

Introduction to Stabilization and Resuscitation: Discussion of ILCOR Guidelines

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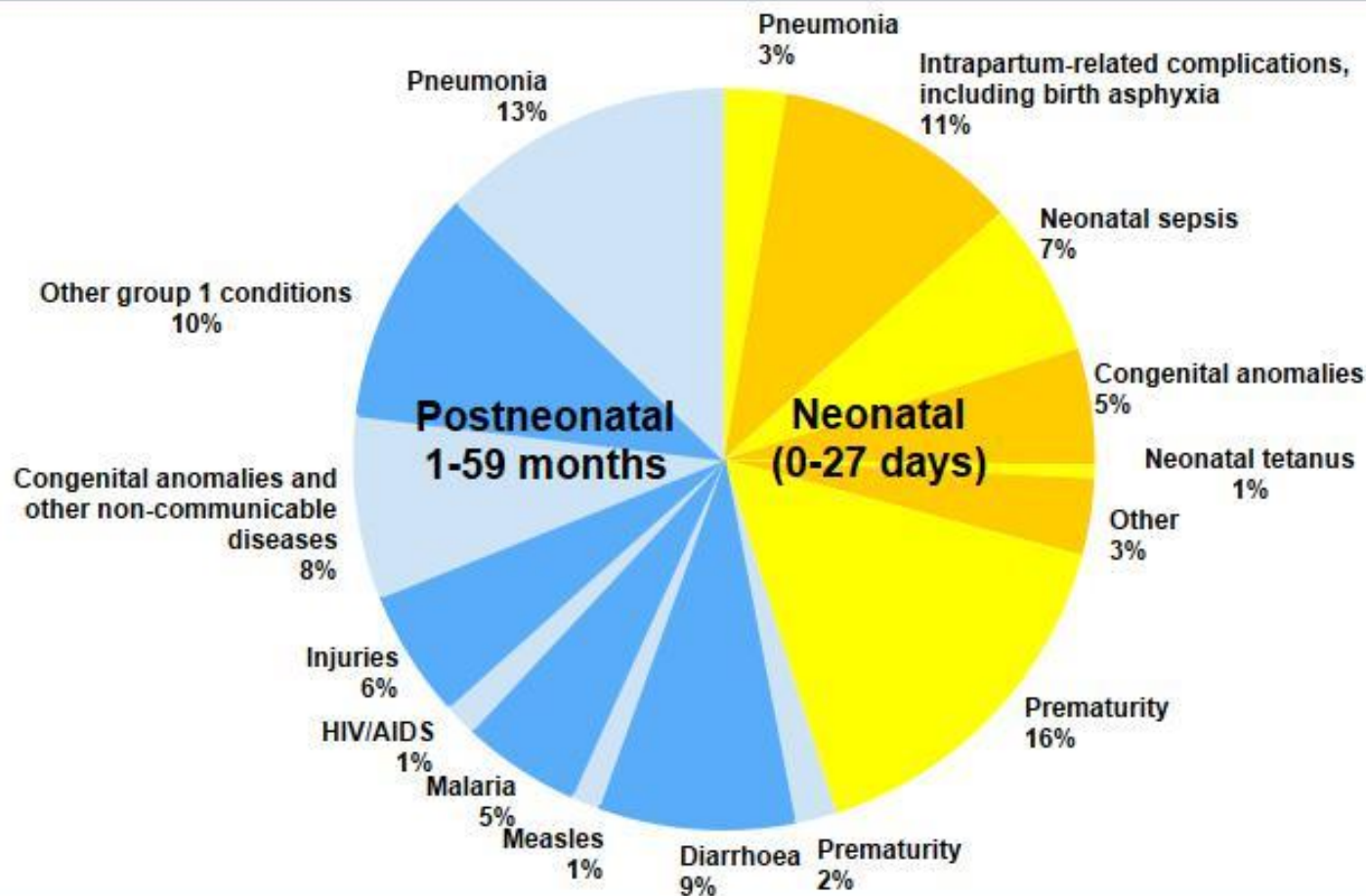
Australia

A light blue world map is visible in the background of the bottom section of the slide.

The BEST of IPOKRATES:
an UPDATE in NEONATOLOGY

Windsor Oceanico Hotel, Barra da Tijuca, Rio de Janeiro, Brazil
June 20 – 23, 2018

Causes of deaths among children under 5 years, 2015



Source: WHO-MCEE methods and data sources for child causes of death 2000-2015 (Global Health Estimates Technical Paper WHO/HIS/IER/GHE/2016.1)

2015 International Liaison Committee on Resuscitation (ILCOR): New Recommendations for Neonatal Resuscitation

Resuscitation. 2015 Oct;95:e169-201.

Circulation. 2015 Oct 20;132(16 Suppl 1):S204-41.

Pediatrics. 2015 Nov;136 Suppl 2:S120-66.

Program

- The process
- The highlights
 - New algorithm
 - New *recommendations*
- A little research

The process

- ILCOR: 5 year cycle, worldwide representation
- Identify questions and assign 2-3 reviewers
- Search strategy designed and implemented with the assistance of librarians
 - Medline, Embase, Cochrane

The process

- Standardised evaluation of the evidence (GRADE)
- Presentation and consensus reached for each question
- Treatment *recommendation* reached (vs Cochrane)

The process

- Publication of ILCOR *guidelines*
- Adapted in national/regional guidelines
 - NRP
 - ERC
 - ARC...
- Adapted in hospital protocols

What is GRADE?

- A method used to assess the quality of evidence and decide whether to recommend an intervention
- Separates *quality of evidence* and *strength of recommendation*
- Quality is assessed for each important outcome
- Evidence can be upgraded (observational studies) or downgraded (RCTs) according to prespecified criteria

Steps of GRADE

1. Assign a priori ranking of quality of the evidence:
RCT “high”, observational “low”
2. Downgrade (e.g. lack of blinding, loss to follow-up)
OR
Upgrade (e.g. large effect, consistency)
3. Assign final grade (high, moderate, low, very low)
4. Consider other factors influencing recommendation
e.g. patient preference, cost
5. Make a strong (“we recommend”) or weak (“we suggest”) recommendation for or against the intervention

