Sepsis Treatment: Is There a Role For Vitamins ?

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Disclosures

Financial

- Grant Support Current
  - FDA/BARDA
  - Marcus Foundation
- Stipend from Critical Care Medicine for work as Associate Editor

Intellectual

- Medical Advisor to Project Hope (ARDS Advocacy Group)
- Member of Surviving Sepsis Guideline Committees (2004, 2008, 2012, 2016, 2020)

Talk Outline

- Review Treatment of Patients with Sepsis
- Review the Benefits and Limitations of Single Center vs Multicenter Clinical Trials
- Discuss the evidence supporting use of Vitamin C, Thiamine, and Steroids in Sepsis
- To Describe the Design of the VICTAS study (Vitamin C, Thiamine and Steroids in Sepsis)

Patient JM

- 66 year old with CML- extra lymphatic involvement S/P ABMT 60 days prior to admission

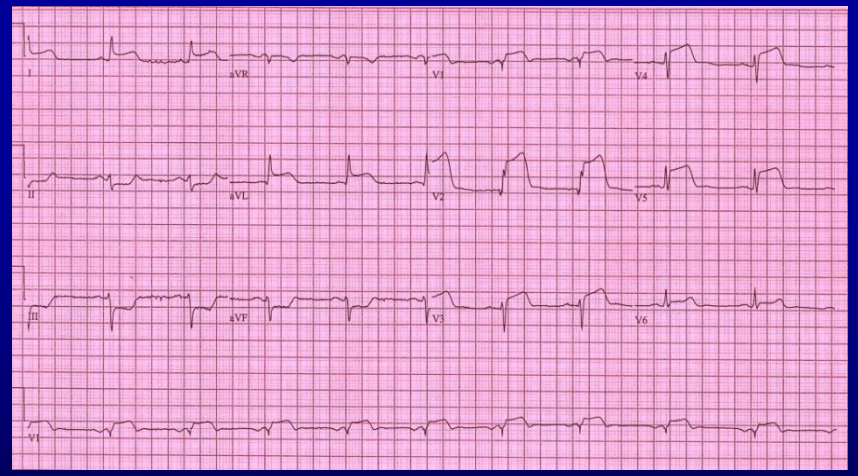
Infection

  - Admitted with GVHD with GI symptoms
  - Noted to have tachypnea to 30's B/P 90/55 pulse 108 T 38.5 wbc 1.2 lactate 4
  - Blood cultures oxidase positive gram negative rods
  - Started on ceftazidime
  - Transferred to ICU when required non-rebreather

Organ failure

Sepsis is a Medical Emergency

Concept Highlighted by Manny Rivers



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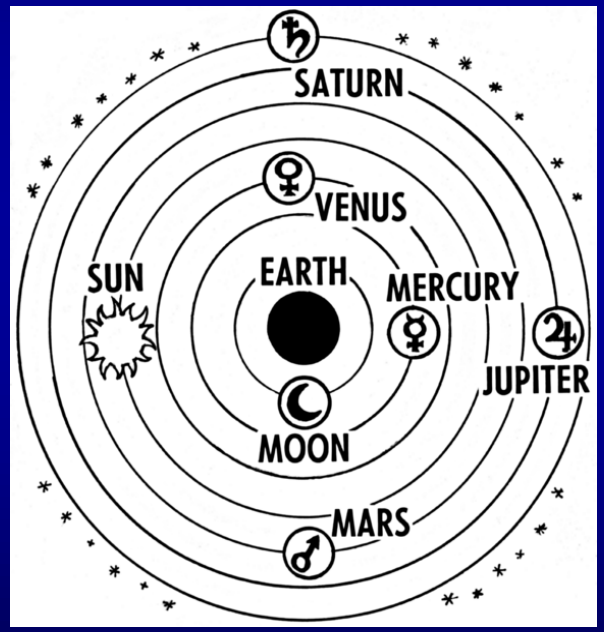
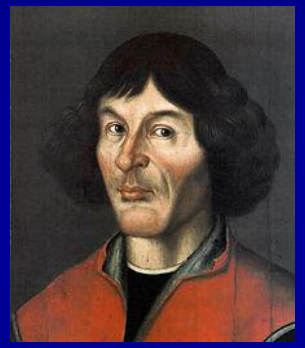
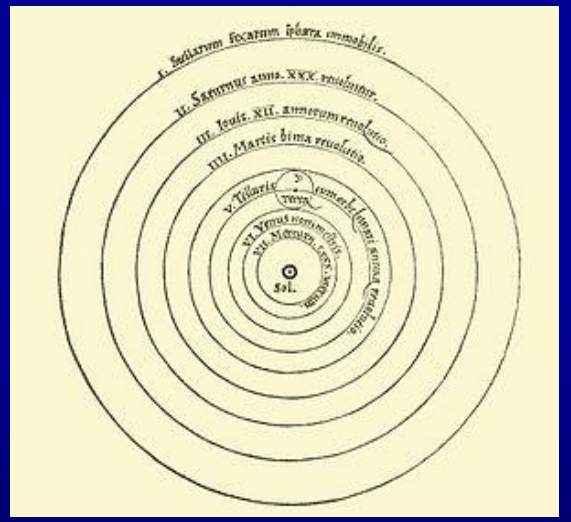
Proper Orientation is Important

Sepsis Care Must Center Around the Patient



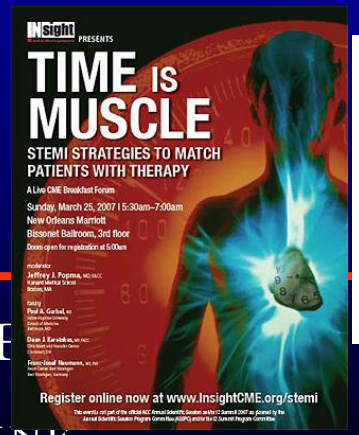


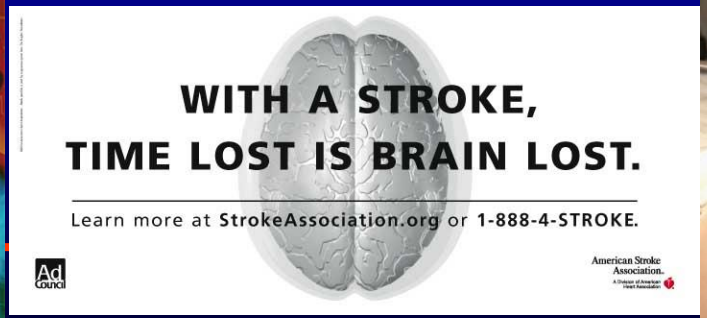


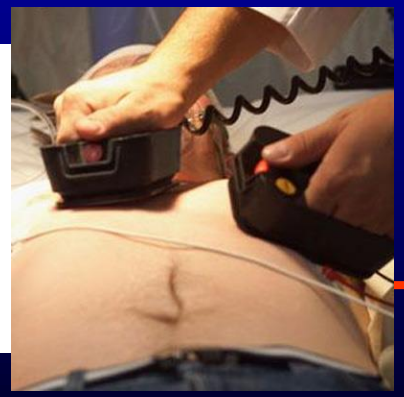
Sepsis is a Medical Emergency

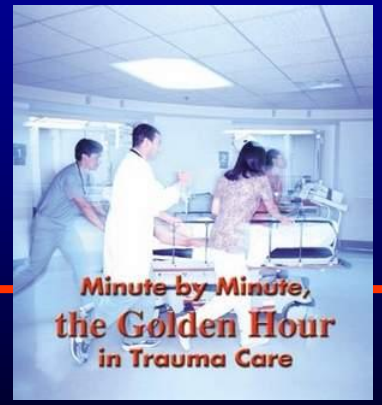
- Treatment

- Similar conditions









Sepsis is…

- Life-threatening organ dysfunction caused by a dysregulated host response to infection[1]
- **Common:** 0.9-3 million cases/yr[2, 3]
- **Life-threatening**: 15-30% mortality[2]
- **Time-sensitive:** 8% mortality increase for every hour delay in initiation of antibiotics[4]
- **A major public health concern:** most expensive reason for US hospitalization[5,6]

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1. Singer et al. JAMA 2016
2. Angus et al. CCM 2013
3. Martin et al. NEJM 2003
4. Kumar et al. CCM 2006
5. Elixhauser et al. AHRQ Report 2011
6. Torio and Andrews. AHRQ Report 2013

