neutrophils
 - Respiratory rate > 20 /min or $\text{paO}_2 < 32$ mmHg

Definitions

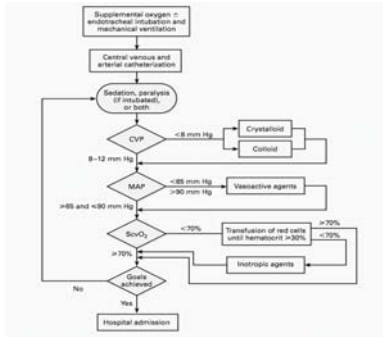
- Sepsis
 - SIRS with presumed or confirmed infection
- Severe Sepsis
 - Sepsis associated with:
 - Organ dysfunction
 - Perfusion abnormalities (altered mental status, oliguria, lactic acidosis, etc.), or
 - Hypotension (MAP < 65mmHg, SBP < 90mmHg, or ↓SBP > 40mmHg)
- SEPTIC SHOCK
 - Sepsis with perfusion abnormalities and hypotension despite adequate fluid resuscitation

Mortality



Laupland K, et al. Infection 2004;32(2):59-64.

Hemodynamic Support



Rivers E, et al. N Engl J Med 2001;345:1368-77.

Vasopressin in Septic Shock

- VP levels rise in early septic shock and remain elevated for up to 12h in animal models after endotoxin infusion
- Patients with late septic shock have a relative deficiency of VP
- Proposed mechanisms of deficiency:
 - Inhibition of VP release by nitric oxide and/or NE
 - Depletion of VP stores

Cooper J, et al. Crit Care Resusc 2006;8:239-40.

Exogenous Vasopressin in Septic Shock

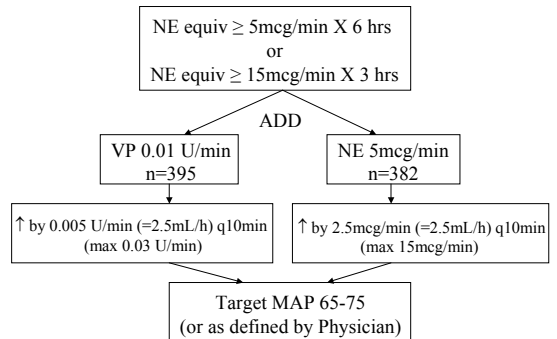
Trials showed rapid and sustained hemodynamic effect

Important clinical outcomes?

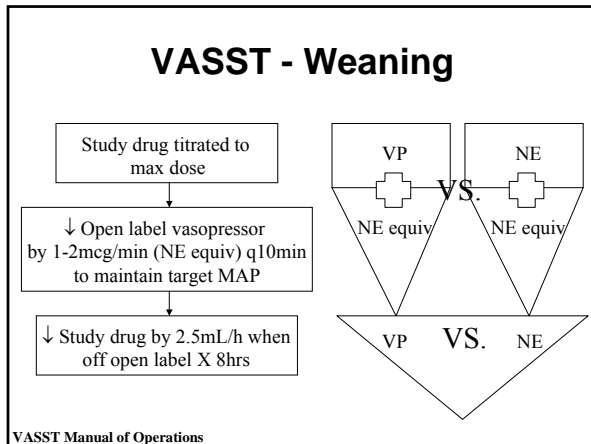
VASST

RCT of the effect of VP vs. NE on 28-day survival in septic shock

VASST



VASST Manual of Operations



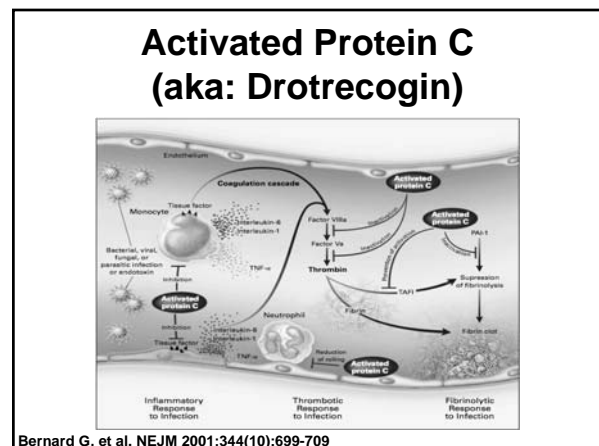
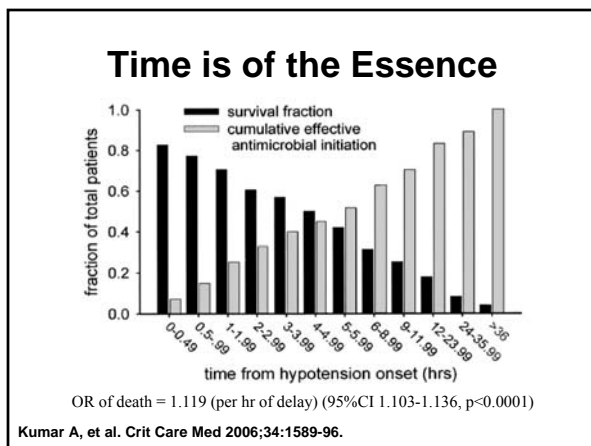
VASST - Results

