An Approach to the Initial Management of Sepsis

Welcome to this series of 3 presentations. Part 1 will look at the new sepsis definitions and clinical criteria and examine why we needed this change. I do not have any conflict of interest regarding the subject matter

GANESAN ABBU
BRANDON PRIMARY CARE CONFERENCE
MAY 2018

CONFLICT OF INTEREST DISCLOSURE

PreOPSYS

Manitoba Health

SMARTabx.ca

OBJECTIVES

Understand the new definitions of Sepsis and Septic Shock

Apply an appropriate Clinical Tool to aid the diagnosis

Consider the 3 most important initial Interventions

What image comes to mind when one says Sepsis? Is it as clearly appreciated as say meningitis or pneumonia. I appreciate that sepsis is more complex, but can we do better!

WHAT IS SEPSIS?

MOST IMPORTANT
MAKE THE DIAGNOSIS!

EXISTING DEFINITION

Lets examine the current definition that has been in use for the last 2 decades. Sepsis is documented or suspected infection with 2 or more SIRS criteria. These criteria are temperature, heart rate, respiratory rate and white blood cell count

UNCHANGED IN LAST 20YRS

Proven or
Presumed Infection
AND
2 or more SIRS Criteria

Temperature	<36c or > 38c
Heart Rate	>90bpm
Respiratory Rate	>20
WBC Count	<4 or > 11

THE CHALLENGE

1. The challenge facing the Sepsis 3.0 team was “ how can we improve the definition of sepsis so that it can satisfy multiple domains of usefulness- helpful for clinicians, researchers and policy makers.
2. Can we describe sepsis in a way that better describes our current understanding of sepsis.
3. Can we differentiate sepsis from uncomplicated infection
4. Can we separate the definition from clinical criteria?

How can we define sepsis so that we can…

1. We know that Infection is the initial trigger that sets in motion a self propagating cascade that drives the process
2. The host response is unlike the normal response to infection and involves both pro and anti-inflammatory cytokines.
3. This intense response eventually leads to organ dysfunction. Not uncommonly, organ dysfunction is the initial presentation and infection and sepsis is a delayed consideration.
4. The final result is an overall higher risk of dying
5. These factors resulted in the final definition of sepsis as " life threatening organ dysfunction that results from a dysregulated host response to infection"
6. Since the definition includes organ dysfunction, the previous category of Severe sepsis becomes redundant.

THE BEST DEFINITION OF SEPSIS

Causes Organ Dysfunction

Sepsis is
life-threatening organ dysfunction
caused by a
dysregulated host response to
infection

Predicated on Infection

Abnormal host response

No need for "Severe Sepsis" category

THE BEST DEFINITION OF SEPTIC SHOCK

The current definition is based on blood pressure and hemodynamics only.

a.How do we better define Septic Shock? Is it all about the cardiovascular systemWhilst blood pressure and the heart are important, the shock state in sepsis involves cellular and metabolic pathways

b.Does the management help differentiate ?

c. Is it possible that the pathobiology is different? We don't know

d.The thing that distinguishes septic shock from sepsis is Mortality

e.Septic Shock is a subset of Sepsis in which profound circulatory, cellular and metabolic abnormalities are associated with a greater risk of mortality than Sepsis alone

Septic Shock
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abnormalities
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mortality than Sepsis alone

Sepsis is
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dysregulated host response to
infection

Limited Practical Utility

Septic Shock
is a subset of Sepsis in which
profound circulatory, cellular and metabolic abnormalities
are associated with a greater risk of mortality than Sepsis alone

“Dysregulated Host Response”
“Organ Dysfunction”

a, If we were granted 3 wishes in this regard; what would we wish for?

We could wish for a diagnostic laboratory test or a screening tool that would either rule in or rule out the diagnosis. The absence of these puts that idea up in smoke so to speak!

b. Fortunately we have 1 wish left, and because we know that patients with sepsis are very sick and at high risk of dying, could we wish for a global risk stratifying tool that was based on clinical criteria, that could be easily done by the triage nurse and perhaps obviating the need for any Laboratory tests.

Wish! Wish!

Diagnostic Laboratory test
Clinical Screening tool

Global Risk Stratification Tool

Clinical Criteria ✓

No Labs ✓

Easily done by Triage Nurse ✓

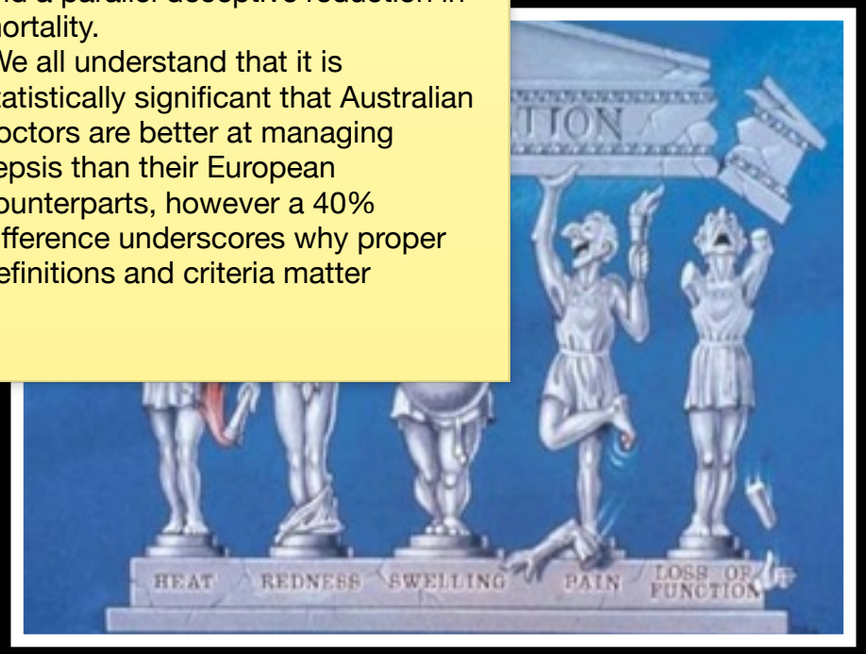
WHATS WRONG WITH SIRS

Lets now examine why these old definitions are problematic. Firstly, our current definition fails to make a distinction between a definition and clinical criteria.It provides a tool to detect sepsis without telling us what sepsis is. Much new information is av
int

1. SIRS criteria were intended as a wide net and the high sensitivity falsely includes far too many patients as septic. Therefore, a high percentage of ICU patients in the US, Euroupe and ANZ would qualify on the basis of 2 or more SIRS criteria.
2. Low entry threshold results in a dramatic increase in less sick patients being
included in the prevalence of sepsis and a parallel deceptive reduction in mortality.
3. We all understand that it is statistically significant that Australian doctors are better at managing sepsis than their European counterparts, however a 40% difference underscores why proper definitions and criteria matter

esumed
on

S Criteria



SIRS
↓
Sepsis
↓
Severe Sepsis
(Sepsis + Organ dysfunction)
↓
Septic Shock

HIGH SENSITIVITY

BUT

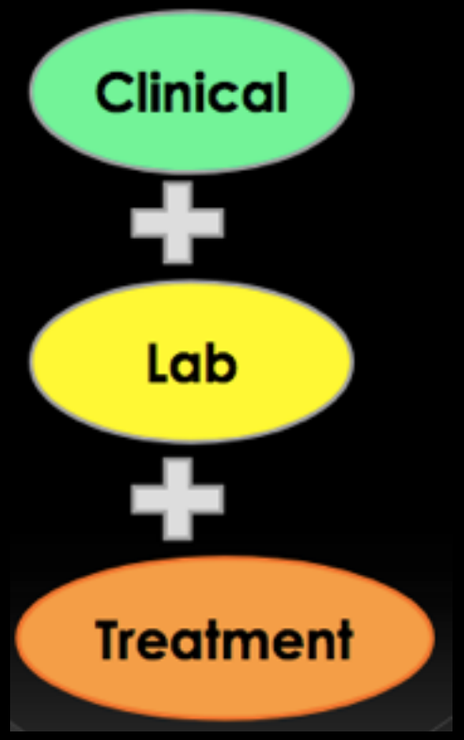
LOW SPECIFICITY

NY Hospitals Screening Tool

ANY 3 OF THE FOLLOWING

1. Any alteration of mental status
2. Temp <36c or >38.3 c
3. Heart rate >90 bpm
4. Systolic BP <90
5. Resp Rate > 20/min
6. SaO_2 <90% on room air
7. Suspected Infection

SOFA



The SOFA score has clinical, laboratory and treatment criteria and is best remembered if one considers a system based approach
CNS……..

Recall, the best we could wish for was a global risk assessment tool and not a screening tool. qSOFA picks out those patients at triage who are at most risk of dying.
Systolic Bp <100, altered mental state and respiratory rate >22 make up qSOFA.
If none of these are present, mortality risk is <1% whilst a score of 3 imparts a 20% risk
Again the major criticism is that there is no prospective validation.

q SOFA is NOT
a screening tool or
a management trigger

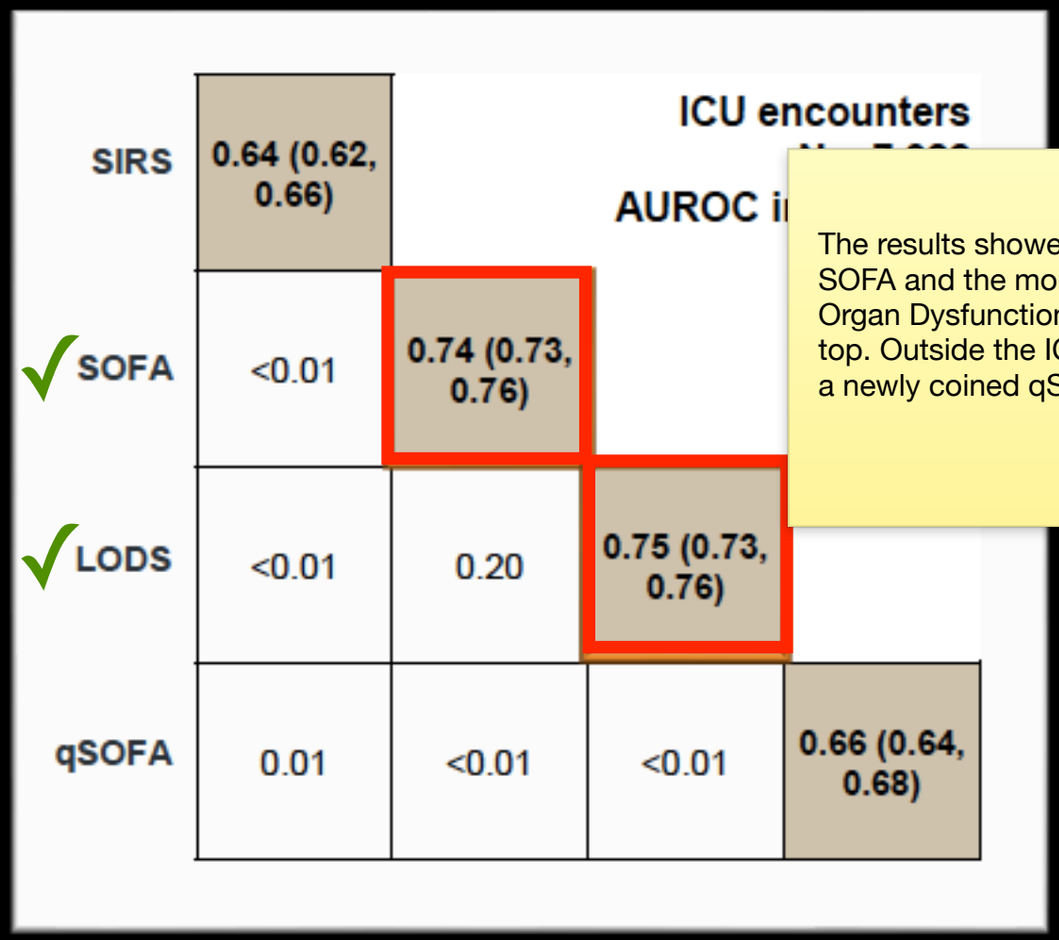
qSOFA is a risk stratifier
Mortality at 6-72 hrs
0/3=<1%
1/3= 2-3%
2/3=8%
3/3=20%