Sepsis is a Syndrome

- Disease

- Known Biomarker
- Diagnostic Test that enables identification

- Syndrome

- Constellation of signs and syndromes that lead to diagnosis

Sepsis Diagnosis- Not Always Simple

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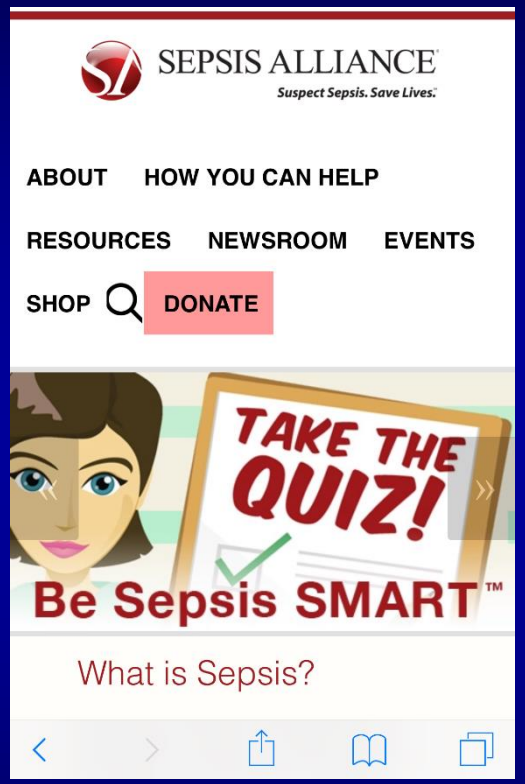
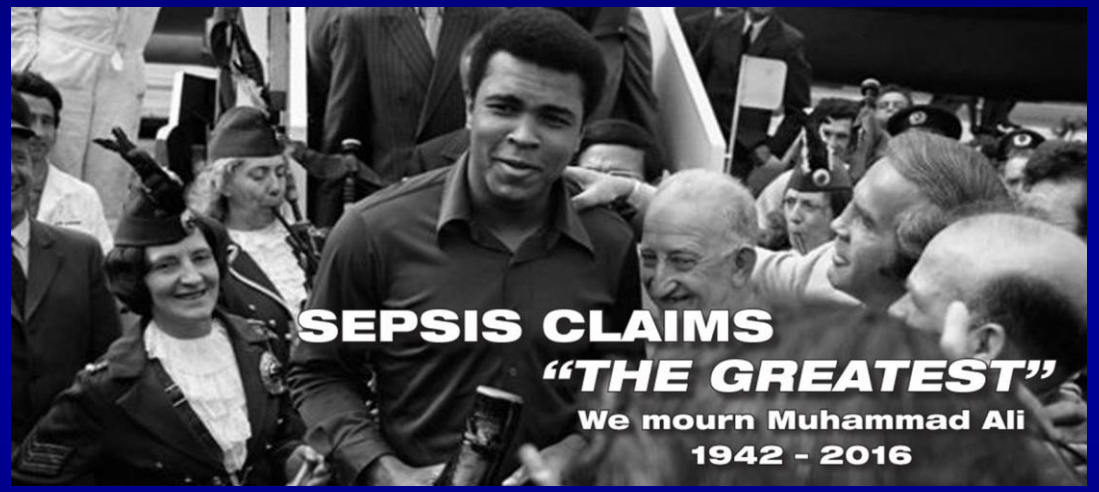
Partnering with Patients and Advocacy Groups



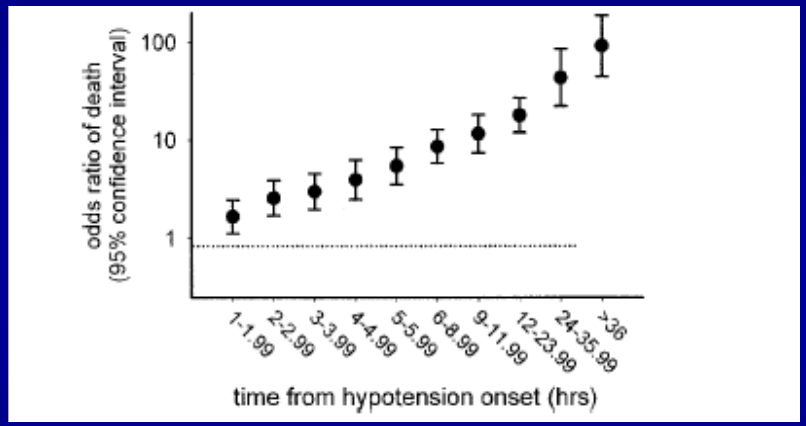


What is in the Sepsis Treatment Toolbox ?

- Early Recognition of Sepsis
- Early Antibiotics and Fluids
- Performance Improvement Projects

Timing of Antibiotics in Sepsis Induced Hypotension

- 2731 Patients with septic shock
- 44% Admissions From ED
  - Lung, Intra-abdominal and Urine most common sites of infection
- Mortality Rate 21% if Effective Antibiotics given within 1 hour
- Mortality Rate 58% if Effective Antibiotics given within 6 hours



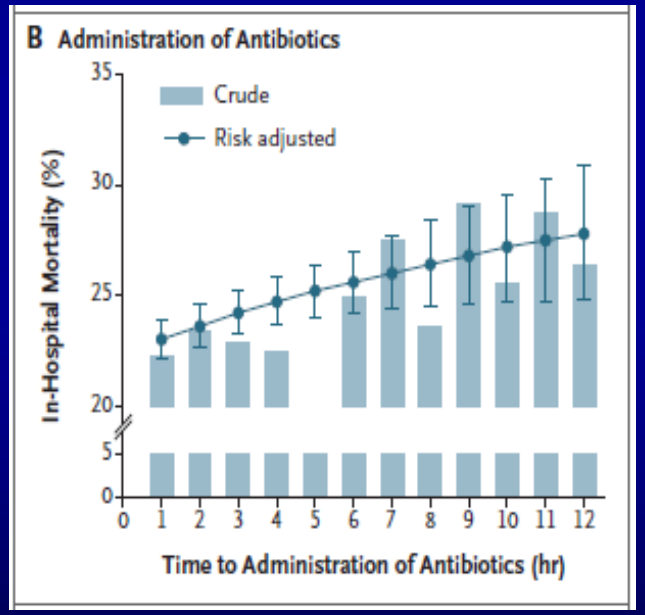
Kumar et al Crit Care Med 2006;34:1589-1596

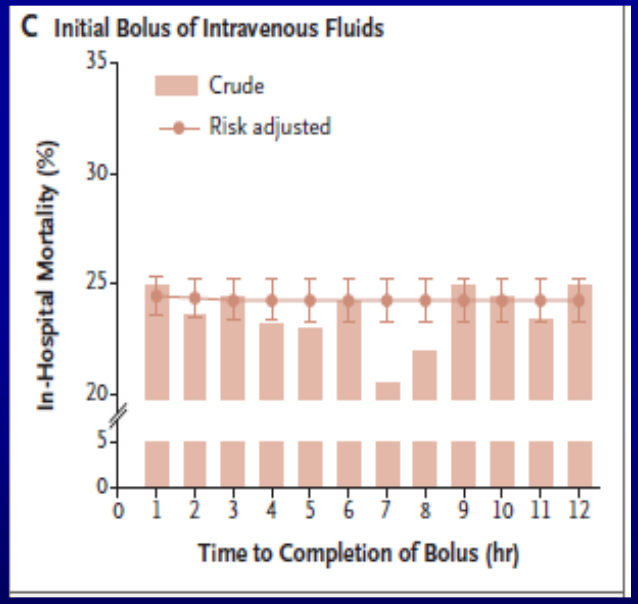
Following Sepsis Guidelines Helps Patients

Not every patient gets treatment consistent with guidelines

Timeliness of Antibiotics associated with mortality

Timeliness of Fluids Not associated with mortality





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New Engl J Med 2017;23;2335-44

Performance of Outcome Measurements: Did the Campaign Work?

Small Increase in Process Measures

Table 5. Impact of the Educational Program on Process-of-Care Measurement and Outcome Depending on Hospital Categorization According to Baseline Compliance With the Guidelines

Type of Measure	Preintervention Cohort	Postintervention Cohort	*P* Value
Category 1 hospitals (n = 20)			
No. of tasks completed, mean (SD) [95% CI]	3.25 (1.56) [3.0-3.4]	4.42 (1.97) [4.2-4.6]	<.001
Resuscitation bundle completed, No. (%) [95% CI]	1 (0.5) [0-1]	16 (4.7) [2-7]	.006
Management bundle completed, No. (%) [95% CI]	13 (6.4) [3-10]	36 (10.6) [7-14]	.10
Hospital mortality, No. (%) [95% CI]	98 (48.0) [41-55]	134 (39.3) [34-44]	.05
APACHE II, mean (SD) [95% CI]	20.6 (7.4) [19.6-21.6]	20.0 (7.3) [19.2-20.8]	.37
Category 2 hospitals (n = 19)			
No. of tasks completed, mean (SD) [95% CI]	4.65 (1.72) [4.46-4.85]	5.22 (1.98) [5.06-5.38]	<.001
Resuscitation bundle completed, No. (%) [95% CI]	11 (3.6) [2-6]	47 (7.8) [6-10]	.02
Management bundle completed, No. (%) [95% CI]	24 (7.9) [5-11]	67 (11.2) [9-14]	.13
Hospital mortality, No. (%) [95% CI]	135 (44.7) [39-50]	245 (40.9) [37-45]	.28
APACHE II, mean (SD) [95% CI]	20.7 (7.3) [19.8-21.6]	21.8 (8.1) [20.9-22.0]	.07
Category 3 hospitals (n = 20)			
No. of tasks completed, mean (SD) [95% CI]	5.90 (1.92) [5.70-6.11]	6.45 (2.00) [6.27-6.62]	<.001
Resuscitation bundle completed, No. (%) [95% CI]	33 (9.5) [6-13]	84 (16) [13-19]	.006
Management bundle completed, No. (%) [95% CI]	56 (16.1) [12-20]	127 (24.2) [21-28]	.004
Hospital mortality, No. (%) [95% CI]	143 (41.1) [36-46]	201 (38.3) [34-42]	.41
APACHE II, mean (SD) [95% CI]	21.5 (7.3) [20.7-22.3]	21.6 (7.7) [21.0-22.0]	.87

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; CI, confidence interval.

