Controversies in Pediatric Resuscitation: 2015

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Janeway CWHP
Kids Rock
Pediatric Emergency
Conference 2015

Conflicts of interest

Financial

- None

Academic/ Intellectual:

- Co-Chair, ILCOR Pediatric Task Force (2006-2015)
- Chair, AHA ‘PALS Guidelines’ Writing Group (2015)
- Member, SCCM/ ACCM Sepsis Guidelines Writing Group (2015)
- Heart and Stroke Foundation of Canada

Objectives

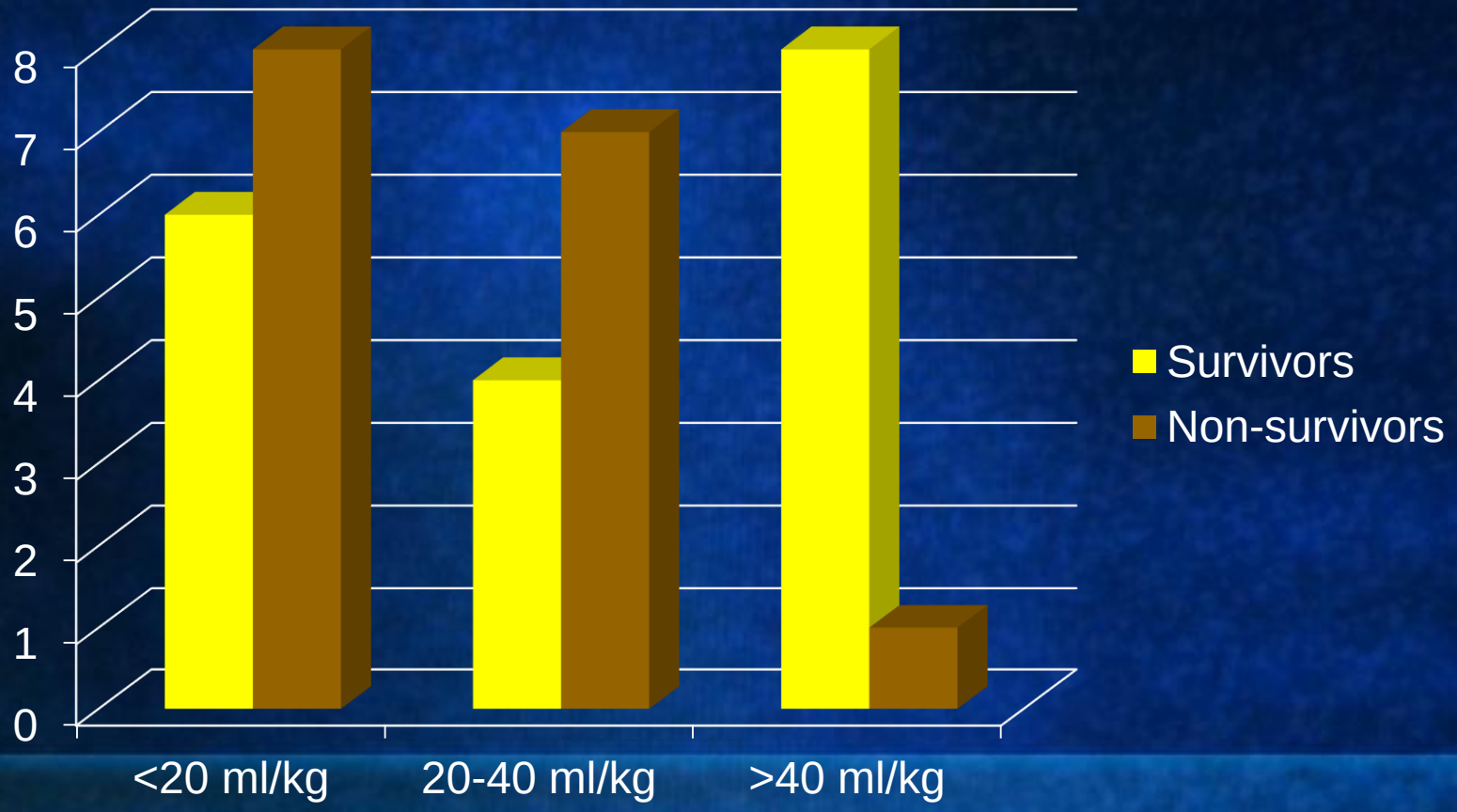
Dismantling dogma in resuscitation

- Fluid for pediatric septic shock
- Epinephrine for cardiac arrest
- Post-cardiac arrest care bundles
  - Temperature
  - Oxygenation
  - Ventilation
  - Blood pressure
- Prognostication post-cardiac arrest

Role of Early Fluid Resuscitation in Pediatric Septic Shock

Joseph A. Carcillo, MD; Alan L. Davis, MD; Arno Zaritsky, MD

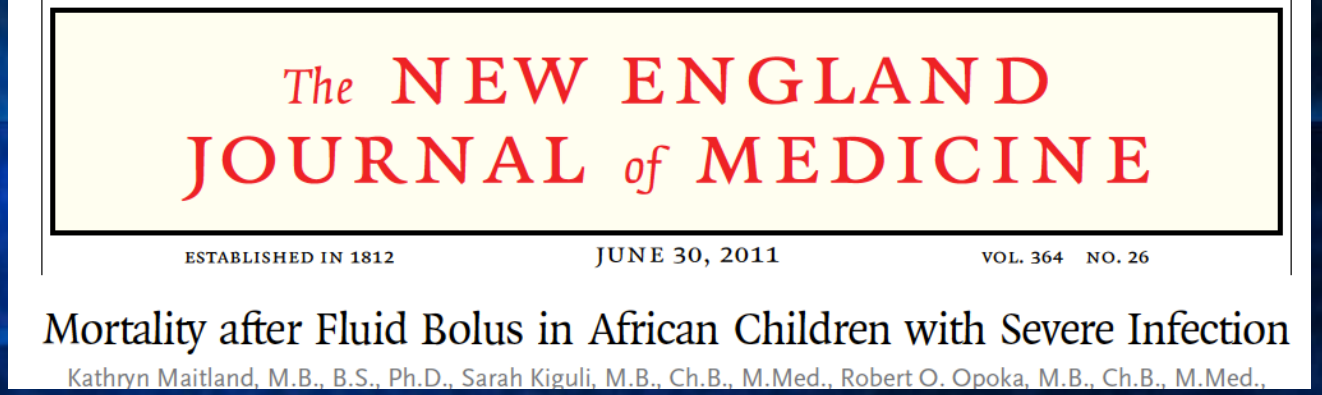
N=34 patients



Early reversal of pediatric-neonatal septic shock by community physicians is associated with improved outcome

Han et al, Pediatrics, 2003

- Retrospective cohort study (1993–2001)
- 91 infants and children presenting to local community hospitals with septic shock and requiring transport to Children's Hospital Pittsburgh
- When resuscitation was consistent with PALS guidelines, a lower mortality was observed
  - 8% vs. 38% mortality non-PALS based therapy



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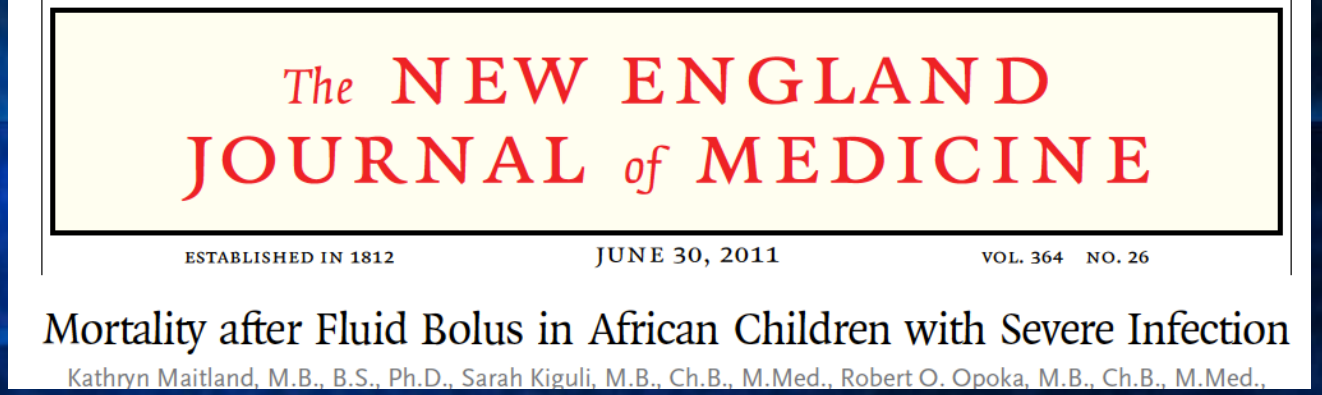
ESTABLISHED IN 1812 JUNE 30, 2011 VOL. 364 NO. 26

