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La neonatologia nel 3° millennio: ruolo ed integrazioni interdisciplinari

La Rianimazione Neonatale: quale Evoluzione?

Daniele Trevisanuto

University of Padova, Italy

Venerdì 24 gennaio 2020

dalle ore 14.15 alle 19.00

Aula Magna
Nuovo Ospedale S. Anna
Cona - Ferrara

EUROPEAN RESUSCITATION COUNCIL

Guidelines for Neonatal Resuscitation (history)

[<1960] Empirical observations

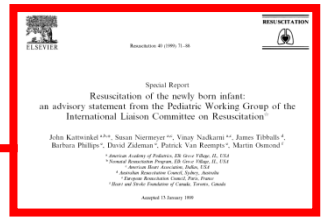
[1966] AHA committee on cardiopulmonary resuscitation (adults)

[1987] Bloom RS, Cropley C, editors. Textbook of neonatal resuscitation

[1992] International Liaison Committee on Resuscitation (ILCOR)

Guidelines for cardiopulmonary resuscitation and emergency cardiac care. Emergency Cardiac Care Committee and Subcommittees, American Heart Association. Part VII. Neonatal resuscitation. (JAMA, Oct 1992)

[2000]


Special Report
Resuscitation of the newly born infant: an advisory statement from the Pediatric Working Group of the International Liaison Committee on Resuscitation

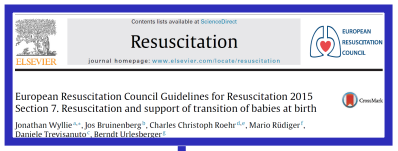
[2005]


2005 American Heart Association (AHA) Guidelines for Cardiopulmonary Resuscitation (CPR) and Emergency Cardiovascular Care (ECC) of Pediatric and Neonatal Patients: Neonatal Resuscitation Guidelines

[2010]


PEDIATRICS
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS
Neonatal Resuscitation: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations

[2015]


Resuscitation
European Resuscitation Council Guidelines for Resuscitation 2015 Section 7. Resuscitation and support of transition of babies at birth

Virginia Apgar

Indicator	
A	Activity (muscle tone)
P	Pulse
G	Grimace (reflex irritability)
A	Appearance (skin color)
R	Respiration

(1952)

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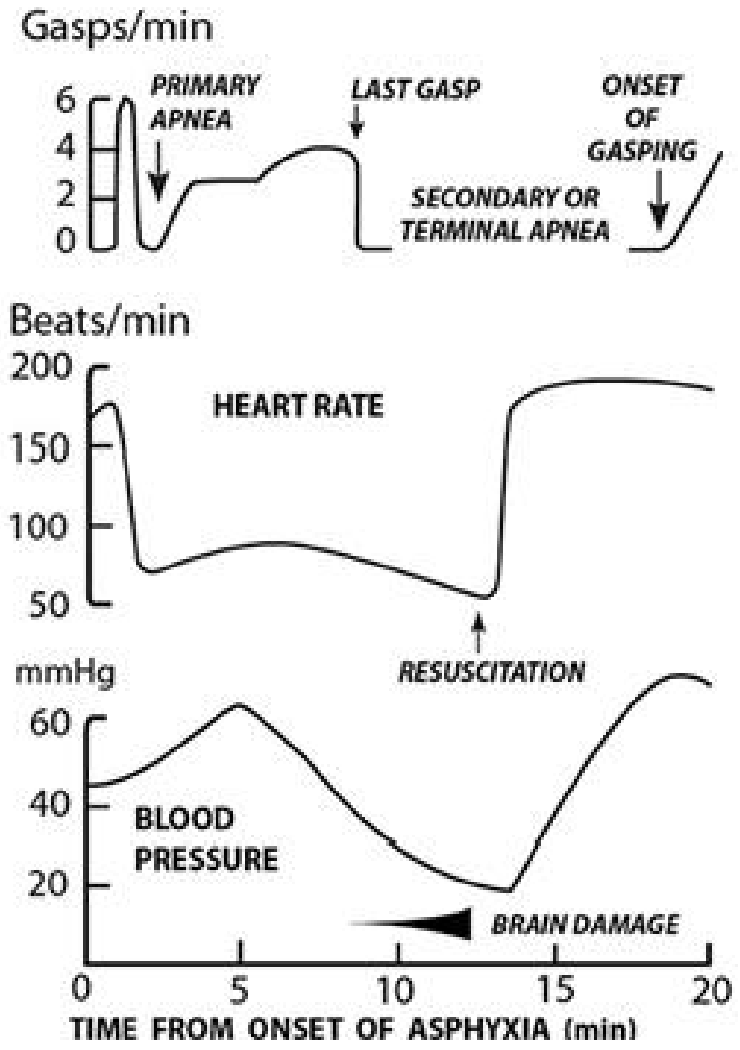
Pco_2	45	100	150	200	40
pH	7.3	7.0	6.8	6.75	7.1



Dawes G, Jacobson H, Mott JC, Shelley HJ, Stafford A. The treatment of asphyxiated, mature foetal lambs and rhesus monkeys with intravenous glucose and sodium carbonate. J Physiol. (1963) 169:167–84.