Decreased Mortality Rate

Table 3. Performance of Outcome Measurements

	Preintervention Cohort (n = 854)	Postintervention Cohort (n = 1465)	*P* Value
Mortality, No. (%) [95% CI]			
Hospital	376 (44.0) [41-47]	580 (39.7) [37-42]	.04
28-d	311 (36.4) [33-40]	456 (31.1) [29-33]	.009
ICU	315 (36.9) [34-40]	474 (32.4) [30-35]	.03
Hospital stay, d[a]			
Mean (SD) [95% CI]	28.7 (23.4) [26.6-30.8]	30.7 (25.7) [29.0-32.4]	.16
Median (IQR)	20.9 (13.5-35.7)	22.8 (13.3-41.4)	.25
ICU stay, d[a]			
Mean (SD) [95% CI]	13.4 (16.0) [11.9-14.0]	13.6 (16.3) [12.5-14.7]	.87
Median (IQR)	7.6 (4.5-15.0)	7.7 (4.0-15.9)	.83

Abbreviations: CI, confidence interval; ICU, intensive care unit; IQR, interquartile range.
[a] Deaths are excluded.

Ferrer, R. et al. JAMA 2008;299:2294-2303.

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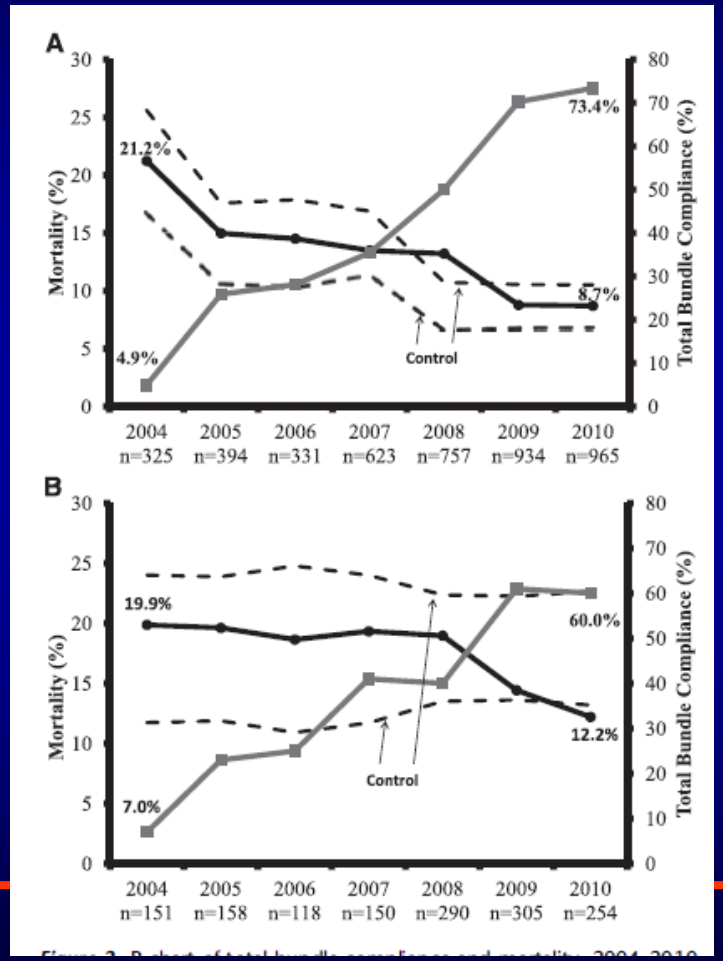
Multicenter Implementation of a Severe Sepsis and Septic Shock Treatment Bundle



- Increasing Compliance with Sepsis Bundle is Associated with Decreasing Patient Mortality
- Compliance with early bundles was associated with decreased need for later intervention
- Lung protective Mechanical Ventilation, inotropes, and steroids were interventions independently associated with mortality

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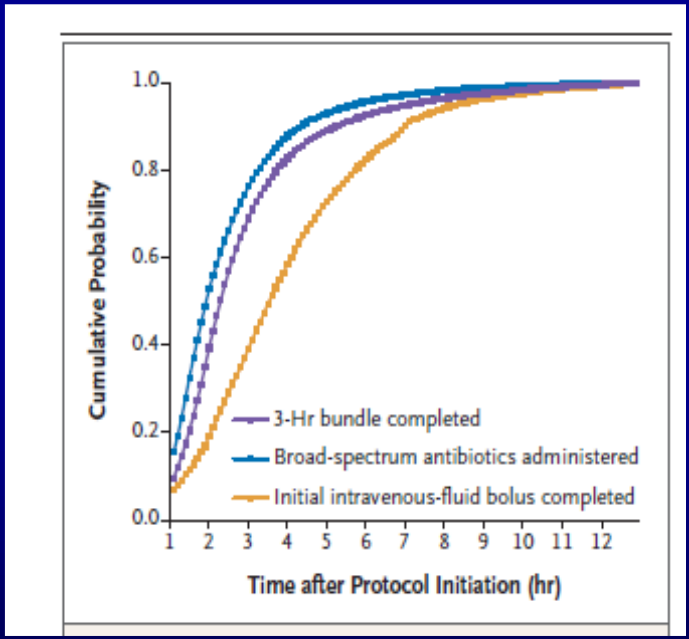
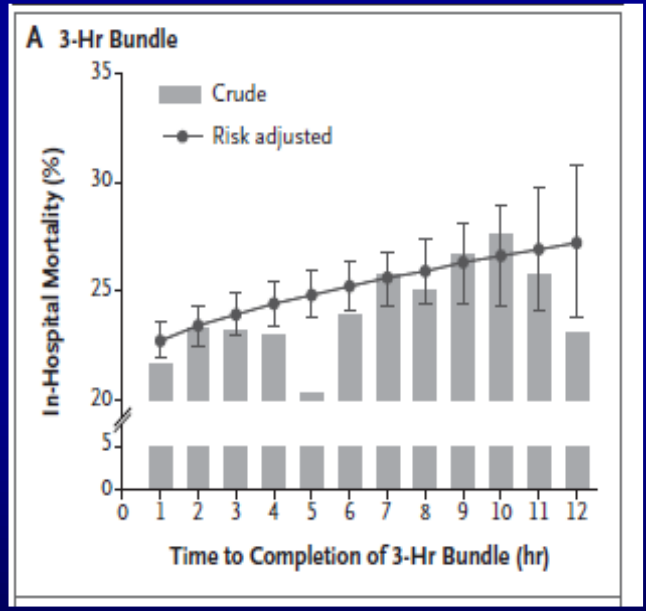
Am J Resp Crit Care Med 2013:188:77-82

Following Sepsis Guidelines Helps Patients

Not all sepsis patients get desired treatment



Time to Completion of 3 hour bundle associated with in hospital mortality



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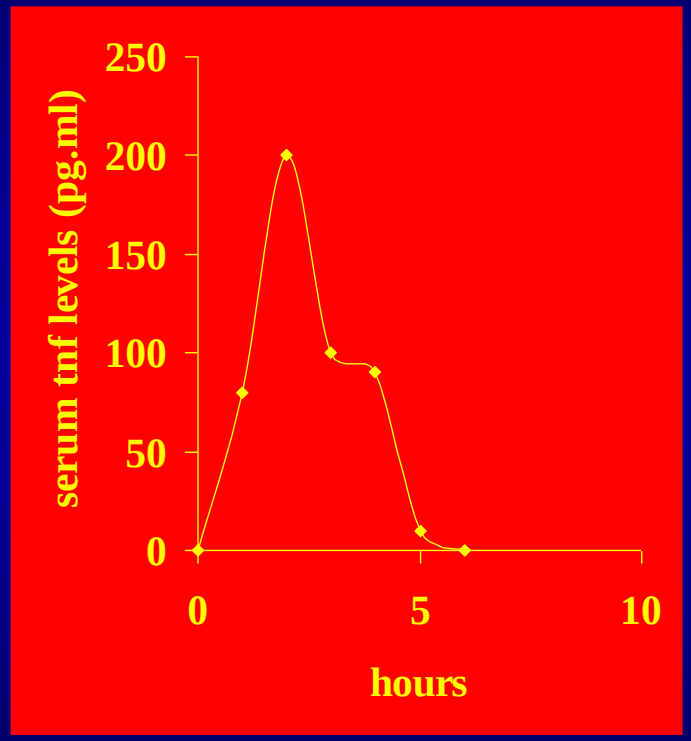
New Engl J Med 2017;23;2335-44

7.5 year Evaluation of a PI project on Sepsis (SSC)

Model	Risk factors[a]	OR (95% CI)	*p*
1. Continuous compliance, either resuscitation or management bundle, as a site-level variable and measured in last 2 quarters of site's SSC participation	For every additional quarter of site participation	0.96 (0.95–0.97)	< 0.001
	10% increase in resuscitation compliance	0.95 (0.94–0.97)	< 0.001
	10% increase in management compliance	0.97 (0.96–0.98)	< 0.001
2. Compliance as a patient-level variable and measuring whether patient's ICU visit was compliant with resuscitation or with management bundle	For every additional quarter of site participation	0.97 (0.96–0.98)	< 0.001
	Resuscitation compliance, yes vs. no	0.82 (0.76–0.88)	< 0.001
	Management compliance, yes vs. no	0.76 (0.71–0.81)	< 0.001