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.,

- Children with severe febrile illness and impaired perfusion upon admission randomly assigned to receive:
  - boluses of 20 to 40 ml/ kg of 5% albumin solution (albumin-bolus group)
  - Boluses of 20 to 40 ml/ kg of 0.9% saline solution
  - No bolus (control group)
- The primary end point was 48-hour mortality



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- The 48-hour mortality:
  - 10.6% in albumin-bolus
  - 10.5% in saline-bolus
  - 7.3% in control

Relative mortality risk for any bolus vs. control: 1.45 (95% CI, 1.13 to 1.86; P = 0.003)

Criticisms of Extrapolating Matiland's Data

Very poor specificity of inclusion criteria…

- The study was not specifically treating shock as currently defined by WHO
  - Cold hands
  - Capillary refill time (CFT) > 2 sec
  - A weak and fast pulse
  - Maitland's criteria were "*One or more* of":
    - Severe tachycardia
    - CFT >2 sec
    - Lower limb T gradient
    - Weak radial pulse volume
- Likely inclusion of numerous patients with malaria and pneumonia, as opposed to true septic shock

A Prospective Randomized Controlled Study of Two Fluid Regimens in the Initial Management of Septic Shock in the Emergency Department

Santhanam, Ped Emerg Care,2008

- Prospective RCT of pediatric septic shock in 147 children (older than 1 month of age) , comparing:
  - 40 mL/kg of fluid over 15 minutes followed, by dopamine
  - 20 mL/kg over 20 minutes up to a maximum of 60 mL/kg over 1 hour, followed by dopamine (control protocol)

A Prospective Randomized Controlled Study of Two Fluid Regimens in the Initial Management of Septic Shock in the Emergency Department

Santhanam, Ped Emerg Care,2008

- No difference in time to achieve therapeutic goals, or in mortality rates (~17%) between two groups
- No difference in intubation rates were the same

(46.5% in control group; 55% in study group; P = 0.28)

- At 20 minutes, hepatomegaly in 35.6% of control group and 70% of study group (P <0.01).

Paediatric community-acquired septic shock: the REPEM Network Study

Van de Vourde, Eur J Pediatr, 2013

- 270,461 (European) paediatric ED consultations screened over 1 year
- 176 cases of septic shock identified
- The median amount of fluid given in the first 6 was 30 ml/kg
- Overall mortality in this sample was 4.5 %
- Mechanical ventilation needed in 25.9 %
- Vasoactive medications needed in 42.9 %

van Paridon *et al. Critical Care* (2015) 19:293
DOI 10.1186/s13054-015-1010-x

CRITICAL CARE

RESEARCH Open Access

Timing of antibiotics, volume, and vasoactive infusions in children with sepsis admitted to intensive care

Bregje M. van Paridon[1], Cathy Sheppard[2], Garcia Guerra G[3], Ari R. Joffe[3,4*] for the Alberta Sepsis Network

- Retrospective single center study of 79 children admitted to a PICU with sepsis or septic shock
- IV volume prior to inotropes was not independently associated with either PICU LOS or ventilator days
- IV volume administered in the first 2 hours of resuscitation *was* an independent predictor of:
  - PICU LOS: 0.22 (95%CI 0.05-0.38)
  - Ventilator days: 0.09 (95%CI 0.02-0.15)

Fluid Bolus Therapy-Based Resuscitation for Severe Sepsis in Hospitalized Children: A Systematic Review

Ben Gelbart, FCICM[1,2]; Neil J. Glassford, MRCP[3,4]; Rinaldo Bellomo, MD[3,4]

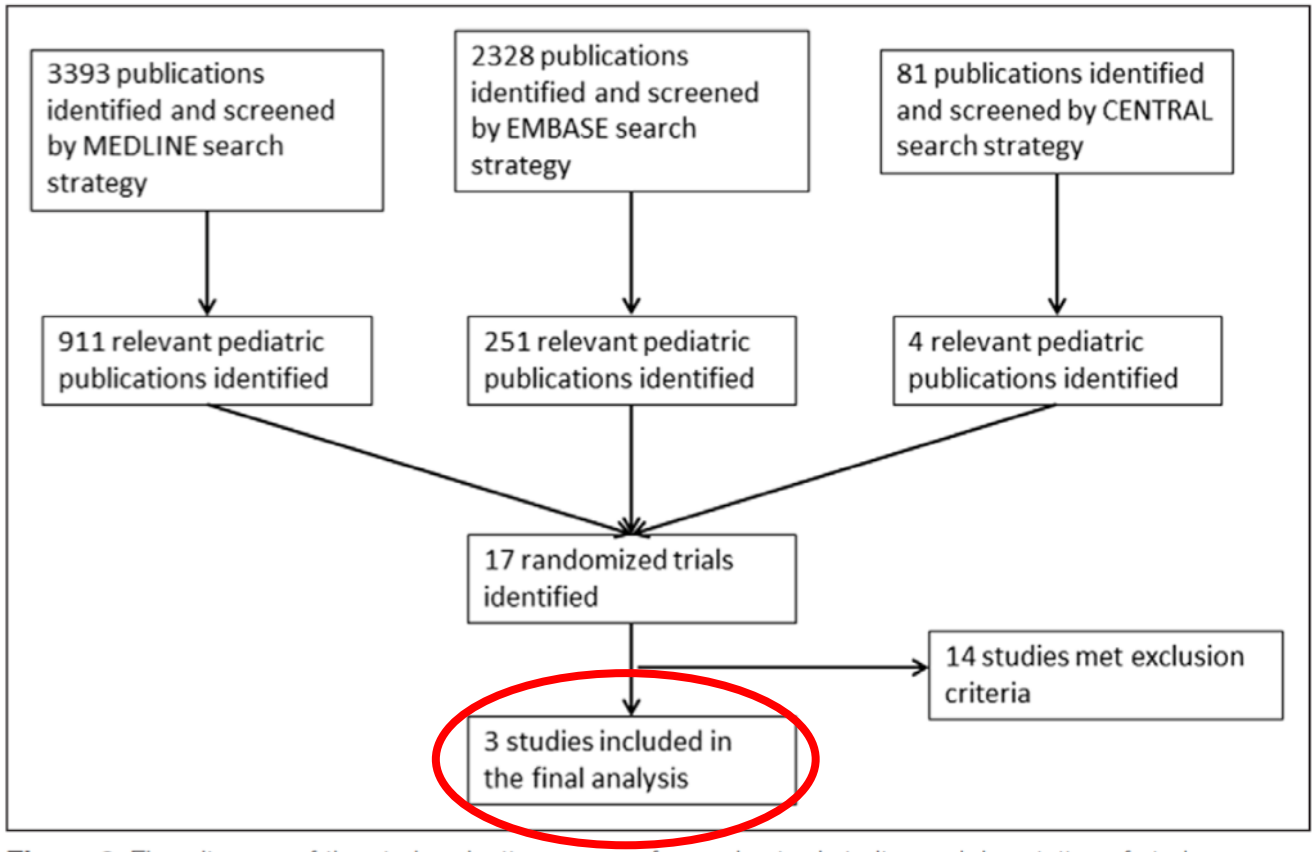


Figure 3. Flow diagram of the study selection process for randomized studies and description of study exclusions.

Still to Come….