EUROPEAN RESUSCITATION COUNCIL

Part 7: Neonatal Resuscitation

2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations

Jeffrey M. Perlman, Co-Chair*; Jonathan Wyllie, Co-Chair*; John Kattwinkel; Myra H. Wyckoff; Khalid Aziz; Ruth Guinsburg; Han-Suk Kim; Helen G. Liley; Lindsay Mildenhall; Wendy M. Simon; Edgardo Szyld; Masanori Tamura; Sithembiso Velaphi; on behalf of the Neonatal Resuscitation Chapter Collaborators

Perlman JM et al. Circulation 2015

Methods

PICO Questions (n. 26)

- Consensus on Science (GRADE)
- Treatment Recommendation
- Values and Preferences
- Knowledge Gaps

[53 pages!]

Perlman J et al. Circulation 2015

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Consensus on Science 2015

Treatment recommendation

- **We recommend…** → in favor… / against…

- **We suggest…** → in favor… / against…

Perlman J et al. Circulation 2015

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Values and Preferences

Justification and Evidence to Decision Highlights

The Task Force recognizes that, while the Treatment Recommendation has not changed, several studies have been added to the literature since the last recommendation was made. While these studies contribute new evidence regarding this topic, the certainty of the findings remains low or very low due to the difficulty of performing unbiased studies of this clinical question as well as failure of the data to reach optimal information size.

In making this suggestion, we place value on both harm avoidance (delays in providing bag-mask ventilation, potential harm of the procedure) and the unknown benefit of routine tracheal intubation and suctioning.

Routine suctioning of non-vigorous infants is more likely to result in delays in initiating ventilation, especially where the provider is unable to promptly intubate the infant or suction attempts are repeated. In the absence of evidence of benefit for routine suctioning, the emphasis should be on initiating ventilation within the first minute of life in non-breathing or ineffectively breathing infants born through meconium-stained amniotic fluid. Some newly born infants may receive tracheal intubation in order to clear a blocked airway or for subsequent ventilation (Edwards 2019 E68, Kalra 2019).

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Knowledge Gaps

Despite the addition of several randomized trials focused on this clinical question, the optimal information size is not achieved even with all of the studies taken together. The difficulties of performing a study while minimizing the risks of bias due to difficulty with blinding and assessment of outcome make accrual of evidence a significant challenge. The priorities for study remain similar to previous versions of the CoSTR:

- Does the potential for harm (i.e. delay in starting positive pressure ventilation or transient bradycardia/hypoxia, mortality, NDI) outweigh the potential for benefit (i.e. reduction of MAS, need for mechanical ventilation or treatment of pulmonary hypertension)?
- Do risks or benefits of intubation with tracheal suctioning vary with any subgroup (gestational age, thickness of meconium, operator experience)?
- Long-term outcomes should be included in future studies.
- The neurodevelopmental, behavioral, or educational assessment for future studies should be at or after 18 months of age and completed with a validated tool.