Resuscitation Compliance includes among other things 30 cc/kg /IVF

Serum Tumor Necrosis Factor Levels After Endotoxin Challenge



- Monoclonal antibodies to TNF given to animals challenged with endotoxin
  - reverse hemodynamic embarrassment
  - improve mortality

Tracey et. al Science 1987;330:662-4

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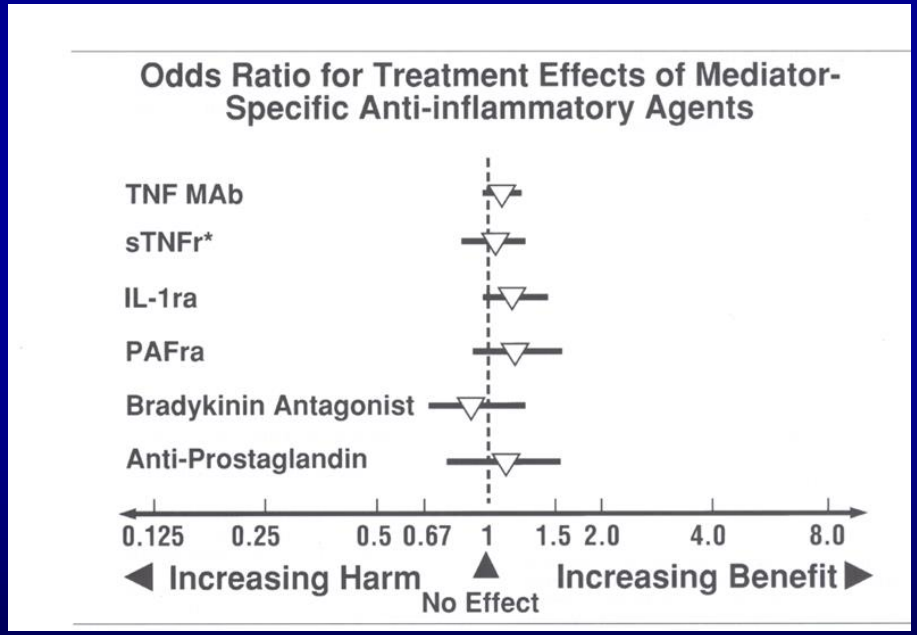
Clinical Sepsis Trials of Monoclonal Antibodies Directed Against TNF

Table 1. Clinical trials of anti-TNF MAb

Therapy (Company) [Reference]	Study design	Inclusion criteria	Control arm deaths/Total (%)	Treatment arm deaths/Total (%)
MAK 195F (Knoll) [12]	Open-label, phase II	Severe sepsis or septic shock (69%)[a]	12/29 (41%)	44/93 (47%)
MAK 195F (Knoll) [13]	Open-label, phase II	Severe sepsis or septic shock	6/12 (50%)	7/27[c] (26%)
MAK 195F (Knoll) [3]	Double-blind, phase III	Sepsis and high IL-6 levels	125/221 (57%)	121/225 (54%)
CDP571 (Celltech) [14]	Open-label, phase II	Septic shock (100%)[a]	6/10 (60%)	20/32[c] (63%)
CB006 (Celltech)[b] [15]	Open-label, phase II	Severe sepsis or septic shock	6/19 (32%)	27/61[c] (44%)
BAYx1351 (Bayer/Miles) [16]	Double-blind, phase III	Severe sepsis or septic shock (49%)[a]	108/326 (33%)	196/645[c] (30%)
BAYx1351 (Bayer/Miles) [17]	Double-blind, phase III	Severe sepsis or septic shock (80%)[a]	66/167 (40%)	144/386[c] (37%)
BAYx1351 (Bayer/Miles) [18]	Double-blind, phase III	Septic shock (100%)[a]	398/930 (43%)	382/948 (40%)
cA2 (Centacor) [19]	Double-blind, phase II	Severe sepsis	11/28 (39%)	10/28 (36%)
Total			738/1742 (42%)	951/2445 (39%)

Treatment Directed at Modulating Inflammation: Not Effective



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Sevransky and Natanson Sepsis 1999:3:11-19

Clinical Sepsis Trials That Did Not Show Beneficial Treatment Effect

Albumin Replacement in Patients

Goal-Directed Resuscitation for Patients

High versus Low Blood-Pressure Target

Early, Goal-Directed Therapy for Septic Shock

Lower versus Higher Hemoglobin Threshold for Transfusion

Hydrocortisone Therapy for Patients with Septic Shock

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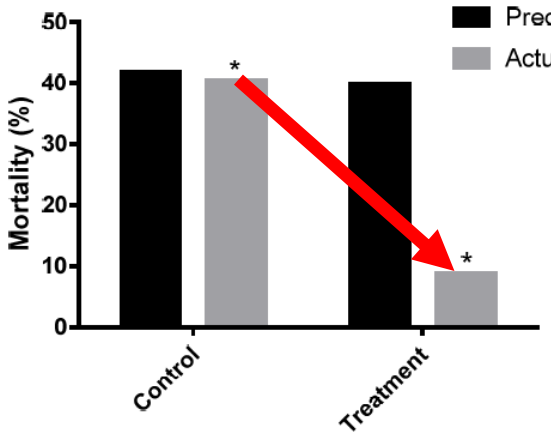
Triple Therapy for Sepsis

Original Research

Hydrocortisone, Vitamin C and Thiamine for the Treatment of Severe Sepsis and Septic Shock: A Retrospective Before-After Study

Paul E. Marik, MD, FCCM, FCCP[1], Vikramjit Khangoora, MD[1], Racquel Rivera, Pharm D[2], Michael H. Hooper, M.D., MSc[1], John Catravas, PhD, FAHA, FCCP[3,4]



CHEST (2017), doi: 10.1016/j.chest.2016.11.036

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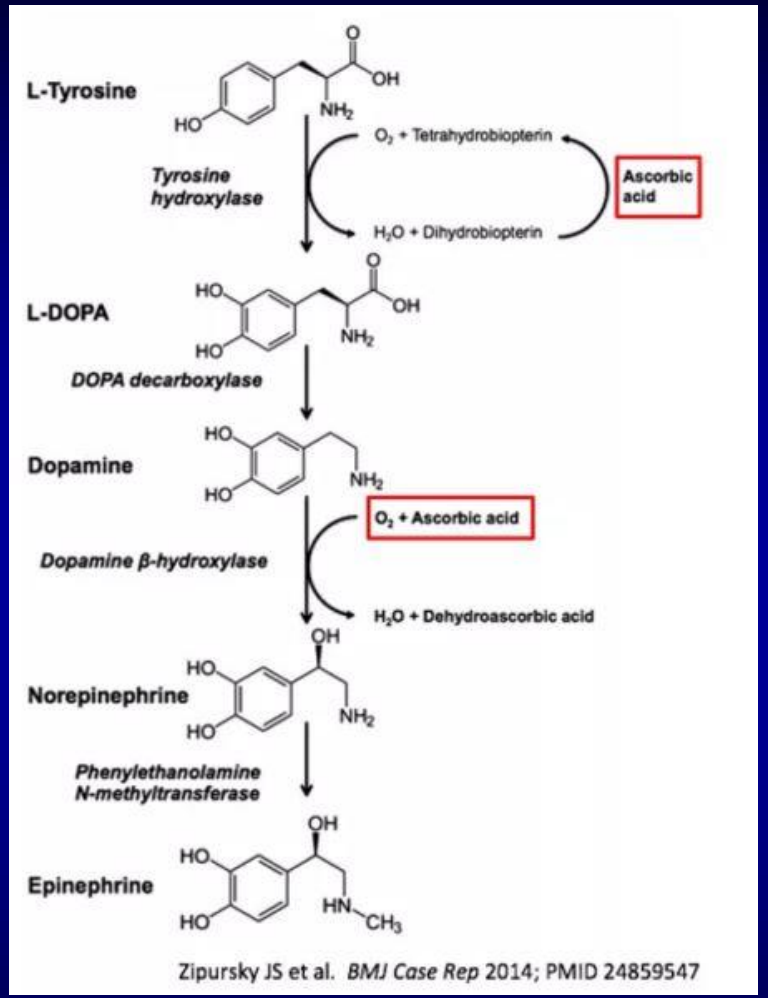
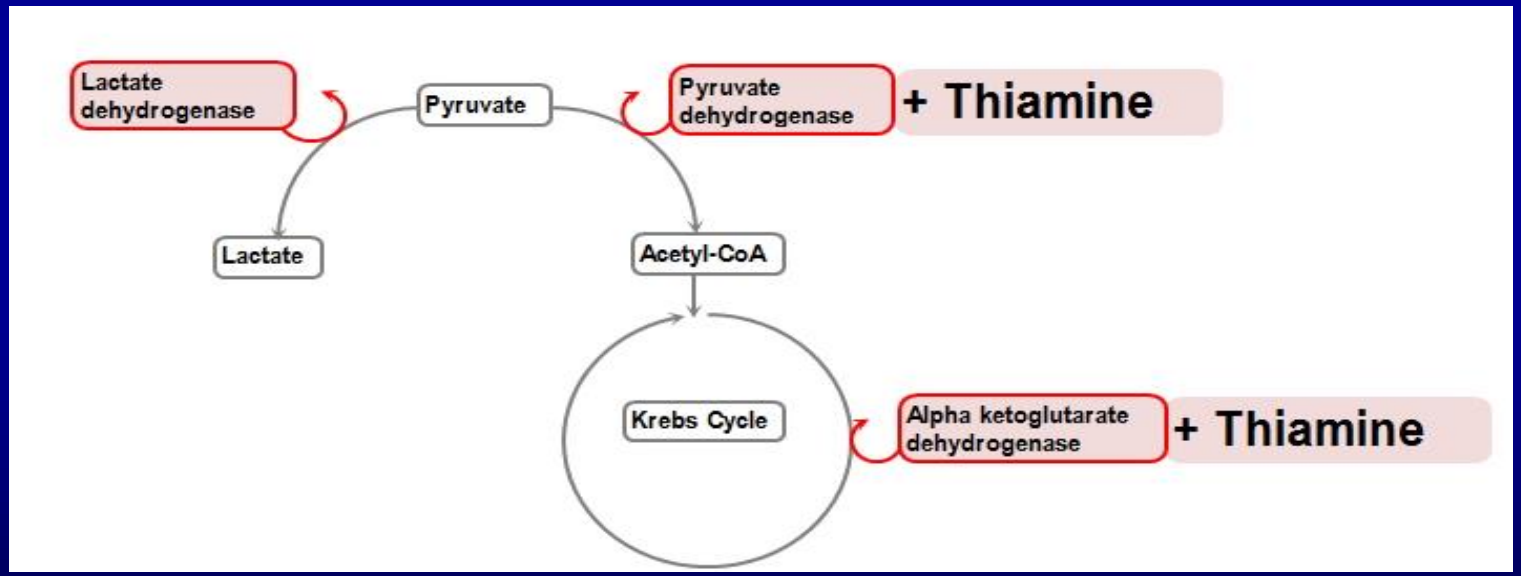
Biologic Rationale Vitamin C in Sepsis