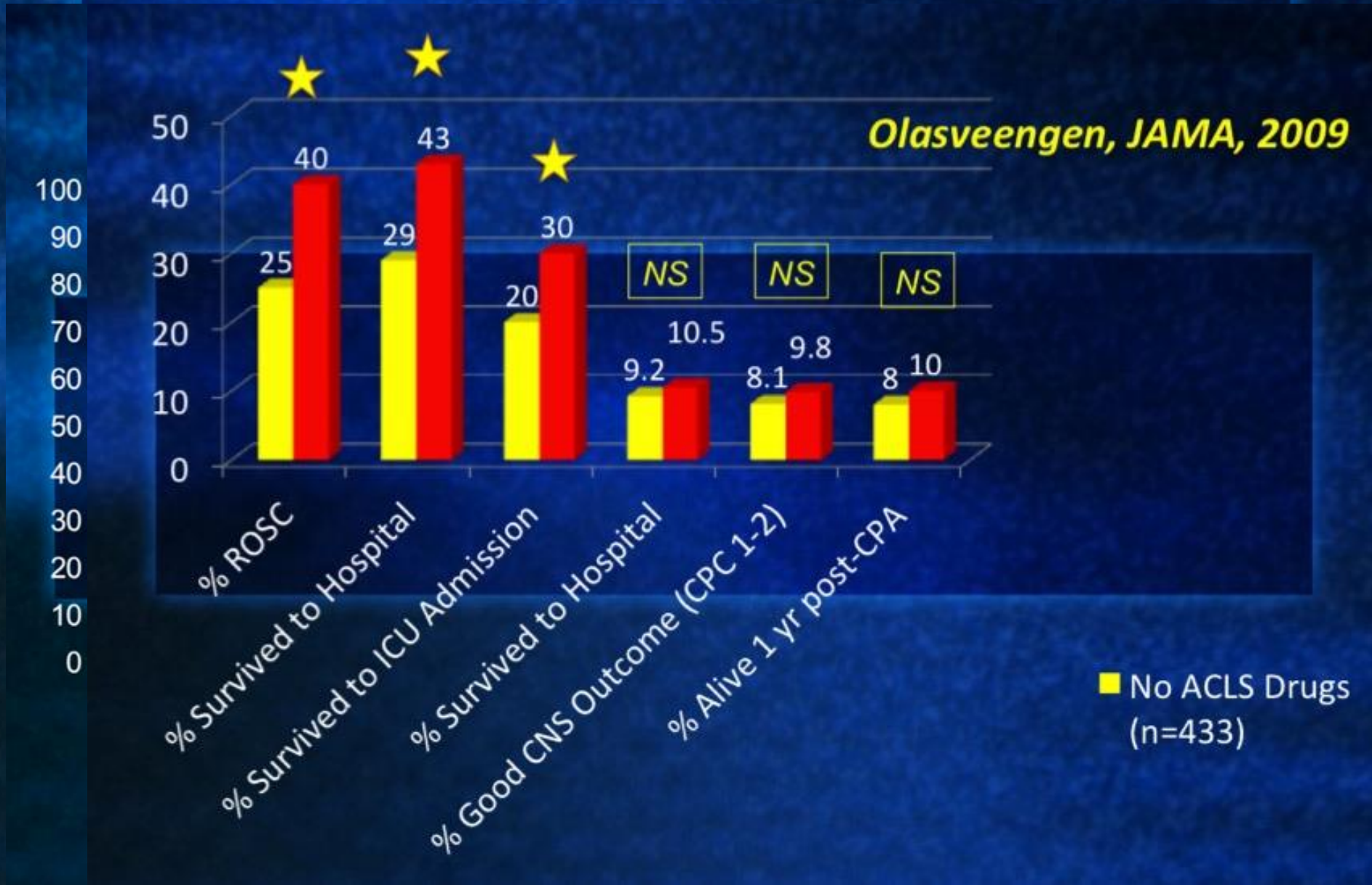
SQUEEZE

Research Questions re: Fluid Resuscitation

- What are the appropriate clinical, hemodynamic and biochemical markers of adequate tissue perfusion?
- When is fluid unresponsiveness an appropriate goal?
- Is fluid resuscitation indicated when a clinical (eg. hypotension) or biochemical (eg. Lactate) problem co-exists with normal perfusion?
- What is the dose response relationship between fluid and outcomes, and what are the side effects/ safety limits of different volumes
- What are the appropriate outcome measures for fluid resuscitation trials?

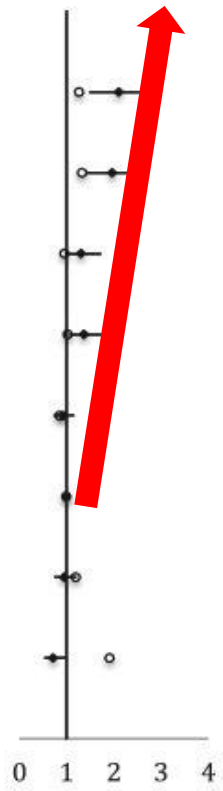
Perner, ICM, 2015

Epinephrine and OHCA Care…




PARAMEDIC2
The Adrenaline Trial

Epinephrine average dosing period	No. of patients	Unadjusted survival to discharge No. (%)	Unadjusted Odds Ratio for Survival (95%CI)	Adjusted Odds Ratio for Survival (95%CI)	Adjusted Odds Ratio for Survival (95%CI) Plotted (○ = unadjusted odds ratio)
9-10 min/dose	796	87(10.9)	1.27 (0.98, 1.65)	2.10 (1.50, 2.93)	
8-9 min/dose	1052	119(11.3)	1.33 (1.04, 1.69)	1.96 (1.47, 2.62)	
7-8 min/dose	1455	122(8.4)	0.96 (0.77, 1.20)	1.31 (1.01, 1.71)	
6-7 min/dose	1987	178(9.0)	1.03 (0.83, 1.27)	1.37 (1.08, 1.74)	
5-6 min/dose	2740	119(11.3)	0.86 (0.72, 1.03)	0.93 (0.75, 1.14)	
4-5 min/dose	2665	233(8.7)	1(ref.)	1(ref.)	
3-4 min/dose	1905	198(10.4)	1.20 (0.99, 1.45)	0.95 (0.76, 1.19)	
1-3 min/dose	989	155(15.7)	1.91 (1.53, 2.38)	0.72 (0.55, 0.95)	
Total	13,589	1,301(9.6)			



Ornato, Resuscitation, 2014

Findings consistent for shockable and non-shockable rhythms

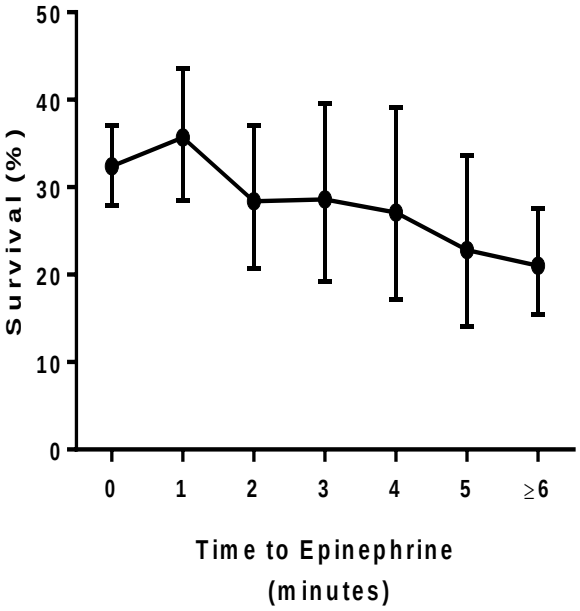
Table 3. Outcomes.*

Outcome	High-Dose Epinephrine (N=34)	Standard-Dose Epinephrine (N=34)	Unadjusted Odds Ratio (95% CI)*	P Value
	no. of patients (%)			
Return of spontaneous circulation	20 (59)	21 (62)	1.1 (0.4–3.0)	0.80
For ≤20 min	4 (12)	6 (18)	1.6 (0.4–6.3)	0.49
For >20 min but <24 hr	15 (44)	8 (24)	0.4 (0.1–1.1)	0.07
Survival at 24 hr	1 (3)	7 (21)	8.6 (1.0–397.0)	0.05
Survival to hospital discharge	0	4 (12)		0.11

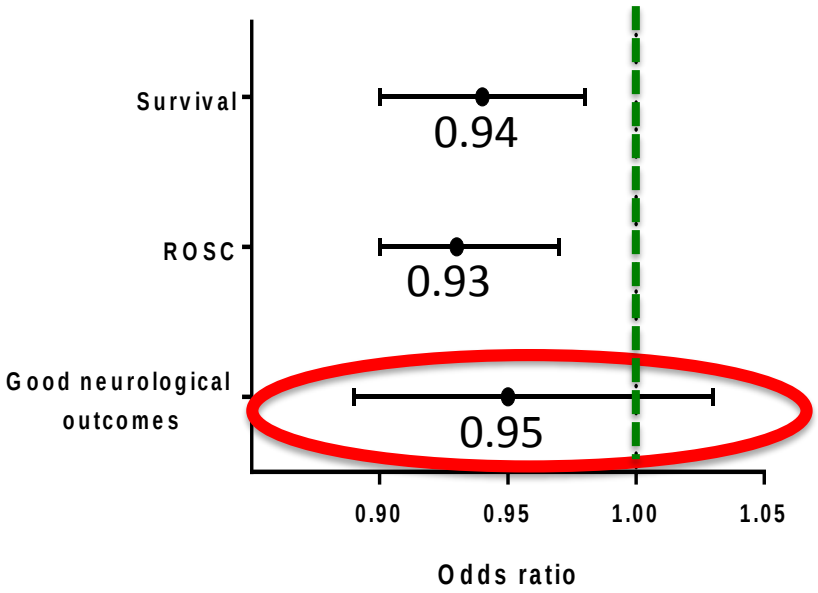
* CI denotes confidence interval.