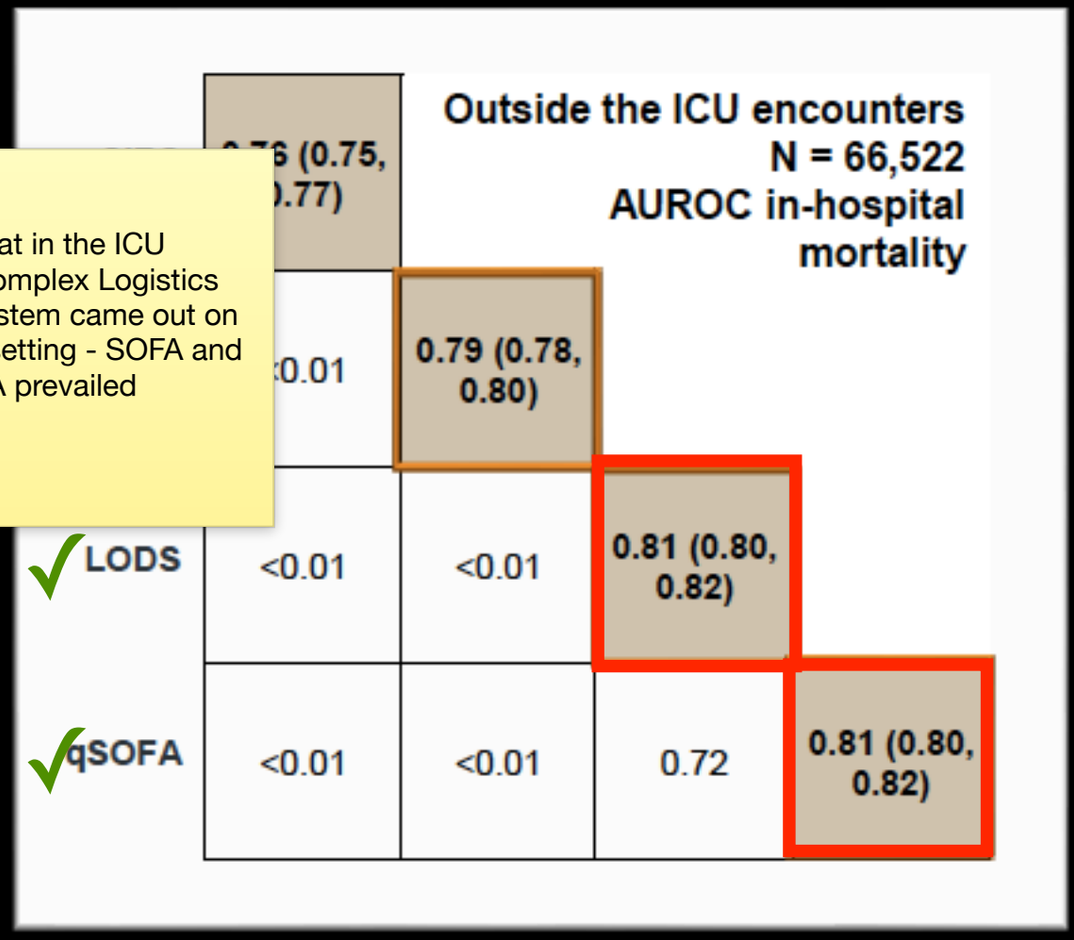
In ICU

Outside ICU

SOFA

qSOFA





The results showed that in the ICU SOFA and the more complex Logistics Organ Dysfunction System came out on top. Outside the ICU setting - SOFA and a newly coined qSOFA prevailed

NATIONAL EARLY WARNING SCORE

Physiological Parameters	3	2	1	0	1	2	3
Respiration Rate (BPM)	≤8		9-11	12-20		21-24	≥25
Oxygen Saturations (%)	≤91	92-93	94-95	≥96			
Any Supplemental Oxygen		Yes		No			
Temperature (°C)	≤35		35.1-36.0	36.1-38.0	38.1-39.0		
Systolic Blood Pressure (mmHg)	≤90	19-100	101-110	111-219			≥220
Heart Rate (BPM)	≤40		41-50	51-90	91-110	111-130	≥131
Level of Consciousness				A			V, P or U

What about other tools that may be better?
NEWS is a British scoring system which holds much promise.
In a retrospective review of 36000 charts at a Chicago Hospital - NEWS fared better than qSOFA or SIRS
However, this was not prospective validation.

Royal College of Physicians

CRITERIA FOR SEPTIC SHOCK

We established that that single factor that discriminates septic shock from sepsis was mortality.
Therefore its logical to look for those clinical criteria that have the highest mortality
If lactate alone is >2 the mortality is 25%. If Fluid refractory hypotension and Vasopressors are required to maintain MAP>65 then mortality is 30%
If all 3 factors are present then the mortality risk is 42%
To diagnose septic shock, we have to adequately fluid resuscitate in the first 3 hours and recheck the serum lactate at the 3h mark and if all 3 criteria are present, only then can we call this septic shock.
To illustrate this with an example- if a patient presents with lactate of 3.8 and is adequately fluid resuscitated and at the 3 hour mark the patient is on vasopressors and MAP is 55 but lactate is 1.7—this is not septic shock. They intended for the criteria to be tight.

M

tate > 2

d Refractory Hypotension
uiring Vasopressor

42%

Fluid Refractory Hypotension
Requiring Vasopressor
Lactate > 2

INITIAL PRESENTATION
MAP = 65
Lactate = 3.8

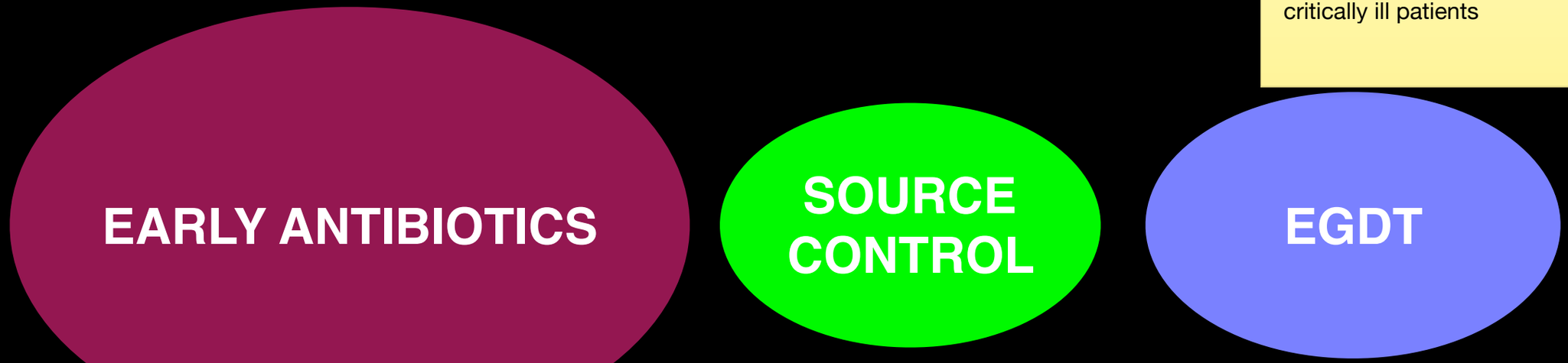
↓

Resuscitated with
30ml/kg normal saline

↓

MORTALITY REDUCTION WITH CRITICAL INTERVENTIONS

THESE ARE ADDITIVE
Today, I plan to focus on these 3 interventions as they contribute the most to survival.I will not discuss some of he other components of managing critically ill patients



50%

12%

16%

ANTIBIOTICS IN SEPSIS

Why antibiotics do we need antibiotics in sepsis?
We know that sepsis is predicated on infection.
The severity of the syndrome would warrant rapid reduction of the antimicrobial load to:
1.prevent injury caused by microbial activity and toxin production
2.prevent or ameliorate harmful host responses to infection

Despite the difference in timing for first antibiotic in these studies, there was no difference in mortality.
Difficult to figure out when time zero for infection was.

This study by Anand Kumar and Dan Roberts in Winnipeg showed that for each hour delay, there was a 7% increase in mortality. However, this has not been replicated.

Stronger evidence over increased mortality after 1 hour of hypotension in sepsis and easier to measure time zero for this event.

inDication

Surviving Sepsis Campaign

2016
Recommendation:
Antibiotics ASAP and preferably within 1 hour from recognition
(Strong Recommendation on Moderate Quality Evidence)

ANTIBIOTICS IN SEPSIS

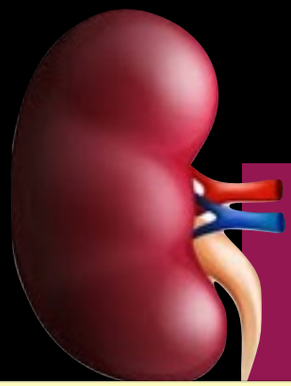
1.Choosing the correct drug the first time is crucial. Getting it right still has high mortality but getting it wrong doubles that number
2. We need to use broad spectrum drugs and by that we mean one that covers many different types of organisms. Combination therapy is suggested and this means 2 drugs from different classes that work against the most likely organs, to accelerate pathogen clearance.
 -eg. beta lactamase plus fluroquinalone, gentamicin or macrolide.
3. How do we go about making those choices? Firstly we have to consider patient factors:
Age - extremes of age pose more problems in terms of choice and resistant organisms
Comorbidities such as diabetes, renal or hepatic dysfunction.
Host immune status - immunocompromised, post splenectomy- more likely encapsulated bacteria
Dialysis patients and PCH- more likely to have resistant organisms
Factors related to the site of the infection if known.
Certain bacteria have predilection for a specific site e.g.. commonest pathogen in pneumonia would be pneumococcus
Bioavailability may be a factor in meningitis as one would want a drug with good penetration of the blood brain barrier.
Lastly, one has to consider the most likely organism in t.he environment
How common is MRSA in the facility- very low for us, what are the local resistance patterns - 80% E.coli would be resistant to amoxycillin so that would not be a good choice for urosepsis

Drug choice

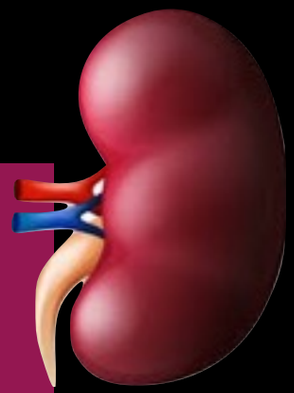
ANTIBIOTIC CHOICE

ANTIBIOTICS IN SEPSIS

Dosage



Increased Volume of Distribution
Augmented Renal Clearance



When considering dosing, 2 things are important: Leaky capillaries and fluid resuscitation cause an increased volume of distribution. Secondly, there appears to be a phenomenon of augmented renal clearance in sepsis. These 2 factors account for suboptimal dosing and a resultant low first peak level, ultimately leading to drug failure. Gentamicin failure is often accounted for by under dosing the first dose. Therefore- recommended one choose a dose at the high end of the spectrum as the first dose and deliver by rbolus or rapid iv infusion regardless of the mechanism of killing

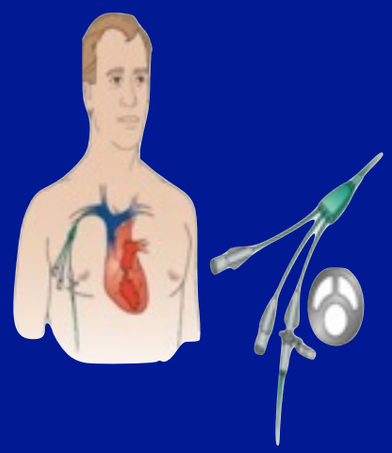
1. Time dependant killing relies on time above MIC —simple infections 60% maybe ok but aim for 100% in sepsis—> therefore continuous infusion may be best.
2. 2 things important with Conc dependant killing, CMax=Peak concentration and AUC(green). once daily dosing at high end of spectrum

