Sepsis Learning Collaborative:

Evidence-based Approaches to Sepsis Resuscitation
Sepsis Resuscitation in Medically Complex Patients

Presenters

Dr. Nathan Shapiro

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Evidence Based Approaches to Sepsis Resuscitation

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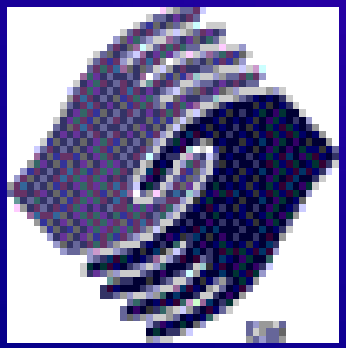
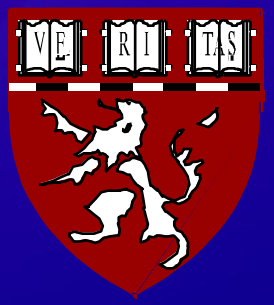




Disclosures

- Industry Research Grants
  - Cheetah Medical, Thermo-Fisher, Astute, Rapid Pathogen Sctreening
- NIH Funding Acknowledgements:
  - 1R01 HL09175701A1 and 1R01HL091757 (PI Shapiro - NHLBI)
  - 1RO1 HL101382 (PI Bennet-Guerrero and Stowell – NHLBI)

The New England Journal of Medicine

EARLY GOAL-DIRECTED THERAPY IN THE TREATMENT OF SEVERE SEPSIS AND SEPTIC SHOCK

EMANUEL RIVERS, M.D., M.P.H., BRYANT NGUYEN, M.D., SUZANNE HAVSTAD, M.A., JULIE RESSLER, B.S., ALEXANDRIA MUZZIN, B.S., BERNHARD KNOBLICH, M.D., EDWARD PETERSON, PH.D., AND MICHAEL TOMLANOVICH, M.D., FOR THE EARLY GOAL-DIRECTED THERAPY COLLABORATIVE GROUP*

VARIABLE	STANDARD THERAPY (N=133)	EARLY GOAL-DIRECTED THERAPY (N=130)	RELATIVE RISK (95% CI)	P VALUE
	no. (%)			
In-hospital mortality†				
All patients	59 (46.5)	38 (30.5)	0.58 (0.38–0.87)	0.009
Patients with severe sepsis	19 (30.0)	9 (14.9)	0.46 (0.21–1.03)	0.06
Patients with septic shock	40 (56.8)	29 (42.3)	0.60 (0.36–0.98)	0.04
Patients with sepsis syndrome	44 (45.4)	35 (35.1)	0.66 (0.42–1.04)	0.07
28-Day mortality†	61 (49.2)	40 (33.3)	0.58 (0.39–0.87)	0.01
60-Day mortality†	70 (56.9)	50 (44.3)	0.67 (0.46–0.96)	0.03

- Early, protocolized resuscitation to targeted physiologic endpoints
- Facilitates early, aggressive resuscitation

Rivers, Nguyen et al NEJM: 354 (19): November 8,2001

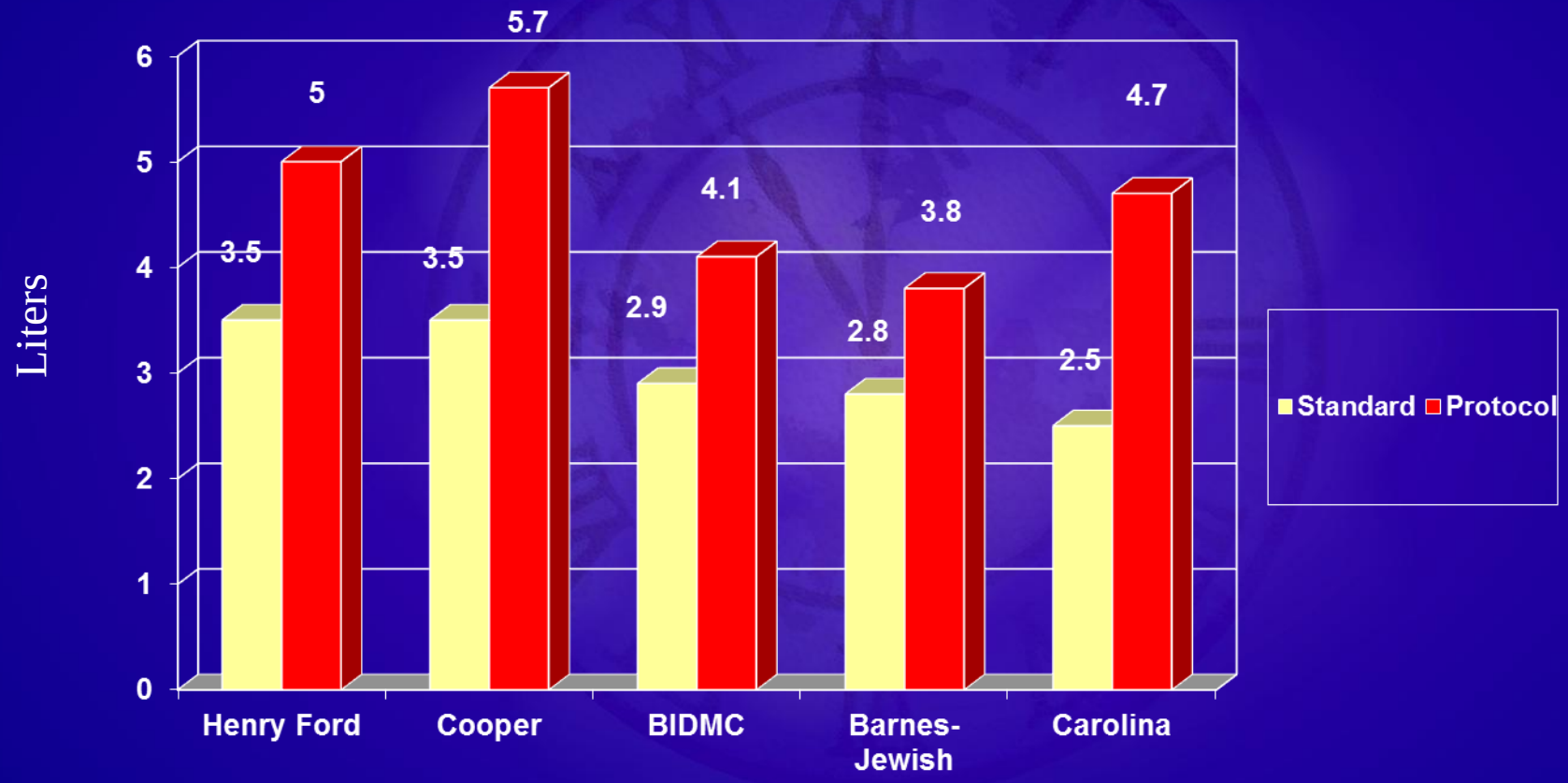
Single Center EGDT Studies

Site	Author	n	design	Protocol
Henry Ford	Rivers	263	Random	EGDT ONLY
Cooper	Trzeciak	38	Hist Control	YES
BIDMC	Shapiro	130	Hist Control	YES
Barnes	Micek	120	Prosp obs	YES
Carolinas	Jones	157	Prosp obs	YES

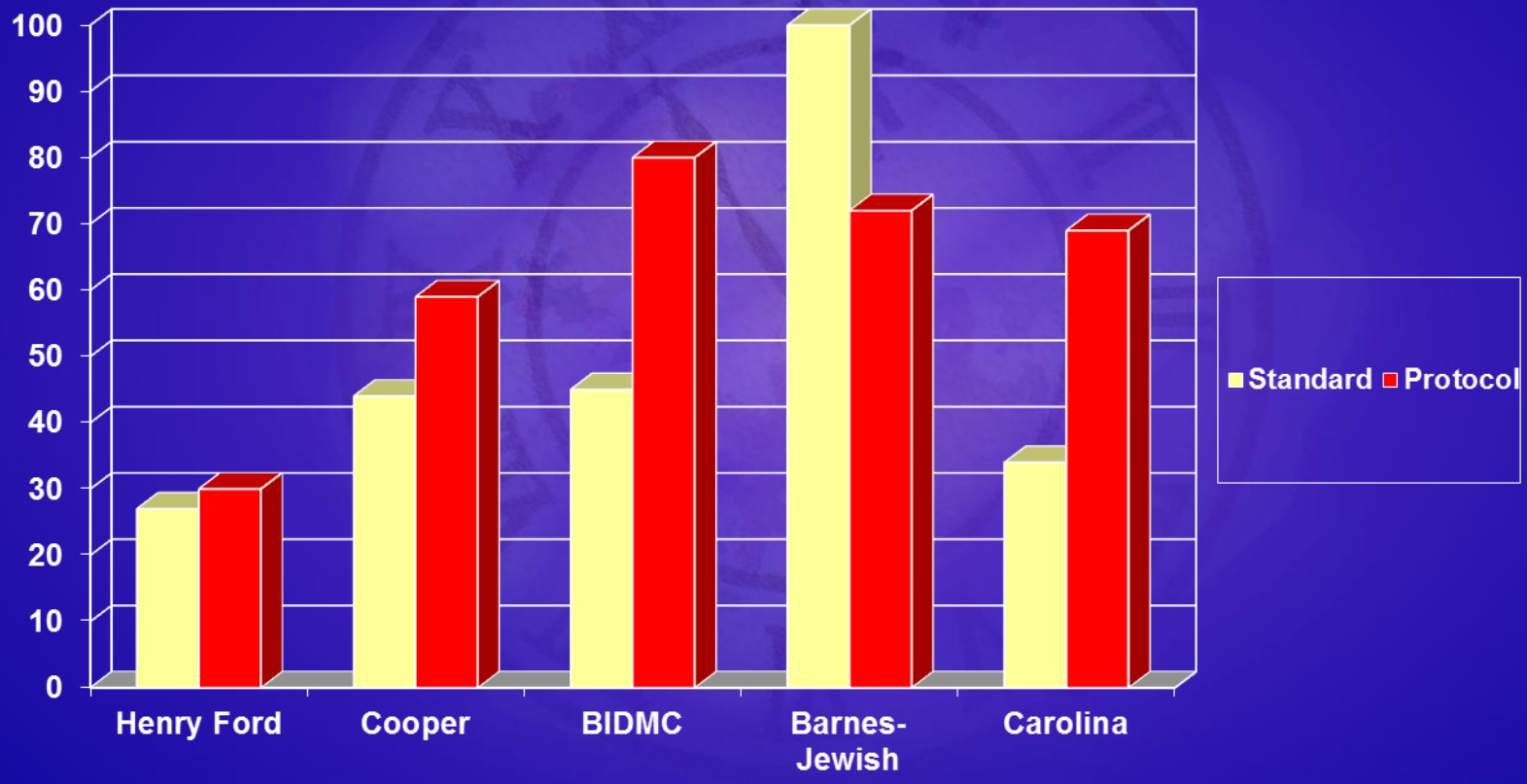
River et al. NEJM 2001;
Shapiro CCM 2006;
Jones et al. Chest 2007

Trzeciak et al. Chest 2006.
Micek CCM. 2007;