JAMA The Journal of the American Medical Association

Unadjusted analysis:



Adjusted* analysis:



* Multivariable logistic regression with generalized estimating equations. Odds ratio per minute delay in epinephrine administration. Adjusted for age, gender, illness category, mechanical ventilation, monitored status, witnessed status, location, time of the day/week, year of arrest, insertion of an airway, initial rhythm, time to initiation of chest compressions, hospital type and teaching status

Andersen, JAMA, 2015

Epinephrine and Cardiac Arrest

- Does the use of epinephrine during cardiac arrest lead to functional outcomes?
- Is demonstrating benefit dependent upon identifying the right:
  - Setting (IHCA vs. OHCA)?
  - Arrest etiology?
  - Timing of delivery?
  - Dose?
  - Frequency of dosing?

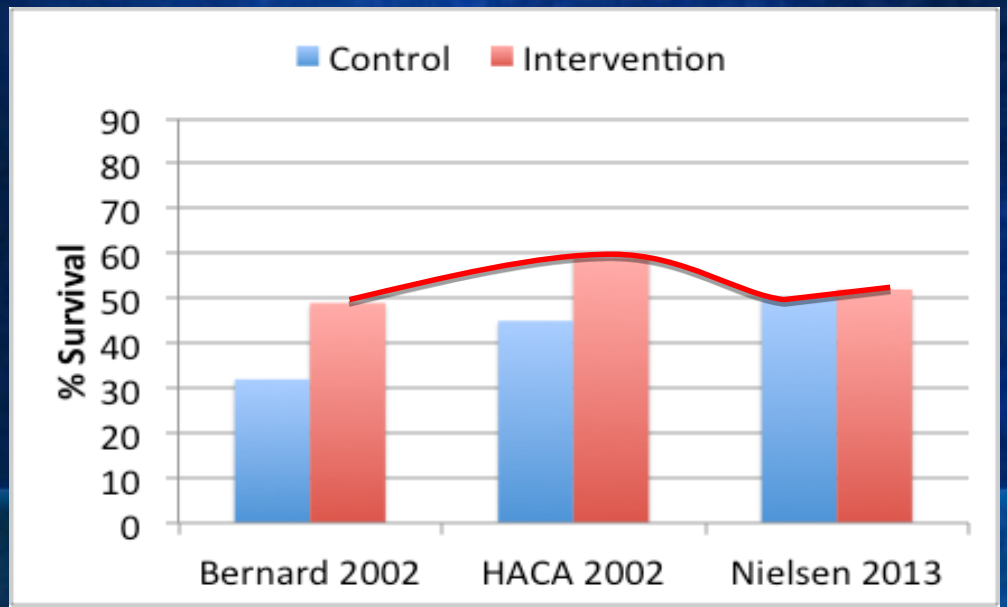
Pediatric Post-Cardiac Arrest Syndrome

% patients	IHCA Non-cv	IHCA CV-postop	IHCA CV-nonsurg	IHCA PICU CV-postop	OHCA
	NRCPR LO, 2011	NRCPR LO, 2011	NRCPR VN, 2006	HSC NdM, 2006	ROC DA, 2009
	N=1109	N=640	N=306	N=91	N=624
(%) Return of spontaneous circulation (ROSC)	53	67	53	82	10
(%) 24 hr survival	37	60	42	66	
(%) Survival to Hospital DC	23	37	28	25	6.4

Nadkarni, JAMA, 2006
De Mos, CCM, 2006
Ortmann, Circulation, 2011
Atkins, Circulation, 2009

Supportive Evidence for TTM (Temperature Targeted Management)

- Adult RCTs: controlling T(33-36ºC) is better than not controlling temperature (37ºC or higher)
  - High Quality Evidence
- Adult RCTs: outcomes (survival and CNS outcome) with 32º-34ºC, 33ºC and 36ºC are similar.
  - High Quality Evidence



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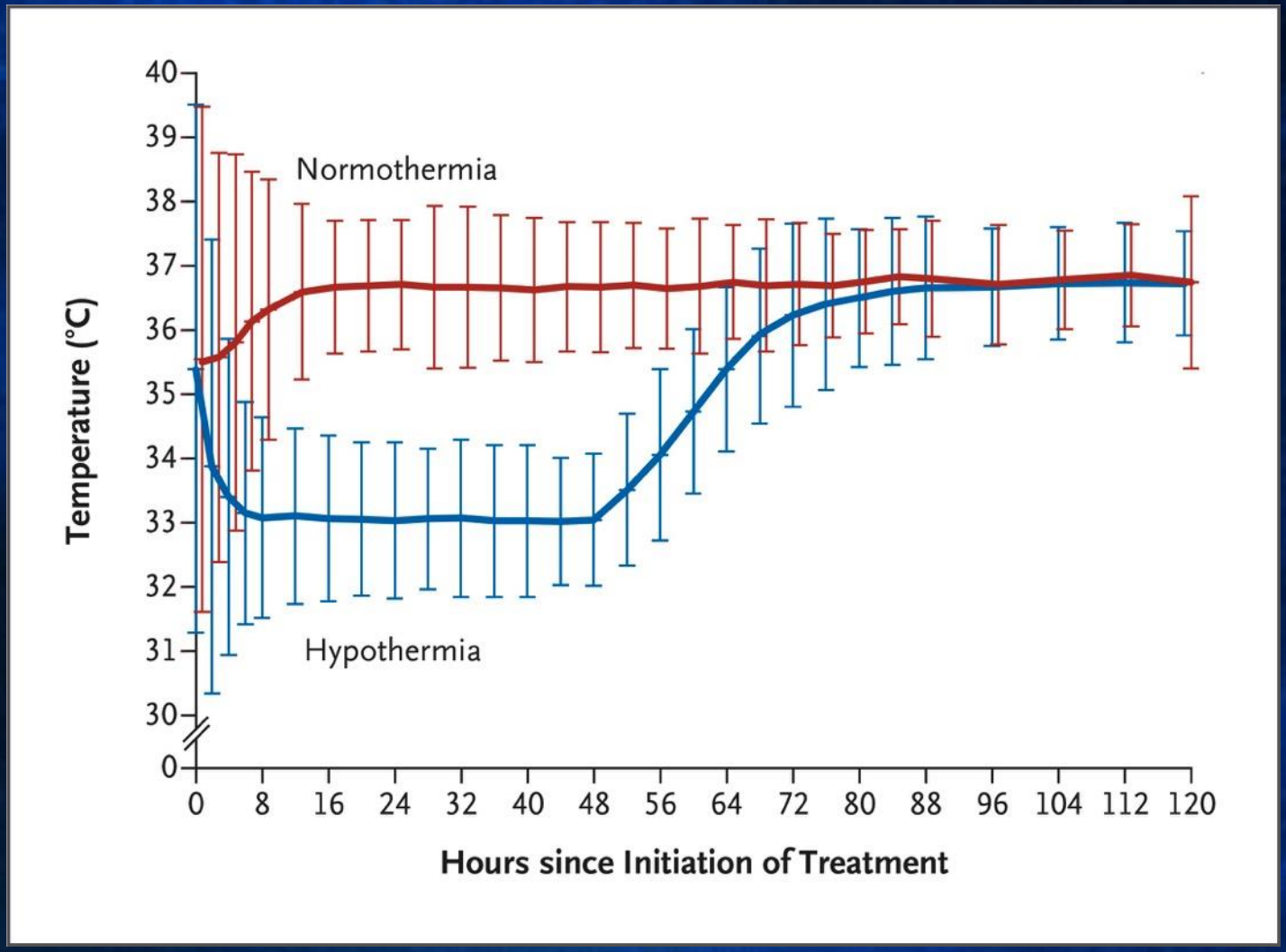