- Antioxidant and enzyme co-factor
  - Activates Nrf2
  - Restores cellular antioxidants
  - Catecholamines
- Anti-inflammatory
  - ↓ NF-κB
- Necessary for tight junctions and microcirculatory flow

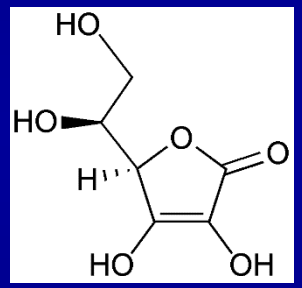


Thiamine

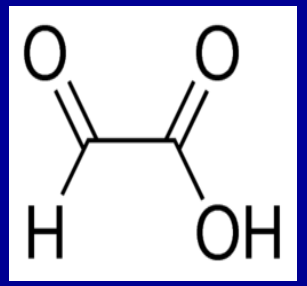
- Essential for aerobic metabolism:
  - Pyruvate dehydrogenase
  - Alpha ketoglutarate dehydrogenase



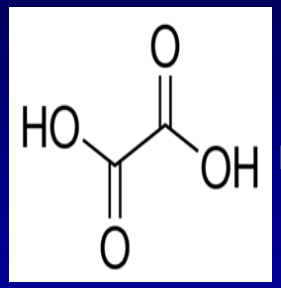
Thiamine and Vitamin C



Vitamin C

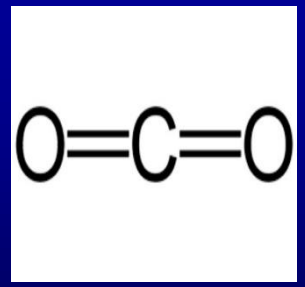


Glyoxalic acid



Oxalic Acid

Thiamine



Carbon Dioxi

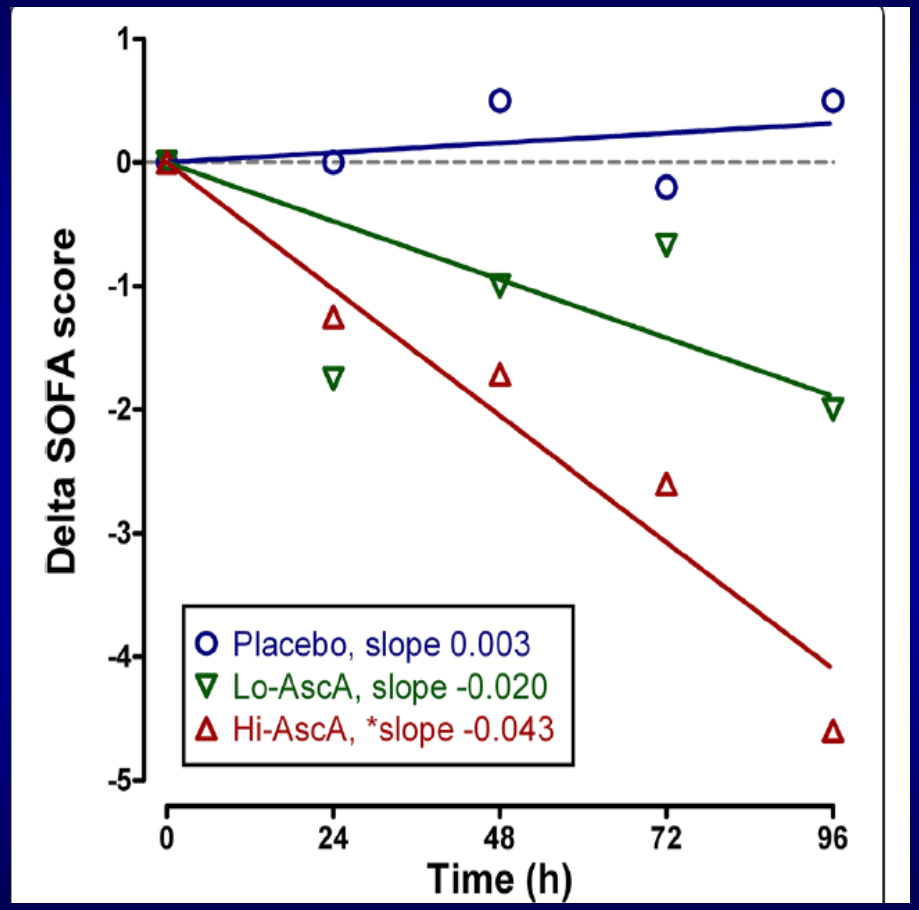
Phase I Study of Vitamin C in Sepsis

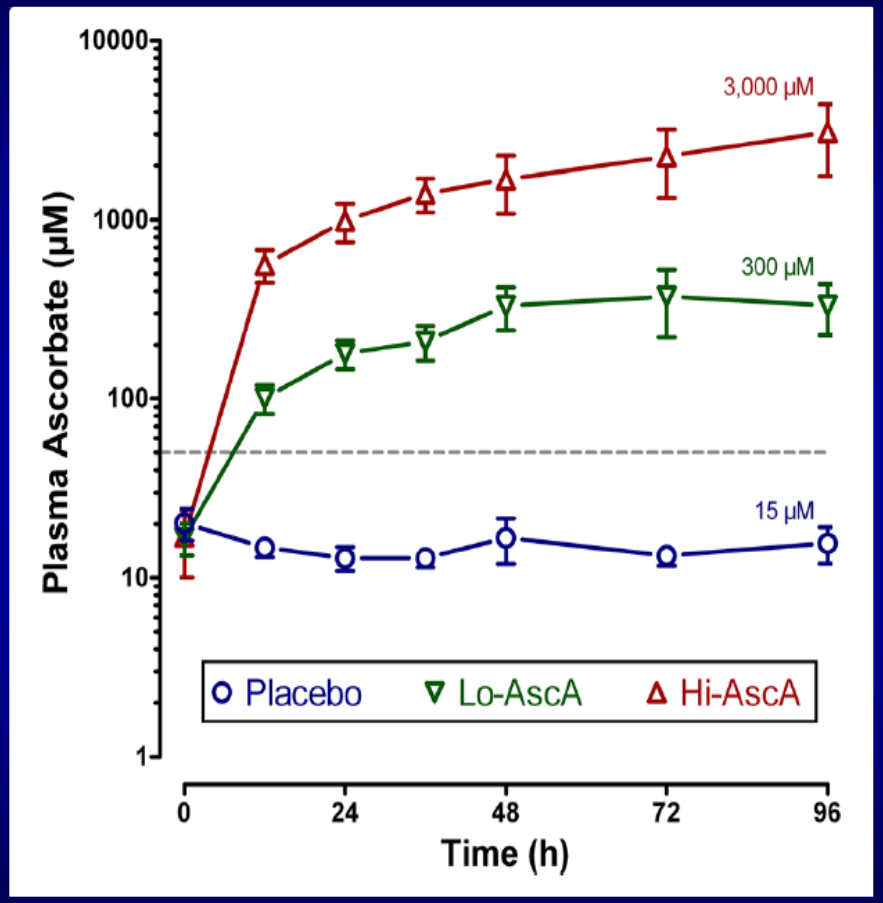
- Patients- 26 Patients with severe sepsis (1.0) at VCU randomized 1:1:1
- Intervention Vitamin C 50 mg/kg/day in divided doses every 6 hours for 96 hours
- Or
- Vitamin C 200 mg/kg/day in divided doses every 6 hours for 96 hours