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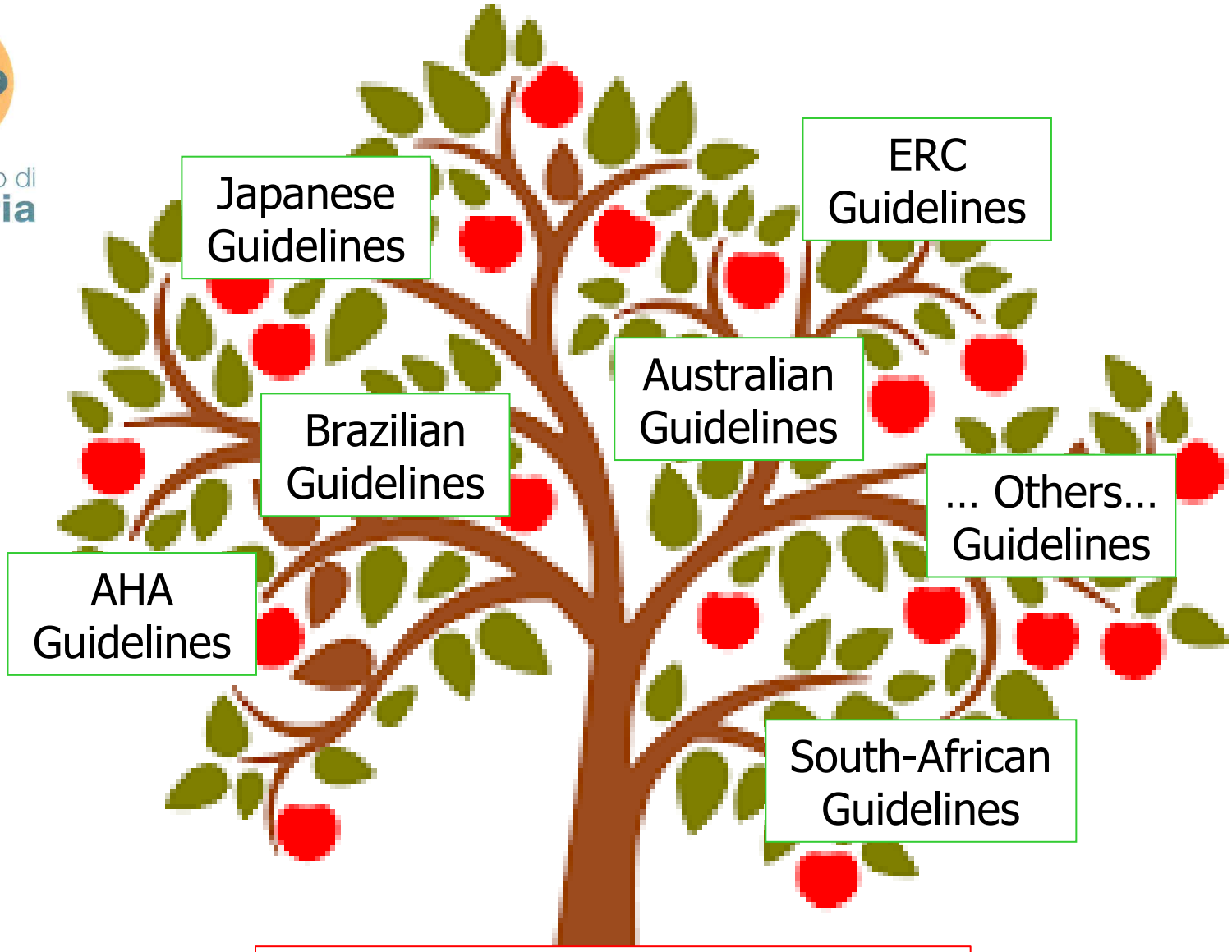
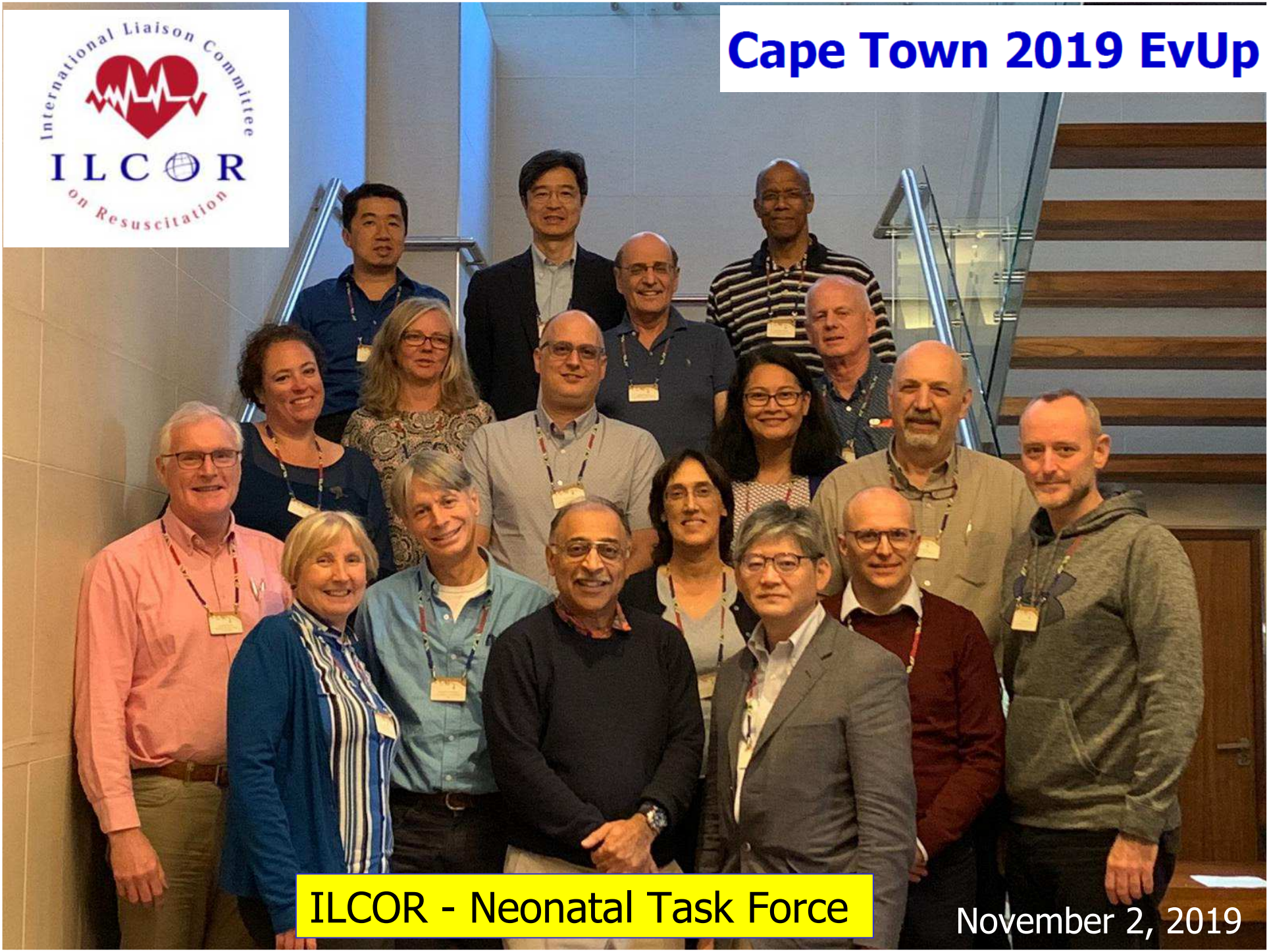