2015 NEONATAL RESUSCITATION ALGORITHM

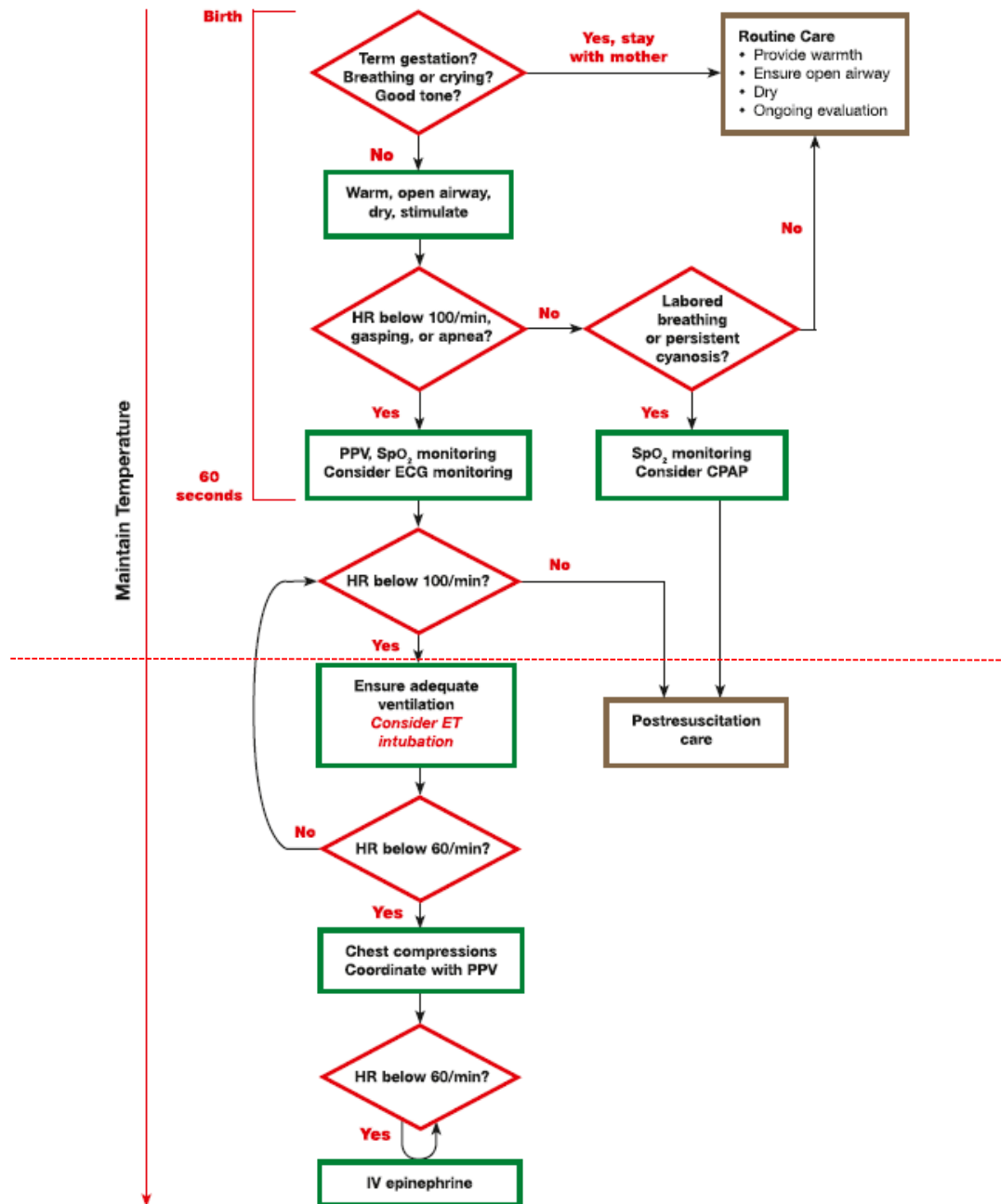
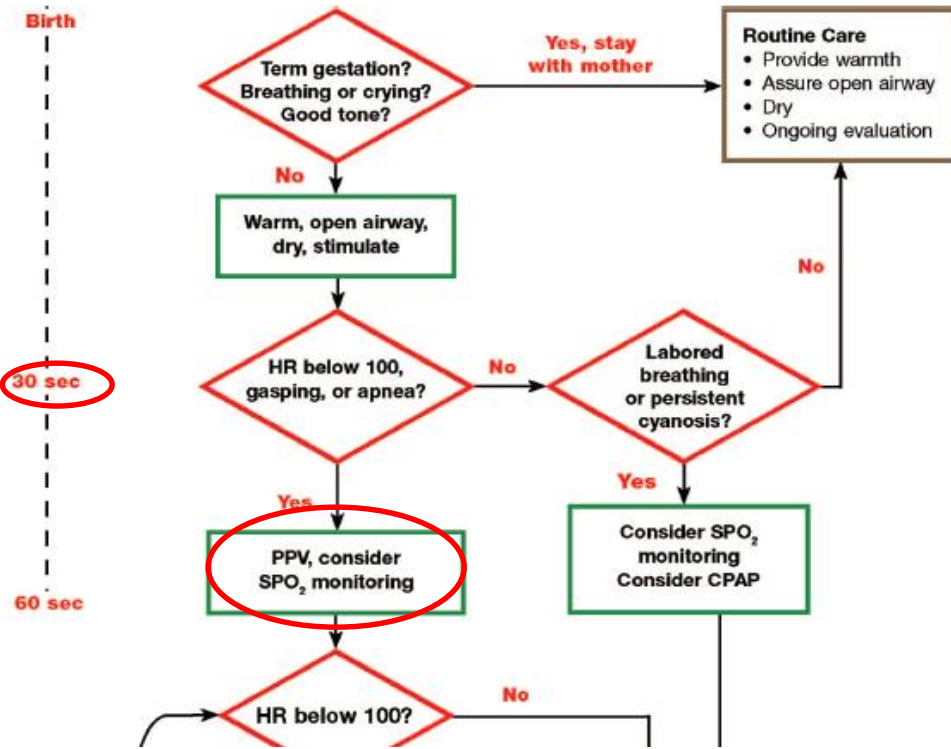
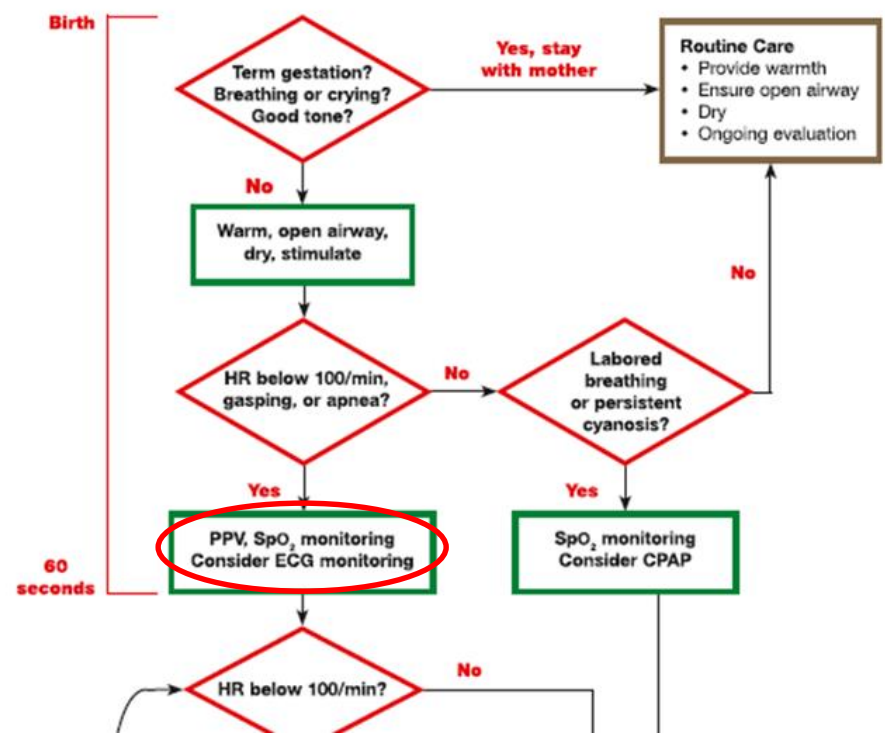


Figure 1
Neonatal Resuscitation Algorithm.