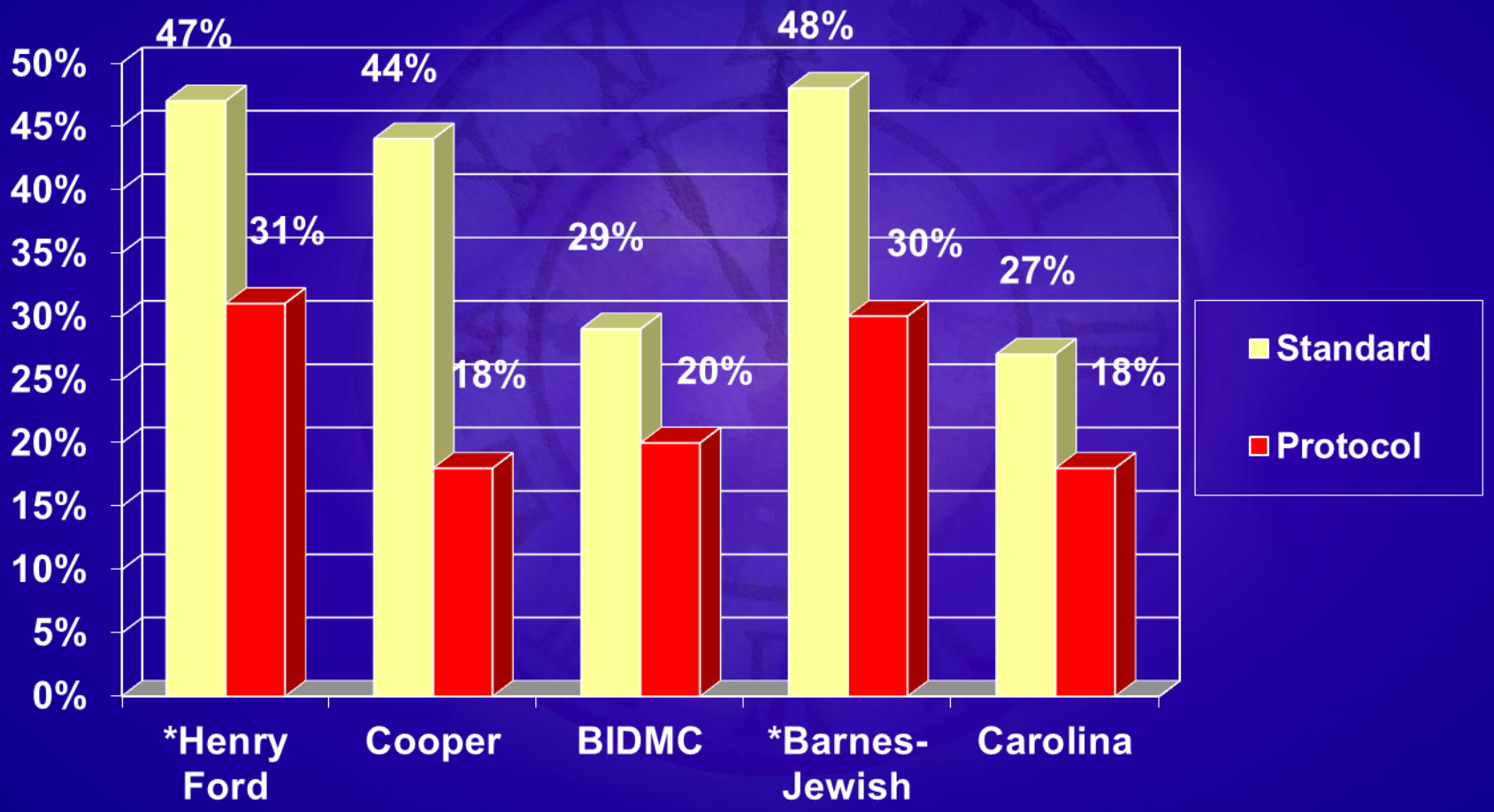
Fluids - Initial



Vasopressor Use



Mortality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*Henry Ford
Cooper
BIDMC
*Barnes-Jewish
Carolina
Standard
Protocol

Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock, 2012

SURVIVING SEPSIS CAMPAIGN CARE BUNDLES

TO BE COMPLETED WITHIN 3 HOURS:

1) Measure lactate level
2) Obtain blood cultures prior to administration of antibiotics
3) Administer broad spectrum antibiotics
4) Administer 30 mL/kg crystalloid for hypotension or lactate ≥ 4 mmol/L

TO BE COMPLETED WITHIN 6 HOURS:

5) Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥ 65 mm Hg
6) In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate ≥ 4 mmol/L (36 mg/dL):
   - Measure central venous pressure (CVP)*
   - Measure central venous oxygen saturation ($ScvO_2$)*
7) Remeasure lactate if initial lactate was elevated*

Dellinger et al Intensive Care Med. 2013:39:165-228

3 EGDT Validation Trials

- ProCESS (United States)
- ARISE (Australia)
- ProMISe (England)

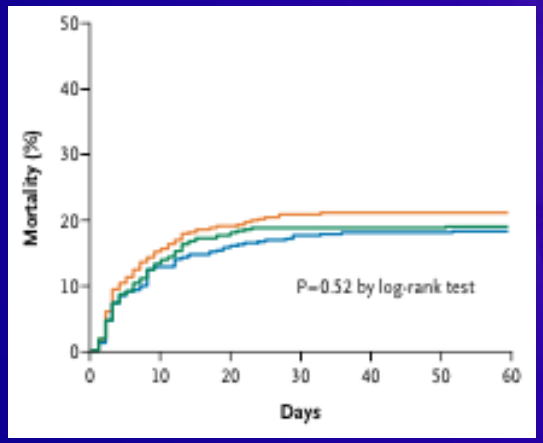
3 EGDT Validation Trials

ProCESS

ORIGINAL ARTICLE

A Randomized Trial of Protocol-Based Care for Early Septic Shock

The ProCESS Investigators*

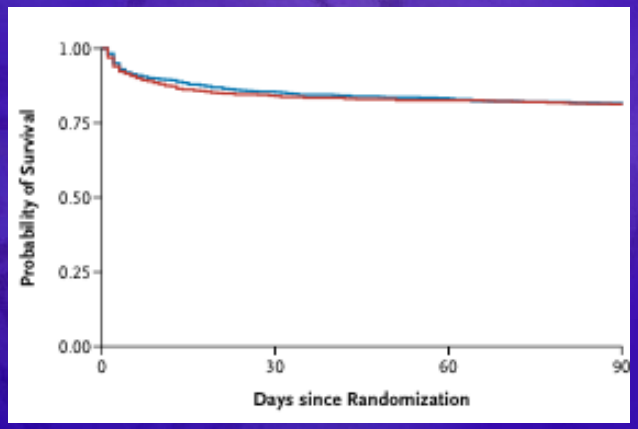


ARISE

ORIGINAL ARTICLE

Goal-Directed Resuscitation for Patients with Early Septic Shock

The ARISE Investigators and the ANZICS Clinical Trials Group*

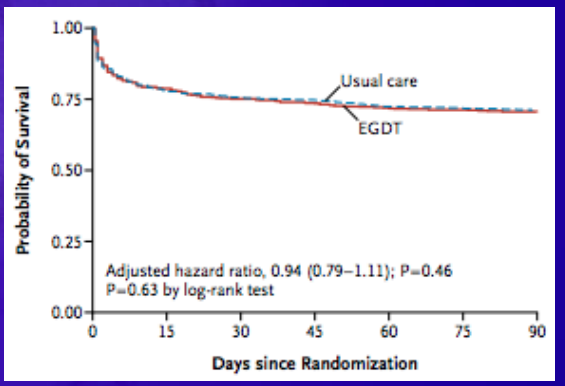


ProMISe

ORIGINAL ARTICLE

Trial of Early, Goal-Directed Resuscitation for Septic Shock

Paul R. Mouncey, M.Sc., Tiffany M. Osborn, M.D., G. Sarah Power, M.Sc., David A. Harrison, Ph.D., M. Zia Sadique, Ph.D., Richard D. Grieve, Ph.D., Rahi Jahan, B.A., Sheila E. Harvey, Ph.D., Derek Bell, M.D., Julian F. Bion, M.D., Timothy J. Coats, M.D., Mervyn Singer, M.D., J. Duncan Young, D.M., and Kathryn M. Rowan, Ph.D., for the ProMISe Trial Investigators*