Moler N Engl J Med 2015

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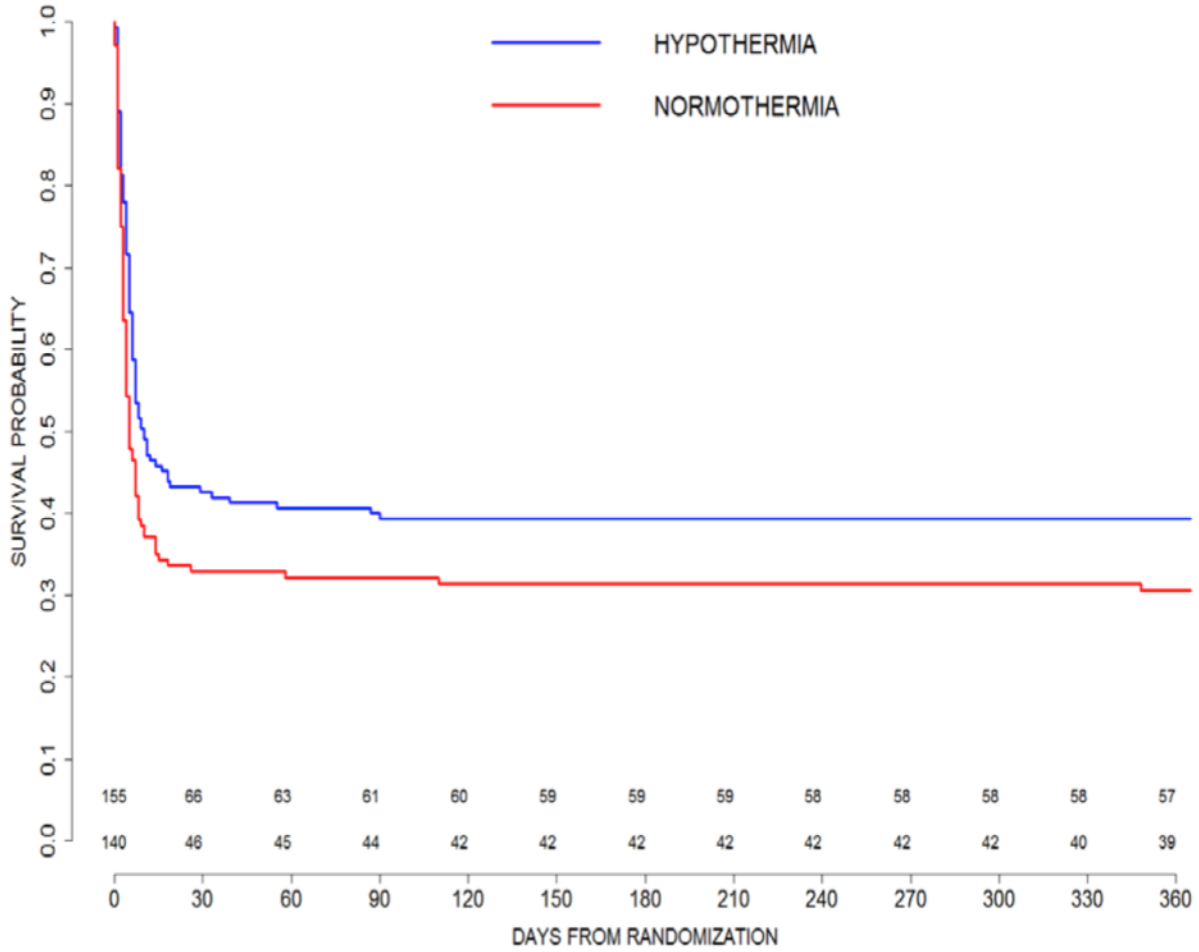
ORIGINAL ARTICLE

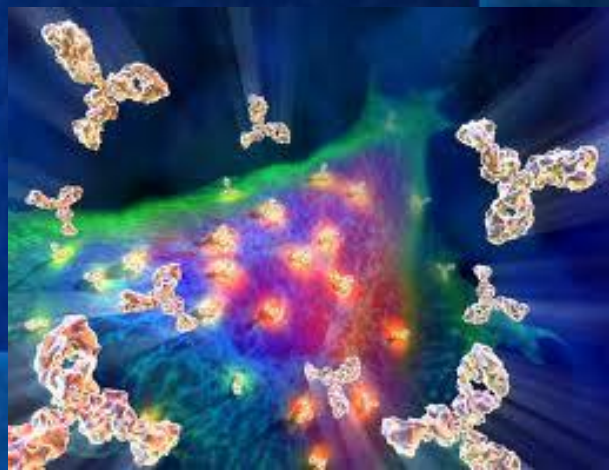
Therapeutic Hypothermia after Out-of-Hospital Cardiac Arrest in Children



Post-ROSC fever associated with worse outcomes (*Bembea, 2010*)

Post-ROSC oxygenation

Multiple animal studies have shown that ventilation with 100% oxygen during and following resuscitation contributes to free radical–mediated reperfusion injury to the brain, and may be associated with more neurologic deficit than ventilation with room air, especially when high Pa02 is experienced in the first hour post-ROSC



Post-ROSC oxygenation

What about neonatal studies?

- Two LOE 5 meta-analyses of several randomized contr… trials comparing neo… resuscitation init… …th room air versus 1… …ygen showed increa… …ival when re… …ion was initiated with … air.

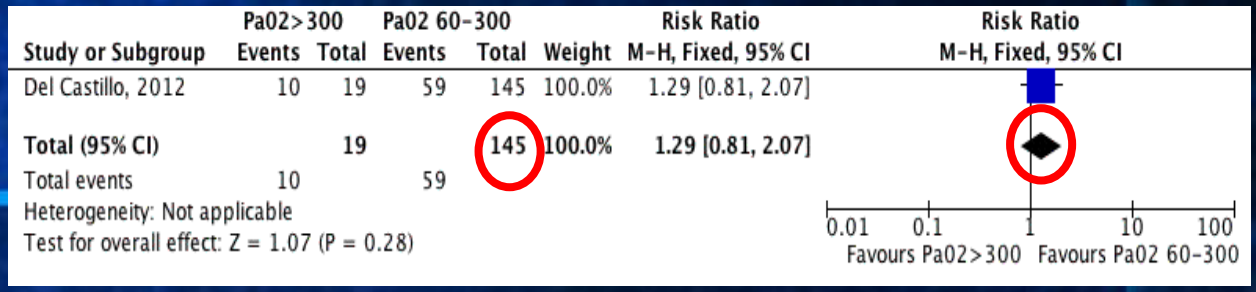
Davis, Lancet, 2004; Rabi, Resuscitation, 2007

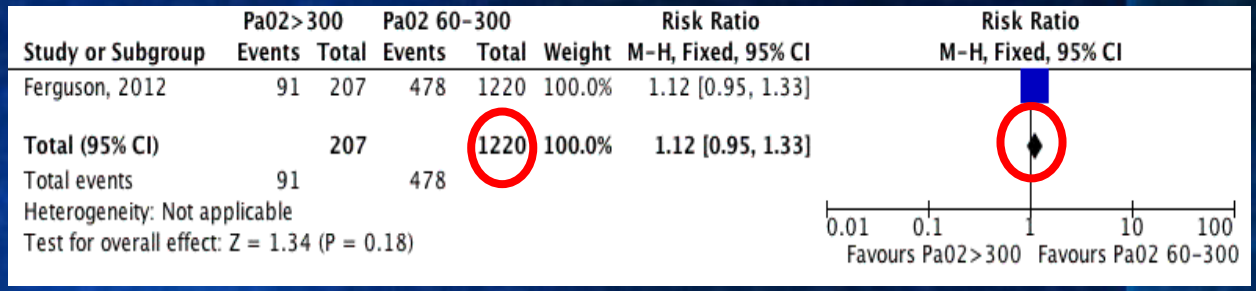
Perinatal HIE is not Cardiac arrest

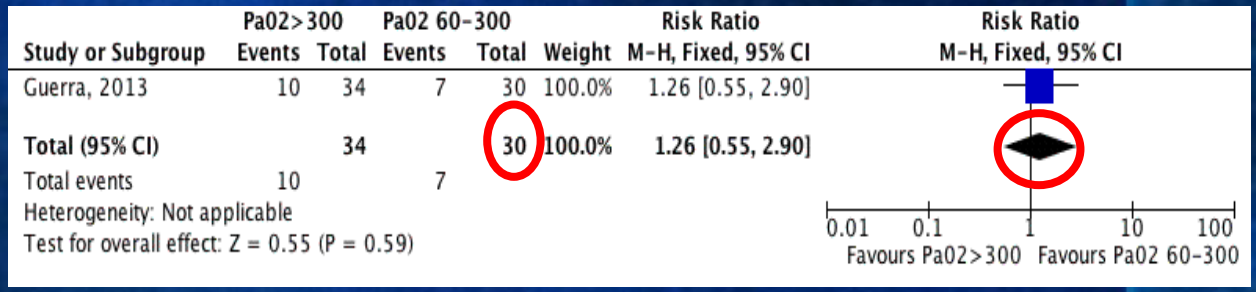
Pediatric Post-ROSC Oxygenation

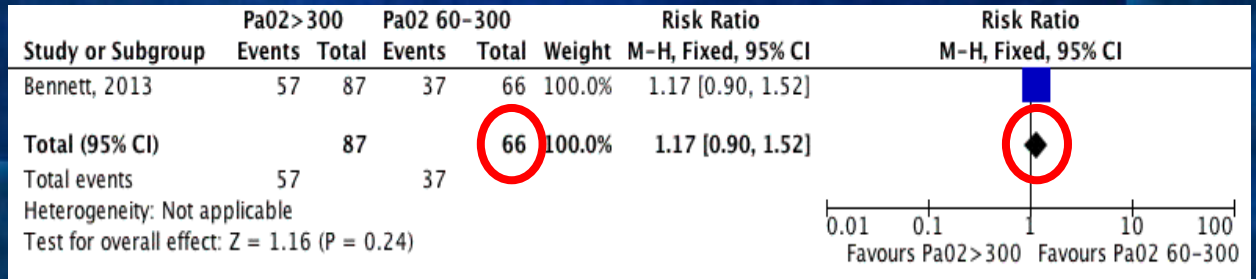
- Pediatric and animal data "disconnect"