2010



2015

2015 RECOMMENDATIONS

Assessing heart rate

- Clinical assessment is inaccurate (underestimates HR)
- Pulse oximetry may take “several minutes” to obtain reliable data
- *Very low quality evidence* that ECG is better (quicker, more accurate early) than PO

Assessing heart rate

Treatment recommendation: In babies requiring resuscitation we *suggest* ECG *can* be used to provide a rapid and accurate estimation of HR

Assessing heart rate

- Values and preferences:
 - ECG is not ready for “prime time”
 - Need to establish trigger points for intervention
 - Risk of inappropriate intervention
 - PO is still important for managing oxygen therapy

Hot off the press: PEA

Pulseless electrical activity

- In a neonatal piglet model of asphyxia:
 - Exposure to 30 min 10% oxygen followed by clamping ETT (10 min or asystole)
 - Cardiac asystole (arrest) defined as zero carotid blood flow
 - Compared carotid blood flow with ECG and auscultation of the piglet's chest

Accuracy of ECG and auscultation vs Carotid blood flow

Electrocardiography (ECG)

	<i>No carotid flow</i>	<i>Carotid flow seen</i>	Predictive values
Asystole on ECG	14	0	Positive 100%
HR present on ECG	23	16	Negative 41%
	Sensitivity 37%	Specificity 100%	

Auscultation

	<i>No carotid flow</i>	<i>Carotid flow seen</i>	Predictive values
No heart sounds	38	0	Positive 100%
Heart sounds heard	0	16	Negative 100%
	Sensitivity 100%	Specificity 100%	

Cord clamping

- Term infants: Delayed cord clamping (DCC) at least 1 minute is appropriate for infants not requiring resuscitation (ILCOR 2010)

Cord clamping

- Preterm infants:
 - Sixteen articles
 - 12 RCTs (n=691)
 - 4 observational studies (n=811)
 - Trials excluded infants receiving resuscitation
 - No difference in mortality or severe IVH
 - No evidence regarding neurodevelopment
 - DCC improves any IVH, hemodynamic stability

Cord clamping

Treatment recommendation: *We suggest* DCC for preterm infants not requiring immediate resuscitation (weak recommendation, very low quality evidence)

Delayed versus Immediate Cord Clamping in Preterm Infants

N Engl J Med 2017; 377:2445-2455

DOI: 10.1056/NEJMoa1711281

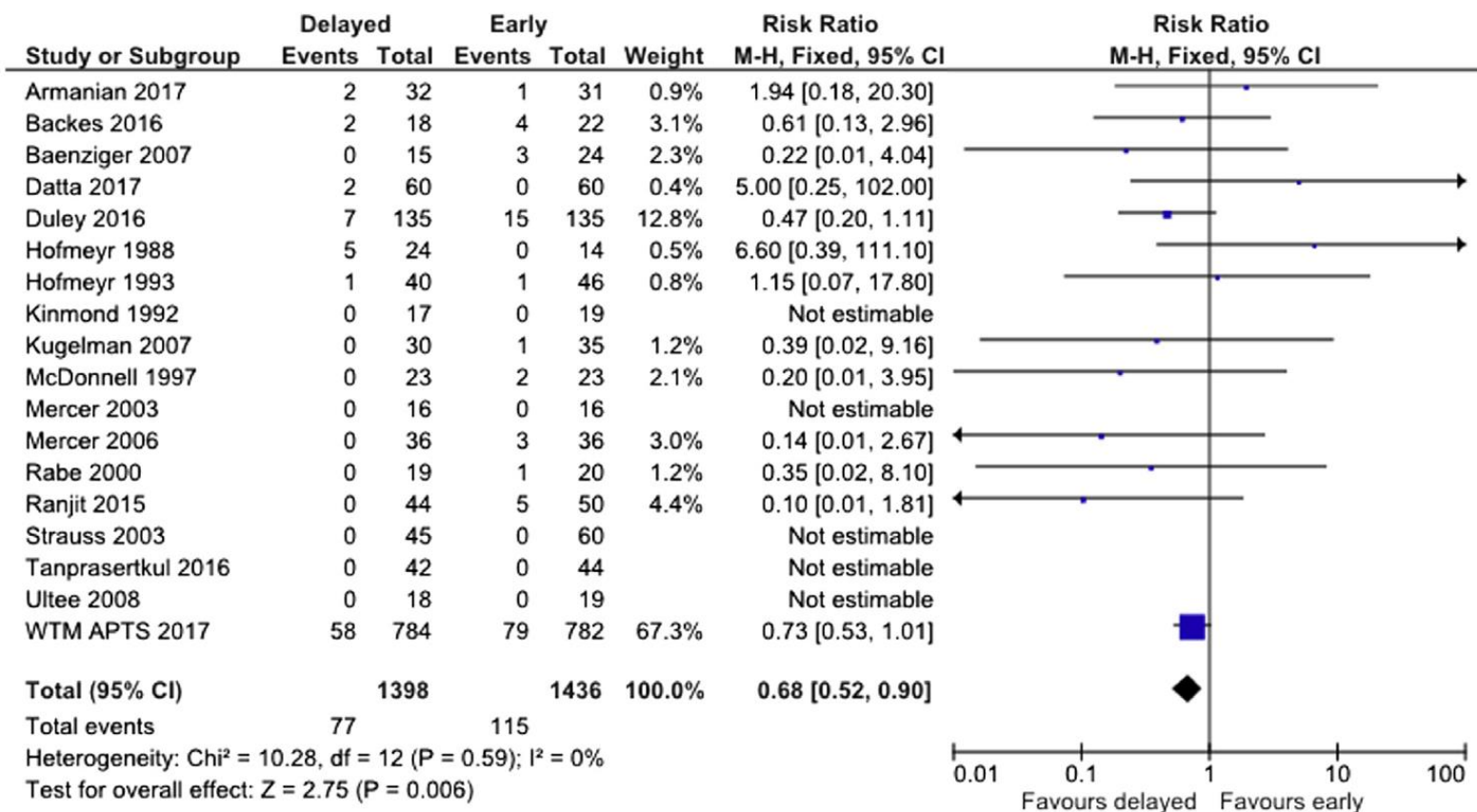
Delayed vs early umbilical cord clamping for preterm infants: a systematic review and meta-analysis