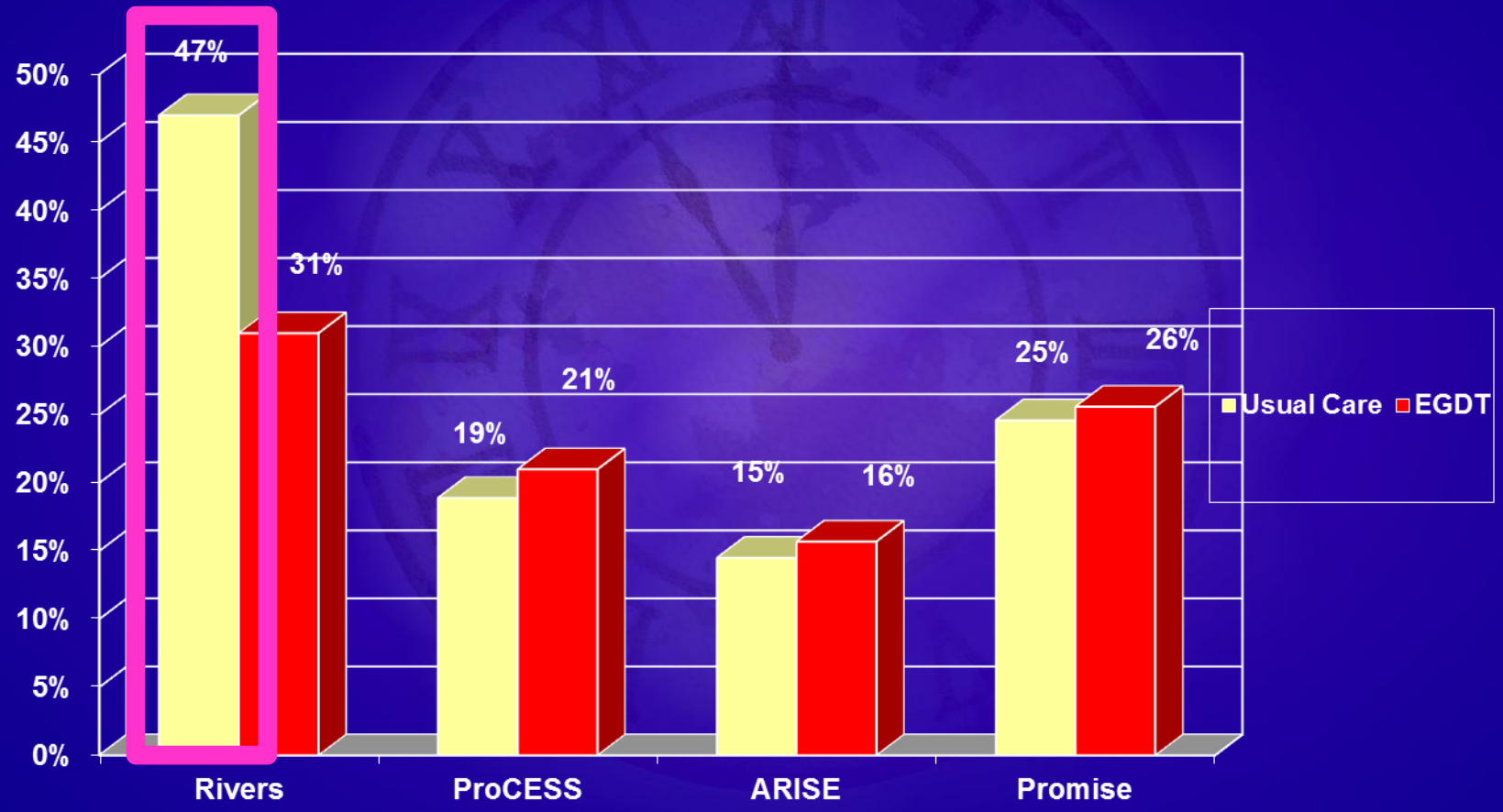


PROCESS Investigators. New England Journal of Medicine. 2014;370(18):1683-93

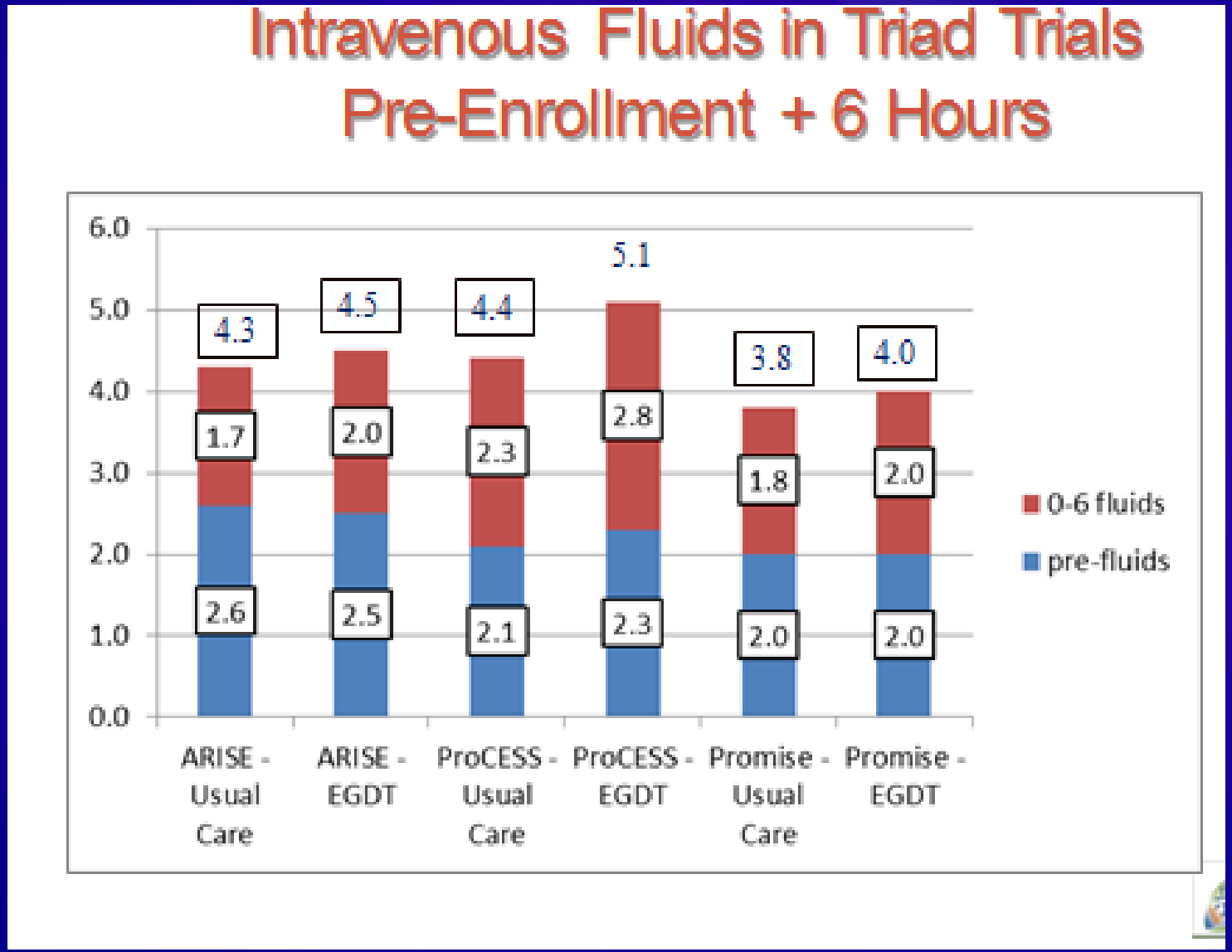
Mouncey PR,, et al. New England Journal of Medicine. 2015.

ARISE Investigators New England Journal of Medicine. 2014;371(16):1496-506.