- Comparator Placebo

- Outcome measure- Sequential Organ Failure Assessment (SOFA scores) and Vitamin C Levels

Phase I Study of Vitamin C in Sepsis





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Journal of Translational Medicine 2014, 12:32

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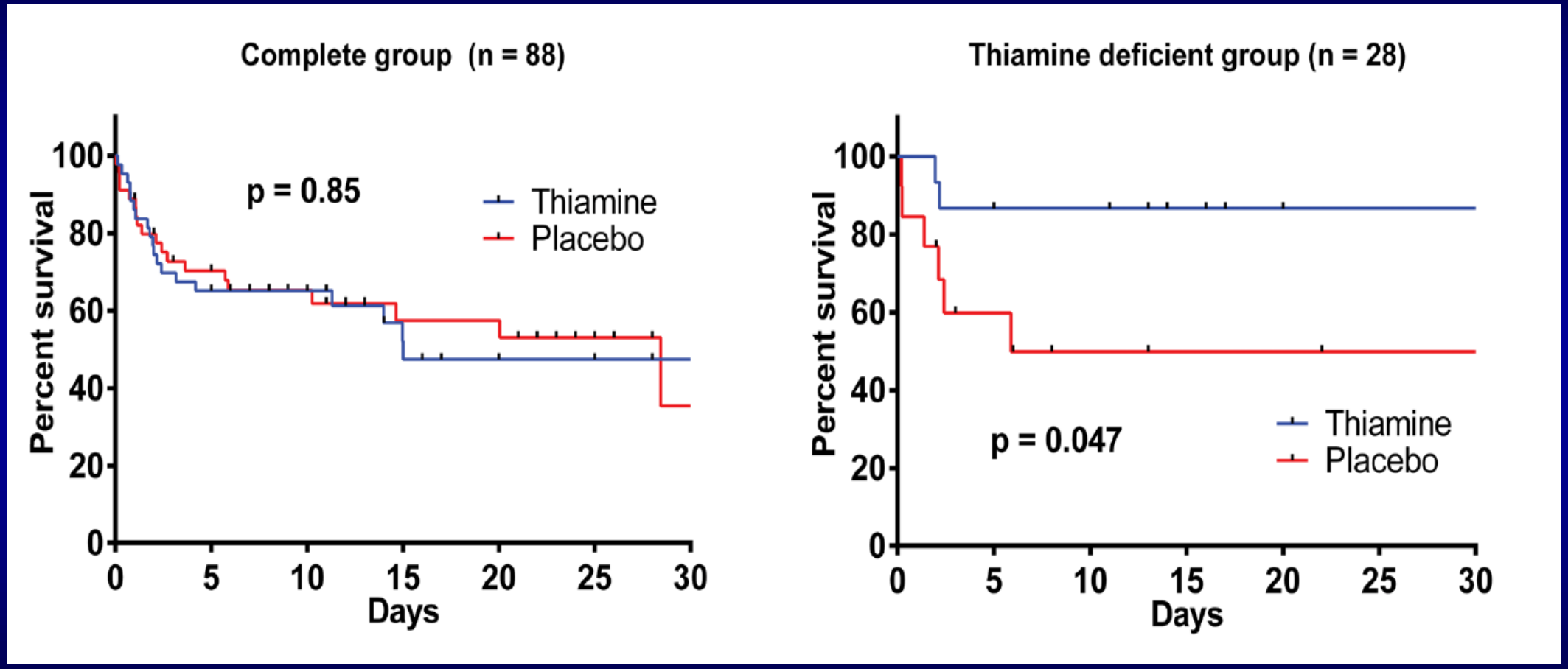
Thiamine in Sepsis

- Patients- Adult patients with septic shock and elevated (> 3 mmol/L) lactate between 2010 and 2014 at 2 hospitals
- Intervention —Thiamine 200 mg twice daily for 7 days or until hospital discharge.
- Comparator- Placebo treated patients
- Outcome Lactate level 24 hours after first study dose

Crit Care Med. 2016 February ; 44(2): 360–367.

Thiamine in Sepsis



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Original Research

Hydrocortisone, Vitamin C and Thiamine for the Treatment of Severe Sepsis and Septic Shock: A Retrospective Before-After Study

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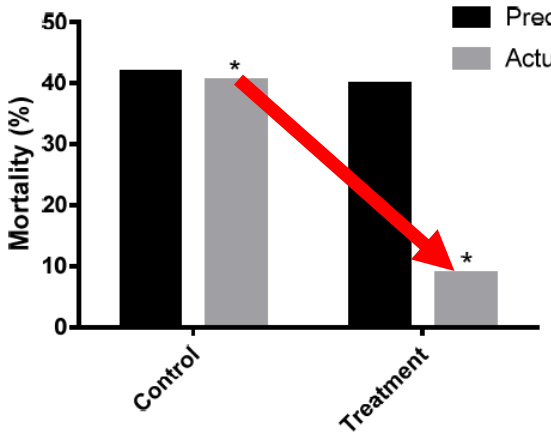

CHEST (2017), doi: 10.1016/j.chest.2016.11.036

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Rationale for Marik study

- Preliminary data
- Patients with sepsis have low serum levels of Vitamin C
- Patients with sepsis have low serum levels of thiamine
- Small studies have shown feasible to give supplemental Vitamin C and thiamine without obvious harm
- Potential synergistic effect of steroids and Vitamin C

Before-After Study

- Patients – 47 consecutive patients admitted to the ICU at Sentara Norfolk General Hospital with a primary diagnosis of severe sepsis or septic shock and a procalcitonin $\geq$ 2ng/ml
- Intervention: intravenous vitamin C (1.5 gm q 6 hourly for 4 days or until ICU discharge), hydrocortisone (50 mg q 6 hourly for 7 days or until ICU discharge followed by a taper over 3 days), intravenous thiamine (200 mg q 12 hourly for 4 days or until ICU discharge).
- Comparator Patients with severe sepsis and septic shock with procalcitonin $\geq$ 2ng/ml treated during previous year without vitamin C or thiamine, but who could receive hydrocortisone per physicians orders
- Outcome Measure Hospital Survival

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Additional analysis

- Propensity score:
  - Probability (0-1) of receiving treatment based on covariates

- Logistic regression for OR mortality
  1. Propensity score
  2. Propensity score + age

Covariates
Age
Weight
Gender
APACHE IV Score
Mechanical Ventilation
Vasopressors
WBC
Lactate
Procalcitonin
Serum Creatinine

Before-After Study

	Treated (n=47)	Control (n=47)
Age	58.3 ± 4.1	62.2 ± 14.3
Sex (male)	27 (57%)	23 (49%)
Comorbidities		
None	2 (4%)	1 (2%)
Diabetes	16 (34%)	20 (42%)
Hypertension	20 (43%)	25 (53%)
Heart Failure	15 (32%)	16 (34%)
Malignancy	5 (11%)	7 (15%)
COPD	8 (17%)	7 (15%)
Cirrhosis	6 (13%)	3 (6%)
CVA	8 (17%)	5 (11%)
CRF	7 (15%)	8 (17%)
Morbid Obesity	6 (13%)	8 (17%)
Immunocompromised	6 (13%)	4 (9%)
Drug addiction	5 (11%)	5 (11%)

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Study Limitations

Single Center before and after study

Complex intervention

Steroids used in comparator arm

Little information about contemporaneous therapies (antibiotics, fluids etc)

Confirmation bias

Large effect size

CHEST (2017), doi: 10.1016/j.chest.2016.11.036

Highly Polarizing Results

- A significant number of professionals immediately began prescribing this as a cure for sepsis
- A significant number of professionals criticized the study very vociferously
- Much of this discussion has been high-level intellectual discourse
- Some of it has not been

Pneumococcal Bacteremia with Especial Reference to Bacteremic Pneumococcal Pneumonia

ROBERT AUSTRIAN, M.D., and JEROME GOLD, M.D.