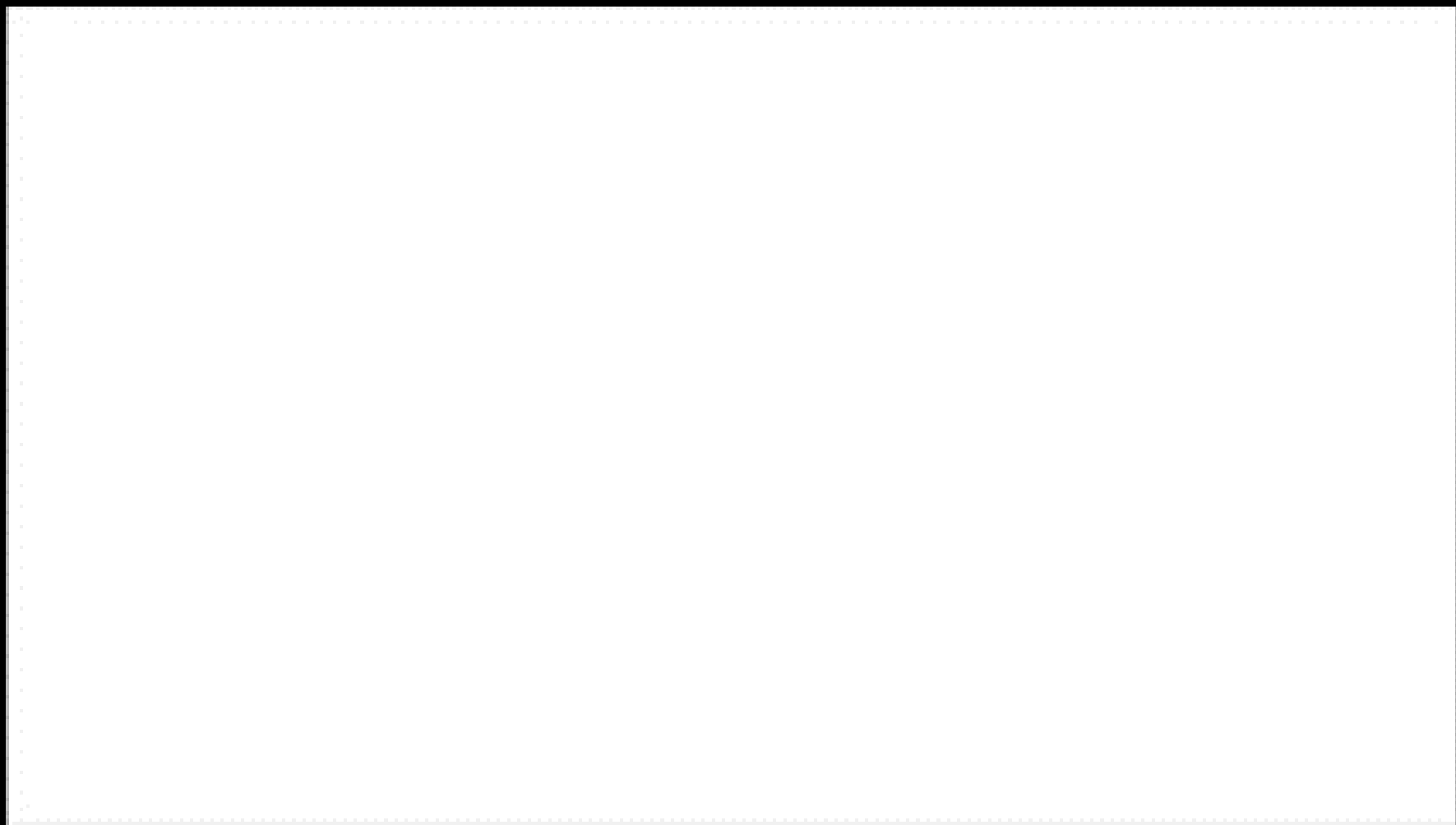
Michael Fogarty; David A. Osborn; Lisa Askie; Anna Lene Seidler; Kylie Hunter; Kei Lui; John Simes; William Tarnow-Mordi

JANUARY 2018 **American Journal of Obstetrics & Gynecology**

FIGURE 3
Meta-analyses showing effect of delayed clamping on mortality



**WHAT'S NEXT: DELAYED CORD
CLAMPING FOR INFANTS RECEIVING
RESUSCITATION?**



Cord Milking (Stripping)

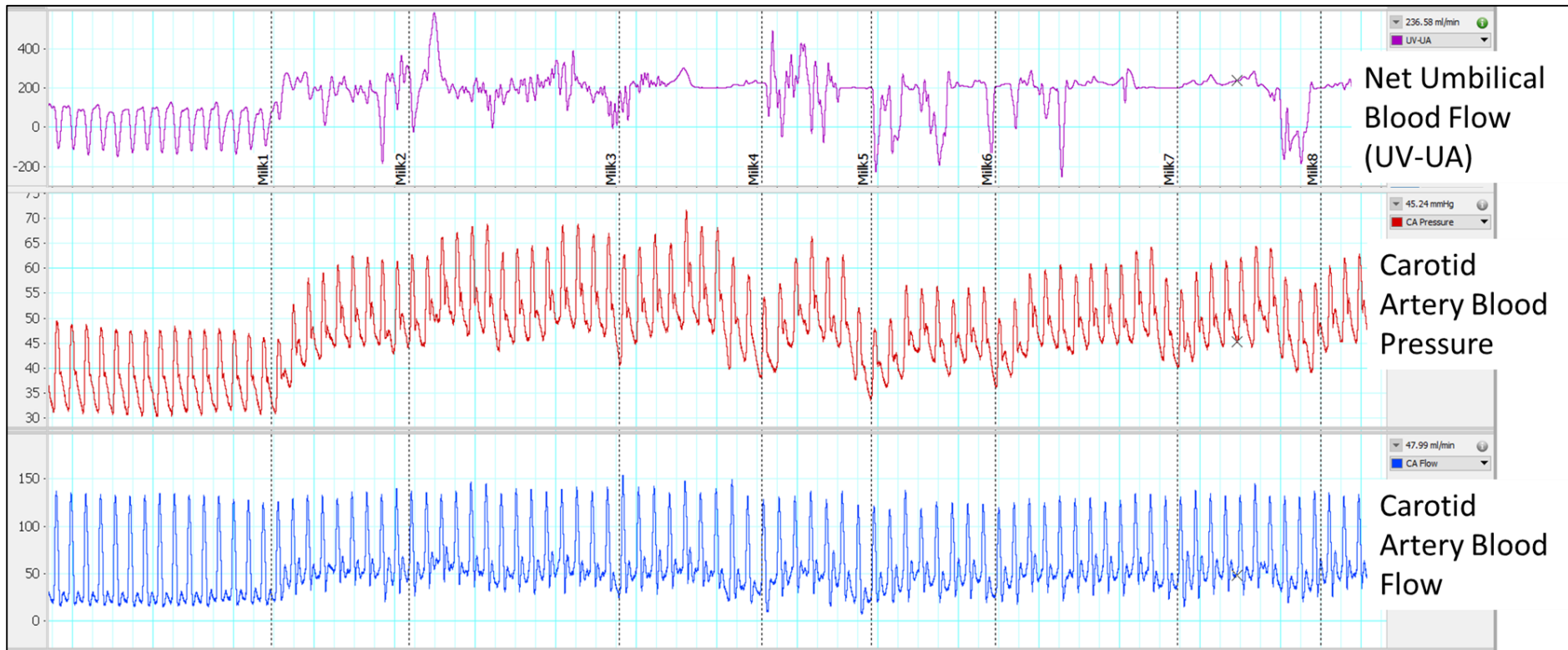
- Biological rationale: quick method of delivering a transfer of blood to the newborn prior to resuscitation
- Evidence base: 4 RCTs, 1 cohort study (200 babies) comparing early clamping with milking i.e. none comparing DCC with milking
- Consensus on science
 - No difference in rates of death
 - No data on neurodevelopment
 - No difference in use of phototherapy
 - Low quality evidence showing a reduction in rates of all IVH

Cord Milking (Stripping)