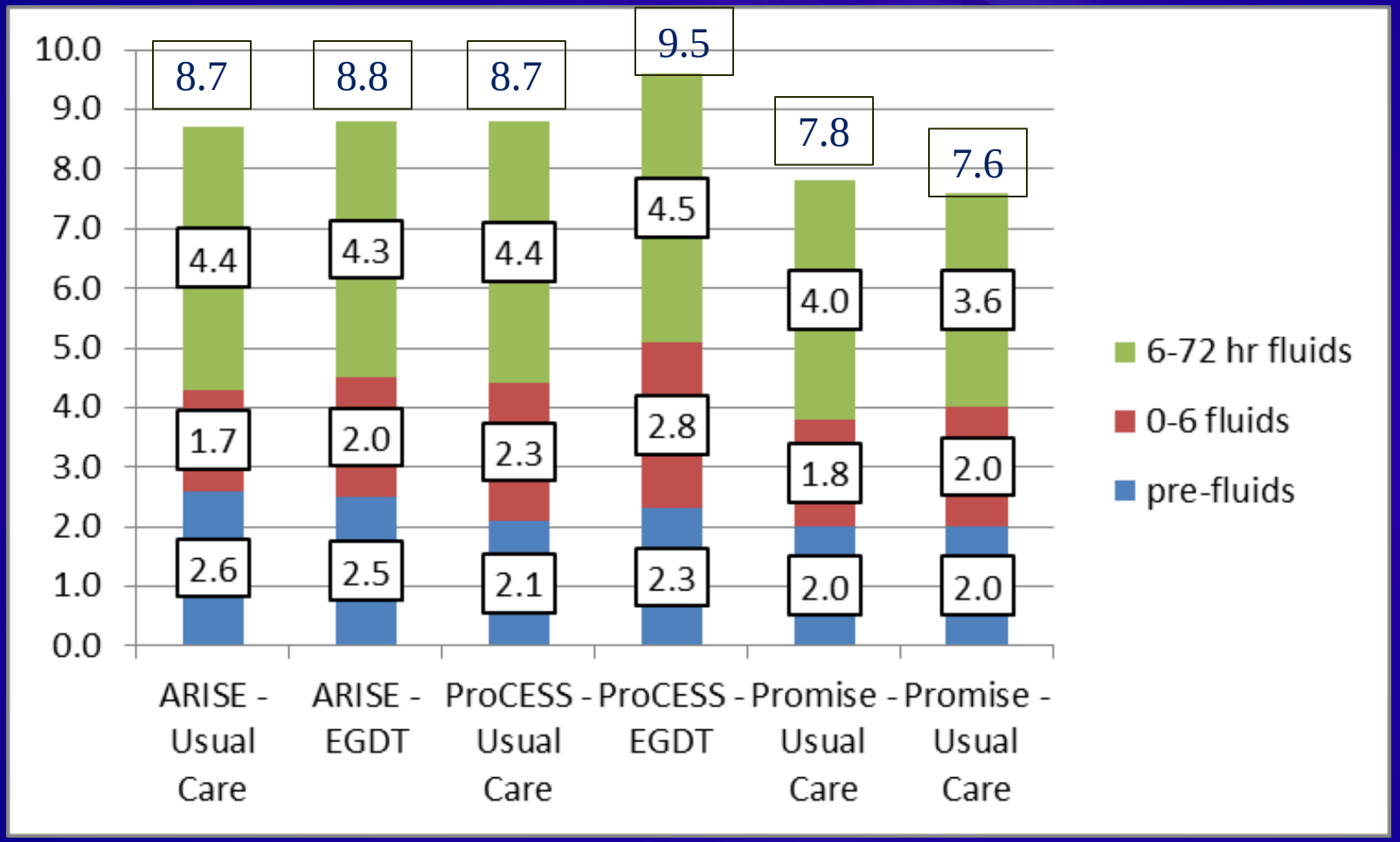
Mortality Rates for EGDT Trials



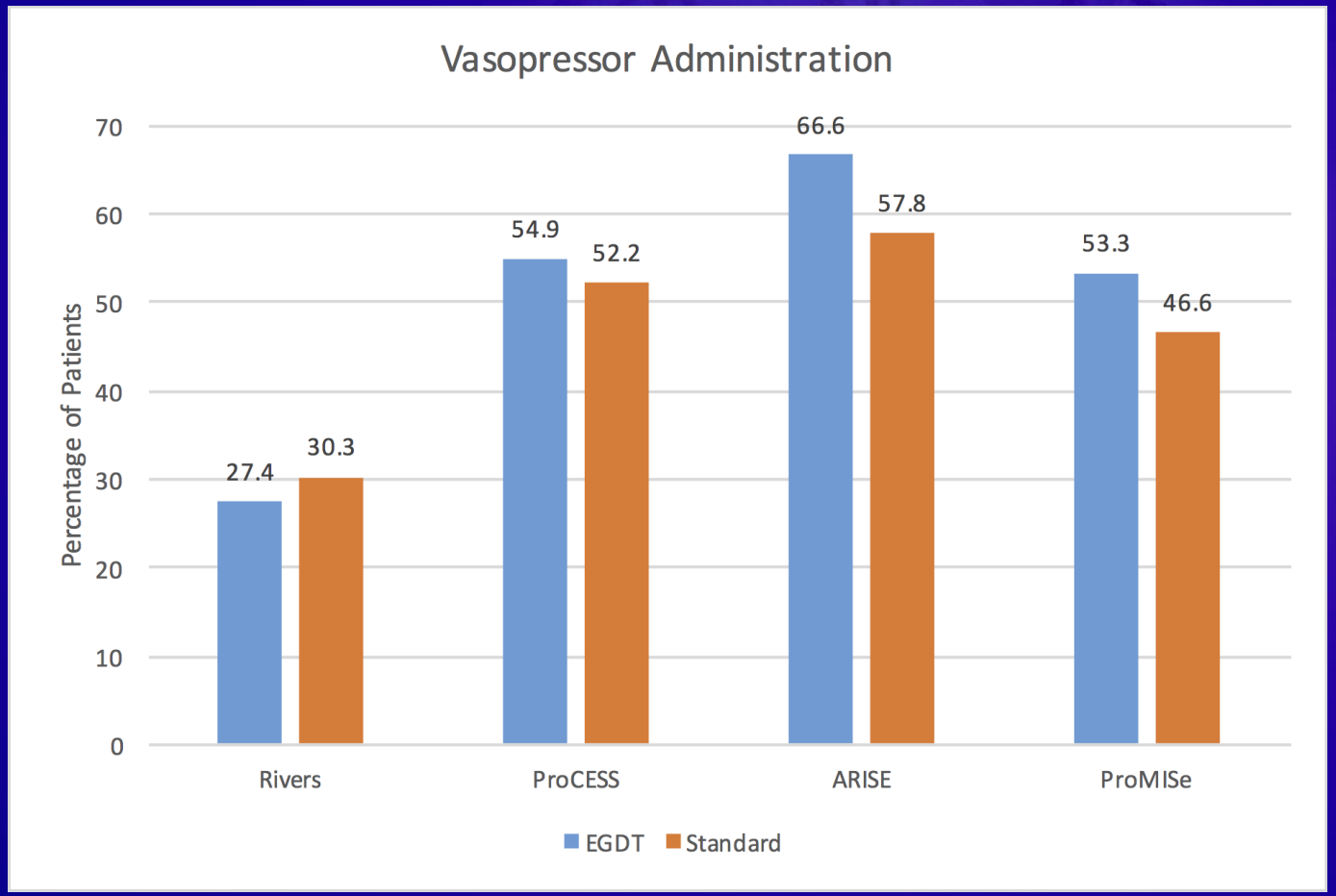
Intravenous Fluids in Triad Trials



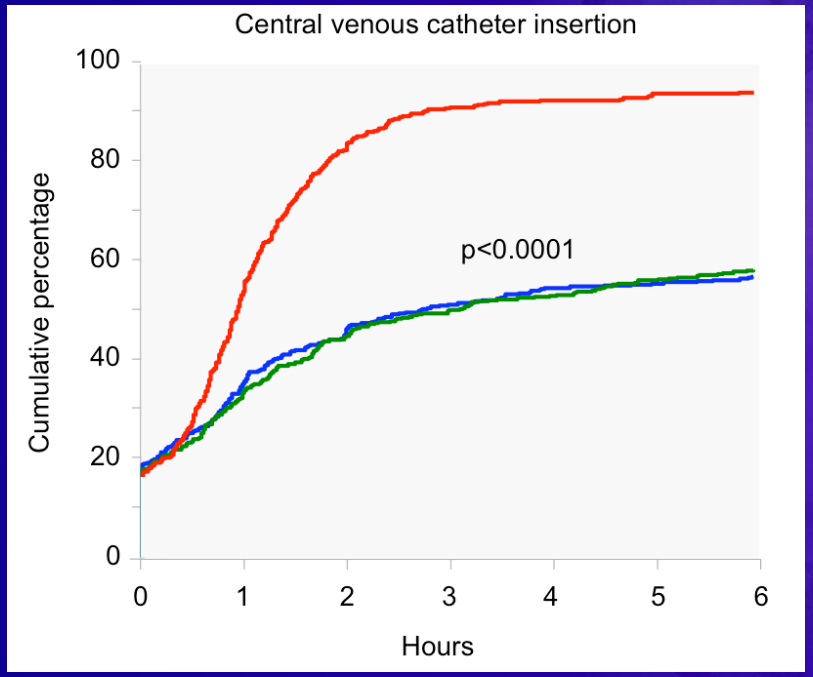
All Fluids Over 72 hours

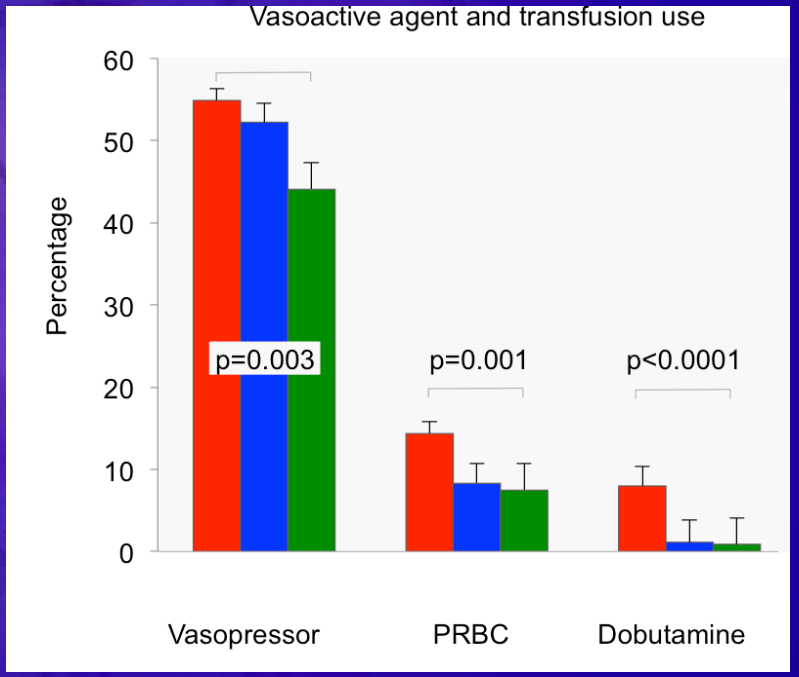


Vasopressor Administration



Other Processes of Care

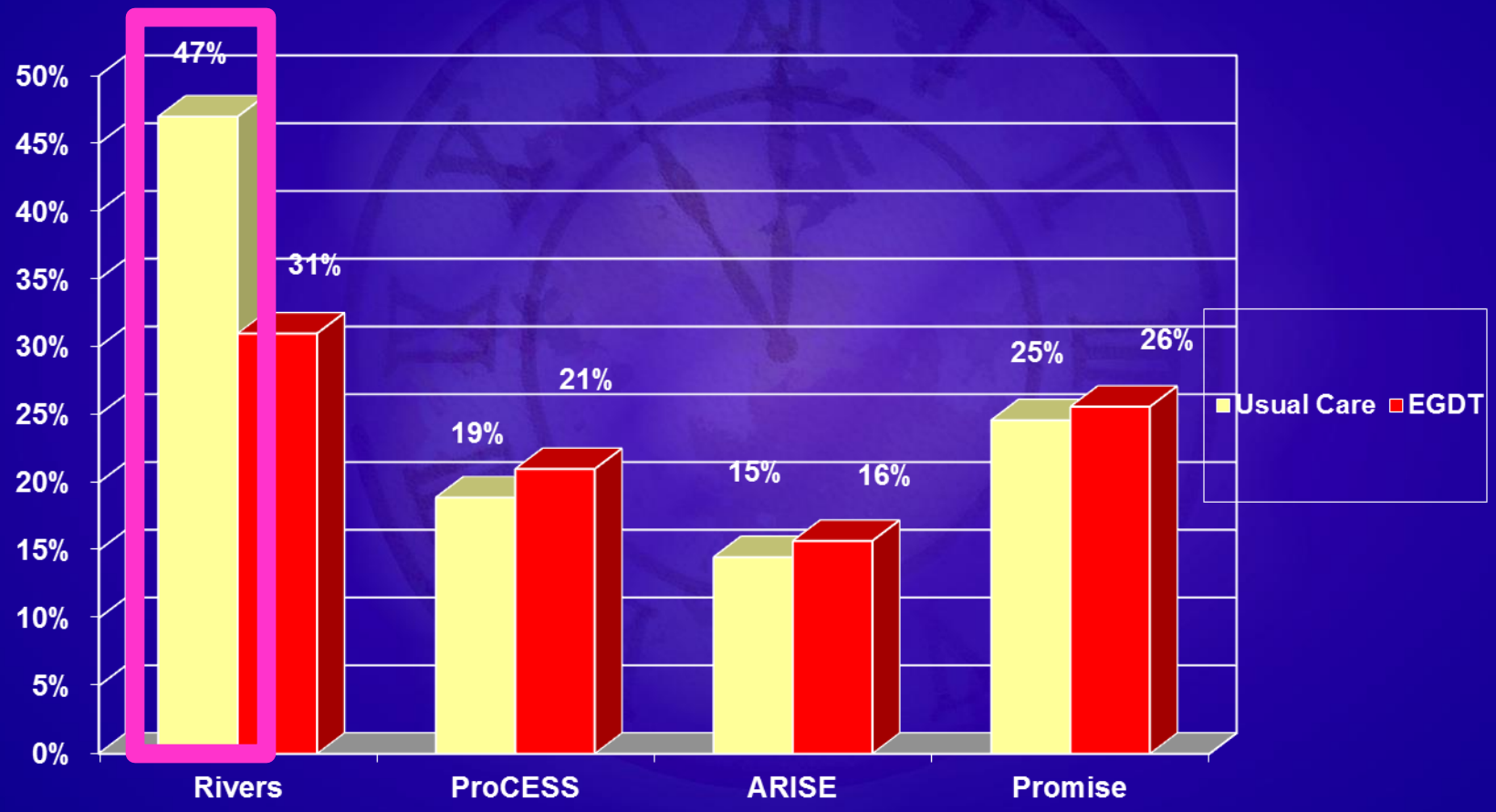




Protocol-based EGDT Protocol-based Standard Therapy Usual care

PROCESS Investigators, A randomized trial of protocol-based care for early septic shock. New England Journal of Medicine. 2014;370(18):1683-93

Mortality Rates for EGDT Trials



Implications of EGDT triad trials

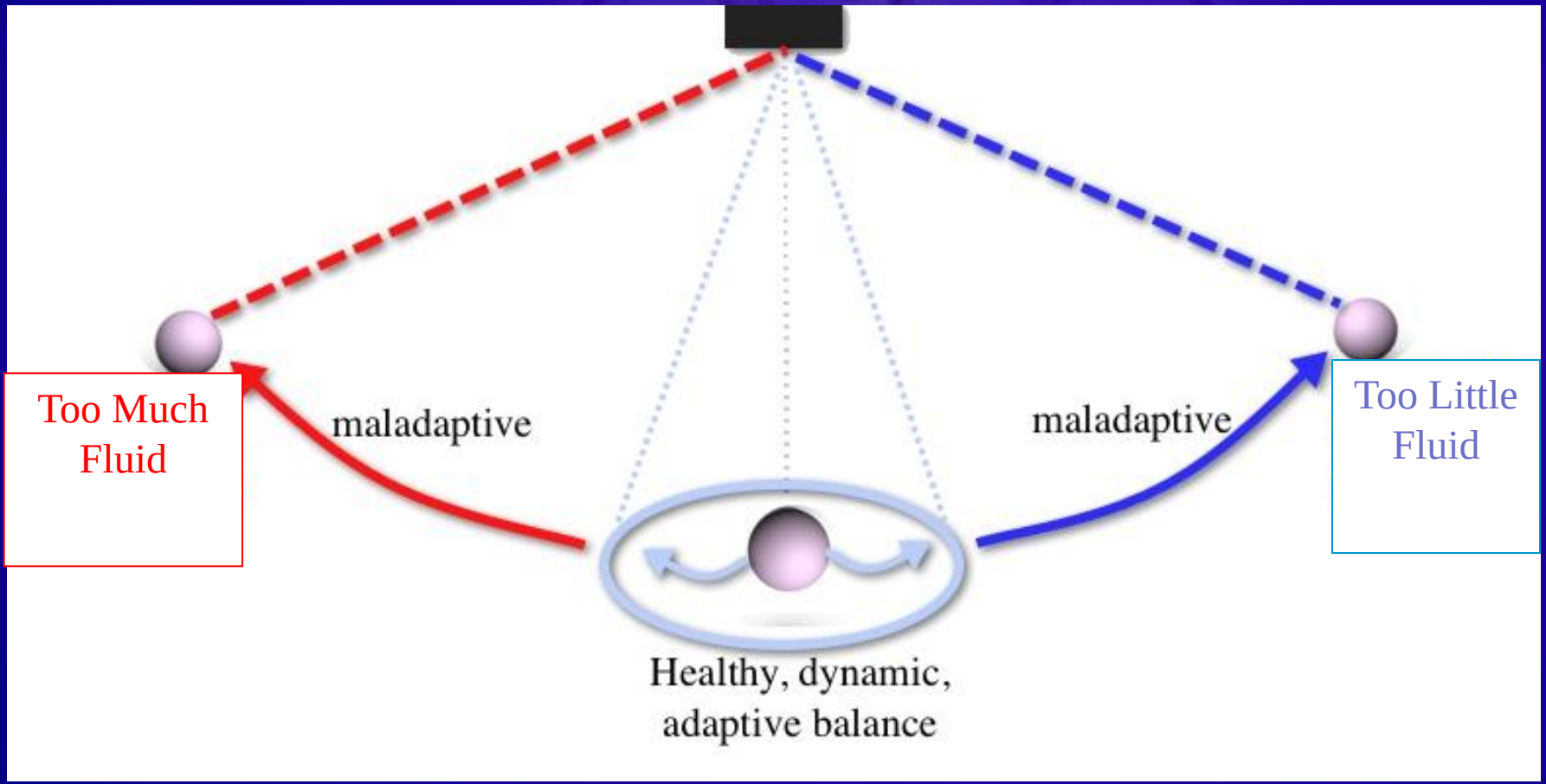
Backdrop: All patients received

- Early Identification
- Aggressive Fluid Resuscitation (about 4-5 liters in first 6 hours)
- Early antibiotics (≥97% all groups)
- Other care elements provided

1. A team based EGDT protocol or empiric structured protocol was not beneficial
2. Systematic Screening and Aggressive treatment is needed to reproduce these findings

Question: How much fluids should we give a patient with Severe Sepsis during the initial phases?