	28-day Mortality (%)		ARR (%)	p-value
	VP	NE		
All (n=777)	35.4	39.3	3.9	0.27
Less Severe Septic Shock (n=400)	26.5	35.7	9.2	0.05
Severe Septic Shock (n=377)	44.0	42.5	-1.5	0.76

Russell J. Society of Critical Care Medicine 36th Critical Care Congress 2007

- ### Antibiotic Initiation
- Use local susceptibility patterns as guide for empirical antimicrobial use
 - Cover broadly considering patient and disease characteristics
 - Narrow spectrum as appropriate
 - Ensure appropriate PK/PD principles are utilized
 - Timeliness of antibiotic initiation

- ### Time is of the Essence
- Kumar A, et al. Crit Care Med 2006;34:1589-96.
- Retrospective cohort (n=2154)
 - Adults with septic shock
 - Not receiving effective antimicrobial prior to hypotension
- | Time from hypotension to antimicrobial administration | Survival |
|---|----------|
| within 1 hr | 79.9% |
| 1-2 hrs | 70.5% |
| 5-6 hrs | 42% |
| 9-12 hrs | 25.4% |



FDA Subgroup Analysis

Table 20. 28-day all-cause mortality for all patients and for subgroups defined by APACHE II as a measure of disease severity

	rhAPC		Placebo		Absolute Mort diff (%)	RR	95% CI for RR
	Total N	N (%)	Total N	N (%)			
Overall	850	210 (24.7)*	840	259 (30.8)	-6.1	0.81	0.70, 0.93
APACHE II quartile (score)							
1 st - 2 nd (3-24)	436	82 (19)	437	83 (19)	0	0.99	0.75, 1.30
3 rd - 4 th (25-53)	414	128 (31)	403	176 (44)	-13	0.71	0.59, 0.85

*P-value for difference between rhAPC and placebo was 0.005, CNMI, stratified by baseline APACHE II, age, and baseline protein C.

Table 23. 28-day all-cause mortality subgroups analyses for number of organ failures

Number of Organ Failure	rhAPC (850)		Placebo (840)		Mort Diff (%)	Relative Risk (RR)	95% CI for RR
	Total N	N (%)	Total N	N (%)			
1	215	42 (20)	203	43 (21)	-1	0.92	0.63, 1.35
2	270	56 (21)	273	71 (26)	-5	0.80	0.59, 1.08
3	214	56 (26)	218	75 (34)	-8	0.76	0.57, 1.02
4	119	46 (39)	116	54 (47)	-8	0.83	0.62, 1.12
5	31	10 (32)	30	16 (53)	-21	0.60	0.33, 1.11

FDA Clinical Review - Xigris™ 2001

‡ NNT=8

Adverse Events

VARIABLE	PLACEBO GROUP (N=840)	DRUG/TRECCOIN ALPHA ACTIVATED GROUP (N=850)	P VALUE
At least one serious adverse event	102 (12.1)	106 (12.5)	0.84
Serious bleeding event*	17 (2.0)	30 (3.5)	0.06
Gastrointestinal	9 (1.1)	9 (1.1)	
Intraabdominal	4 (0.5)	3 (0.4)	
Intrathoracic	1 (0.1)	6 (0.7)	
Retroperitoneal	0	4 (0.5)	
Intracranial	1 (0.1)	2 (0.2)	
Skin or soft tissue	0	2 (0.2)	
Genitourinary	0	2 (0.2)	
Source unidentified†	2 (0.2)	2 (0.2)	
Thrombotic events	25 (3.0)	17 (2.0)	0.20