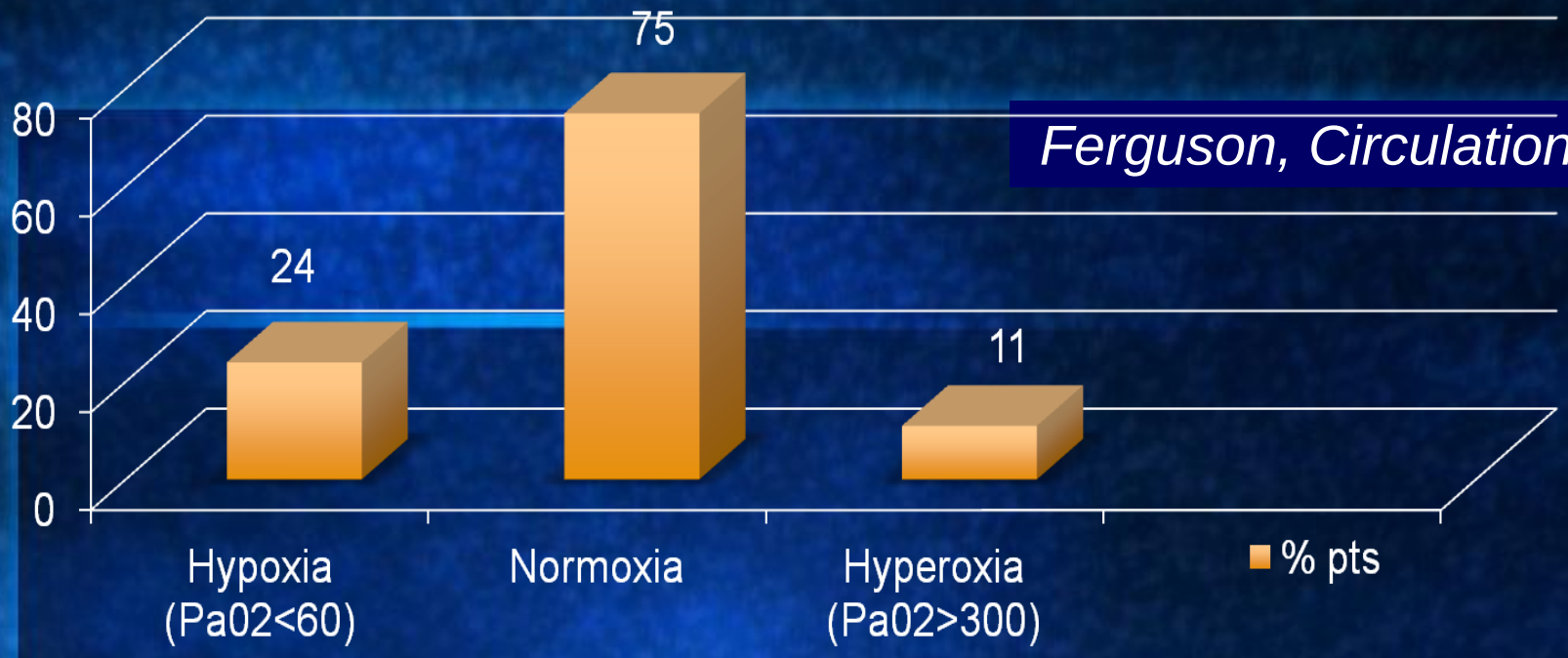
Hypoxemia post-ROSC is bad, but Hyperoxemia has less significant association with outcomes