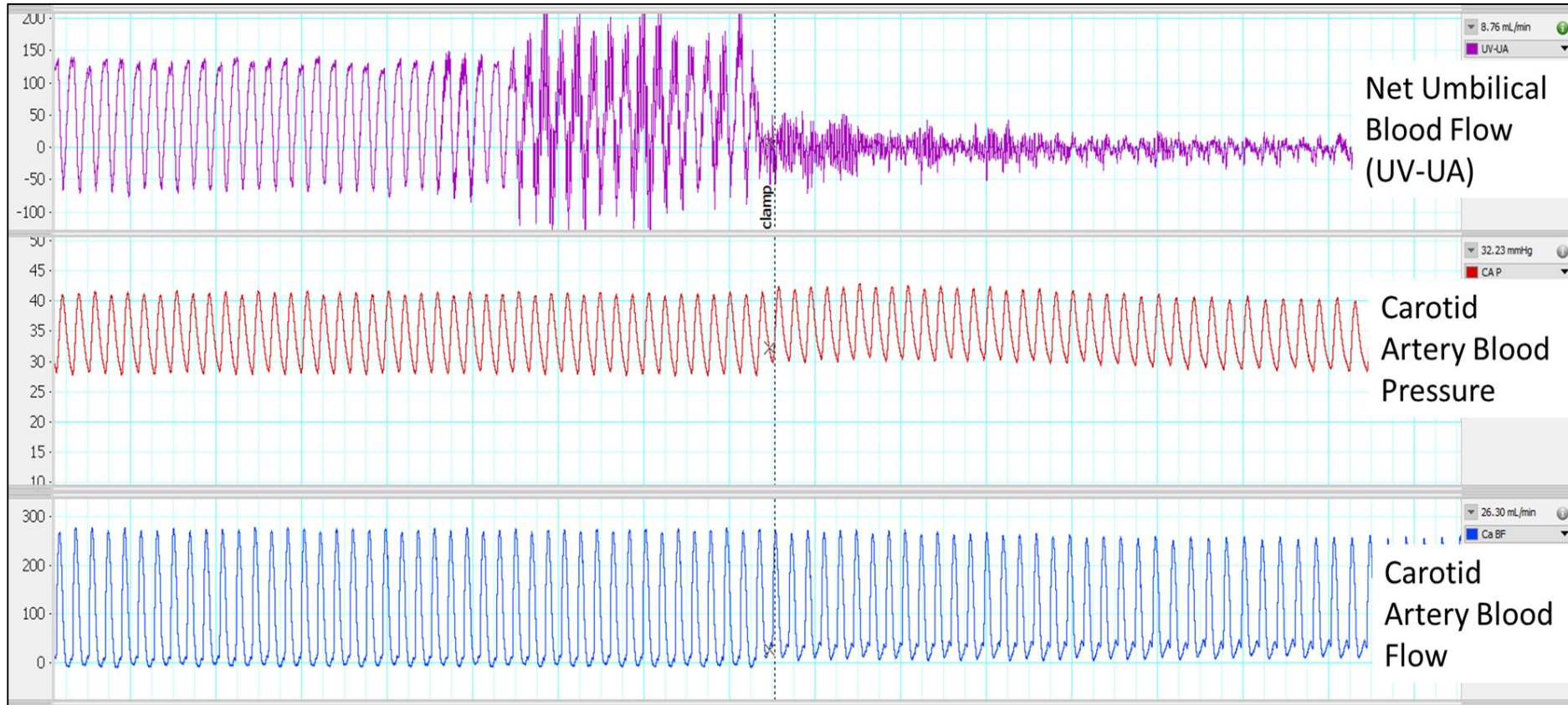
Treatment recommendation: *We suggest against the routine use* of cord milking for infants born ≤ 28 weeks

Trials are underway that should fill this gap by 2020.

Lamb model of cord milking



Lamb model: Ventilation then cord clamping



Temperature

- 36 observational studies showed an increased risk of mortality associated with hypothermia at admission (low quality evidence upgraded to moderate quality due to effect size, dose-effect relationship and consistency of direction of evidence)

Temperature

We recommend that the temperature of newborn infants be maintained between 36.5 and 37.5C (strong recommendation, very low quality evidence)

Maintaining temperature: Strategies in preterm infants

- Strategies available
 - Radiant warmer, thermal mattress, plastic wrap, environmental temp ($>26^{\circ}\text{C}$), heated humidified gases
- Evidence
 - Small RCTs, low quality of observational studies

Maintaining temperature: Strategies in preterm infants

For newborn infants <32 weeks under radiant warmers we *suggest* using a combination of interventions to reduce hypothermia (environmental temp, plastic wraps, caps, thermal mattress)

We *suggest* that hyperthermia (>38C) be avoided due to associated risks

CPAP and IPPV

- Consensus on science
 - Moderate quality evidence from 3 RCTs (2358 infants)
- Death or BPD: potential benefit for CPAP RR 0.91 (0.83-1.00)
- Death: no benefit RR 0.82 (0.66-1.03)
- BPD: no benefit RR 0.92 (0.82-1.03)
- Air leak: no benefit (or harm) RR 1.24 (0.91-1.69)

CPAP and IPPV

Treatment recommendation: for spontaneous breathing preterm infants with respiratory distress requiring respiratory support in the DR we *suggest* initial use of CPAP rather than intubation and IPPV (weak recommendation, moderate evidence)

Sustained inflations (SI)

- Rationale: rapid establishment of FRC will improve outcomes following resuscitation. Strong evidence from animal (lamb and rabbit) models that SI are safe and effective



Sustained inflations (SI)

- Rationale: rapid establishment of FRC will improve outcomes following resuscitation. Strong evidence from animal (lamb and rabbit) models that SI are safe and effective
- 3 RCTs (404 infants) and 2 cohort studies (331 infants)
 - No benefit for mortality, BPD, air leak
 - Low quality evidence of a decreased need for mechanical ventilation

Sustained inflations (SI)

Treatment recommendation: we *suggest against* the routine use of initial SI (>5 sec) for preterm infants without spontaneous respirations but may be considered in individual circumstances or research settings (weak recommendation, low quality evidence)

- Values and preferences
 - Absence of long term benefits, lack of clarity on how to administer SI
 - Large RCT (SAIL) is underway

The International 'Sustained Aeration for Infant Lung' (SAIL) Randomized Trial

PAS 2018



1-U01-HD072906-01A1

THE **S**USTAINED **A**ERATION OF **I**NFANT **L**UNGS (SAIL) STUDY:
RANDOMIZED CLINICAL TRIAL



Conclusions

- In this population of extremely preterm infants who required resuscitation, up to two SIs at these pressures and durations did not reduce the combined rate of BPD or death.
Note that these 2 SIs were not prophylactic.
- There was an elevated risk of death within 48 hours with SI, with no evidence of benefit.

PEEP

- Consensus on science:
 - low quality evidence from 2 RCTs, 596 babies
- Death: no benefit RR 0.62 (0.27-1.38)
- BPD: no benefit RR 1.15 (0.71-1.87)
- Need for drugs/CPR: no benefit RR 1.47 (0.55-3.92)
- Need for intubation: no benefit RR 1.21 (0.91-1.61)
- Maximum oxygen required: PEEP 48% vs no PEEP 53% (p=0.005)

PEEP

Treatment recommendation: *We suggest* using PEEP for premature infants during DR resuscitation (weak recommendation, low quality evidence)

- Values and preferences
 - Based on animal evidence showing a benefit for PEEP and small difference in maximum oxygen required

Non-vigorous infants born through meconium stained AF

- Routine suctioning of vigorous babies no longer recommended
- Consensus on science: based on 1 RCT (n=122), and multiple observational studies
 - No evidence of improved survival and/or MAS with intubation

Non-vigorous infants born through meconium stained AF

Treatment recommendation: there is insufficient evidence to suggest tracheal intubation for suctioning of meconium in non-vigorous infants born through MSAF

Values and preferences

- Driven by harm avoidance – delayed PPV, trauma from procedure vs unknown benefit of the intervention
- Still need a provider capable of intubating and ventilating a baby born through MSAF

Oxygen concentration for preterms

- 2010 recommendation for term infants: start in 21% oxygen and titrate according to saturations to match saturations of healthy term babies
- Benefits and risks are different for preterms
- Evidence base: 7 RCTs (607 infants), 1 cohort study (125 infants)
- Consensus on science
 - No benefit of high oxygen for death, BPD, IVH, ROP