Part 7: Neonatal Resuscitation

2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations

Jeffrey M. Perlman, Co-Chair*; Jonathan Wyllie, Co-Chair*; John Kattwinkel; Myra H. Wyckoff; Khalid Aziz; Ruth Guinsburg; Han-Suk Kim; Helen G. Liley; Lindsay Mildenhall; Wendy M. Simon; Edgardo Szyld; Masanori Tamura; Sithembiso Velaphi; on behalf of the Neonatal Resuscitation Chapter Collaborators

Cape Town 2019 EvUp



ILCOR - Neonatal Task Force

November 2, 2019

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Gaps of knowledge
2015 → 2020

- Algorithm
- Initial evaluation
- Meconium aspiration syndrome
- Oxygenation
- Ventilation
- Chest compressions
- Ethics
- Cord clamping
- Education

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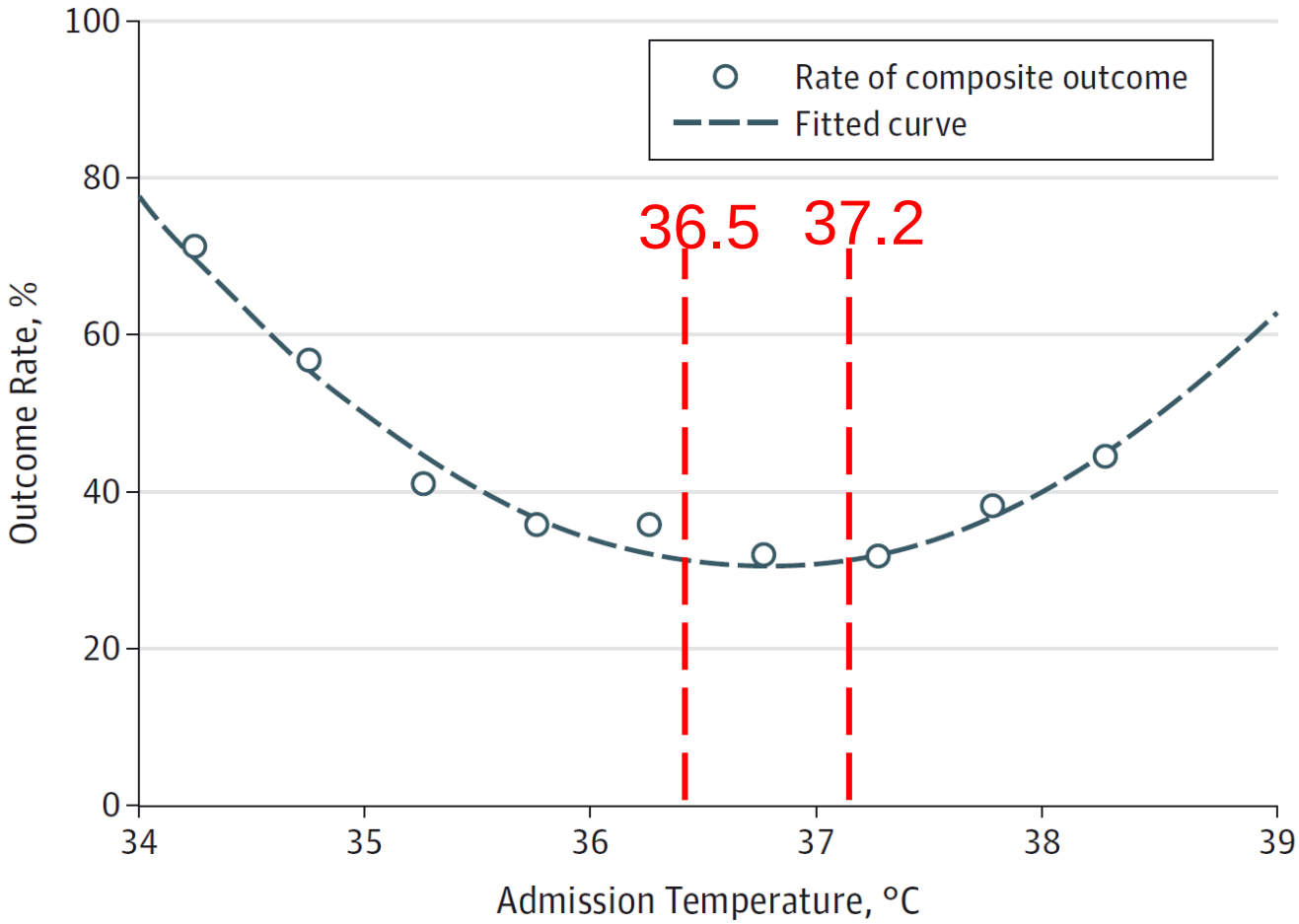
Gaps of knowledge
2015 → 2020