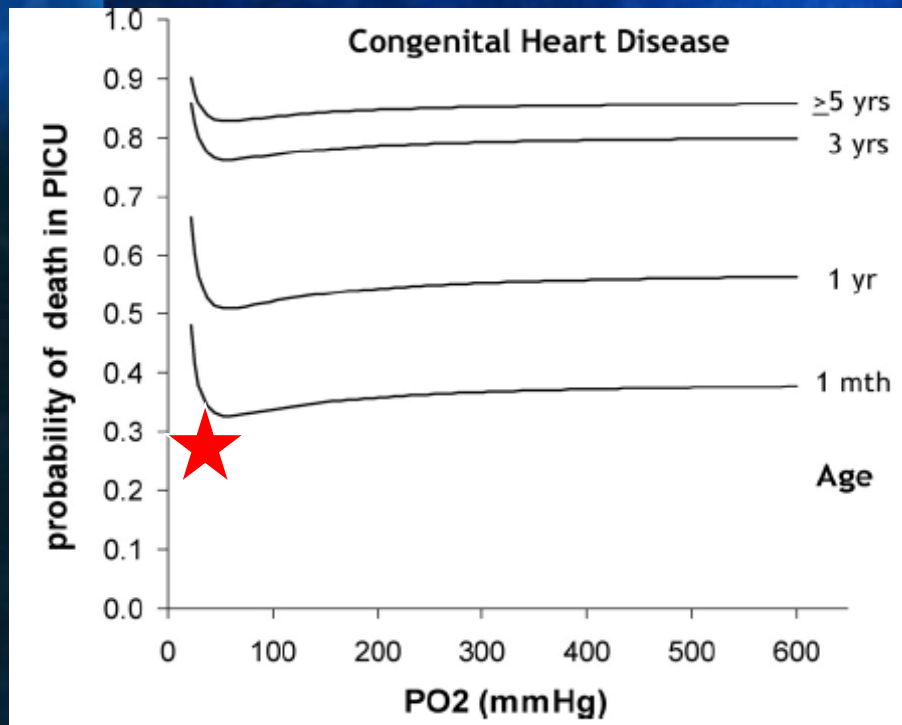


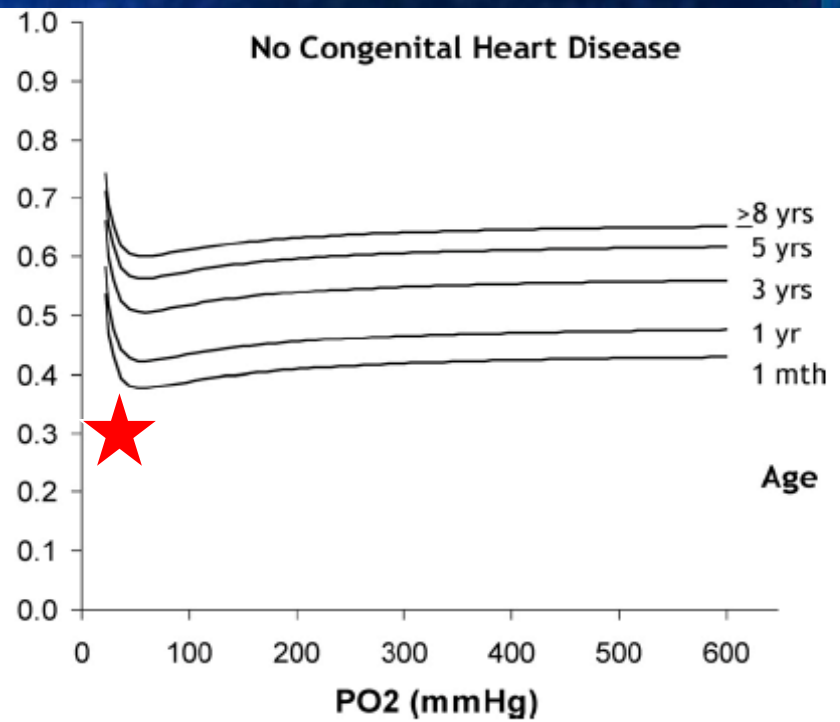




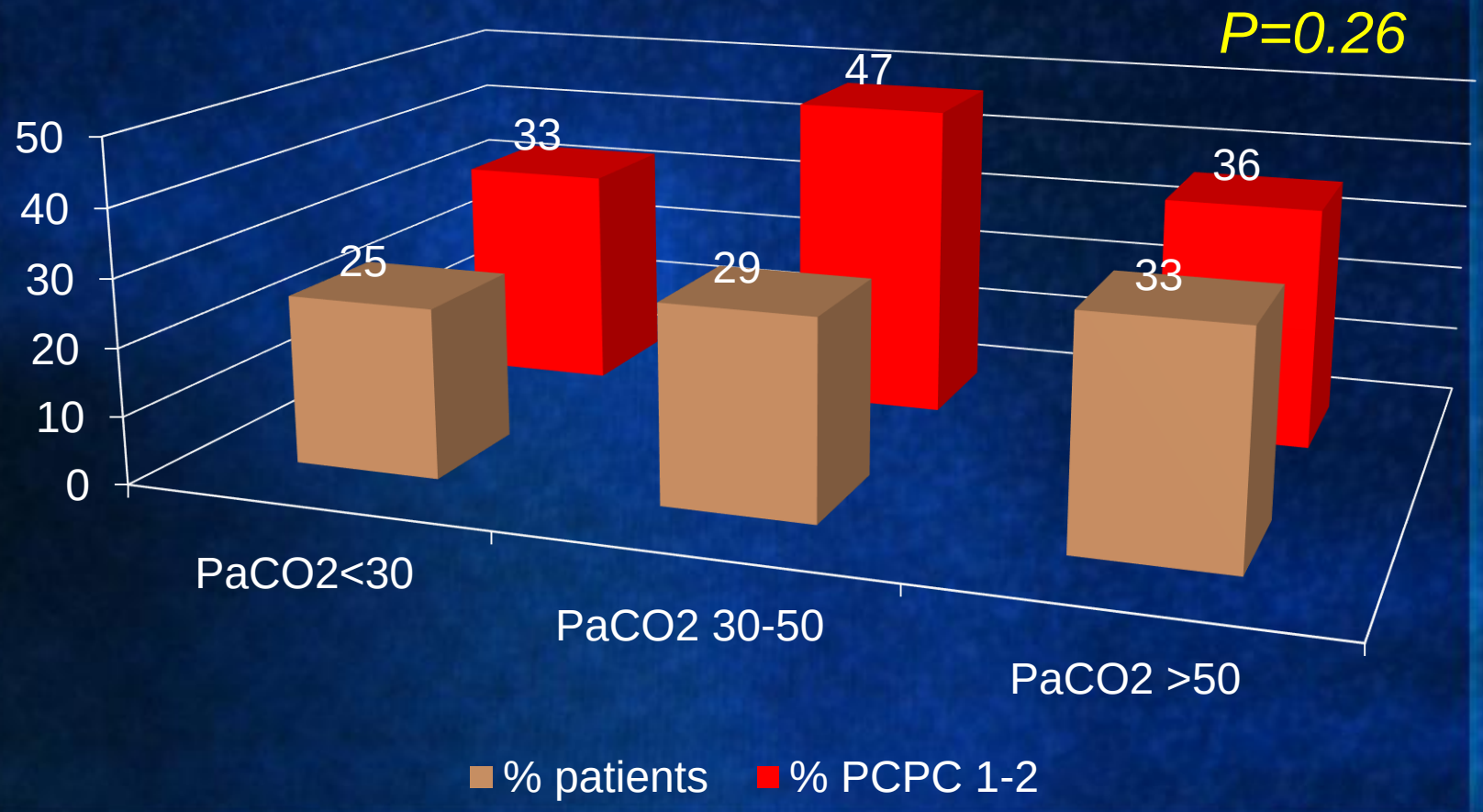


Ferguson, Circulation, 2012



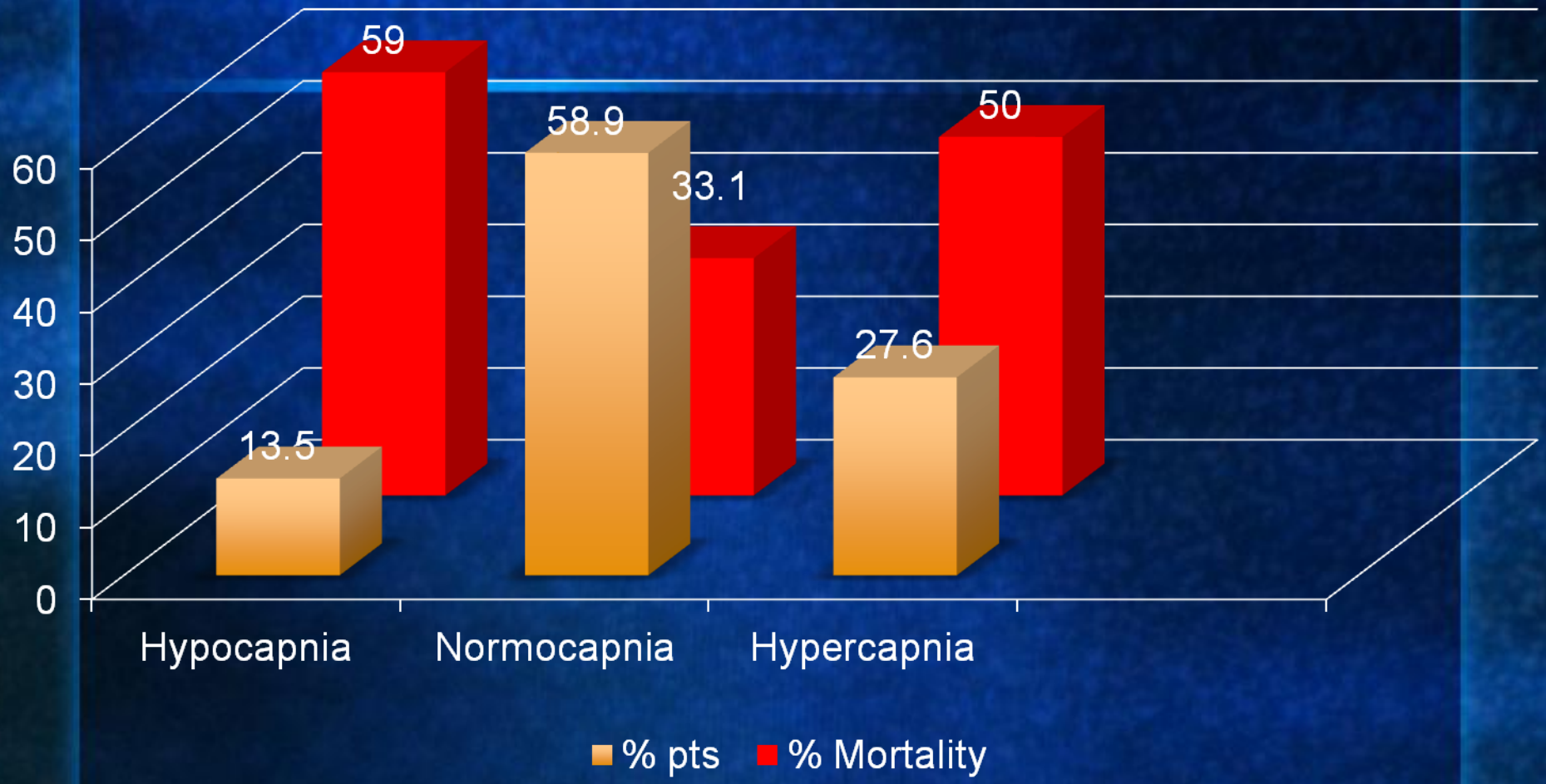


Bennett, CCM, 2013



N=195 patients

del Castillo et al, Resuscitation, 2012

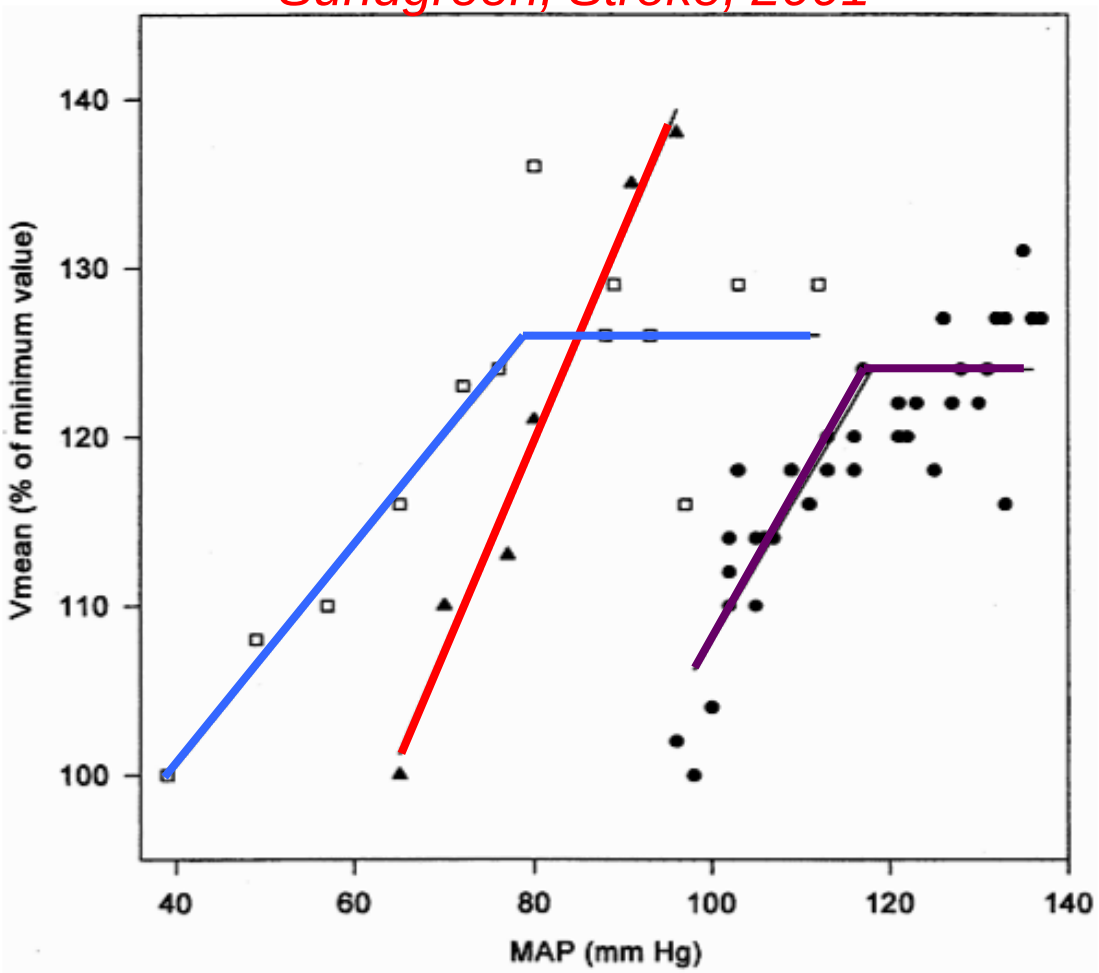


Cerebrovascular reactivity to changes in arterial carbon dioxide tension is preserved in comatose patients post-ROSC

Buunk Stroke 1997

Examples of TCD Profiles (n=18 patients)

Sundgreen, Stroke, 2001



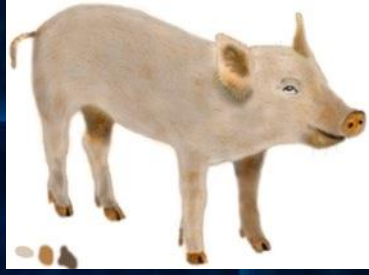
Impaired CBF autoregulation

- Autoregulation with no identifiable lower limited
- Right-shifted autoregulation

Claus, Stroke 2001

"…should MAP be kept at a higher level than commonly accepted"; but how high and for how long?

PCAS: Myocardial Dysfunction



Animal models (VF)

- *Myocardial stunning*, with an onset within 30 min post-ROSC, and function returning to normal within 24-48 hours of the insult
- Systolic and diastolic dysfunction (biventricular)
- Recovery of systolic and diastolic function can be hastened by dobutamine, low dose epinephrine, milrinone or levodimendan