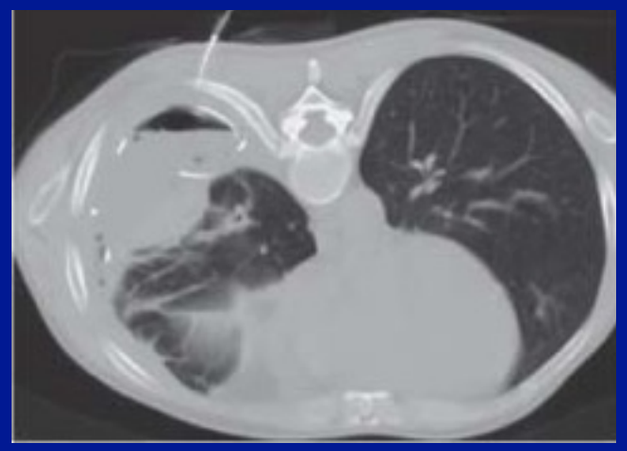
SOURCE CONTROL

Optimize within 12 hours

SOURCE CONTROL

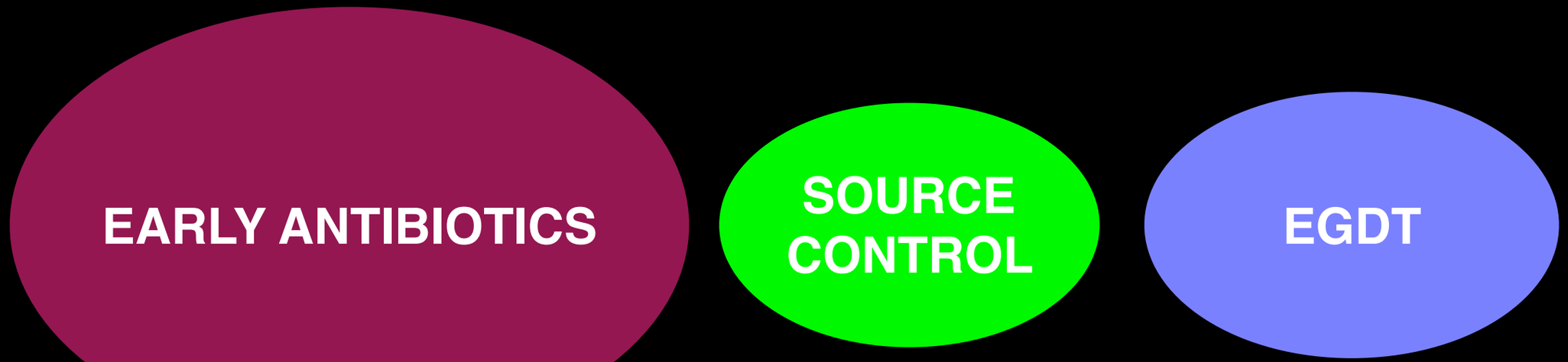
Remove Indwelling Catheters





Non Invasive Intervention Preferred

MORTALITY REDUCTION WITH CRITICAL INTERVENTIONS



50%

12%

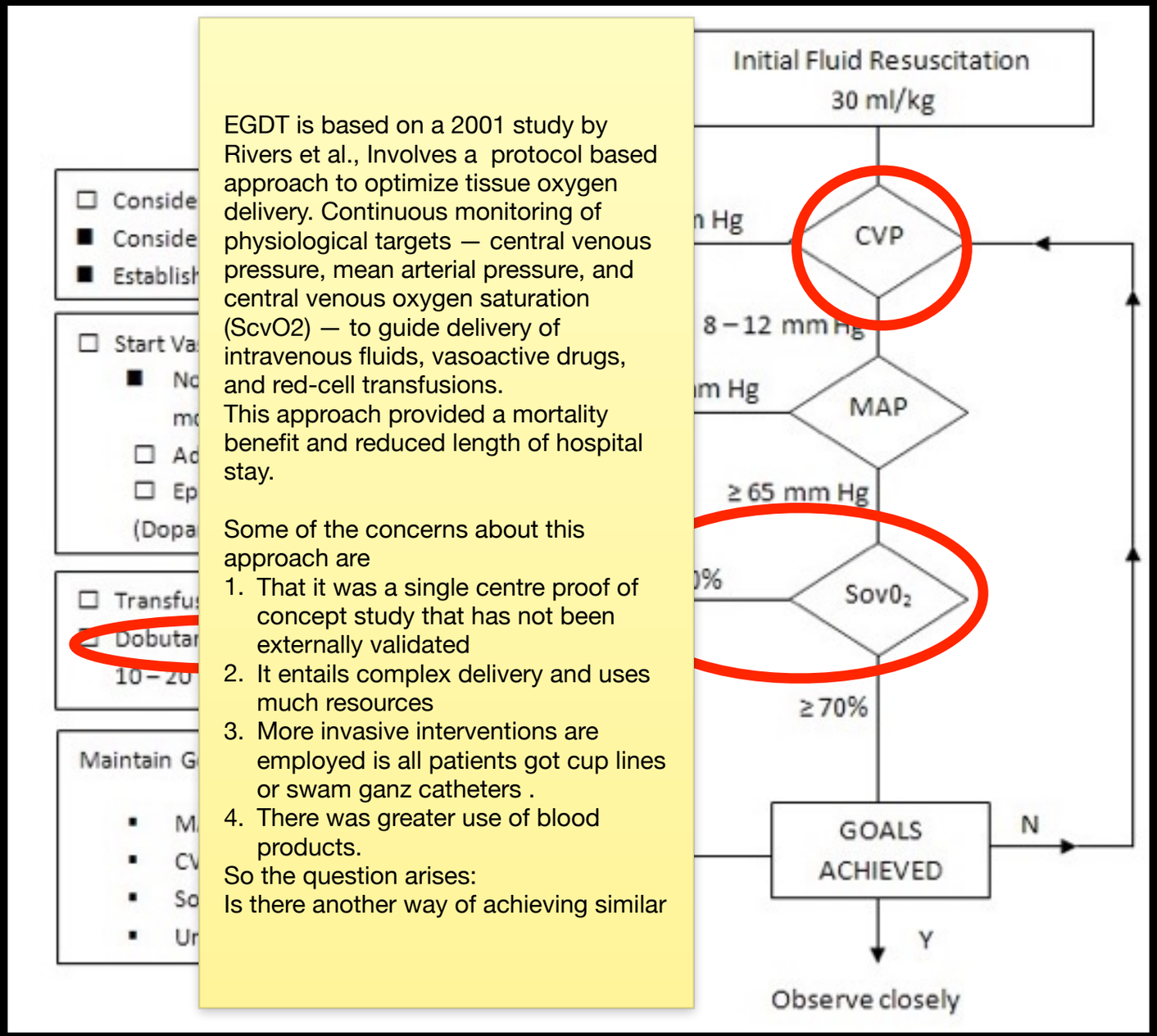
16%

EARLY GOAL DIRECTED THERAPY

(RIVERS AND RIVERS - 2001)

Single Centre Proof of Concept Study

Complex Delivery Much resources



EGDT is based on a 2001 study by Rivers et al., Involves a protocol based approach to optimize tissue oxygen delivery. Continuous monitoring of physiological targets — central venous pressure, mean arterial pressure, and central venous oxygen saturation (ScvO2) — to guide delivery of intravenous fluids, vasoactive drugs, and red-cell transfusions.
This approach provided a mortality benefit and reduced length of hospital stay.

Some of the concerns about this approach are

1. That it was a single centre proof of concept study that has not been externally validated
2. It entails complex delivery and uses much resources
3. More invasive interventions are employed is all patients got cup lines or swam ganz catheters .
4. There was greater use of blood products.

So the question arises:
Is there another way of achieving similar

More invasive interventions

Greater use of Blood products

SEPSIS “TRIALogy”

PROTOCOL

bottom line - these trial showed that there was equivalent results with less interventions, complications and costs.

VS.

Process
Multicentred academic hospital study comparing EGDT to usual care
X plain what was usual care- whatever the attending saw necessary- low sats- give oxygen, low bp give fluids, start vassopressors
Criticism- academic hop study

ARISE
Multicentred academic and non academic hospital study
Criticism - patients not as sick

Promise looked at very sick group of patients and evaluated the cost effectiveness and QOL outcomes

USUAL CARE

2014
ProCESS
Lactate
± CVP
± $ScVO_2$

2014
ARISE
Lactate
No CVP
No $ScVO_2$

2015
ProMISe
Lactate
No CVP
No $ScVO_2$

2001
EGDT
Protocol
CVP
$ScVO_2$

SEPSIS “TRIALogy”

VARIABLE	RIVERS(EGDT)	PROCESS	ARISE	PROMISE
	4.3% (60d)	18.9 vs 21% (60d)	18.8 vs 18.6% (90d)	29.2 vs 29.6% (90d)
	6H	3h	1.2	1.3
	-	2L	2.5L	2L
	5L	2.8L	1.7L	2.0L

1. IIf we look at the trial parameters we notice that age, time to id and goal MAPs were not statistically different.
2. Mortality in the comparative trials in 2014/15 were similar but much lower than the original Rivers trial.
3. One could argue that patient in the Rivers trial were more sick as they had lower ScVO2 and higher lactates - the Promise trial had equally sick patients but the main reason is….
4. Patients in the newer trials were given antibiotics earlier and received fluids earlier so that even pre randomization the lactate and Scvo2 became less
5. This tells us that giving antibiotics and fluid early is the key rather than a strict protocol driven approach.
6. ASIDE—What we re comparing here is the arms of the 3 new trial versus the original Rivers trial - therefore fluids pre randomization would not be relevant for rivers trial.

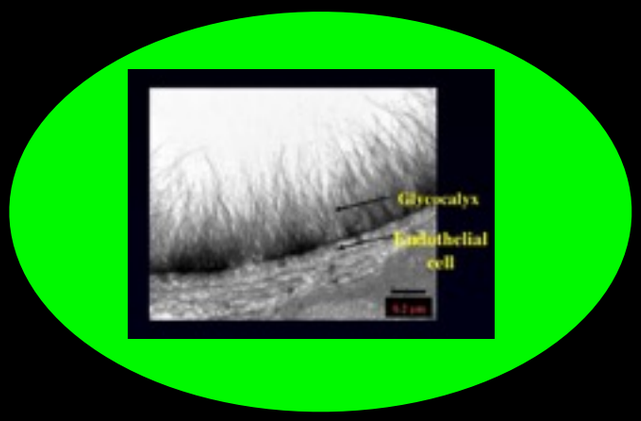
now what?

If Early goal directed therapy is too much trouble, how do we approach the management of septic patients

HEMO ENSATION IN SEPSIS

Start this section by describing the hemodynamic deficits in sepsis.
You will discuss each in more detail.
2001 Rivers trial EGDT tried to give this a structured approach.
What this meant in term of intervention and a goal. Great idea but does it really make a difference; especially in terms of invasive interventions and excessive use of blood transfusions

HYPOVOLEMIA



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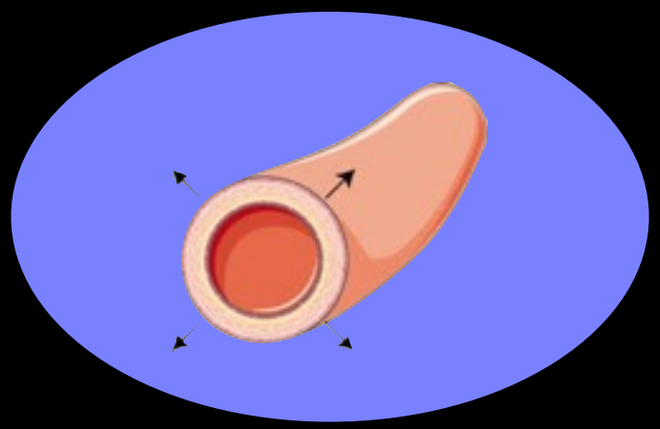
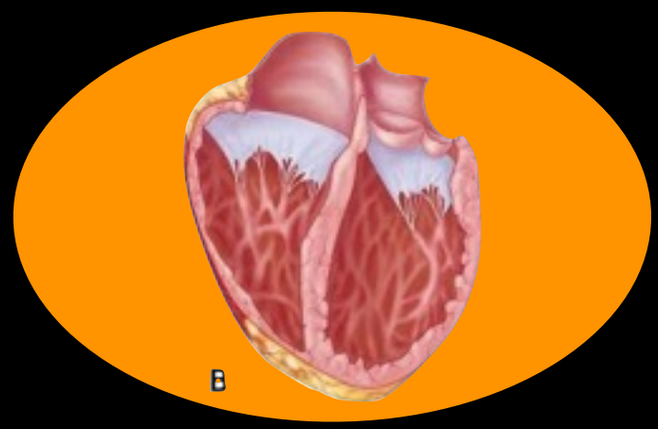


MYOCARDIAL DYSFUNCTION



Restore Fluid Volume Avoid Tissue Edema

vasodilation mediated by nitric oxide
Leaky capillaries because TNF denudes the glycocalyx.