Oxygen concentration for preterms

Treatment recommendation

- *We recommend against* initiating resuscitation of preterm newborns with high supplementary oxygen concentrations (65%-100%)
- *We recommend* initiating resuscitation with low oxygen concentration (21%-30%) (strong recommendation, moderate quality evidence)

Oxygen concentration for preterms

- Watch this space
 - More trials are coming (Torpedo etc)

Chest compressions

- Weak recommendations based on very low quality evidence (animal models, mannikins, older infants)
- *We suggest*
 - Delivery by 2-thumb method with hands encircling the chest
 - Delivery to the lower third of the sternum
 - 3:1 compression to ventilation ratio

Oxygen during CPR

- No human data
- Animal data suggests no advantage to using 100% oxygen
- “We are making a recommendation independent of the evidence”

“It would seem prudent to try increasing the supplementary oxygen concentration”

Cooling for hypoxic ischemic encephalopathy: ILCOR 2010 Treatment Recommendation

- Term and near-term with moderate to severe HIE should be offered cooling
- Whole body and selective head cooling are both appropriate
- Cooling should be initiated and conducted in neonatal intensive care facilities using the protocols used in the RCTS (begin within 6 hours of birth, continue for 72 hours after birth, and rewarm over at least 4 hours).
- Monitor for adverse effects: thrombocytopenia and hypotension
- All treated infants should be followed up longitudinally

Barriers to application in resource limited settings

- Lack of suitable cooling equipment (\$)
- Lack of skilled personnel
- Higher rates of sepsis (neutrophil function)
- Lack of facilities for disabled children
- Lack of ventilatory support

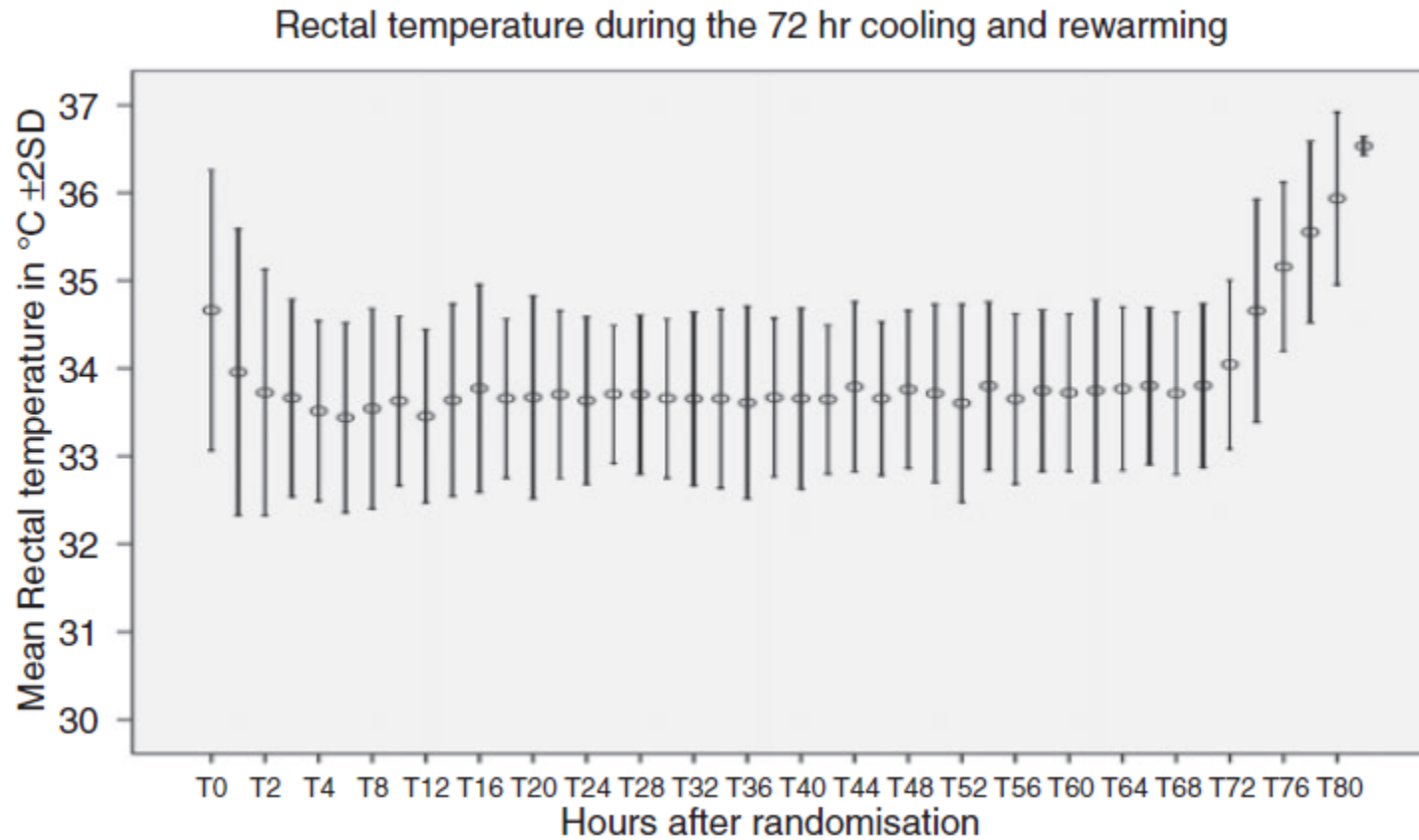
Effectiveness vs efficacy

- Can accurate/reliable cooling be achieved with ice packs and passive cooling?
- Does this method of cooling improve long term outcomes?
- Is it safe?
 - Infection
 - Coagulopathy
 - ...