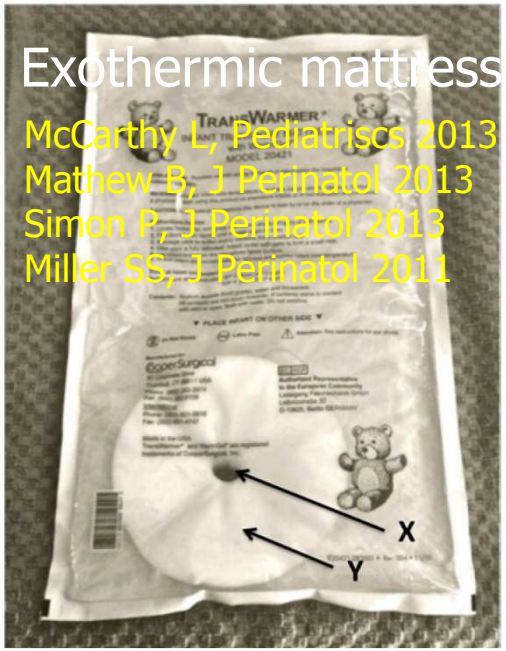
- Flow-chart
- **Initial steps (temperature,** HR detection**)**
- Meconium aspiration syndrome
- Oxygenation
- Ventilation
- Chest compressions
- Ethics
- Cord clamping
- Education

Figure 2. Association of Admission Temperature With a Composite Mortality/Morbidity Outcome



- Mortality
- Severe neurological injury
- Severe ROP
- NEC
- BPD
- Nosocomial infection

Unadjusted data for rate of a composite mortality/morbidity outcome plotted against admission temperature and fitted with a curve indicating the U-shaped relationship between admission temperature and the composite outcome. Lyu Y, JAMA Pediatr 2105



Trevisanuto D et al. Semin Fetal Neonatal Med 2108

Dallas 2015

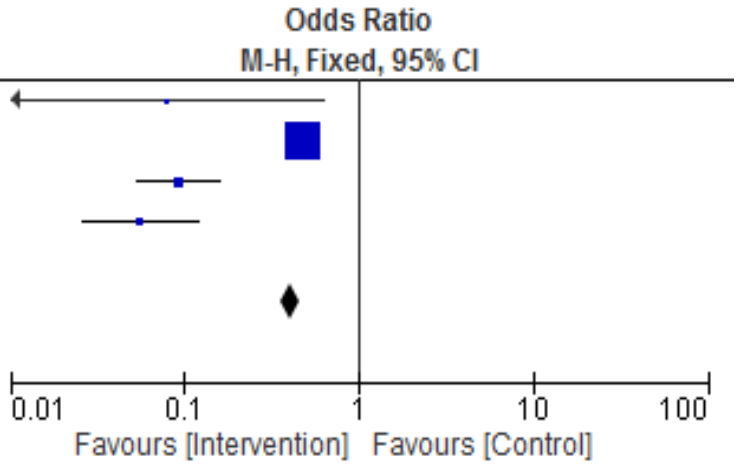
Combination of interventions + check lists + feed-backs