Goal MAP ≥ 65

The heart, is exquisitely sensitive to increases in microvascular permeability and interstitial oedema . Whereas some organs can cope with profound increases in the interstitial fluid volume without a compromise in function, heart function is significantly compromised with only a few percent increase in the interstitial fluid volume.
The ability of the LV to dilate appears to be protective in Sepsis and the interstitial deem compromises this

Improve Stroke Volume

SUMMARY OF HEMODYNAMIC INTERVENTIONS

INOTROPES

FLUIDS

C R R A P

VASOPRESSORS

Emphasize that Strong recommendation on low quality evidence

Surviving Sepsis Campaign

2016

1. **Treatment and Resuscitation begin Immediately**

Best Practice Statement

2. **At least 30ml/kg Crystalloid be given in the 1st 3h**

Strong Recommendation. Low Quality Evidence!!

3. **Additional fluids based on frequent reassessment of Hemodynamic Status**

Best Practice Statement

FLUIDS

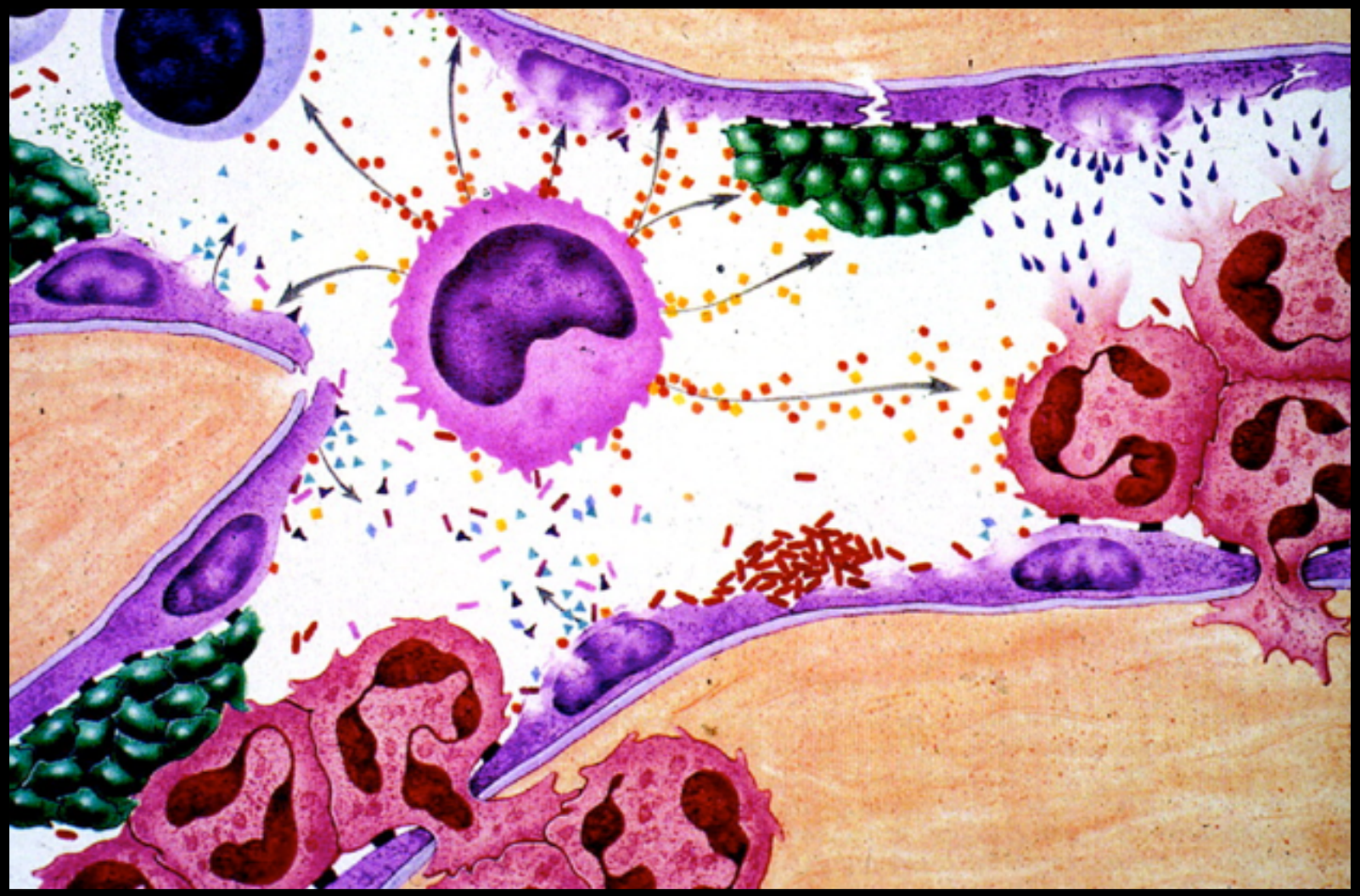
WHY ?

WHAT ?

HOW MUCH ?

1. Need to replace intravascular volume because of capillary leakage and v/d that increases venous capacitance- holds more

WHY FLUIDS ?



WHAT FLUID?

after distribution slides
Ask 3 questions?
1.Why not give everyone blood?
2.choice between colloids and crystalloids?
3.are all crystalloids equivalent?

CRYSTALLOIDS

COLLOIDS

BLOOD

DEXTROSE
ABNORMAL SALINE
RINGERS LACTATE

HYDROXY-ETHYL STARCH
ALBUMIN

PRBC

80ml

250ml

1000ml

COLLOIDS VS. CRYSTALLOIDS

6S TRIAL

	MORTALITY	p VALUE
6% HES	51%	0.03
RINGERS	43%	

CHEST TRIAL

	RENAL IMPAIRMENT	p VALUE
TETRA STARCH	7%	
0.9% NS	5.8%	

The SAFE trial showed no difference in mortality between albumin and normal saline. Subgroup analysis demonstrated a trend toward less mortality in the albumin group.
One cant put much trust into subgroup analysis so The Albios trial was done to investigate this
Whilst serum albumin and bp increased, there was (Proof that one cannot trust subgroup analysis) no diff in mortality at 28 and 90d
In most cases avoid albumin as initial fluid resuscitation.
May consider it in a restrictive fluid strategy in ARDS and in sepsis with abdominal compartment syndrome

H ...LOIDS

RECOMMENDATION A

- **No mortality ben**
- **Increased coagu**
- **Increased renal c**
- **Costs more**

Appeal to colloids was that they had larger macromolecules that remained intravascular and kept fluids intravasc as well. Furthermore, there was a perception that we needed 1/3 or 1/4 of the equiv vol of crystalloid to get the same effect. More recent studies put this ratio at 1/1.3
Colloids cause transient inc in intravasc volume that does not translate to better outcomes

ARE ALL CRYSTALLOIDS EQUIVALENT?

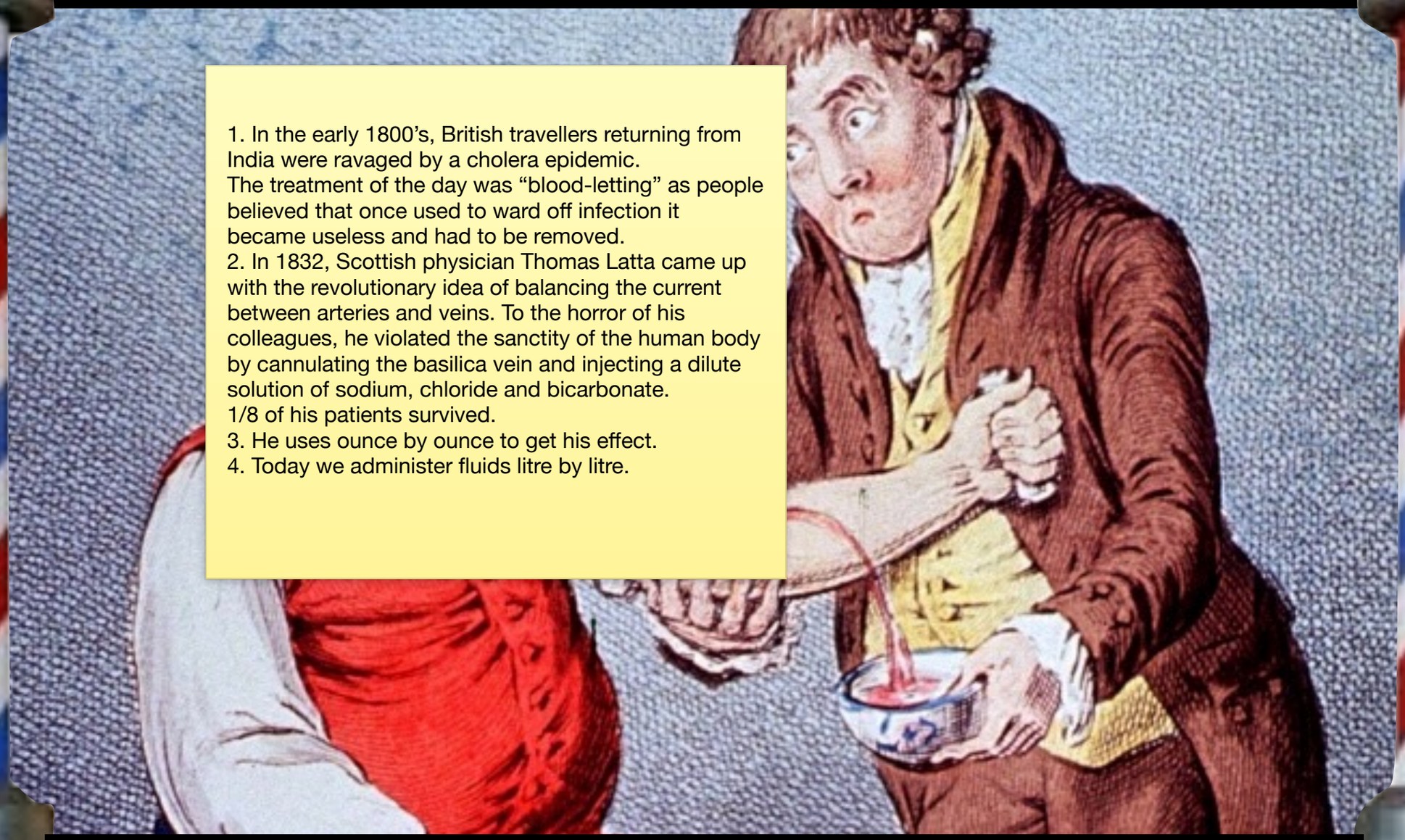
If crystalloids are the answer, then it begs the question " are all crystalloids equivalent/"
Normal saline has been the go to drug largely because of cost. However, the current cost difference is negligible.
Saline is really abnormal saline as it differs moocher widely from plasma than ringers lactate.

NS causes a non AG hyperchloremic metabolic acidosis and in small head to head studies trended toward greater renal injury.
Saline would be the ideal drug in severe vomiting-rx the low sodium, chloride and metal alkalosis.

In most situations balanced crystalloids such as RL would be preferable.
Ringers cant be used together with blood transfusions because the calcium will chelate blood.
RL may not be the best choice for TBI because of its lower osmolality.

Na	Cl	pH	Osm.	Cost
140	103	7.4	290	
154	154	5.7	308	$1.23
130	109	6.5	273	$1.45

HOW MUCH FLUID?



1. In the early 1800's, British travellers returning from India were ravaged by a cholera epidemic.
The treatment of the day was "blood-letting" as people believed that once used to ward off infection it became useless and had to be removed.
2. In 1832, Scottish physician Thomas Latta came up with the revolutionary idea of balancing the current between arteries and veins. To the horror of his colleagues, he violated the sanctity of the human body by cannulating the basilica vein and injecting a dilute solution of sodium, chloride and bicarbonate.
1/8 of his patients survived.
3. He uses ounce by ounce to get his effect.
4. Today we administer fluids litre by litre.

ARDS

Crit Care Med. 2013 Feb;41(2):472-80. doi: 10.1097/CCM.0b013e3182a8ab77.

Extravascular lung water is an independent prognostic factor in patients with acute respiratory distress syndrome.