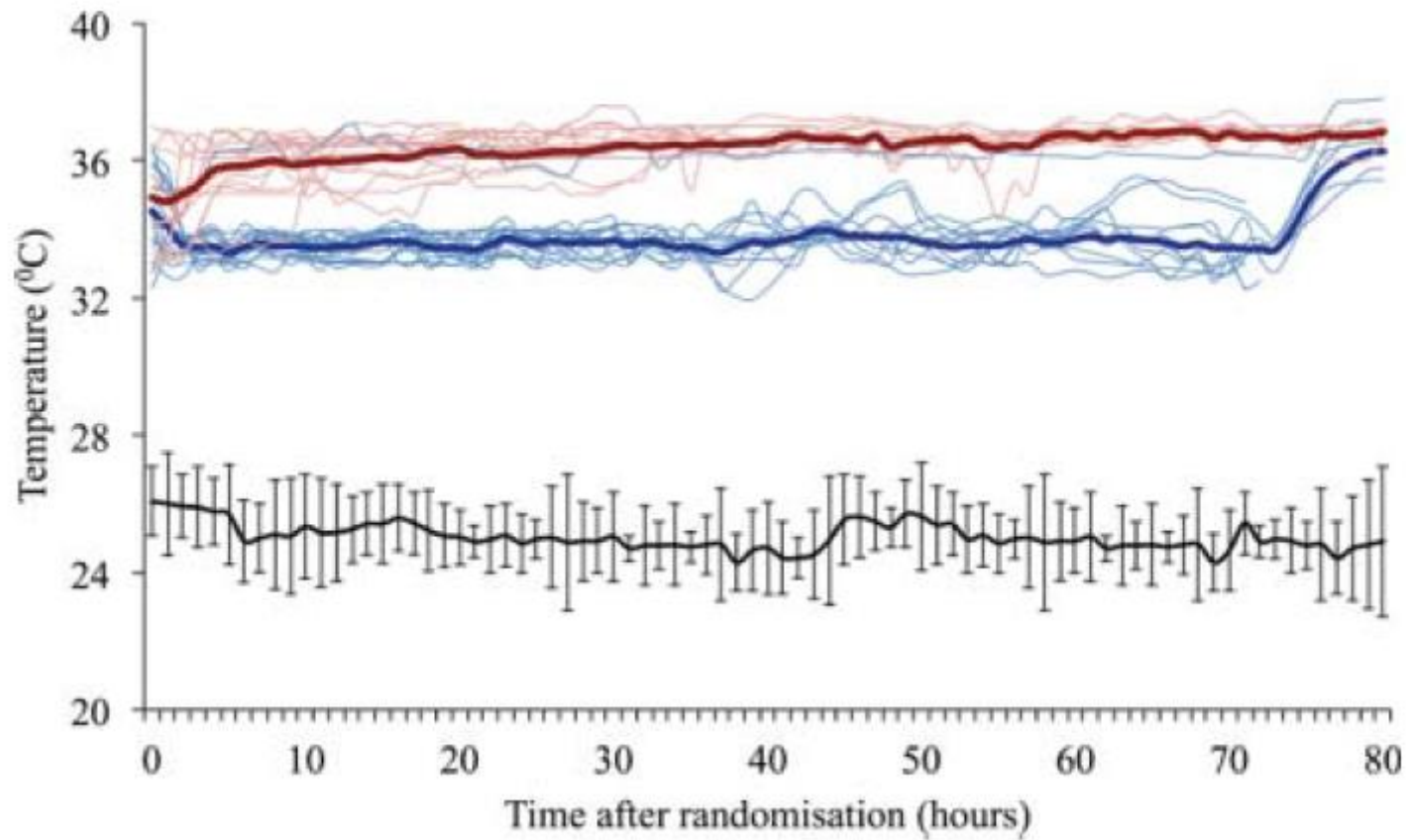
Evidence pertinent to resource limited settings

- 4 RCTs
 - ICE Trial: gel packs, advanced setting
 - Bharadwaj (2012) India: gel packs
 - Thayyil (2013) India: phase changing material mattress
 - Robertson (2011, 2008) Uganda: water bottles