OUTCOME: **Hypothermia at NICU admission (temp<36.0° C), OBS**

Study or Subgroup	Intervention Events	Intervention Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
DeMauro SB, 2013	1	80	11	80	1.5%	0.08 [0.01, 0.63]
Lee HC, 2014	328	4132	633	4179	80.6%	0.48 [0.42, 0.56]
Pinheiro JMB, 2014	20	440	56	164	10.8%	0.09 [0.05, 0.16]
Russo A, 2014	12	193	36	66	7.0%	0.06 [0.03, 0.12]
Total (95% CI)		**4845**		**4489**	**100.0%**	**0.40 [0.35, 0.46]**
Total events	361		736			

Heterogeneity: Chi² = 62.53, df = 3 (P < 0.00001); I² = 95%

Test for overall effect: Z = 13.38 (P < 0.00001)



[GA<32 weeks]

Trevisanuto D, De Almeida MF, ILCOR Meeting, Feb 2015, Dallas

Trevisanuto D et al. Semin Fetal Neonatal Med 2108

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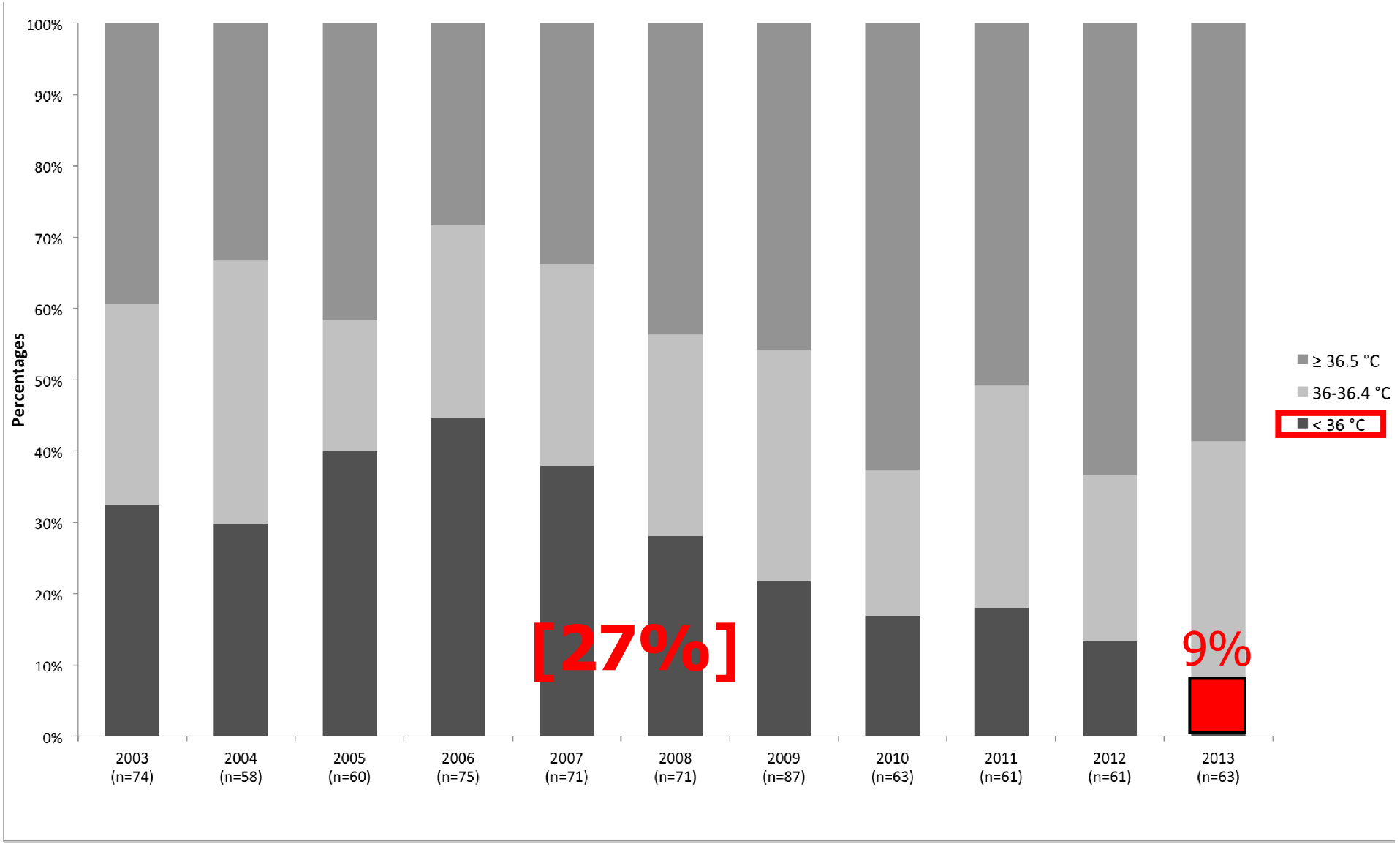
BW<1000 g and/or ≤28 weeks gestation
Temperature at NICU Admission (n. 726)