Jozwiak M[1], Silva S, Persichini R, Anguel N, Osman D, Richard C, Teboul JL, Monnet X.

n=200
70% Mortality if EVLW>21 ml/kg
40% Mortality if EVLW <21ml/kg

There's good evidence that more fluid in ARDS is bad. When extravascular lung water exceeds 21ml/kg, mortality increased 30%

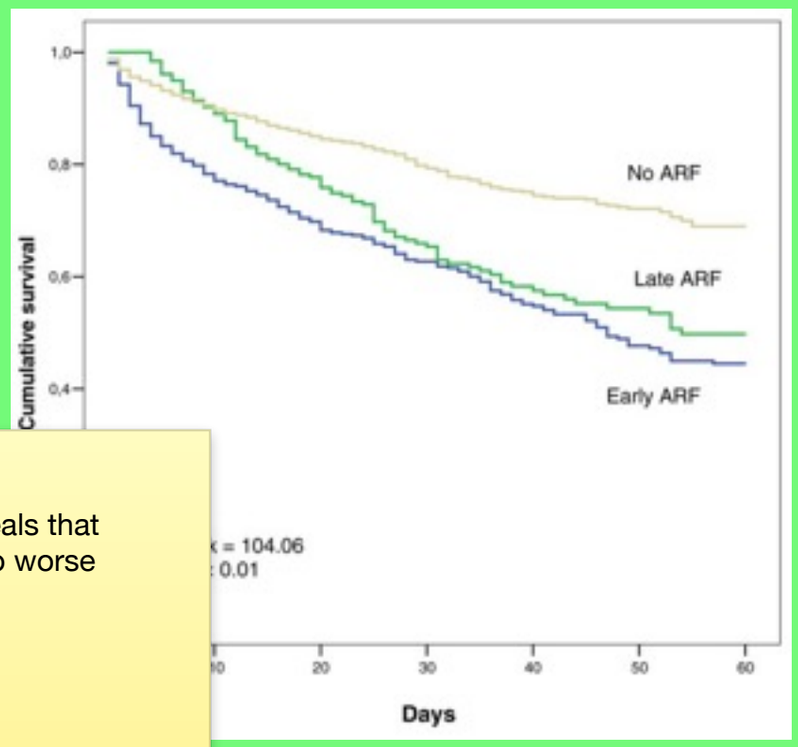
ARDS

More Fluids = ↑ Mortality

Crit Care. 2008;12(3):R74. doi: 10.1186/cc6916. Epub 2008 Jun 4.

A positive fluid balance is associated with a worse outcome in patients with acute renal failure.

Payen D[1], de Pont AC, Sakr Y, Spies C, Reinhart K, Vincent JL; Sepsis Occurrence in Acutely Ill Patients (SOAP) Investigators.



The graph on the right reveals that positive fluid balance led to worse survival in AKI

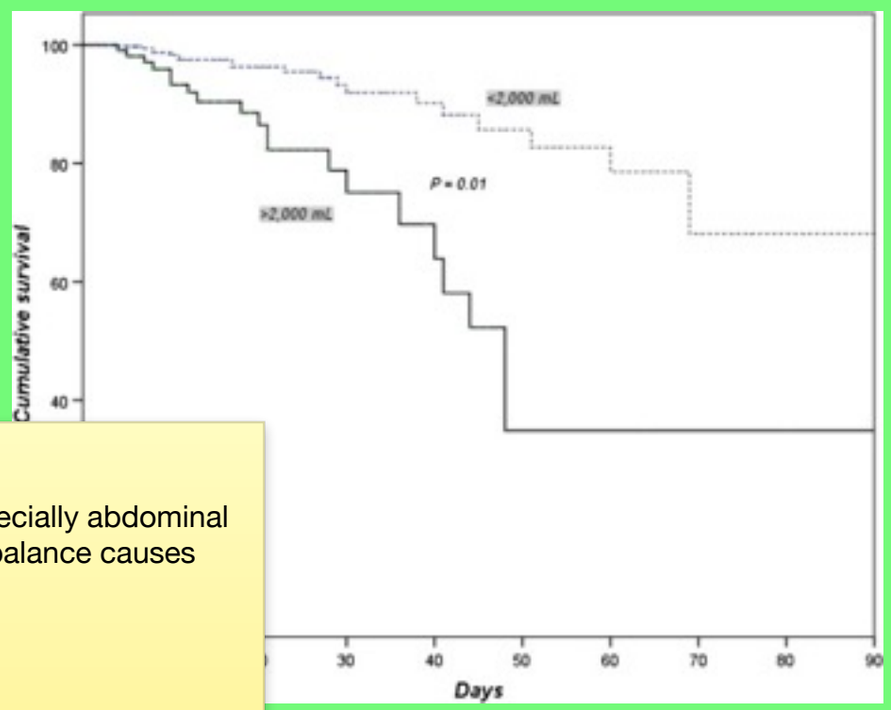
ACUTE KIDNEY INJURY

More Fluids = ↑ Mortality

Crit Care. 2013; 17(6): R288. PMCID: PMC4057181
Published online 2013 Dec 10. doi: 10.1186/cc13151

The effect of excess fluid balance on the mortality rate of surgical patients: a multicenter prospective study

João M Silva, Jr.,[1,2,4] Amanda Maria Ribas Rosa de Oliveira,[2,3] Fernando Augusto Mendes Nogueira,[1] Pedro Monferrari Monteiro Vianna,[1] Marcos Cruz Pereira Filho,[1] Leandro Ferreira Dias,[1] Vivian Paz Leão Maia,[1] Cesar de Souza Neucamp,[1] Cristina Prata Amendola,[3] Maria José Carvalho Carmona,[2] and Luiz M



In general surgery, especially abdominal surgery; positive fluid balance causes decreased survival

GENERAL SURGERY

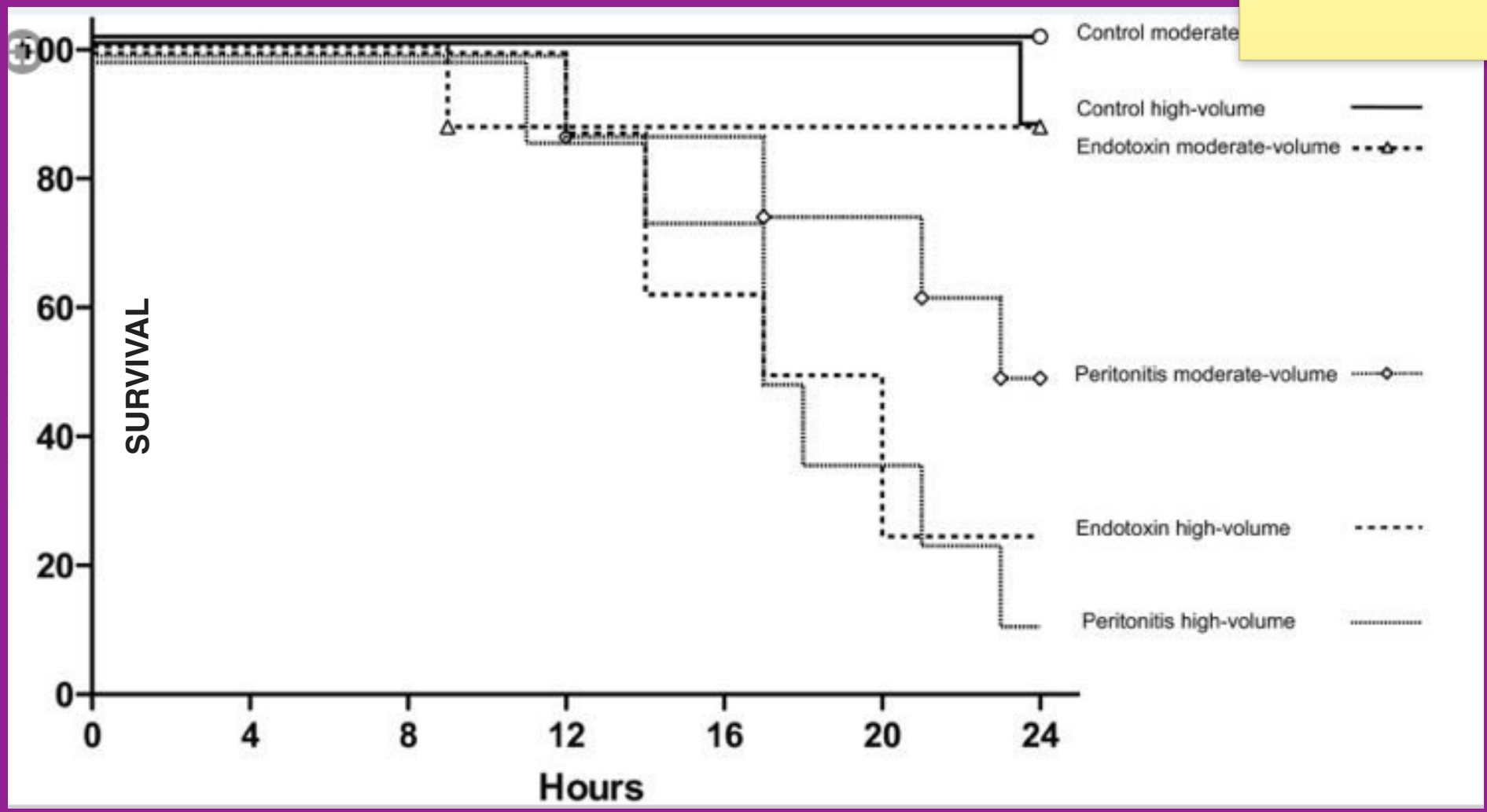
More Fluids = ↑ Mortality

“THE” ENDOTOXIC PIGS

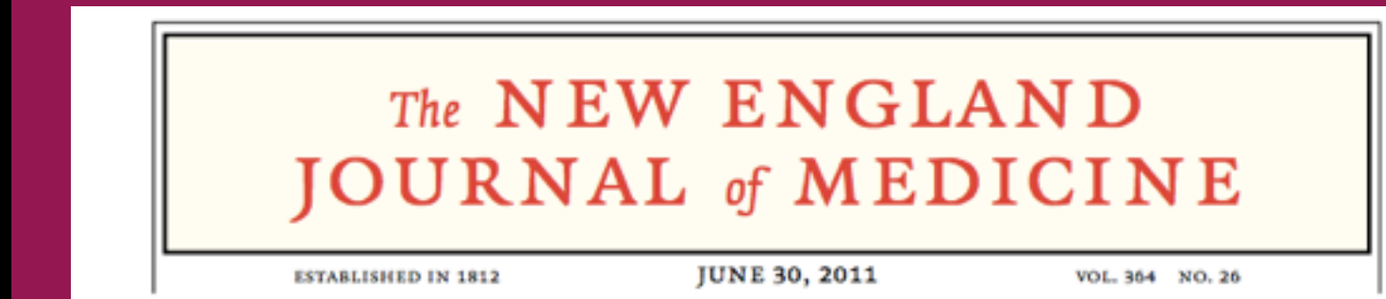
Crit Care. 2009;13(6):R186. doi: 10.1186/cc8179. Epub 2009 Nov 23.

Effect of fluid resuscitation on mortality and organ function in experimental sepsis

Brandt S[1], Regueira T, Bracht H, Porta F, Djafarzadeh S, Takala J, Gorrasi J, Borotto E, Krejci V, Hiltebrand LB, Bruegger LE, Beldi G, Lepper PM, Kessler U, Jakob SM.



Ok so we've proved that liberal fluid strategy is bad. Then is a conservative strategy better.In this study 48 pigs randomised to 3 groups of 16.
A control group, endotoxin and fecal peritonitis grip.
Each subdivided to receive 10ml/kg/hr R?L or 20ml/kg/hr RL
In each of the groups the conservative strategy led to better outcomes.
A man may be a pig but pigs are not human!