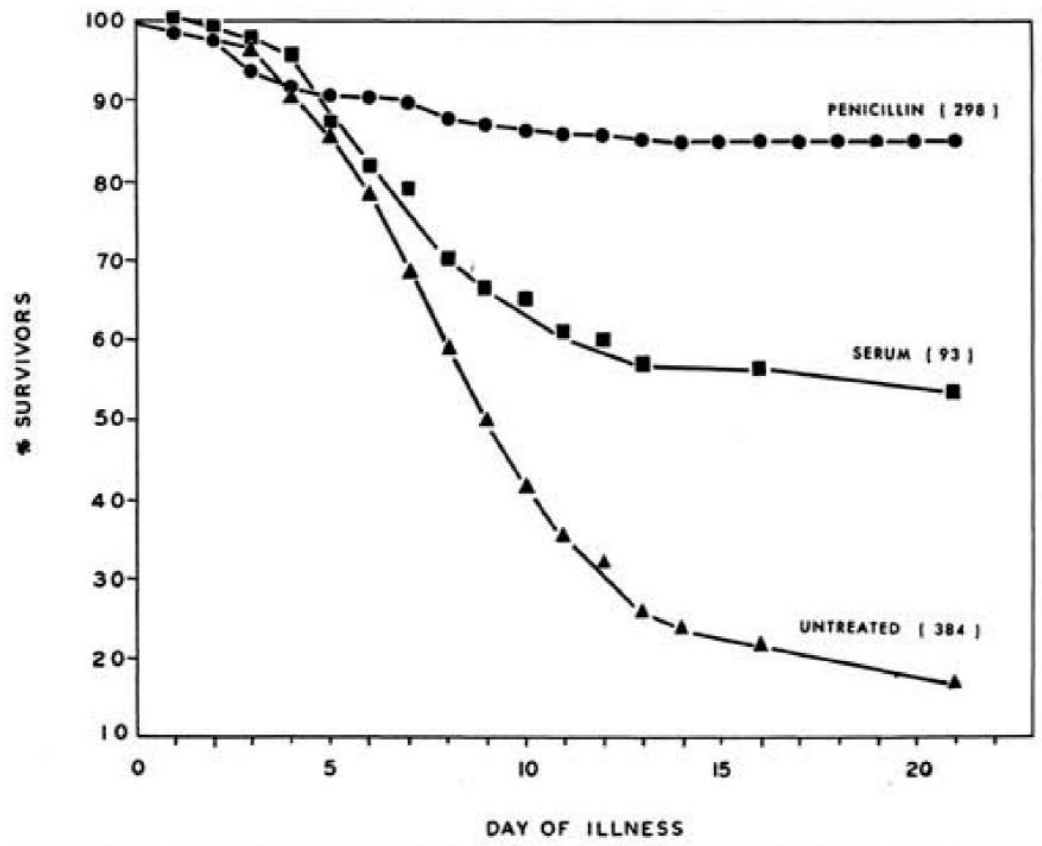

FIGURE 6. Numbers in parentheses indicate size of each group of patients. Data for untreated and serum-treated patients (capsular Types I and II only) from Tilghman and Finland (1).

Ann Int Med 1964:759-776

38% ARR

27% ARR

Single Vs Multicenter Trials

Phase II Single Center Trials

- Test potential novel therapies
- Show potential risks and benefits
- Easier to do/Cheaper
- May change practice at one site or with some physicians
- May have large treatment effects

Phase III Multicenter Trials

- Test Potential new therapies
- Show potential risks and benefits
- Harder to do/More expensive
- The gold standard for changing clinical practice
- Usually with smaller treatment effects

Why We Need a Clinical Trial

Vitamin C Is Not Ready for Prime Time in Sepsis but a Solution Is Close

To the Editor:

We read with interest the report by Marik et al[1] published in *CHEST* (June 2017). However, the study lacked blinding, randomization, concurrent control subjects, and case-control propensity matching; it also had a small sample size, thus substantially increasing the risk of false benefits due to confounding combined with selection and ascertainment biases. Many

resolution in an even shorter time.[5] Considering this poor evidence on the safety and efficacy of vitamin C and how swiftly an adaptive RCT can be done, we believe that there is no ethical or scientific justification to use vitamin C outside of a clinical trial at this time.

DOI: http://dx.doi.org/10.1016/j.chest.2017.05.025

Why We Need a Clinical Trial

Viewpoint 1

- To my knowledge, we have had zero patients treated at Vanderbilt. But Jon, you should emphasize this does not reflect any lack of enthusiasm for conducting a proper study, it reflects Vanderbilt's long-standing conservatism regarding "new" or "exciting" therapies, i.e., we believe it is proper to wait until there is sufficient high quality data to begin routinely using these treatments on everyday patients.
- Gordon Bernard MD

Viewpoint 2

- "It might help- that's why I used it"

- I'm on service right now and thought I'd relay an event that occurred simultaneous to the foundation presentation. We have a patient who was found down and seems to have acute on chronic liver disease with septic shock, AKI, DIC and ARDS. She was given thiamine because of the alcoholism and steroids because of refractory shock (vasopressin and 50+ mcg of norepinephrine). Because she was doing poorly despite a couple of days of maximal therapy the resident (all credit due) decided to add Vitamin C to the steroids and thiamine already being given. Within 24 hours her vasopressin was turned off and her norepinephrine was 2-5mcg. In full disclosure she also got NAC and albumin because of liver disease and possible HRS, but still!

What Kind of Evidence Should Change Practice ?

1- Single Physician and Single Patient

2- Single Institution

3- Most Patients

4- Treatment Guidelines

- Clinical Experience, Literature
- Clinician Agreement + Data Showing that Practice Change Works in that Institution
- > 1 RCT in a similar patient population
- >1 RCT in similar patient population + evaluation of quality of RCT + cost and downside of intervention

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Phase III Multicenter Trials Change Practice

An Analogy For Multicenter vs. Single Center Trials

New York Knicks vs Cleveland Cavaliers Oct 30th 2017 NY 114 –Cleveland 95

- A multicenter trial is more likely to be reproduced than is a single center trial, just as a 7 or 82 game series is more likely to give the same result if repeated.

Trial Design- What Patient Population to Pick

Critically Ill Patients:

Mortality Endpoint

- More likely to immediately change practice
- Simpler Enrollment Criteria

- Fewer patients
- More sites required
- May take longer to complete

Very Sick but Not Yet Critical:

Rates & Speed of Improvement Endpoint

- Preventing progression to Critically Ill-

-May be appealing to Patients

- Applies to More Patients

- More complicated enrollment criteria
- Could be less compelling for immediate practice change

Consider nested study including both populations

Design Considerations

- Patients- which patient population are your studying
- Intervention- What are You Giving
- Comparator- What Treatment does the non-intervention arm get
- Outcome – What is the primary outcome measure

Victas PICO Questions

- Patients- Up to 2000 Adult patients with confirmed or suspected infection and evidence of respiratory or cardiovascular organ dysfunction (e.g. adult sepsis)

- Intervention Intravenous vitamin C (1.5 grams every 6 hours), thiamine (100 mg every 6 hours), and hydrocortisone (50 mg every 6 hours), will be administered in divided doses each day for 4 days or until ICU discharge.

- Comparator Placebo (unless clinical team desires to give steroids)

- Outcome- Vasopressor and Ventilator Free Days
  - 30 day mortality

Inclusion Criteria

- Patients > 18 with confirmed or suspected infection and evidence of respiratory or cardiovascular organ dysfunction
- Confirmed or suspected infection :ordering of blood cultures and administration of at least one antimicrobial agent
- Respiratory Dysfunction
  - Positive pressure ventilation (invasive or non invasive)
  - High Flow Nasal Cannula (>=45 L >=45%%)
- Cardiovascular Dysfunction
  - Vasopressors

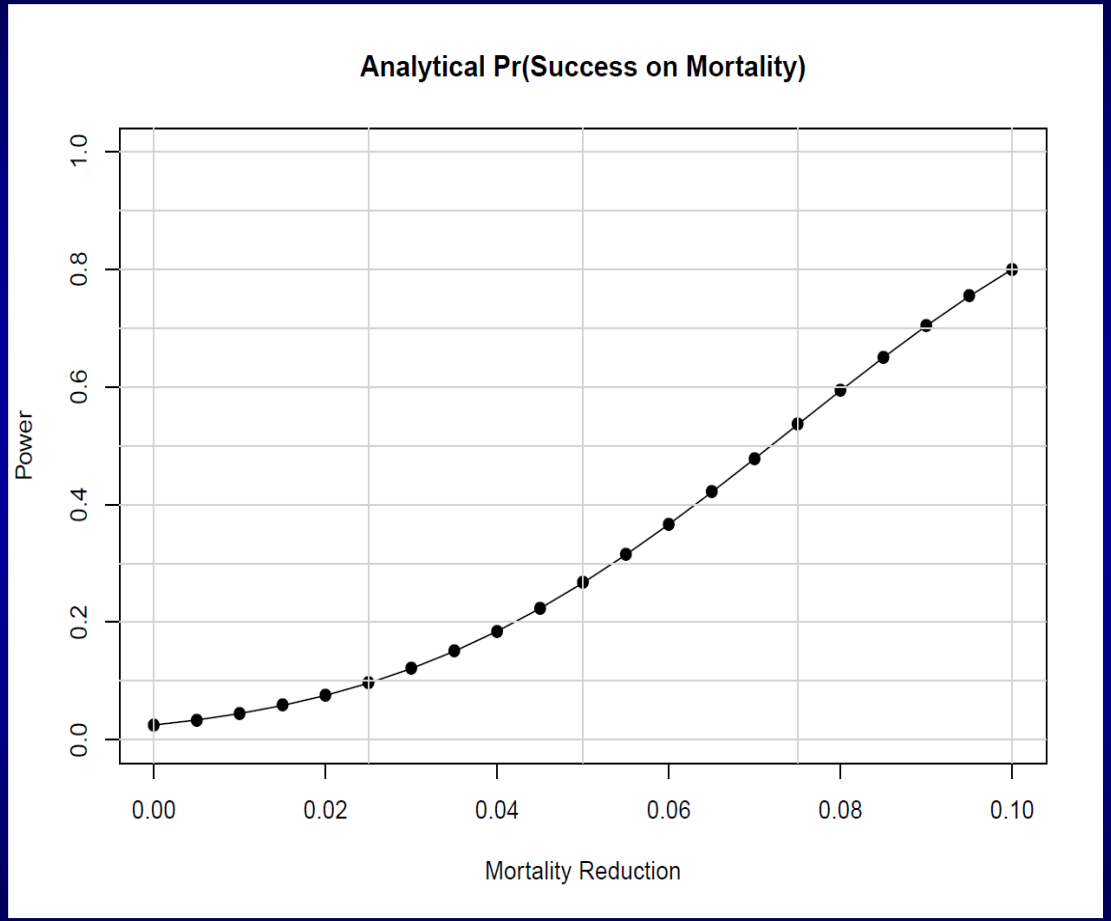
Exclusion Criteria

Designed to limit exclusions and make the study as pragmatic as possible

- Patients that are too ill from other causes in which the treatment is unlikely to fix the other problems (e.g., end stage cancer)
- Patients who refuse to participate
- Patients who are allergic to any of the treatments
- Patients with medical conditions that would make treatment higher risk (kidney stones, problems metabolizing calcium)
- Patients who are participating in another study

Sample Size

500 Patients- Simulation Data



If the Mortality Difference is 10% between groups, 500 patients would have 80% power to show it.