The Pendulum is Swinging



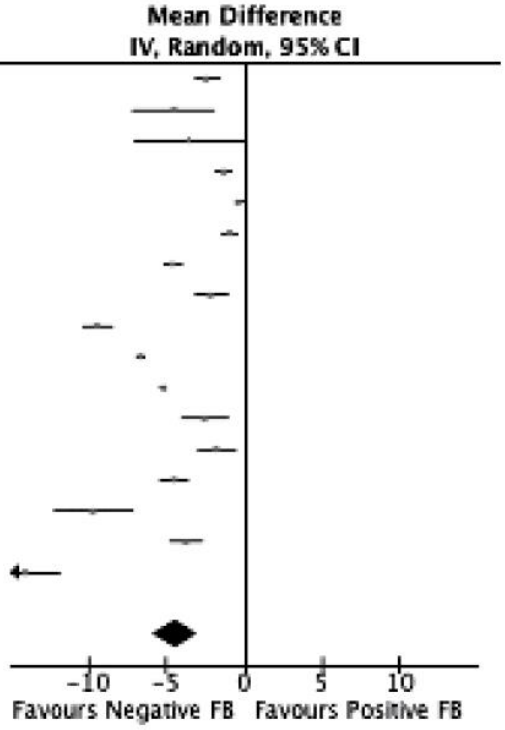
Each Has Theoretical Advantages

Liberal Fluids	Conservative Fluids
Augment preload to increase CO and organ perfusion	Reduce overall fluids and positive fluid balance
Decrease vasopressor use and its detrimental effects	Early vasopressors to treat vasodilation
?Increase Microcirculatory Flow	Prevent worsening of pathologic edema (due to sepsis-induced barrier dysfunction)
Current early empiric approach	Observational studies of Fluid and Fluid Balance Associated with Poor Outcomes

Negative Fluid Balance is Associated with **Better** Outcomes

Study or Subgroup	Survivors Mean	SD	Total	Nonsurvivors Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Alsous 2000	0.05	0.4	16	2.4	1.7	20	6.1%	-2.35 [-3.12, -1.58]
Cordemans 2012 (CLI)	4.971	7.737	58	9.503	6.91	65	5.1%	-4.53 [-7.14, -1.93]
Cordemans 2012 (PAL)	3.419	7.842	70	6.982	9.875	44	4.5%	-3.56 [-7.01, -0.12]
Dabrowski 2014	-0.963	1.089	24	0.333	0.401	6	6.2%	-1.30 [-1.84, -0.75]
Goldstein 2005	0.457	0.403	60	0.805	0.858	56	6.3%	-0.35 [-0.59, -0.10]
Kuzkov 2006	0.893	0.668	16	1.782	0.75	15	6.2%	-0.89 [-1.39, -0.39]
Malbrain 2005	1.643	1.5	192	6.214	2.143	73	6.2%	-4.57 [-5.11, -4.04]
Malbrain 2014	3.862	6.904	314	5.994	7.546	413	6.1%	-2.13 [-3.19, -1.08]
Micek 2013	2.709	2.585	162	12.124	5.463	163	6.1%	-9.42 [-10.34, -8.49]
Murphy 2009	9.25	0.625	125	15.875	1.125	87	6.3%	-6.63 [-6.89, -6.36]
Rosenberg 2009	5.154	0.769	159	10.308	1.923	635	6.3%	-5.15 [-5.35, -4.96]
Sakr 2005	1.4	6.5	239	3.9	7.8	153	5.9%	-2.50 [-3.99, -1.01]
Schuller 1991	0.25	1.6	43	2	2.8	26	6.0%	-1.75 [-2.93, -0.57]
Shum 2011	0.88	2.32	505	5.41	5.05	134	6.1%	-4.53 [-5.41, -3.65]
Simmons 1987	7.5	4.09	11	17.22	2.045	26	5.2%	-9.72 [-12.26, -7.18]
The RENAL Study 2012	-1.94	11	808	1.755	9.061	644	6.1%	-3.69 [-4.73, -2.66]
Vidal 2008	2.1	3.9	34	16.1	6.4	49	5.4%	-14.00 [-16.22, -11.78]
Total (95% CI)			**2836**			**2609**	**100.0%**	**-4.43 [-5.83, -3.04]**

Heterogeneity: $Tau^2 = 8.09$; $Chi^2 = 1894.59$, df = 16 ($P < 0.00001$); $I^2 = 99\%$
Test for overall effect: Z = 6.23 ($P < 0.00001$)



Manu L.N.G. Malbrain et al., Fluid overload, de-resuscitation, and outcomes in critically ill or injured patients

Anaesthesiol Intensive Ther 2014, vol. 46, no 5, 361–380

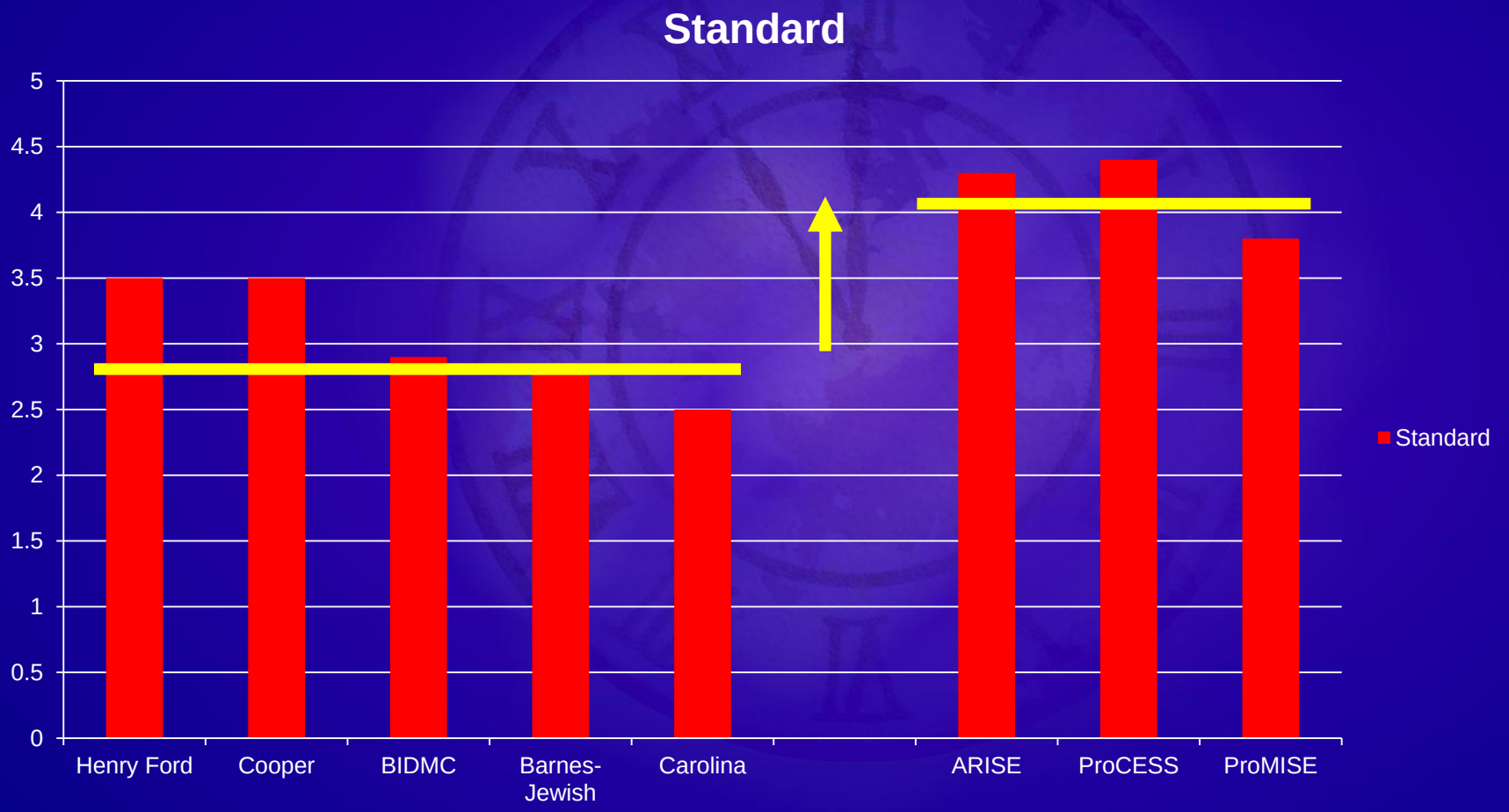
Data in support of Conservative Approach ?

- Observational Studies finding Association between fluid volume/balance and Adverse Outcome
  - Confounding by Indication
  - Fluid Administration is really, really good biomarker of illness severity
  - Association does not equal causation
- FEAST trial provocative but different population/setting

Support for a Liberal Approach ?

- Physiologically logical
- Historical Shifts and Mortality trends support this approach

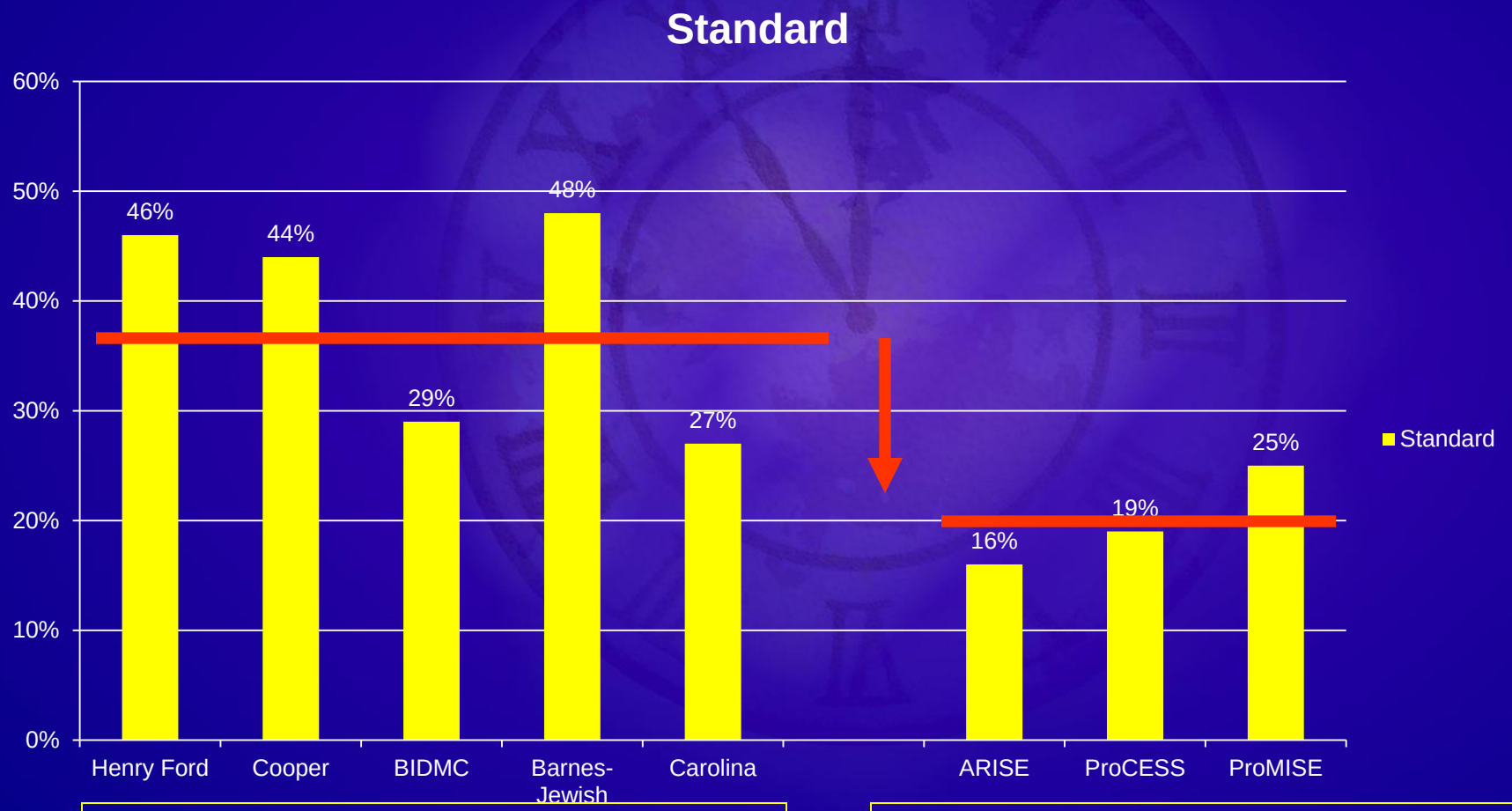
Fluids in Usual Care
Pre- and Post- Rivers



Pre-Rivers

Post-Rivers

Mortality in Usual Care Pre- and Post- Rivers



Pre-Rivers

Post-Rivers

Limitations and Opportunity

- Studies are Largely observational
- Well conducted trials are needed

Challenge to the EDs and ICUs

- Early Identification
- Assure “appropriate” fluid resuscitation in all patients (~ 4 liters in ED)
- Assure early/appropriate antibiotics
- Optimize other care elements
- We cannot return to Sepsis Circa 2000

Systematically in ALL patients!!!