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 30, 2011 VOL. 364 NO. 26

Mortality after Fluid Bolus in African Children with Severe Infection

Kathryn Maitland, M.B., B.S., Ph.D., Sarah Kiguli, M.B., Ch.B., M.Med., Robert O. Opoka, M.B., Ch.B., M.Med.,

DESIGN

n=

Mu

6 cent

Saharan

Tanzan

This human study was done by Kathryn Maitland in sub-saharan Africa- multi centre RCT with 3 groups
Albumin bolus, saline bolus and no bolus of 20ml/kg and maintenance of 2.5-4ml/kg
She looked at mortality at 48h and 4 weeks.
I am sure you guessed that the no bolus group fared the based.
The critical care world really does not know what to do about this study because it was well designed but could never be replicated in North America
The criticism of course was that it was in children and done in Africa

INTERVENTION

Albumin bolus (n=1,050)
Saline bolus (n=1,047)
No bolus (n=1,044)

20ml/kg bolus
2.5-4ml/kg maintenance

Acheampong and Vincent *Critical Care* (2015) 19:251
DOI 10.1186/s13054-015-0970-1

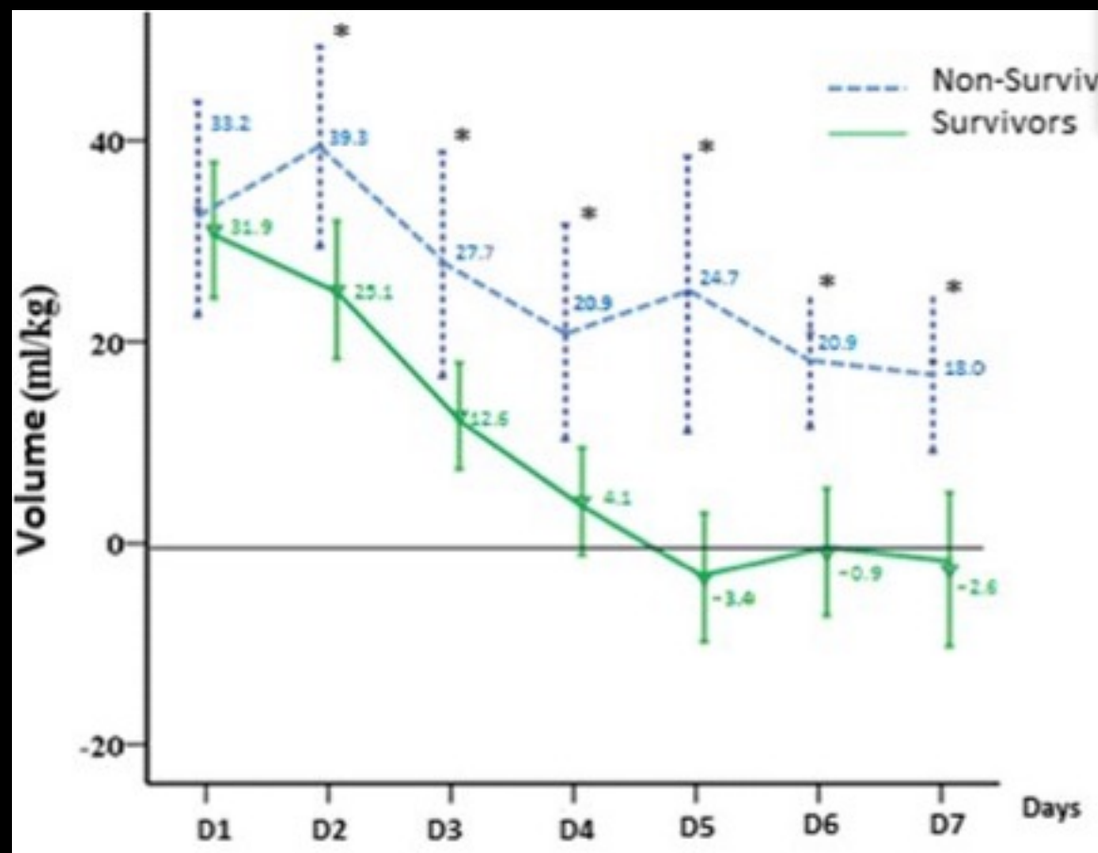
CRITICAL CARE

RESEARCH Open Access

A positive fluid balance is an independent prognostic factor in patients with sepsis

Angela Acheampong and Jean-Louis Vincent*

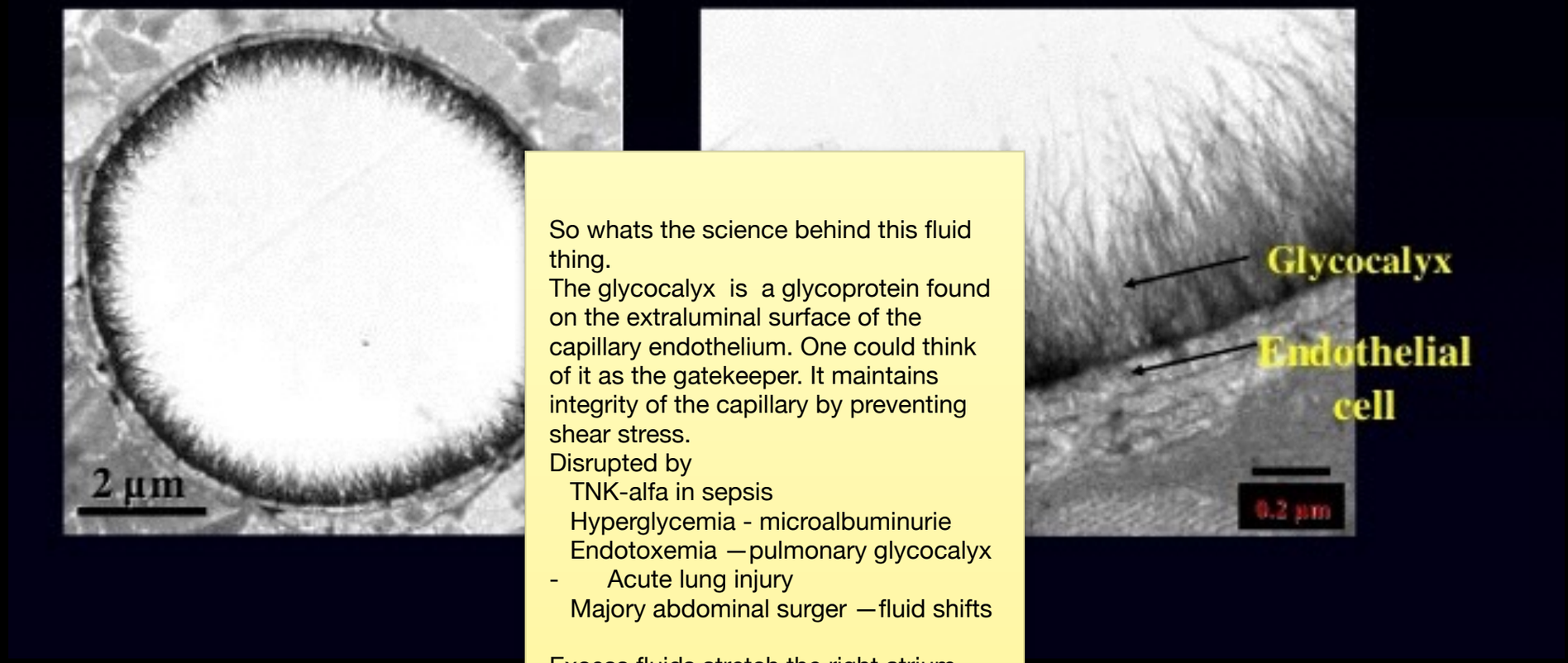
This small Belgian studyof 173 ICU patients demonstrated that a positive fluid balance as shown in the upper blue line, leads to greater mortality (different from the other graphs that depicted survival



Number of patients per day							
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
NS	59	59	59	51	43	38	31
S	114	114	114	96	75	64	49

THE GLYCOCALYX

van den Berg et al
Circ Res 92:592;2003



So whats the science behind this fluid thing.
The glycocalyx is a glycoprotein found on the extraluminal surface of the capillary endothelium. One could think of it as the gatekeeper. It maintains integrity of the capillary by preventing shear stress.
Disrupted by
TNK-alfa in sepsis
Hyperglycemia - microalbuminurie
Endotoxemia —pulmonary glycocalyx
- Acute lung injury
Majory abdominal surger —fluid shifts

Excess fluids stretch the right atrium—>greater release of ANP that denudes the glycocalyx—

Net effect of disrupting the glycocalyx is

WHEN TO STOP FLUIDS?

Fluid that does not contribute to increased stroke volume leaks through into interstitial space and worsens edema

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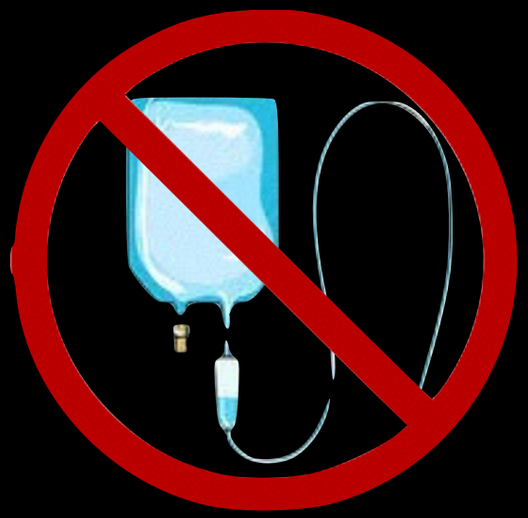


NO LONGER
PRELOAD RESPONSIVE

When more fluid does not cause a commensurate increase in stroke volume

WHAT ABOUT CVP MONITORING?

there is no
CVP meas
cardiac ou
[2]. A meta
investigati
to predict
blood volu
under the
indicating

The 7 flawed assumptions in assuming that the CVP predicts fluid responsiveness

CVP ≈ RVEDP ≈ PAD ≈ PCWP ≈ LAP ≈ LVEDP ≈ LVEDV ≈ Fluid responsiveness

RV compliance	Pulm Vasc resistance	Airway pressure	Mitral valve	LV compliance	LV function

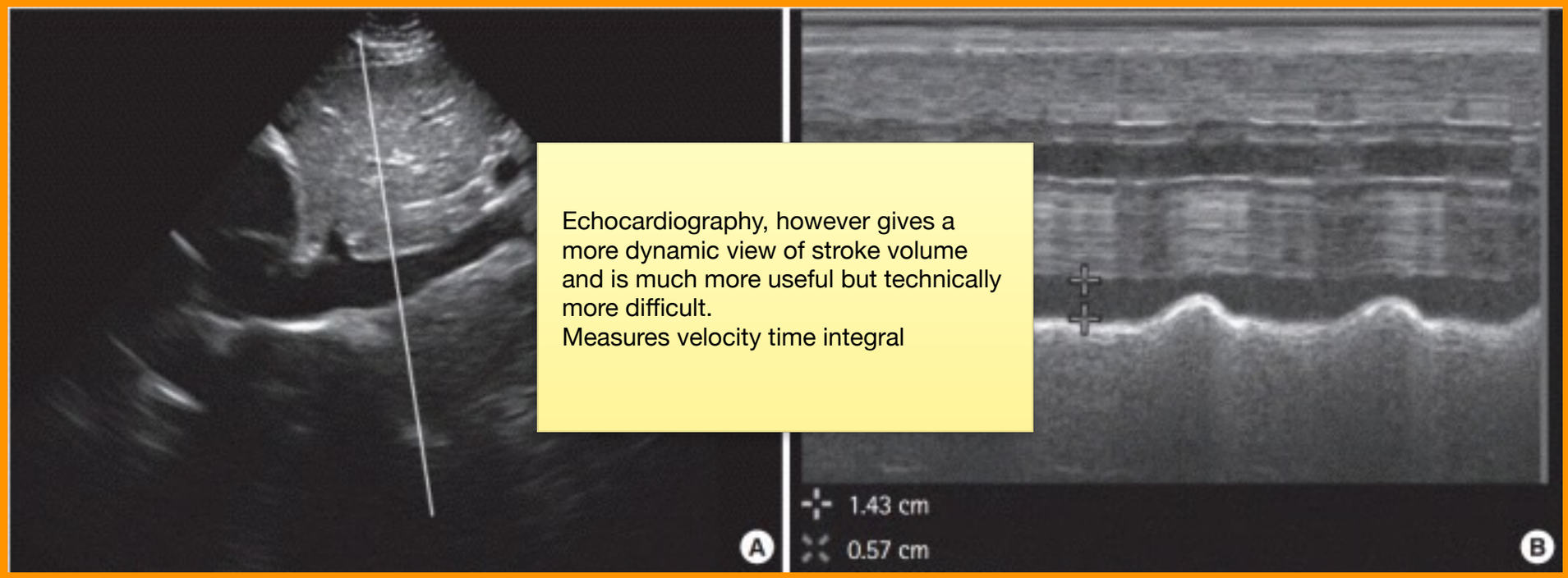
rx—> worse

delines

the
contrary,SSC strongly supported CVP and ScVO2 in their 2012 guidelines but retracted to suggest dynamic rather than static measures of fluid responsiveness

Long axis view of the IVC distal to convergence of hepatic vein held some promise in ventilated patients. Diameter and compressibility were surrogate markers of CVP. However, recent studies have found this to be not useful because the critical thing is does the inc volume translate to increased SV-

IVC DIAMETER



Echocardiography, however gives a more dynamic view of stroke volume and is much more useful but technically more difficult.
Measures velocity time integral

HOW DO WE DETERMINE PRE-LOAD RESPONSIVENESS

NB. These clinical markers are only surrogates and may not reveal an accurate picture. (For organ perfusion one needs flow and pressure)
e.g. BP
60% patients were preload responsive
fluid
ow