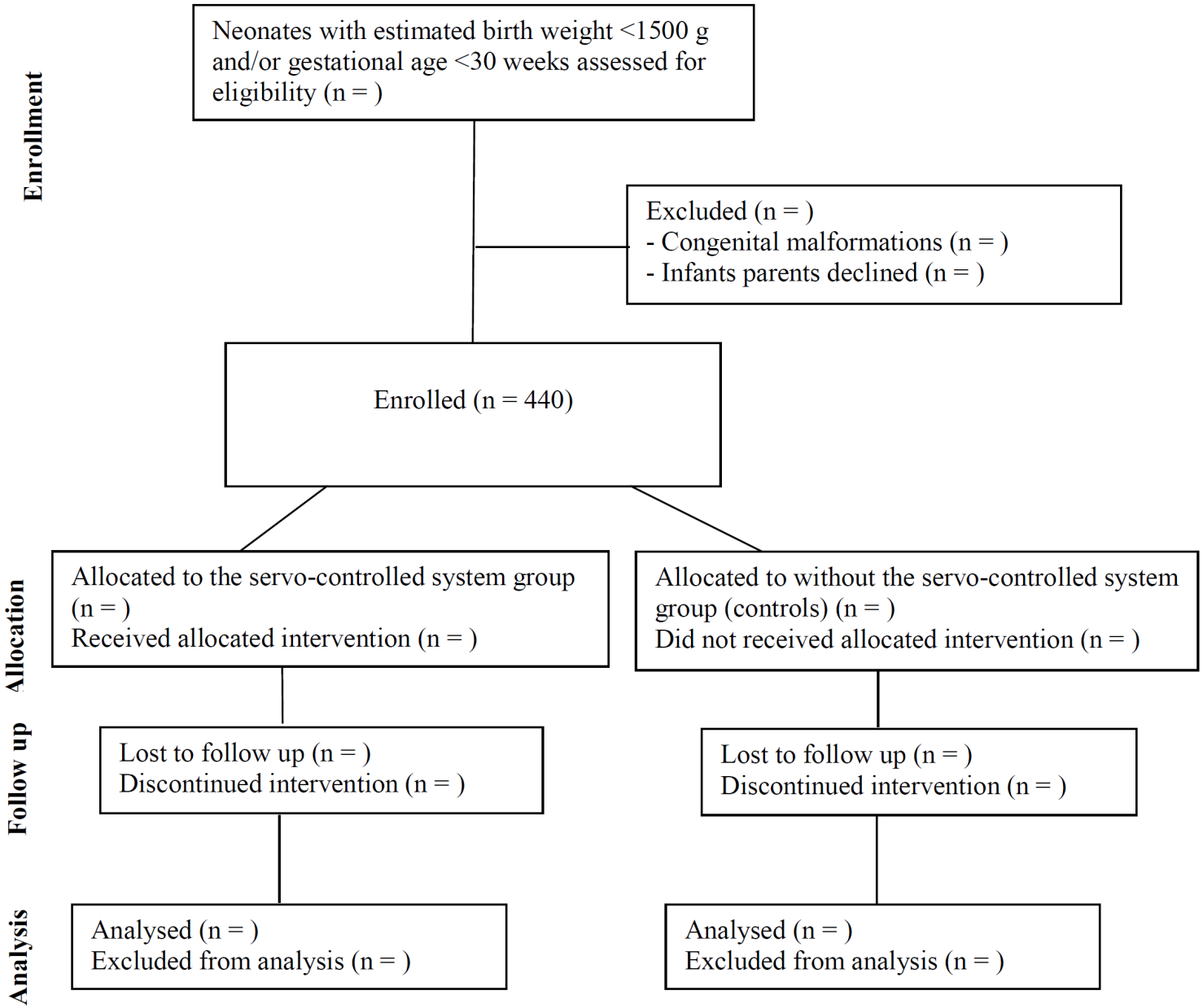
Rech Morassutti F et al. J Pediatr 2015

Servo COntrol in PRreterm Infants
SCOPRI study

Effect of a servo-controlled system on heat loss at birth in very low birth weight infants: a multicenter, randomized, controlled trial