Rectal temperature: Bharadwaj

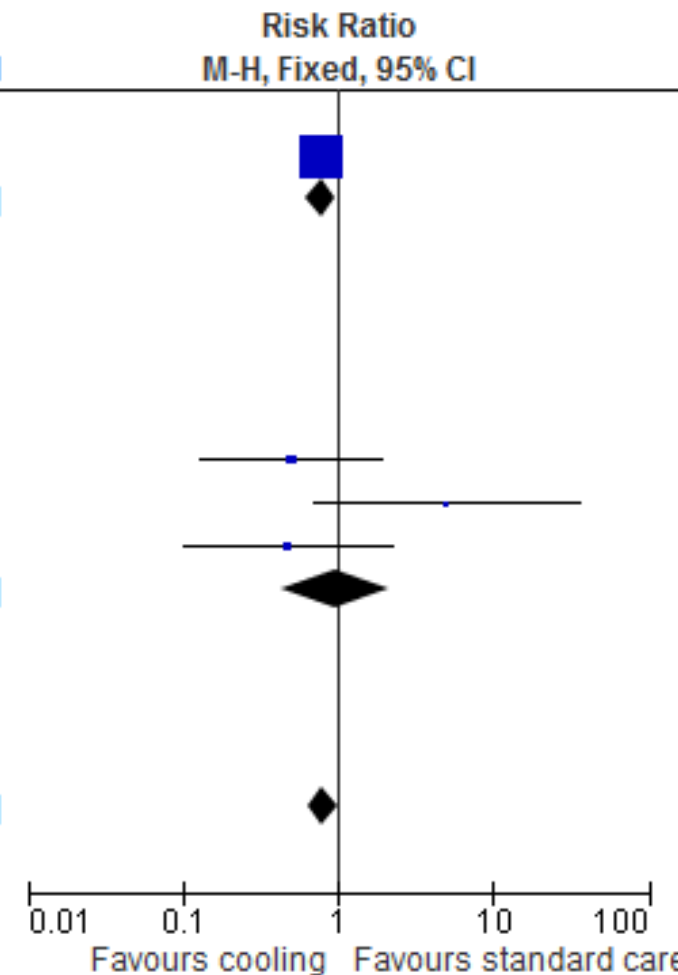


Rectal temperature: Thayyil

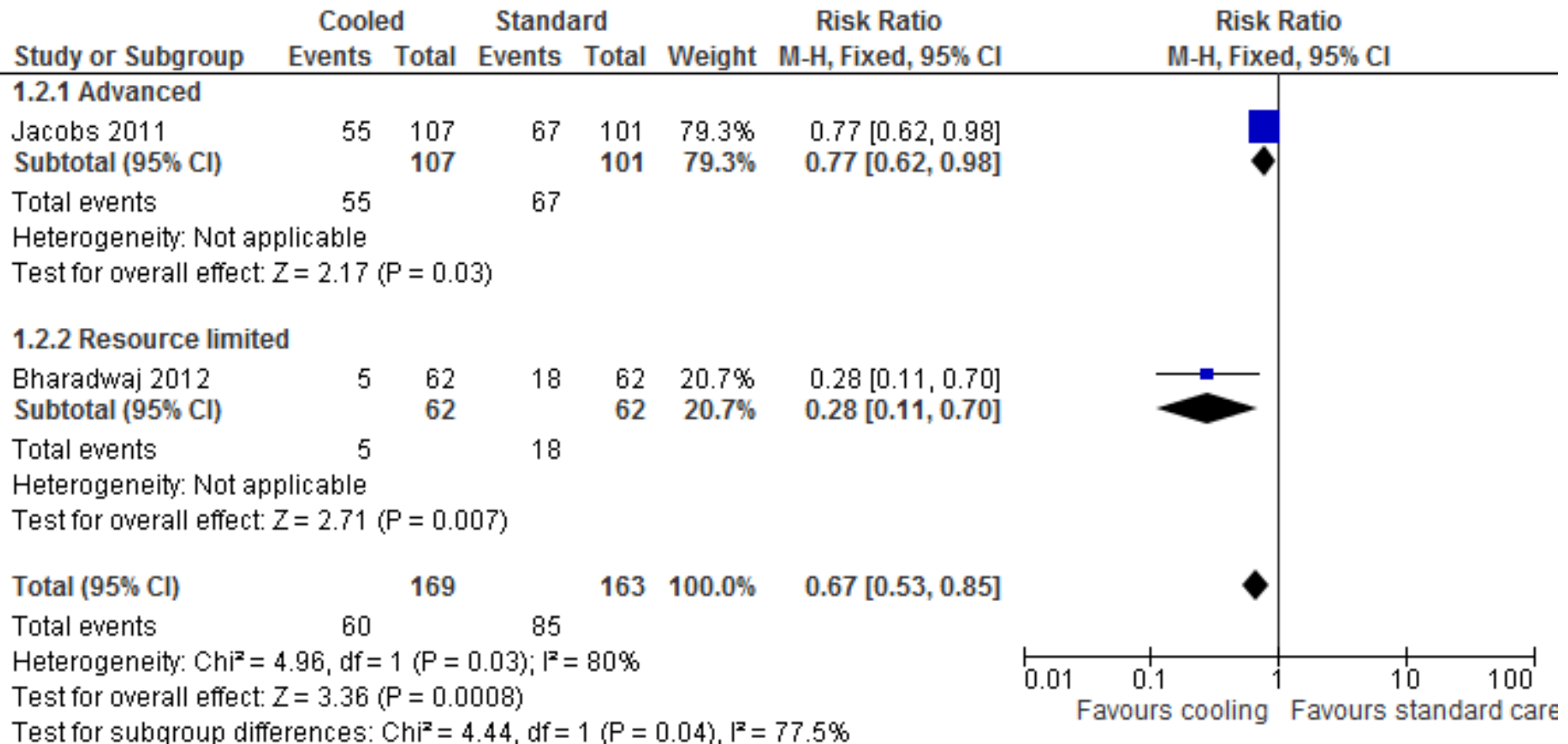


Simple whole body cooling: Death

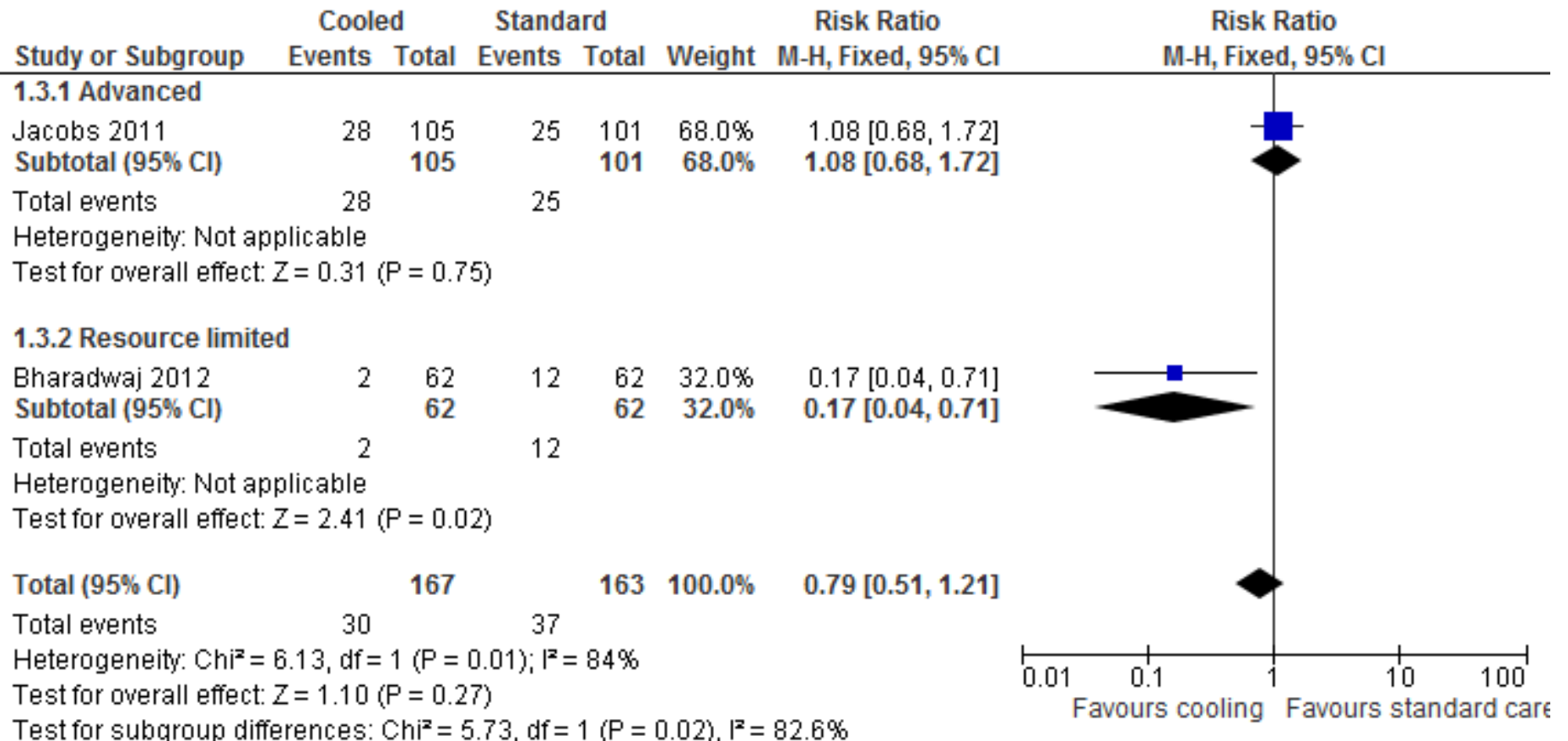
Study or Subgroup	Cooled		Standard		Weight	Risk Ratio M-H, Fixed, 95% CI
	Events	Total	Events	Total		
1.1.1 Advanced						
Jacobs 2011	55	107	67	101	85.9%	0.77 [0.62, 0.98]
Subtotal (95% CI)		107		101	85.9%	0.77 [0.62, 0.98]
Total events	55		67			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.17 (P = 0.03)						
1.1.2 Resource limited						
Bharadwaj 2012	3	62	6	62	7.5%	0.50 [0.13, 1.91]
Robertson 2008	7	21	1	15	1.5%	5.00 [0.69, 36.50]
Thayyil 2013	2	17	4	16	5.1%	0.47 [0.10, 2.23]
Subtotal (95% CI)		100		93	14.1%	0.95 [0.43, 2.13]
Total events	12		11			
Heterogeneity: Chi ² = 4.36, df = 2 (P = 0.11); I ² = 54%						
Test for overall effect: Z = 0.11 (P = 0.91)						
Total (95% CI)		207		194	100.0%	0.80 [0.64, 1.01]
Total events	67		78			
Heterogeneity: Chi ² = 4.26, df = 3 (P = 0.23); I ² = 30%						
Test for overall effect: Z = 1.89 (P = 0.06)						
Test for subgroup differences: Chi ² = 0.24, df = 1 (P = 0.63), I ² = 0%						



Death or disability



Disability



***Bharadwaj – assessed at 6 months**

Results

- Simple cooling delivers reasonably precise and accurate whole body hypothermia
- The technique reduces death (and death or disability) in a developed world setting (ICE)
- No evidence of benefit or harm (mortality) in resource limited setting

Treatment recommendations

We *recommend* that term and near –term infants with moderate to severe HIE born in limited resource settings may be treated with therapeutic hypothermia (weak recommendation, low quality evidence)

- Consider only if
 - Clearly defined protocols (similar to RCTs)
 - Multidisciplinary neonatal care
 - Intravenous therapy, respiratory support, pulse oximetry, antibiotics, anticonvulsants and pathology services

Discontinuing resuscitation

- Very low quality evidence from “nested” studies within cooling RCTs
- Very controversial, much disagreement
“spirited debate”

Discontinuing resuscitation

Treatment recommendations

- It may be reasonable to stop resuscitation at 10 minutes with an Apgar score of 0 at 10 minutes (i.e. no heart rate). The decision should be individualised: quality of the resuscitation, availability of advanced neonatal care, known timing of insult, wishes of family
- In resource limited settings we *suggest* that it may be reasonable to stop assisted ventilation in babies with no spontaneous breathing despite a heart rate (Apgar score 1-3) at 20 minutes

WHAT HASN'T CHANGED

Ventilation, ventilation, ventilation

- “Ventilation of the lungs is the single most important and most effective step in the resuscitation of the compromised newborn”