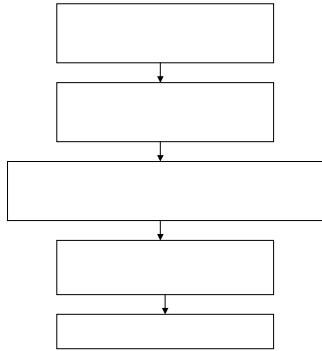
NNH=66

Bernard G, et al. NEJM 2001;344(10):699-709

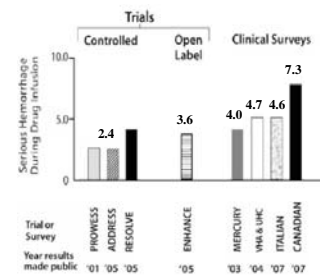
	APACHE II 3-25		APACHE II 25-53	
	rhAPC (436)	Placebo (437)	rhAPC (414)	Placebo (403)
Bleeding AE	74 (17)	37 (9)	86 (21)	54 (13)
Bleeding SAE	11 (3)	5 (1)	9 (2)	3 (1)

FDA Clinical Review - Xigris™ 2001

APC Research History



Major Bleeding



Eichacker P, et al. Intensive Care Med 2007;33:517-23.

Ontario/Quebec

	Ont/Que	ENHANCE	PROWESS
Severity of Illness:			
• APACHE score	31	22	24.6
• Organ failures	3.4	2.7	2.4
Mortality (%)	45*	25.3*	24.7*
Serious Adverse Bleeding Events (%)	7.3	3.6	2.4
Relative Contraindications (%)	20%	NA	NA

Kanji S, et al. Intensive Care Med 2007;33:517-23.

Vincent JL, et al. Crit Care Med 2005;33:2266-77.

Bernard G, et al. NEJM 2001;344(10):699-709

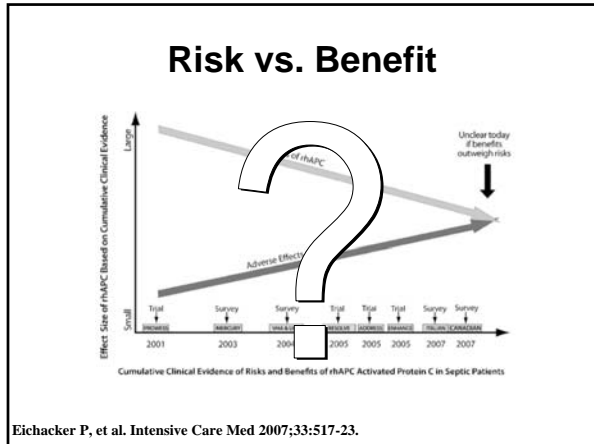
‡hospital mortality
*28 day mortality

Time to APC Initiation

- PROWESS
 - APC administration within 48 hrs of first organ failure
⇒ Mean = 17.5 hrs
- ENHANCE
 - Mortality if > 24 hrs = 27.4%
 - 0 - 24 hrs = 22.9%
- Kanji, et al.
 - Mortality if > 12 hrs = 51.8%
 - 0 - 12 hrs = 33%

Vincent JL, et al. Crit Care Med 2005;33:2266-77.

Kanji S, et al. Intensive Care Med 2007;33:517-23.



- ## Actions of Glucocorticoids
- **1. Metabolic**
 - Increased BG levels, facilitating delivery of glucose to cells during acute and chronic stress
 - **2. Cardiovascular**
 - Synthesis of catecholamines and their receptors
 - Decrease production of nitric oxide → decreased vasodilation and vascular permeability
 - **3. Immunosuppression/Anti-inflammatory**
 - Decrease accumulation and function of cytokines
- Marik P, et al. Chest 2002;122:1784-96.

- ## Corticosteroids in the Critically Ill
- Why would they be of potential use?
 - Incidence of adrenal insufficiency in critically ill patients: ~30%
 - Incidence in septic shock: ~50-60%
 - Minor degrees of adrenal insufficiency
 - ↑ mortality of critically ill patients
- Marik P, et al. Chest 2002;122:1784-96.

Cortisol & Prognosis

Risk Level	Baseline Cortisol (nmol/L)	Δ Cortisol* (nmol/L)	% patients	28-d mortality
Low	≤ 940	> 250	30	26%
Intermediate	≤ 940 > 940	≤ 250 > 250	50	67%
High	> 940	≤ 250	20	82%

*As a result of ACTH stim test

Annane D, et al. JAMA 2000;283:1038-45.