The pa
approx
extrem
venous
PLR is
can be
sponta
[19-21]
use of
clinicia
and po
whethe
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Passiv
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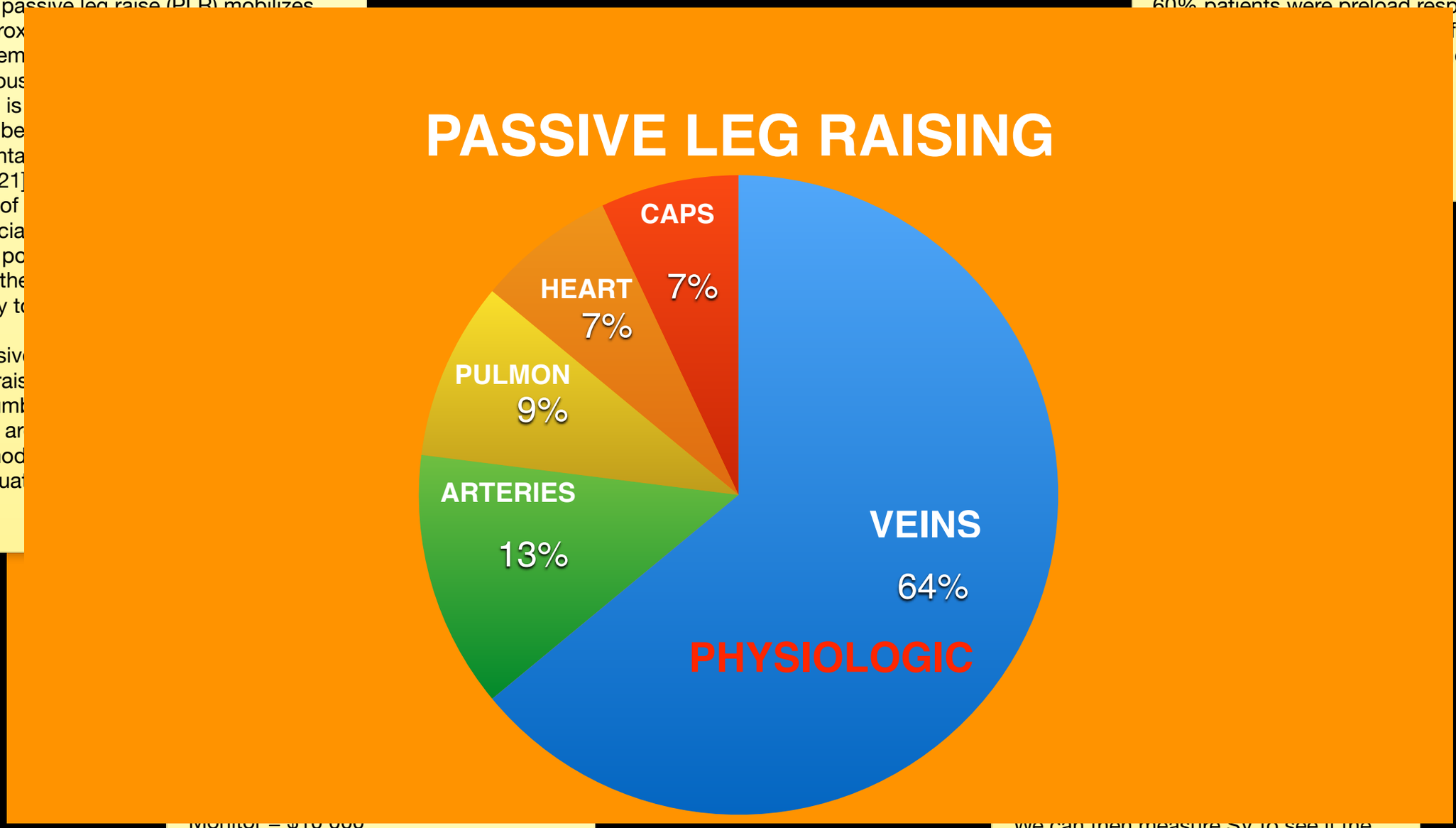
evaluat



Monitor = $10 000
Sensors - $110 x ?1
need 4 sensors

We can then measure SV to see if the patient is preload responsive

SUMMARY - FLUIDS

Do we need fluid in Sepsis?

✓

How much fluid?

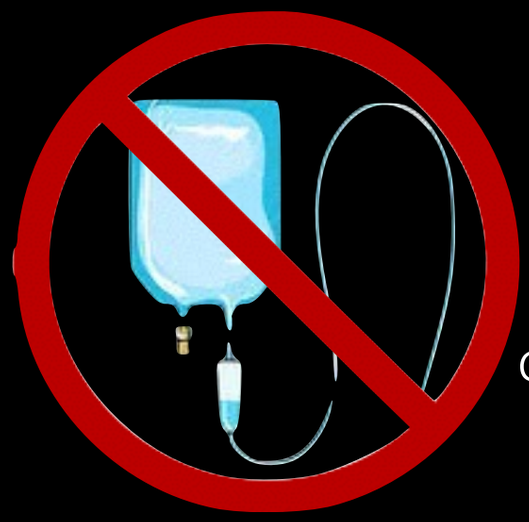
30ml/kg in first 3 hours

"think ounce by ounce"

500ml by 500ml

GCS
↓HR
↓PP
↑BP
↑UO

When do we STOP?



NO LONGER PRELOAD RESPONSIVE

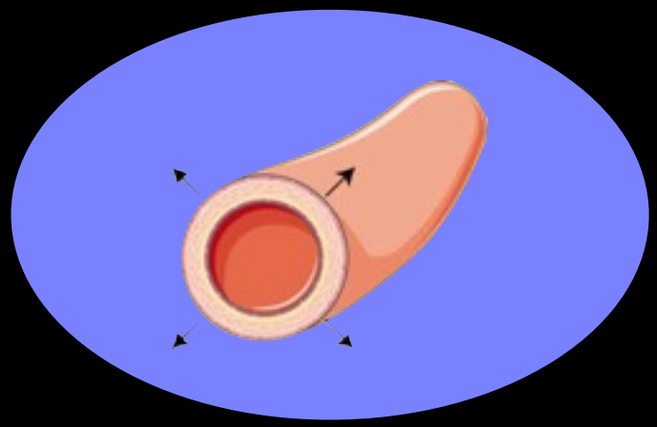
When more fluid does not cause a commensurate increase in stroke volume

HEMODYNAMIC DECOMPENSATION IN SEPSIS

HYPOVOLEMIA

Restore Fluid Volume
Avoid Tissue Edema

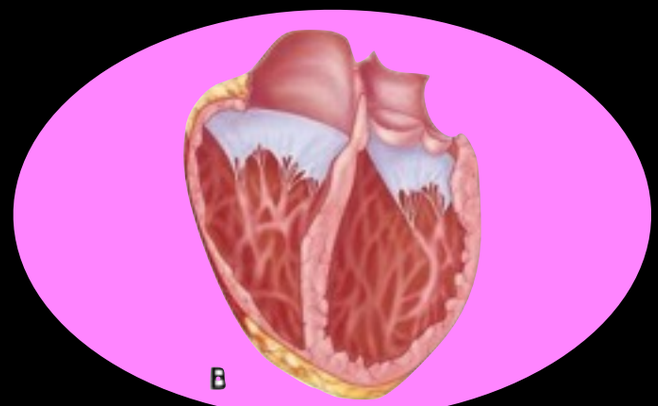
VASODILATION



Goal MAP ≥ 65

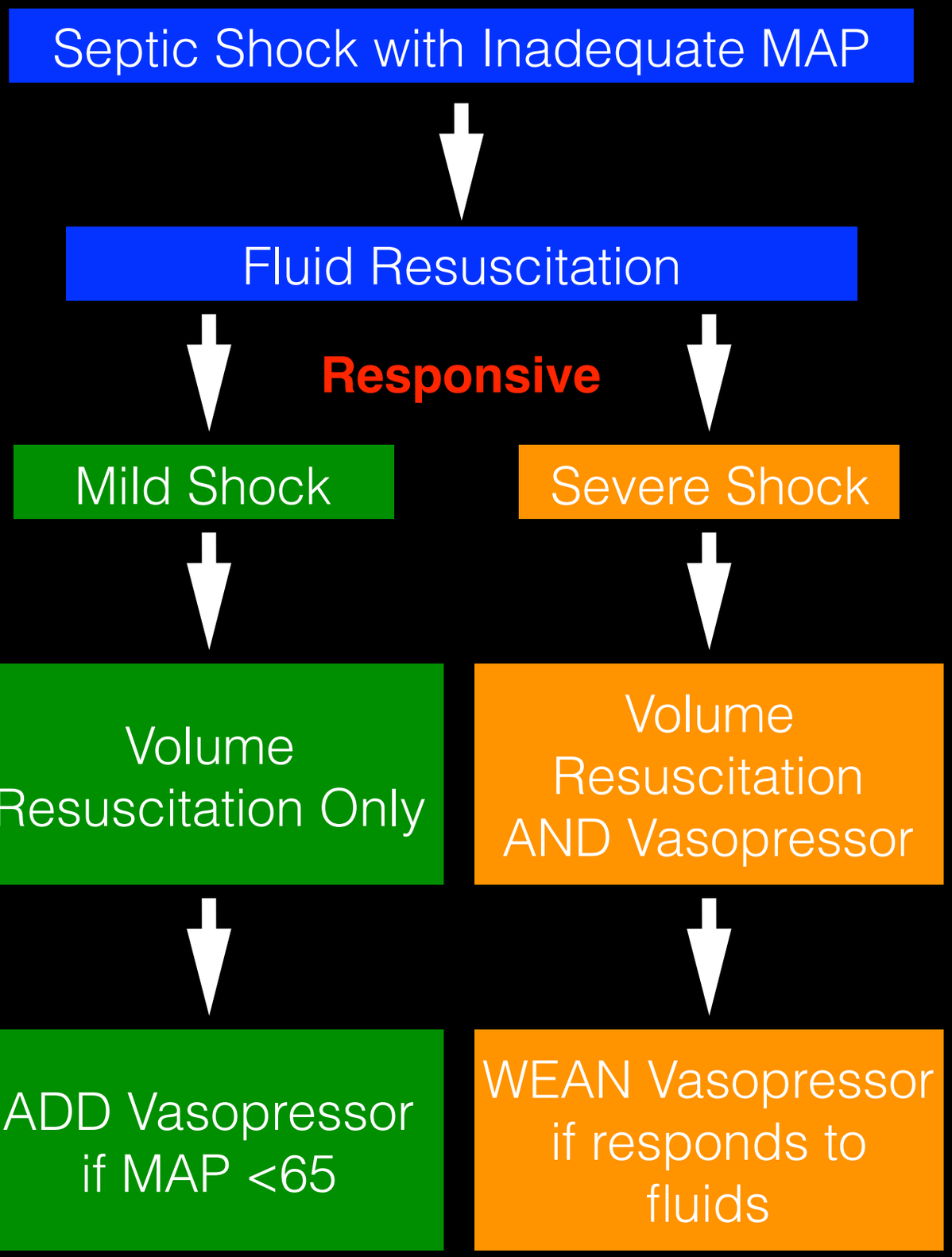
vasodilation mediated by nitric oxide
Leaky capillaries because TNF denudes the glycocalyx.