EFFECTIVE SEPSIS RESUSCITATION IN MEDICALLY COMPLEX PATIENTS

LAURENCE DUBENSKY, MD
ASSISTANT PROGRAM DIRECTOR
RESIDENCY IN EMERGENCY MEDICINE

Aventura Hospital and Medical Center

DISCLOSURES:

- None

DISCLAIMER:

- Expert opinion / consensus recommendations
- Actively evolving evidence

OBJECTIVES

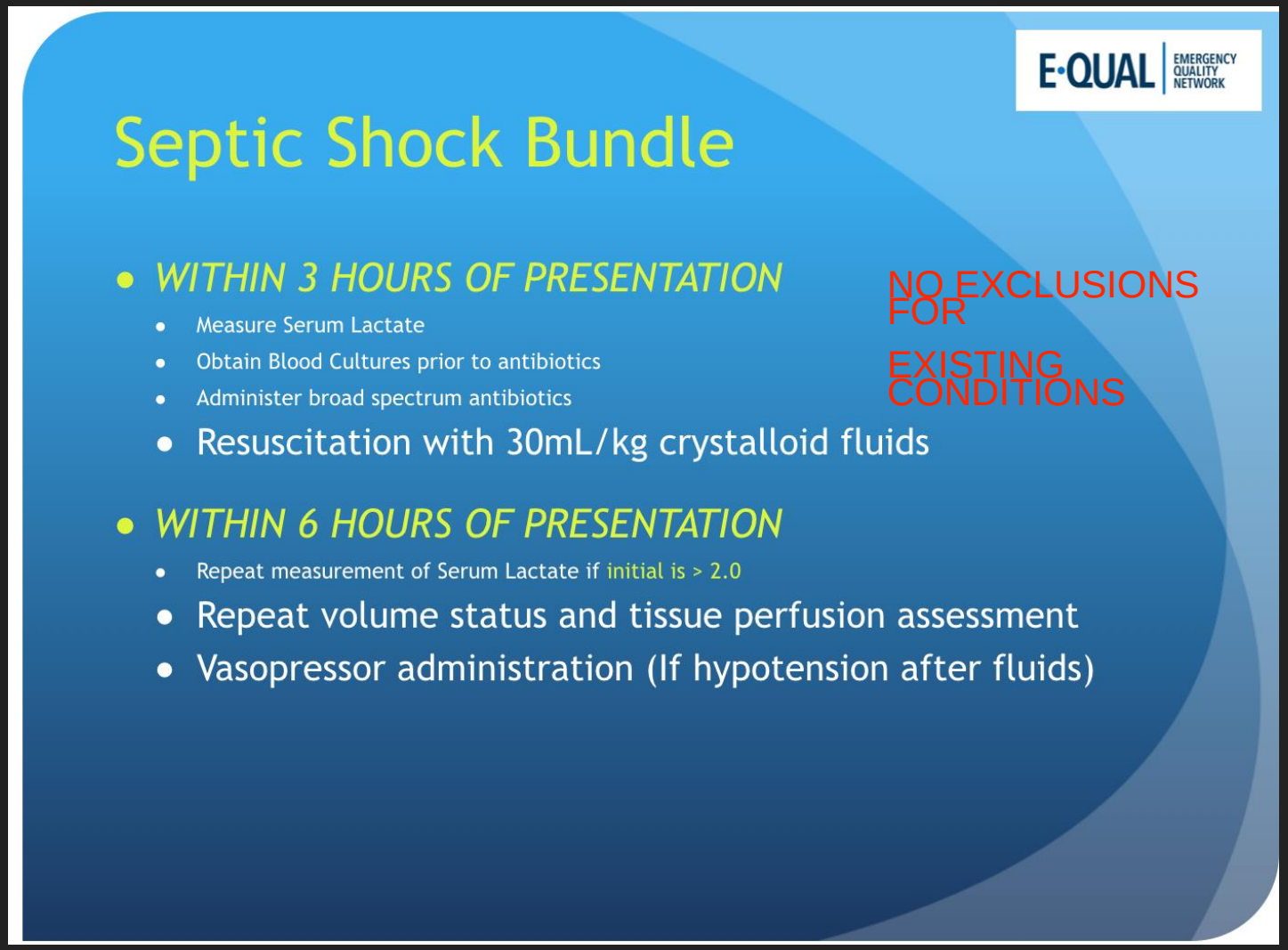
- Address provider concerns about medically complex care:
  - Volume overload - liberal vs conservative
  - POCUS - ECHO
  - Early vasopressors in fluid restricted models

- CHF - right heart failure and pulmonary HTN
- ESRD - hemodialysis and peritoneal dialysis
- Cirrhotic / Liver disease
- Goals of Care

Chest. 2014 Jun;145(6):1407-18

REFRESHER

- SEP-1 measures:



FLUID RESPONSIVENESS

REVIEW ARTICLE

A rational approach to fluid therapy in sepsis

P. Marik[1,*] and R. Bellomo[2]

[1]Division of Pulmonary and Critical Care Medicine, Eastern Virginia Medical School, 825 Fairfax Av, Suite 410, Norfolk, VA 23507, USA, and [2]Intensive Care Unit, Austin Health, Heidelberg, Victoria, Australia

- Increase in SV by 10-15% in response to 250-500cc bolus
- Important to assess fluid tolerance and responsiveness before fluid loading
- Venous capacitance and myocardial dysfunction
- <40% of patients are fluid responders

FLUID RESPONSIVENESS

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STATIC ASSESSMENT	DYNAMIC ASSESSMENT
Clinical endpoints (HR, Cap Refill, UO)	**Passive leg raise (PLR)**
CVP	**IVC / Lung POCUS**
CXR	**Pulse pressure variation**
Lactate / SvO2	**ECHO w/ VTI**

HEART FAILURE & PULMONARY HTN

- Types of heart failure
  - Systolic vs diastolic
  - Left, right and biventricular
- Beside ECHO or recent ECHO is key
- Volume responsiveness
- Considerations in right heart failure and pulmonary HTN

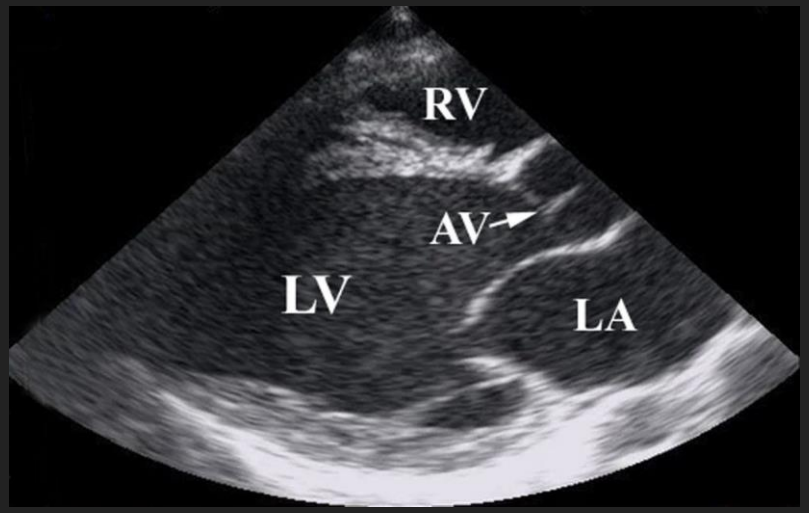
Annals of the American Thoracic Society, Vol. 11, No. 5 (2014), pp. 811-822.

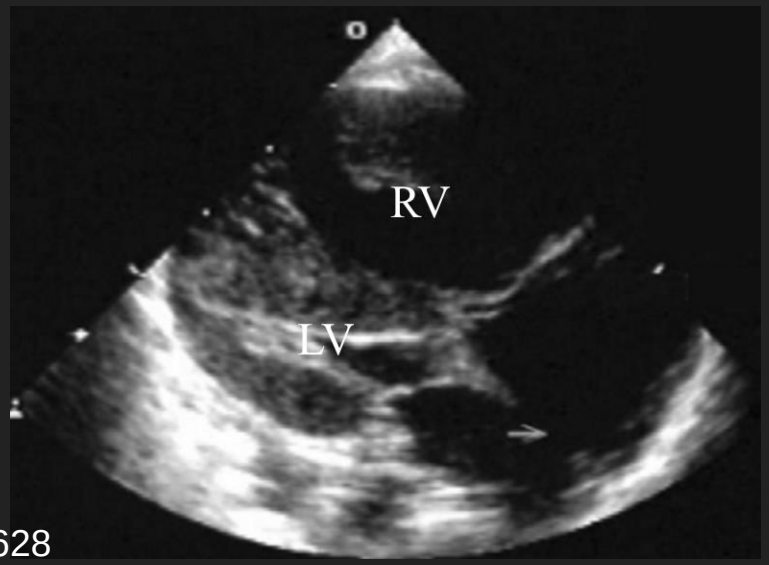
HEART FAILURE & PHYSIOLOGY

- LV tolerates ▲ afterload but not preload
- RV tolerates ▲ preload but not afterload
  - Limited contractile reserve
  - Pulmonary hypertension
- Significantly decreased physiologic reserve
  - Off Frank-Starling curve
- Cannot ▲ CO to compensate (innate or fluid)
- Exacerbated by myocardial dysfunction in sepsis

RIGHT HEART FAILURE & PHYSIOLOGY

- ECHO guided resuscitation
- LV only pumps what it receives
- Isolated right heart failure will not show “CHF” on CXR
- Does not respond well to aggressive fluid resuscitation
- Intubation is associated with increased mortality