Annane 2002 RCT - Results

Variable	No. (%)		Adjusted OR (95% CI)	P Value
	Placebo	Steroids		
Nonresponders				
No. of patients	115	114		
28-day mortality	73 (63)	60 (53)	0.54 (0.31-0.97)	.04
ICU mortality	81 (70)	66 (58)	0.50 (0.28-0.89)	.02
Hospital mortality	83 (72)	70 (61)	0.53 (0.29-0.96)	.04
1-Year mortality	88 (77)	77 (68)	0.57 (0.31-1.04)	.07
Responders				
No. of patients	34	36		
28-Day mortality	18 (53)	22 (61)	0.97 (0.32-2.99)	.96
ICU mortality	20 (59)	24 (67)	0.99 (0.31-3.16)	.99
Hospital mortality	20 (59)	25 (69)	1.20 (0.38-3.76)	.75
1-Year mortality	24 (71)	25 (69)	0.70 (0.20-2.40)	.57
All Patients				
No. of patients	149	150		
28-Day mortality	91 (61)	82 (55)	0.65 (0.39-1.07)	.09
ICU mortality	101 (68)	90 (60)	0.61 (0.37-1.02)	.06
Hospital mortality	103 (69)	95 (63)	0.67 (0.40-1.12)	.12
1-Year mortality	112 (75)	102 (68)	0.62 (0.36-1.05)	.08

Annane D, et al. JAMA 2002;288:862-71.

CORTICUS

Population	<ul style="list-style-type: none"> • Targeted n=800 → recruited 499* • Inclusion: <ul style="list-style-type: none"> • Clinic evidence of infection • 2 SIRS criteria • Septic shock onset within 72hrs of randomization*
Intervention	• Hydrocortisone 50mg IV q6h X 5d → q12h X 3d → q24h X 3d*
1° Outcome	<ul style="list-style-type: none"> • 28d all cause mortality in non-responders • Stratified to responders and non-responders*

* Key differences from JAMA 2002

www.clinicaltrials.gov

CORTICUS

	Steroid (n=251)	Placebo (n=248)	p-value
28-Day Mortality (%)			
· All	33.5	31	0.57
· Non-responders	37.6	35.2	0.79
Shock Reversal (%)			
· All	80.5	74.6	0.14
· Non-responders	76.8	70.4	0.34
Time to shock reversal (days)			
· All	3.1	5.7	0.003
· Non-responders	3.7	6	< 0.05

Sprung CL, et al. European Society of Intensive Care Medicine 20th Annual Congress 2007

CORTICUS - ADRs

	Steroids (n=251)	Placebo (n=248)	p-value
Superinfection (%)	33	26	NS
ICU polyneuropathy (%)	1	2	NS
Hyperglycemia (%)	84	72	-

Sprung CL, et al. European Society of Intensive Care Medicine 20th Annual Congress 2007

Summary

Early Initiation of Antibiotics	✓
EGDT Principles	✓
Use of Vasopressin	?
Use of Activated Protein C	✓
Use of Corticosteroids	?

Future Research

- Await completion of TESST trial
- RCT of vasopressin in less severe septic shock?
- Update on Kumar's ever expanding database
- Retrospective look at contraindications for associations with bleeding risk
- Determine usefulness of ACTH stimulation test

References

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15. Annane D, Sebille V, Charpentier C, Bollaert PE, Francois B, et al. JAMA 2002;288:862-71.
16. ClinicalTrials.gov - CORTICUS
17. Sprung CL, et al. Corticosteroid therapy of septic shock (CORTICUS). Abstracts of the European Society of Intensive Care Medicine 20th Annual Congress; October 7-10, 2007; Berlin, Germany.

Contraindications to APC Use

- Absolute
 - Evidence/concern for internal bleeding
 - Platelet count < 30,000
 - Recent hemorrhagic stroke
 - Recent intracranial or intraspinal surgery
 - Epidural catheter
 - Recent severe head trauma
 - CNS mass lesion or cerebral herniation
 - Sepsis-induced organ failure > 48 hours
 - Moribund state
 - Family or physician not in favour of aggressive treatment
 - 28-day survival not expected due to underlying condition
- Relative
 - Therapeutic anticoagulation
 - INR > 3
 - Recent GI bleed
 - Trauma
 - Recent thrombolytics
 - Recent oral anticoagulants or GP IIb/IIIa inhibitors
 - Recent ASA >650mg/d or other platelet inhibitors
 - Recent ischemic stroke
 - Intracranial arteriovenous malformation or aneurysm
 - Severe hepatic disease
 - Known bleeding diathesis
 - Significant bleeding hazard
 - Patients who are pregnant or breastfeeding