MYOCARDIAL DYSFUNCTION



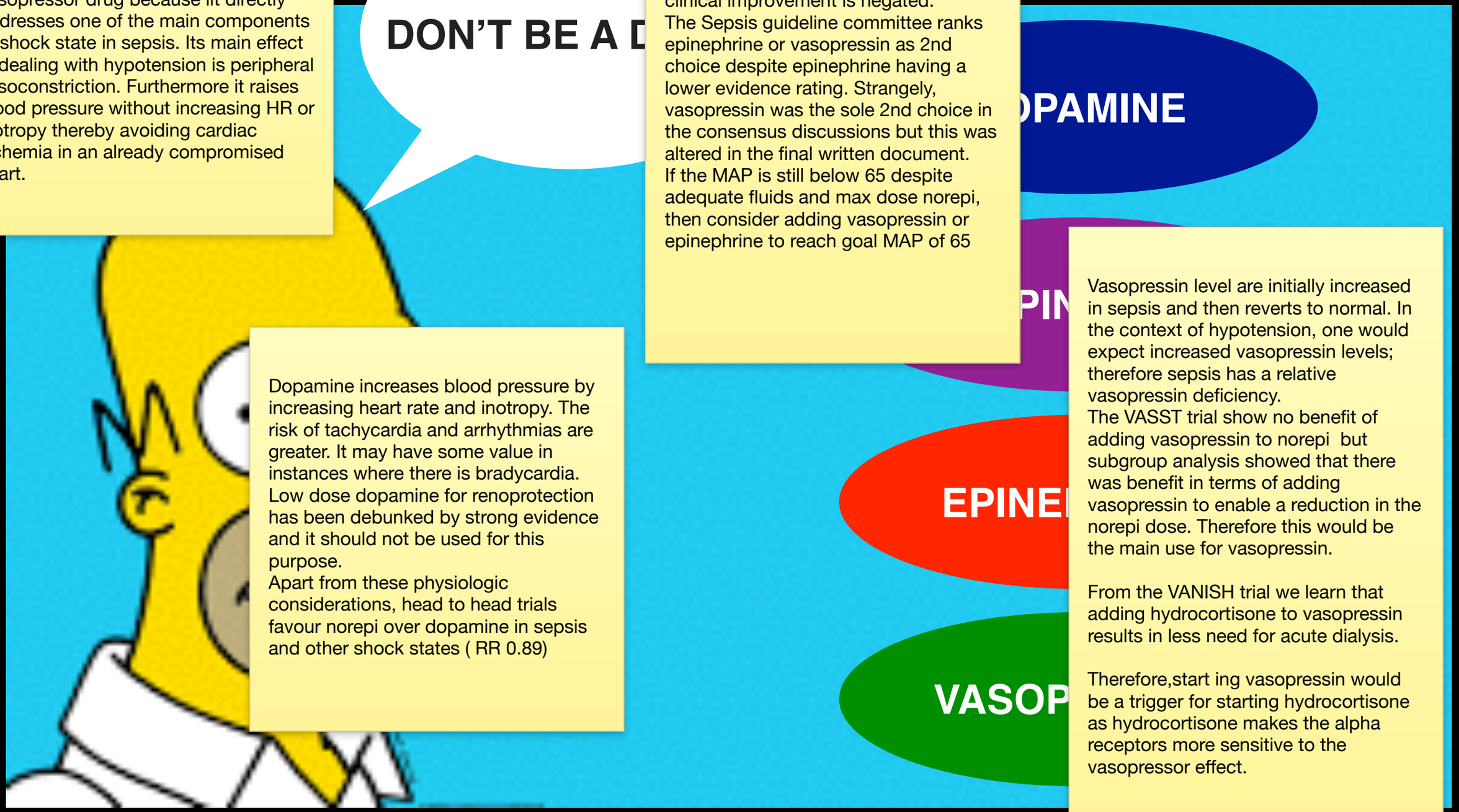
Improve Stroke Volume

RAPID SUPPORT OF MAP IN SEPTIC SHOCK



Norepi is clearly the best option as a vasopressor drug because iit directly addresses one of the main components of shock state in sepsis. Its main effect in dealing with hypotension is peripheral vasoconstriction. Furthermore it raises blood pressure without increasing HR or inotropy thereby avoiding cardiac ischemia in an already compromised heart.

Epinephrine exerts its effect primarily by its increase on HR and contractility. It reduces sphlacnic circulation and increase serum lactate by its beta 2 effect on skeletal muscles. Therefore lactate clearance as a measure of clinical improvement is negated.
The Sepsis guideline committee ranks epinephrine or vasopressin as 2nd choice despite epinephrine having a lower evidence rating. Strangely, vasopressin was the sole 2nd choice in the consensus discussions but this was altered in the final written document.
If the MAP is still below 65 despite adequate fluids and max dose norepi, then consider adding vasopressin or epinephrine to reach goal MAP of 65



Dopamine increases blood pressure by increasing heart rate and inotropy. The risk of tachycardia and arrhythmias are greater. It may have some value in instances where there is bradycardia.
Low dose dopamine for renoprotection has been debunked by strong evidence and it should not be used for this purpose.
Apart from these physiologic considerations, head to head trials favour norepi over dopamine in sepsis and other shock states (RR 0.89)

Vasopressin level are initially increased in sepsis and then reverts to normal. In the context of hypotension, one would expect increased vasopressin levels; therefore sepsis has a relative vasopressin deficiency.
The VASST trial show no benefit of adding vasopressin to norepi but subgroup analysis showed that there was benefit in terms of adding vasopressin to enable a reduction in the norepi dose. Therefore this would be the main use for vasopressin.

From the VANISH trial we learn that adding hydrocortisone to vasopressin results in less need for acute dialysis.

Therefore,start ing vasopressin would be a trigger for starting hydrocortisone as hydrocortisone makes the alpha receptors more sensitive to the vasopressor effect.

SUMMARY OF HEMODYNAMIC INTERVENTIONS

INOTROPES

FLUIDS

C R R A P

VASOPRESSORS

TO WHAT ENDPOINT DO WE RESUSCITATE?

Michelle Hay
Boosting oxy
supernormal
patients caus

Surviving Sepsis Campaign

i cps up regulation
t increases the
to produce more
actate.
AEROBIC

2016

uiding resuscitation to normalize la
ients with elevated lactate levels
as a marker of tissue hypoperfusion

(weak recommendation, low quality of evidence).

proof that there is no tissue hypoxia
Normal number of ATP molecules in septic tidssue

Increased lactate is produced by skeletal muscle, the liver and the oxygen rich lungs and serves as an important and more efficient biofuel for the heart and kidneys

ARE WE MISSING SOMETHING?

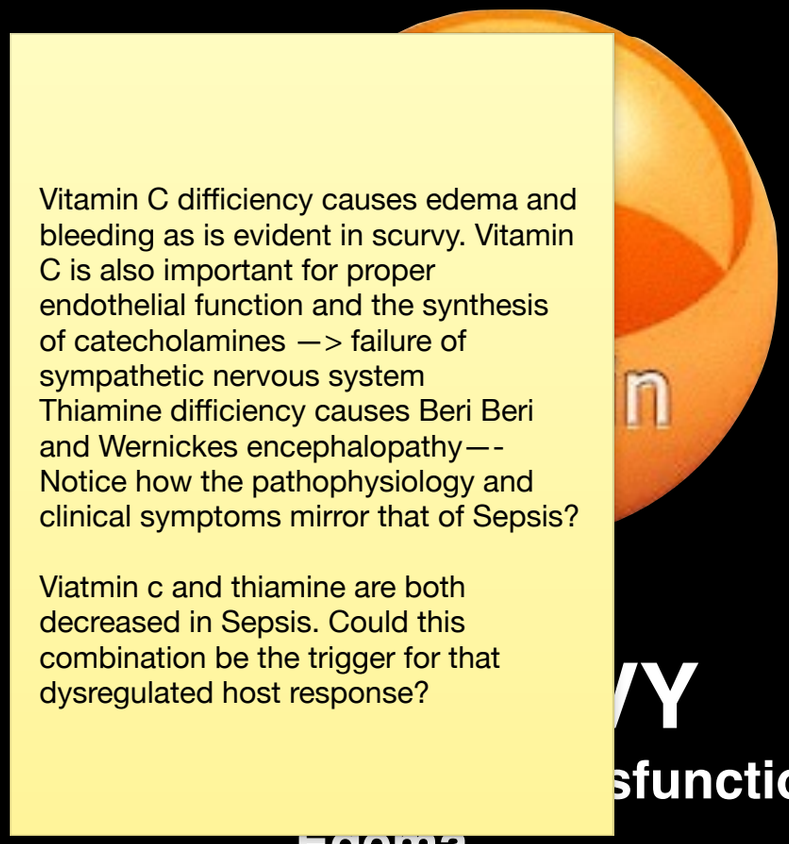
Sepsis resuscitation focuses on hemodynamics and tissue oxygen delivery. We can deliver all the oxygen we want but it would be useless if the mitochondria cannot utilize it.

The question is, are we missing something more basic?

Interesting question that warrants more investigationf

Vitamin C difficiency causes edema and bleeding as is evident in scurvy. Vitamin C is also important for proper endothelial function and the synthesis of catecholamines —> failure of sympathetic nervous system
Thiamine difficiency causes Beri Beri and Wernickes encephalopathy—-
Notice how the pathophysiology and clinical symptoms mirror that of Sepsis?

Viatmin c and thiamine are both decreased in Sepsis. Could this combination be the trigger for that dysregulated host response?



VY

sfunction

Edema
Bleeding
Failed Sympathetics
Vasodilation

BERI BERI
Distributive shock
Increased Lactic Acid

WERNICKE'S
Delirium

METABOLIC RESUSCITATION: DOES IT WORK?

1.THIS 2016 study shows the effect of low and high dose vitamin c on SOFA scores - see marked reduction in score with high dose vitamin c.
2, Another 2016 study looked at thiamine in sepsis and found no mortality benefit. However in considering only those patients with thiamine difficiency, there was a benefit
3. This study by Marik et Al is creating all the buzz in the Sepsis world. Their small randomized control trial had 47 patients in each arm. They used a iv cocktail of vit c 1.5g q 6h, thiamine 200mg q 12h and hydrocortisone 50mg q 6h. HC was added for its synergistic effect with vit c in protecting the endothelium.
They showed a mortality reduction
4. Earlier weaning of vasopressors despite less overall fluids given
5. and improvement in SOFA scores and Procalcitonin levels over time

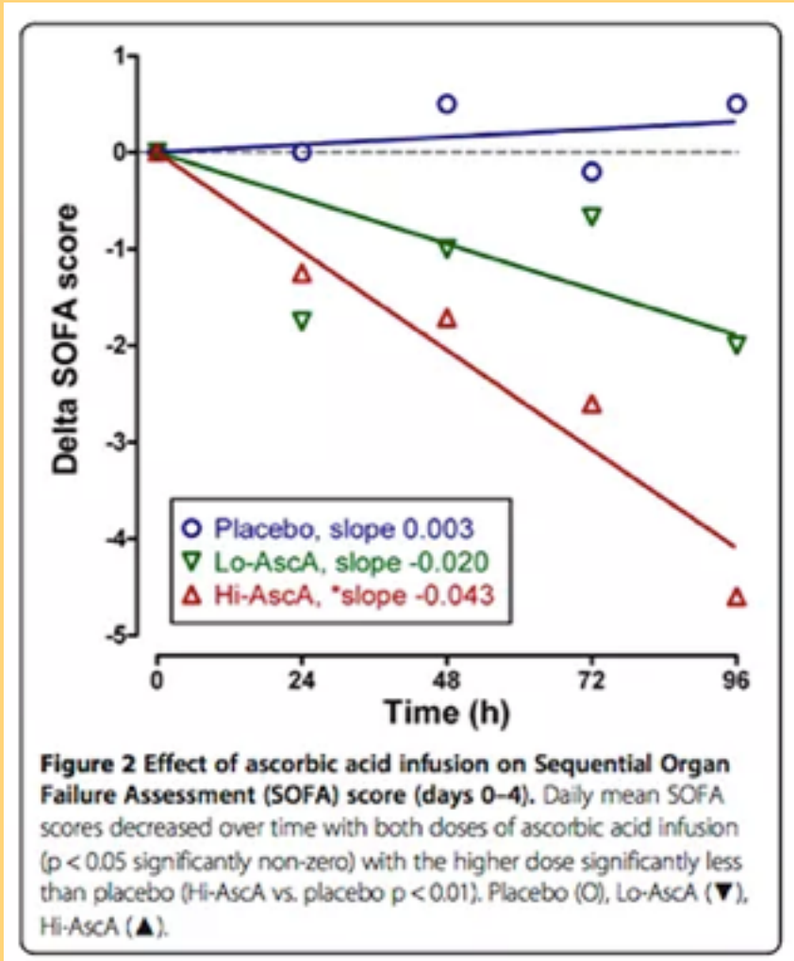


Figure 2 Effect of ascorbic acid infusion on Sequential Organ Failure Assessment (SOFA) score (days 0–4). Daily mean SOFA scores decreased over time with both doses of ascorbic acid infusion ($p < 0.05$ significantly non-zero) with the higher dose significantly less than placebo (Hi-AscA vs. placebo $p < 0.01$). Placebo (O), Lo-AscA (▼), Hi-AscA (▲).

Zabet MH et al 2016:
Effect of high-dose ascorbic acid on vasopressor requirement in septic shock

Gracias!

Dankie

Thank You!

நன்றி
nanṟi

Mahalo!

谢谢
Xiexie

Ngiyabonga

shukriya

Danke

Merci!

ありがとう
Arigatō