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Estimates of Patients Needed

According To Differences in Mortality Between Treatment Groups

Treatment Effect	Patients Needed to Show Treatment Effect	
32%	72	← Marik Manuscript Treatment Effect
20%	250	
10%	500	
5%	2000	

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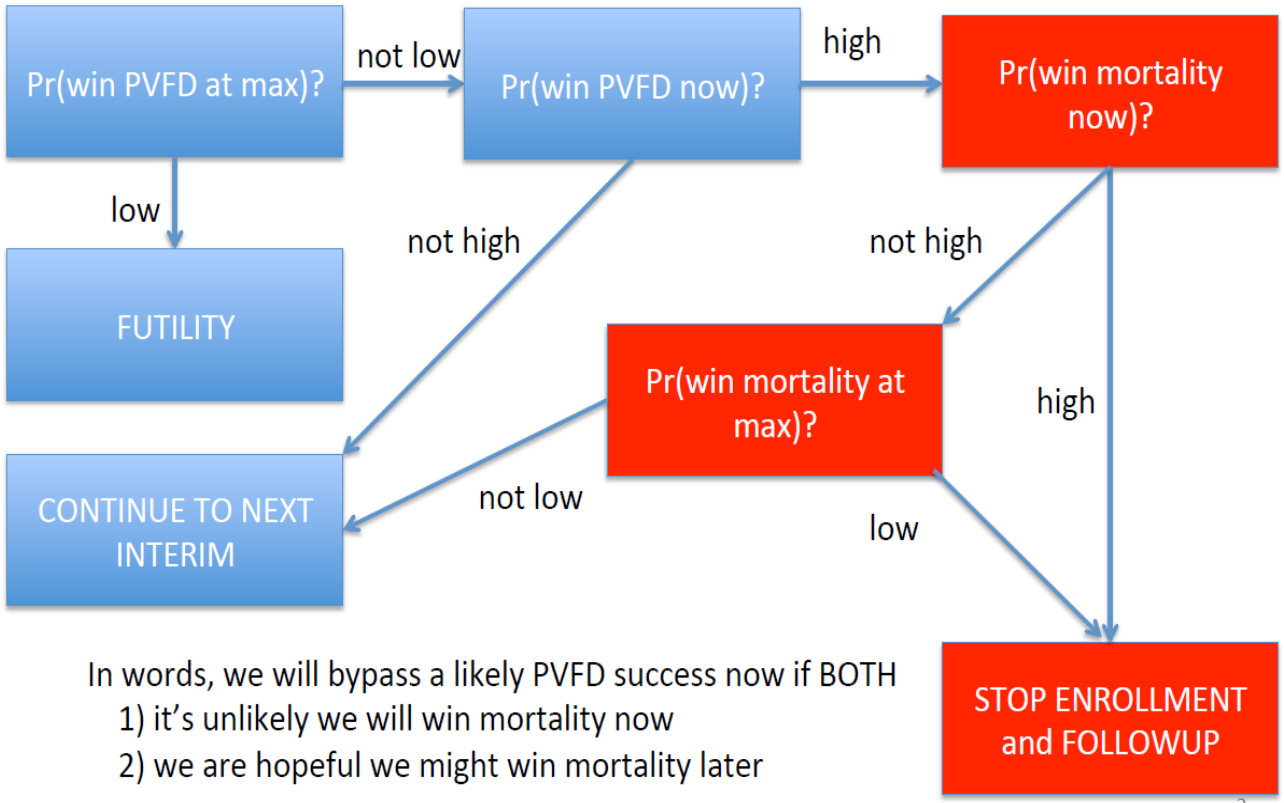
Estimates Dependent Upon Mortality Rates in Control Group

Interim Analysis Decision Tree ("bypass" Goldilocks)



In words, we will bypass a likely PVFD success now if BOTH
1) it's unlikely we will win mortality now
2) we are hopeful we might win mortality later

Pr=Probability
PFVD- vasopressor and ventilator free days (i.e alive and off vasopressors and ventilators)

Analytic Plan

- Final analysis will be done after all enrolled subjects are followed to Primary Endpoint
- For Vasopressor and Ventilator Free Days will use a Wilcoxon Rank Sum Test, using 1 sided alpha of 0.022 (to adjust to control Type I error rate at 0.025)
- In final analysis, patients who died are treated as though they had zero Ventilator and Vasopressor Free Days
- Managed with DCC, with assistance from Berry Consultants

VICTAS Trial Sites: 46 Enrolling Sites

Vitamin C, Thiamine and Steroid
VICTAS
A clinical trial evaluating the treatment of sepsis

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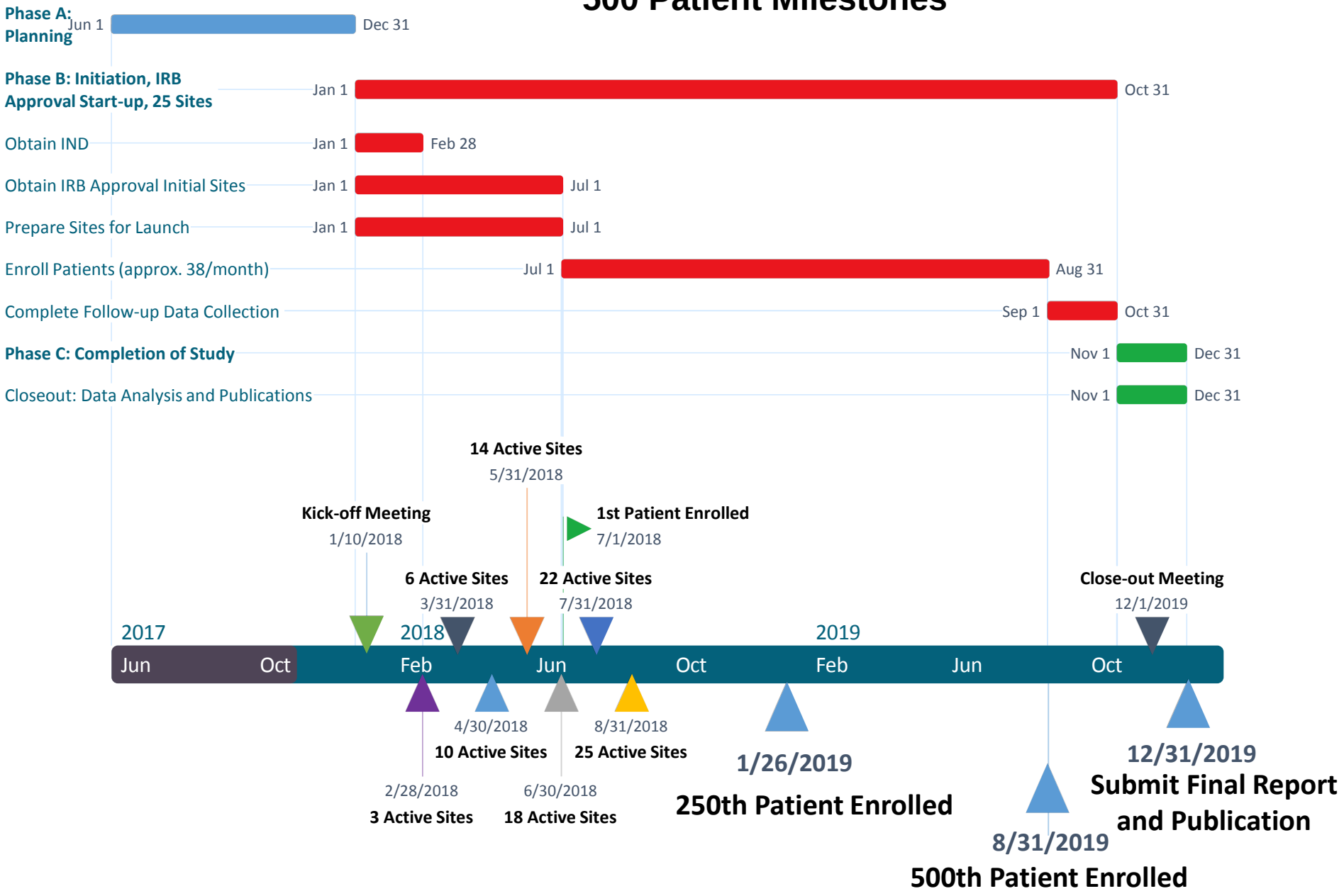
500 Patient Milestones



- Thank you

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