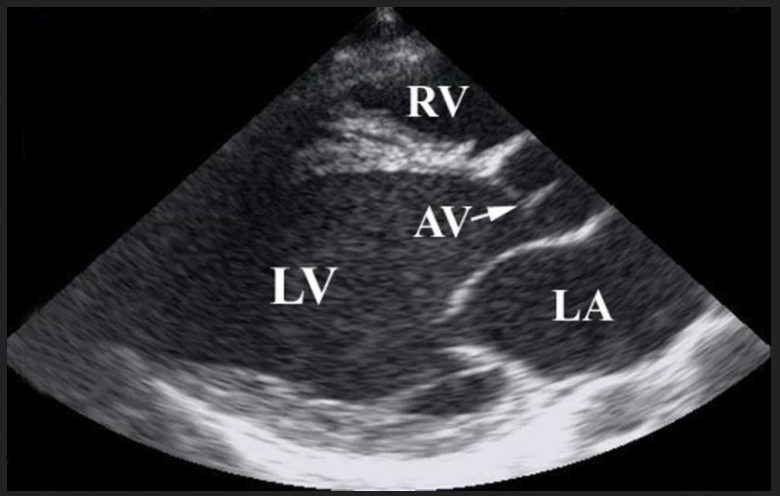


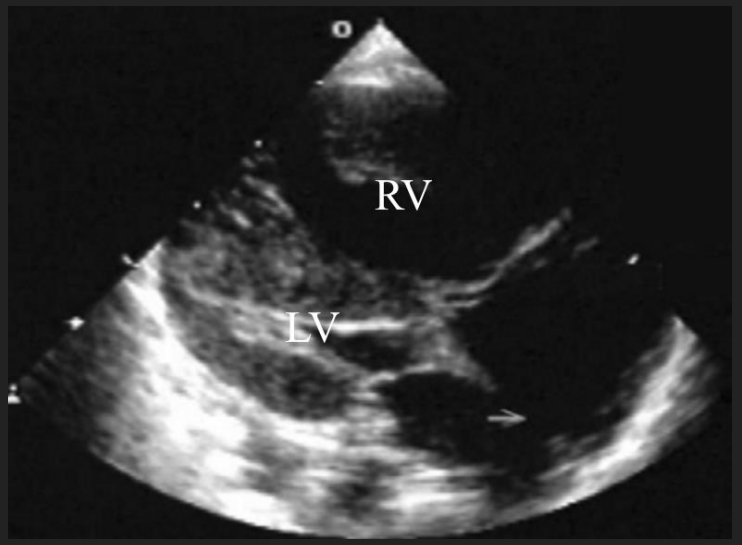


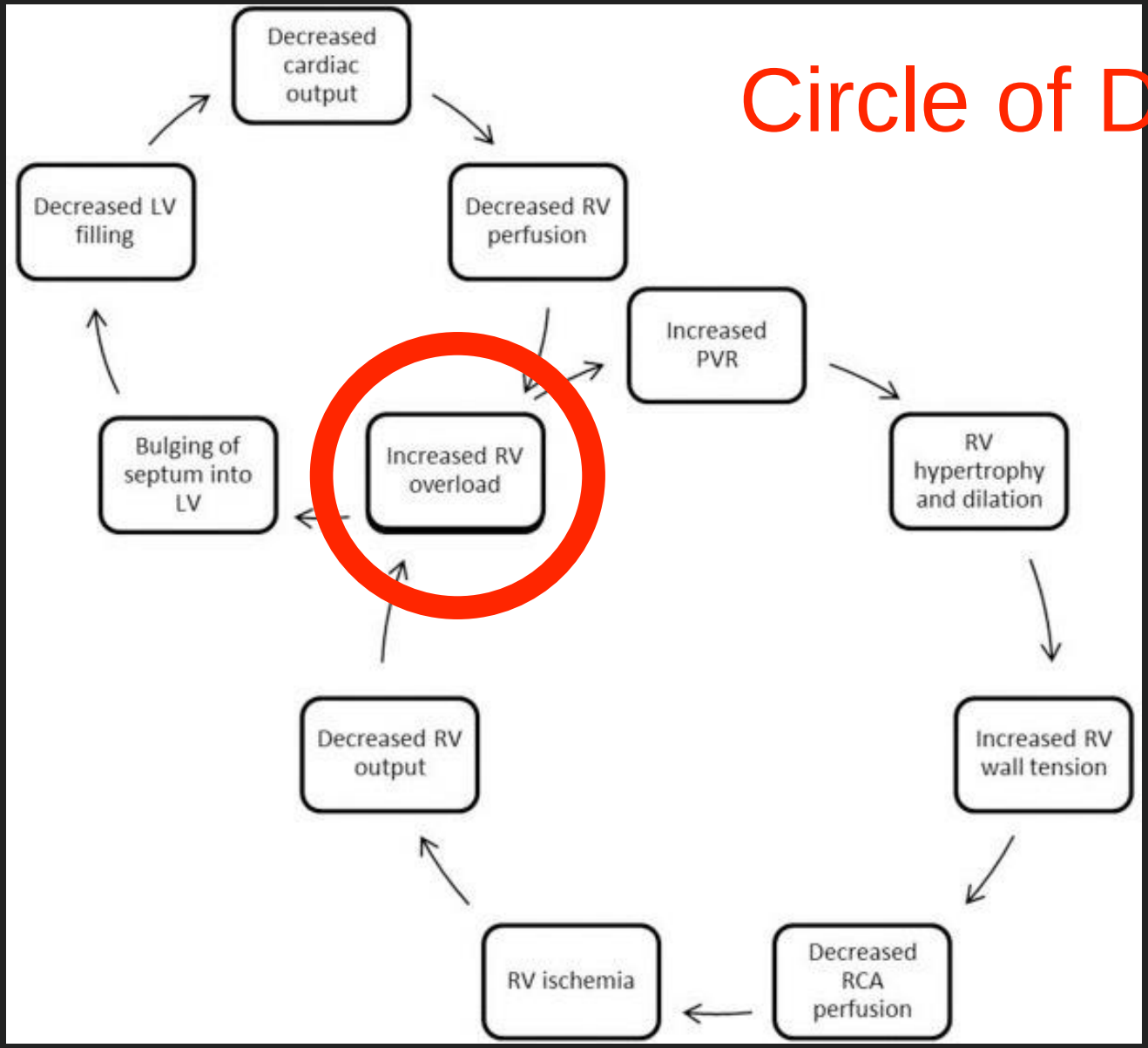
Annals of Emergency Medicine , Volume 66 , Issue 6 , 619 - 628

RHF / PAH & SEPSIS

- Fragile patient population
- Most common causes are LHF & COPD
- Exacerbated by:
  - Hypoxia
  - Acidosis (lactate / hypercarbic)
  - Excess fluid
  - Hypothermia
  - Anemia
- Unable to tolerate permissive hypercapnia or acidosis







Circle of Death!

RHF / PAH & SEPSIS

- Early vasopressors
  - Norepinephrine / Epinephrine
  - Vasopressin (pulmonary vasodilator)
    - Decrease RV afterload
- Dobutamine in isolation should be avoided (beneficial as combo therapy)
- Avoid phenylephrine
- May add iNO (even non ventilated patients), PDEi

RHF / PAH & SEPSIS

- Down regulation of Beta receptors
- Many patients with PPM
- Able to augment CO by raising HR on PPM
- ECMO and RVAD for refractory patients

RHF / PAH & INTUBATION

- Avoid at all costs
- Profound hemodynamic effects
  - Loss of sympathetic tone
  - Increased thoracic pressure
  - RSI medications
- Risks weighed against hypoxia & hypercarbia
- ARDS type management but low PEEP
- NIV is the better choice

RHF / PAH: SUMMARY

- Fluids are high risk
- Early pressors / inotropes
- Avoid hypoxia, acidosis, hypothermia
- Avoid intubation
- Pulmonary vasodilators
- ECMO / RVAD
- Goals of Care Discussions

END STAGE RENAL DISEASE

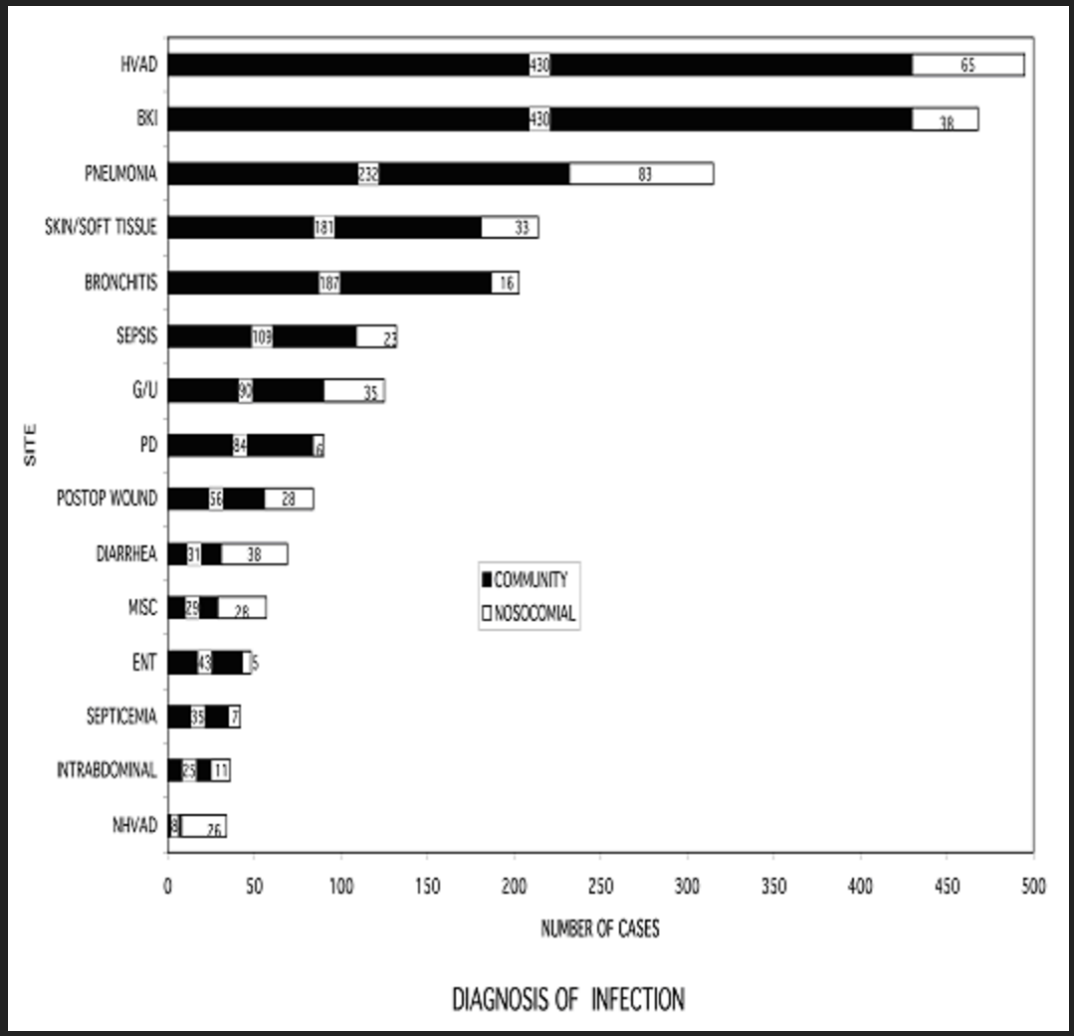
- Marked increased risk for infection
  - Immunocompromised state
- Baseline fluid overload
  - fragile volume status
- Many co-morbid/causative conditions
  - DM, HTN, CHF
- Access is often infectious source

Adv Chronic Kidney Dis. 2013 Jan;20(1):102-9

FLUIDS & END STAGE RENAL DISEASE

- Fluid limited / restricted
- Volume assessment / Intravascularly volume depleted
  - fragile volume status
- Choice of crystalloid (NS, LR, balanced)
  - Plasmalyte / Normsol
  - Avoid large volume NS

SOURCE & END STAGE RENAL DISEASE



SOURCE & END STAGE RENAL DISEASE

- Dialysis access until proven otherwise
- Source control
- May limit ability for dialysis during resuscitation
  - fragile volume status
- Blood cultures from temporary access
- All treated as Health Care Associated Infections

MISCELLANEOUS

- Unable to use urine output as quantitive goals

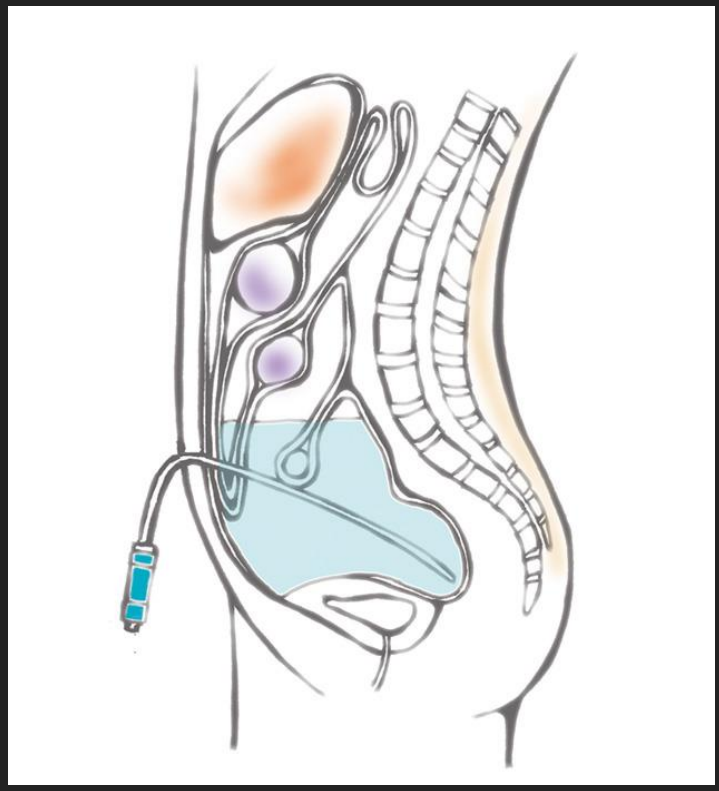
- Be mindful of patients that produce urine

END STAGE RENAL DISEASE: SUMMARY

- Very sick population, high mortality
- Source control
- Fluid responsiveness essential
- Early vasopressors / Dobutamine
- NIV, High Flow O2 > ETT
- Consider: Avoiding NS as crystalloid (acidemia)

PERITONEAL DIALYSIS

- Intra-abdominal static fluid infections
- Tolerate more fluid
- Peritonitis
  - Get fluid sample (PD nurse)
  - Intra-abdominal antibiotics
- Skin or Catheter Infection
  - IV antibiotics