Kern, Circulation, 1997

Kern, J Am Coll Card, 1996

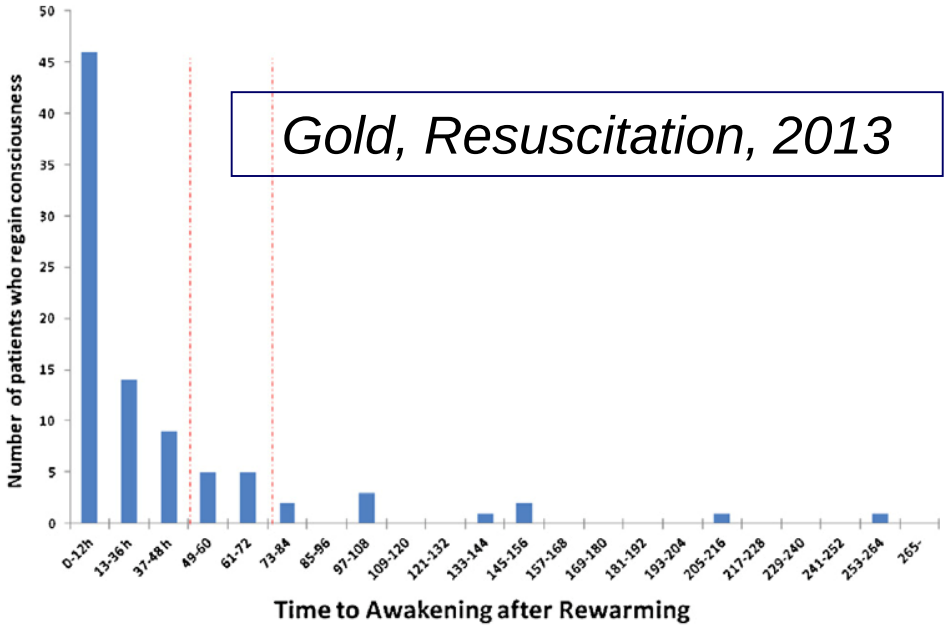
Pediatric Post-ROSC Hypotension

Topjian, CCM, 2014

After controlling for patient and cardiopulmonary arrest characteristics, hypotension in the first 6 hours following ROSC was associated with:

- Significantly increased odds of in-hospital mortality (adjusted odds ratio = 1.71; *p* = 0.042)
- Increased odds of unfavorable outcome (adjusted odds ratio = 1.83; *p* = 0.032).

- Marker of severity, or a Target for management?
- How best to treat, what best to target (BP vs. perfusion indices), post-ROSC mechanical support?

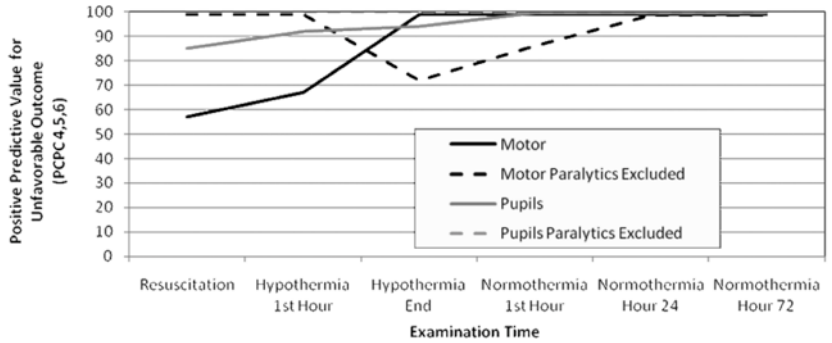


Gold, Resuscitation, 2013

Fig. 2. Time to awakening after rewarming. Dashed lines indicate the 48 and 72 h timepoints.

Timing of Prognostication Post ROSC

Abend, Peds CCM, 2012



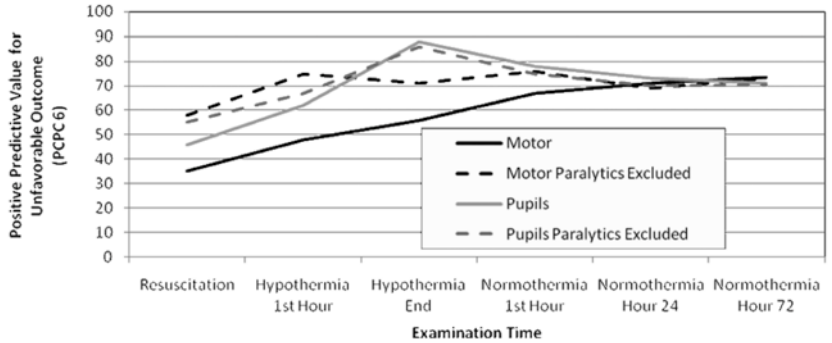


Figure 1. Examination times during the course of therapeutic hypothermia after cardiac arrest.

Thank You for your attention!

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