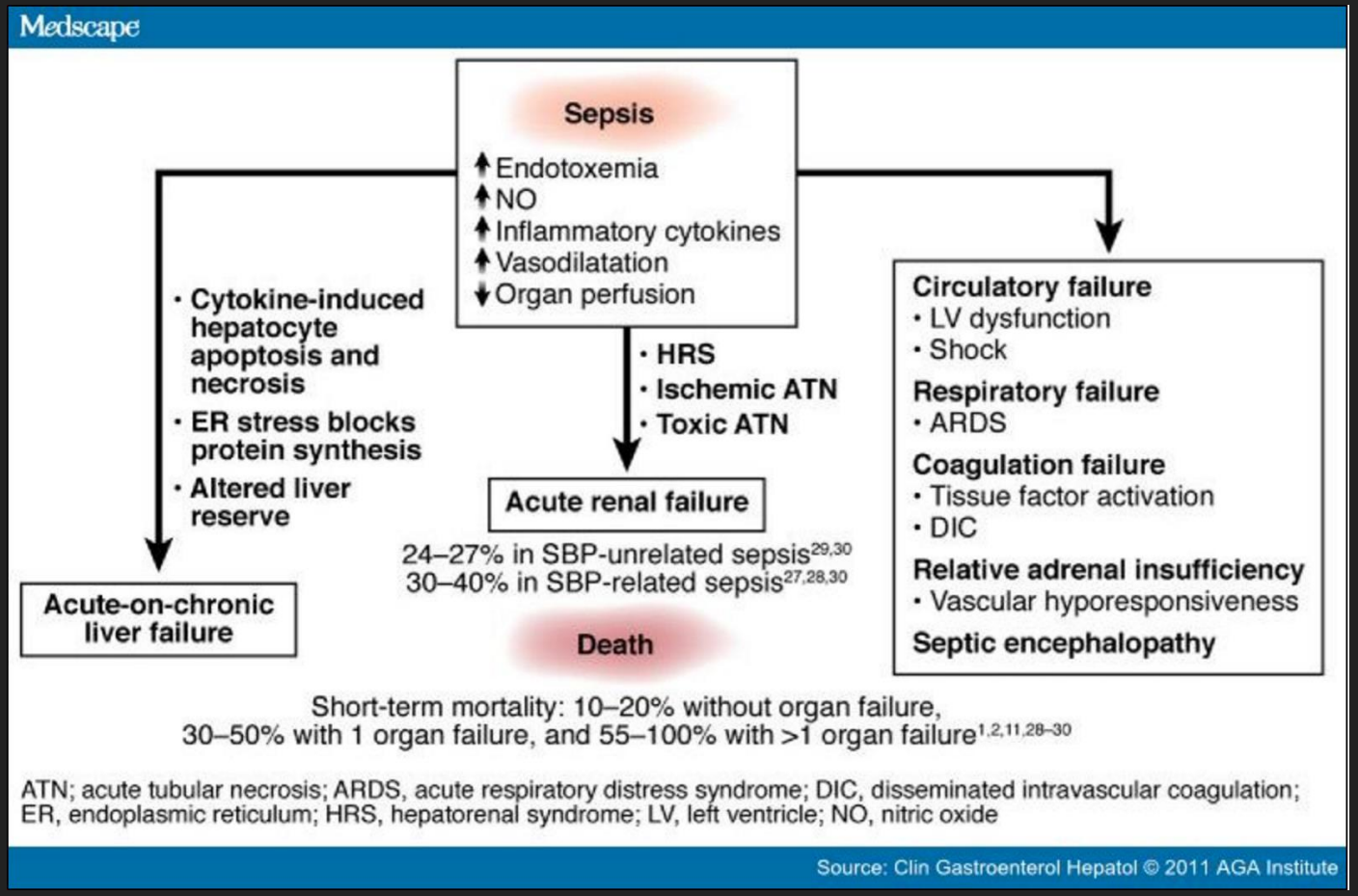
CIRRHOSIS AND LIVER DISEASE

- Marked increased risk for infection
- Chronic alcohol abuse - independent risk factor for septic shock
- Advanced disease is associated with increased risk for SBP and infection
- Advanced disease, Child-Pugh C & MELD >17 associated with increased mortality

Medicine. 2016;95(8):e2877

Critical Care. 2013;17(2):R78. doi:10.1186/cc12687.

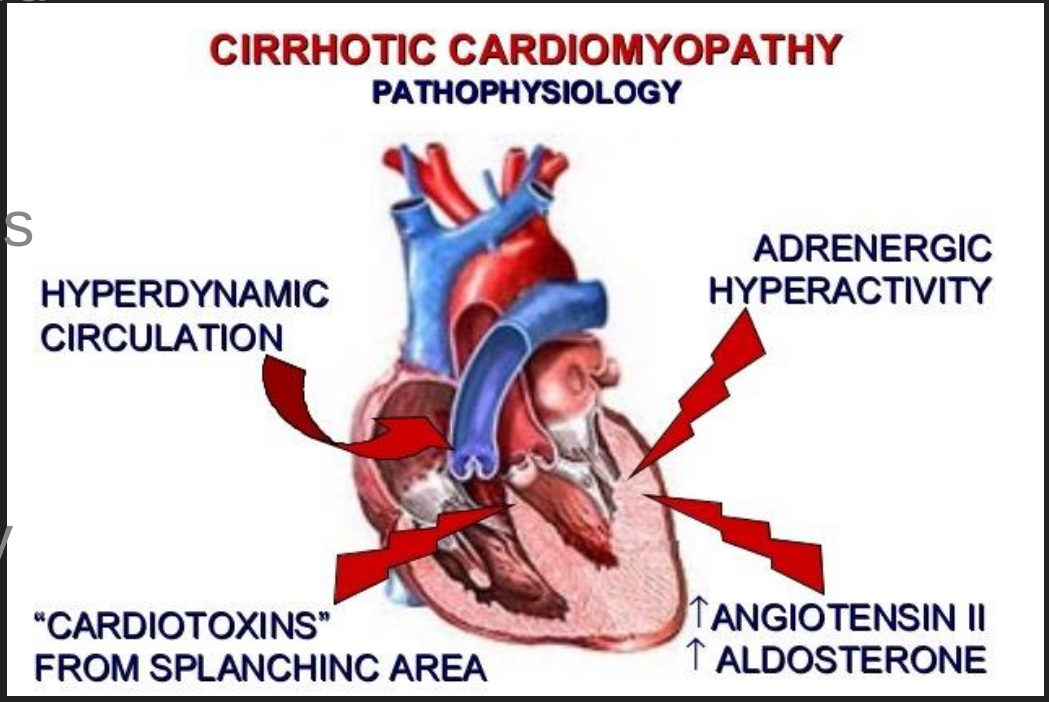
CIRRHOSIS / ACLD



Clin Gastroenterol Hepatol. 2011;9(9):727-738

CIRRHOSIS AND THE HEART

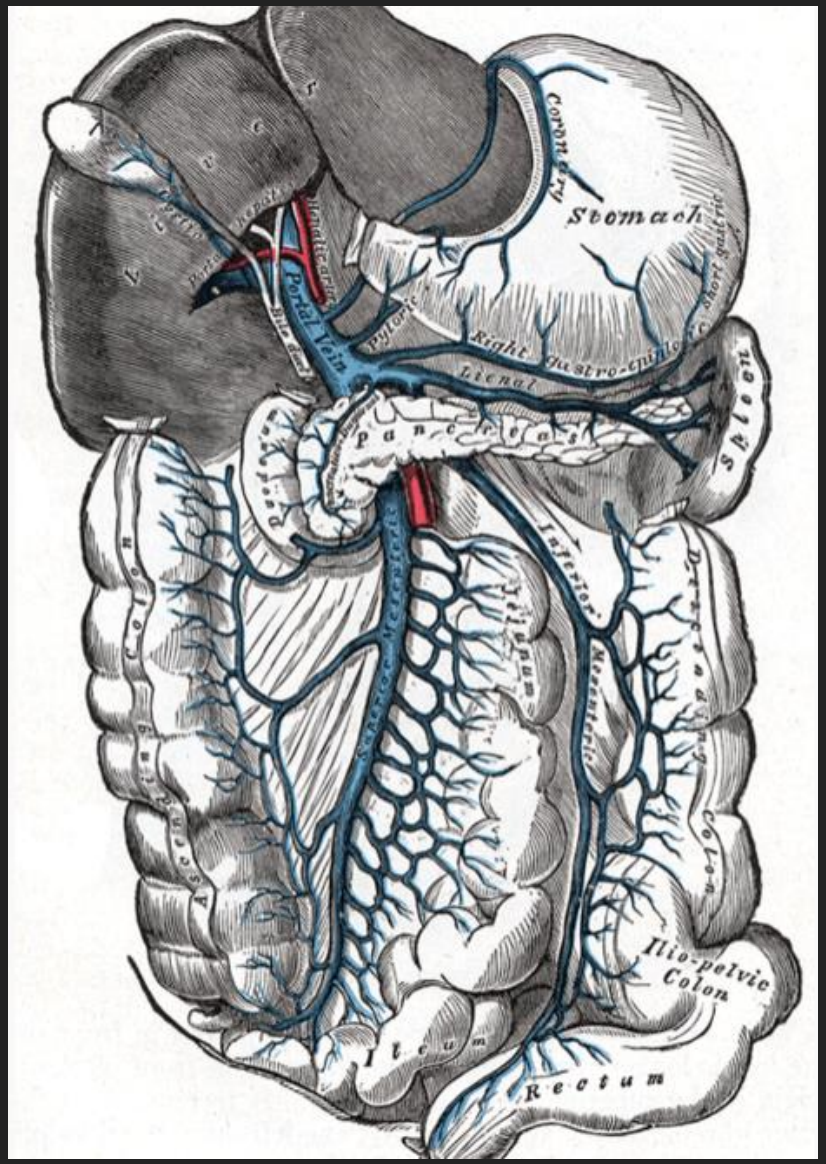
- Largely volume overloaded
- Cardiomyopathy: Cirrhosis - 50% (alcoholic)
- Hyperdynamic Circulatory Syndrome
- Beta-Blocker use



Hepatol Int. 2011 Sep;5(3

CIRRHOSIS AND FLUIDS MECHANICS

- Splanchnic vasodilation
- Hypoalbumenemia
- Type of crystalloid
- Vasopressors and Inotropes



WJG. 2014;20(10):2555-2563.

CIRRHOSIS : MISCELLANEOUS

- Lactic Acidosis without shock
  - Use other markers for shock evaluation
  - Fluid responsiveness, tolerance assessment
- Found to have adrenal insufficiency or RAI more frequently than non-cirrhotics (up to 65% in sepsis)
  - Role for corticosteroids
- SBP should be considered early
  - Antibiotics

CIRRHOSIS AND COLLOIDS

- Increased survival with colloids
  - Extrapolated from SBP
- Decreased risk for AKI and RRT
  - AKI significantly increased mortality
- No consensus on algorithm

CIRRHOSIS : SUMMARY

- Very sick population, high mortality
- Fluid responsiveness essential
- Consider colloids (improve mortality, decrease AKI/RRT)
- Consider corticosteroids
- Early vasopressors / Vasopressin (hyporesponsive)
- Consider: Variceal bleeding & Abdominal Compartment Syndrome

GOALS OF CARE : HIGH RISK POPULATIONS

Exclusions

- Patients under the age of 18
- Patients with LOS greater than 120 days
- Directive for comfort measures within 3 hours of presentation of severe sepsis
- Directive for comfort measures within 6 hours of presentation of septic shock
- Transfer in from another acute care facility
- Patients with severe sepsis who expire within 3 hours of presentation
- Patients with septic shock who expire within 6 hours of presentation
- Patient/caregiver refusal for care that must be documented by provider
- Patients receiving IV antibiotics for more than 24 hours prior to presentation

QUESTIONS?

- Fluids are high risk
- Early pressors / inotropes
- Case specific, patient specific management
- Avoid intubation / Use NIV
- Goals of Care Discussions