ClinicalTrials.gov Identifier: NCT03844204

Fig. 1 Flow diagram of patient randomization



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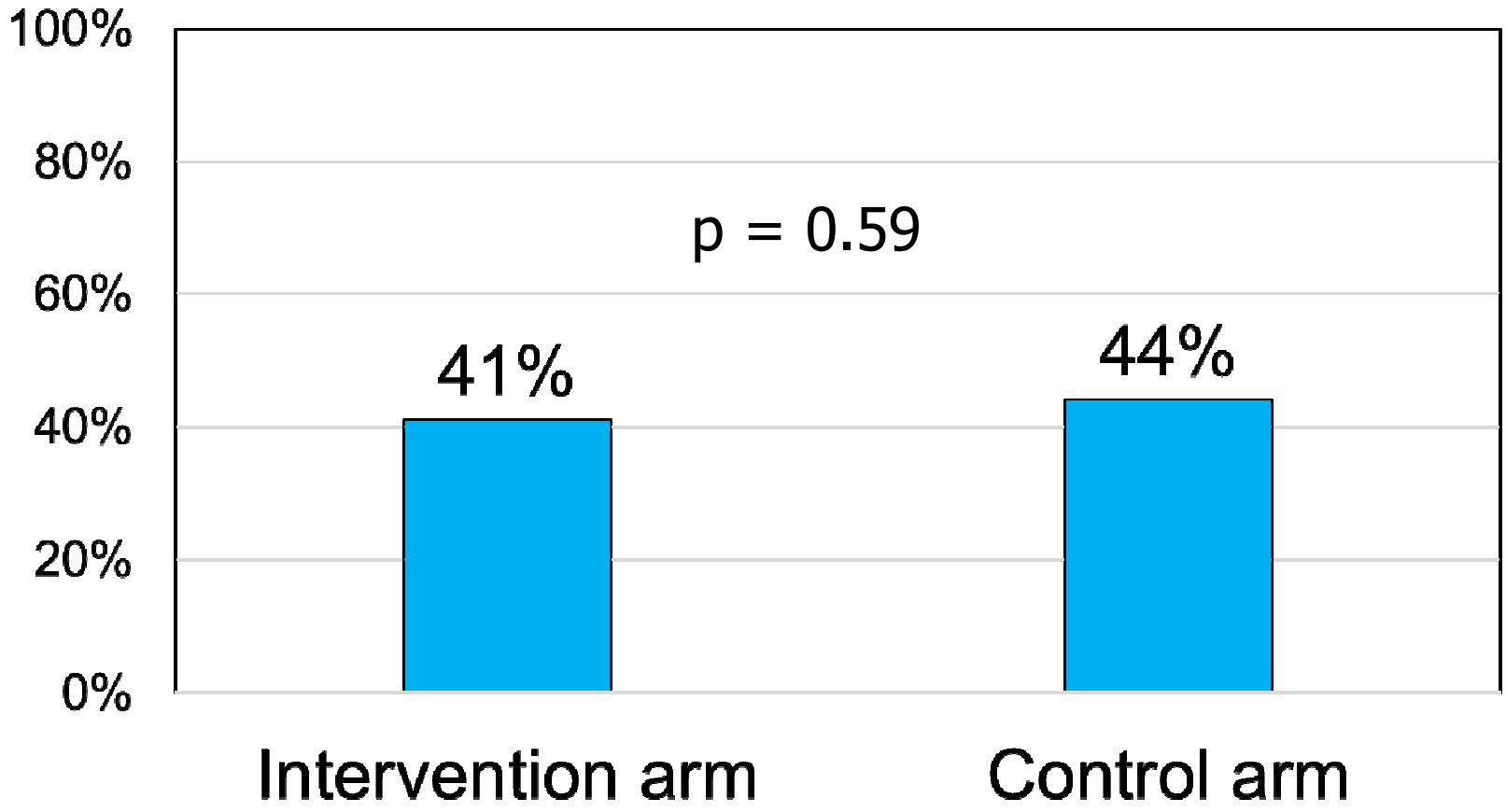
Neonatal temperature at admission 36.5-37.5°C (Primary outcome)



Secondary outcome measures (temperature)

	Intervention arm, n(%)	Control arm, n(%)	p-value	Risk ratio (95% CI)
Neonatal temperature at admission<36°C	52 (27%)	49 (25%)	0.72	1.08 (0.77 to 1.52)
Neonatal temperature at admission 36-36.4°C	58 (30%)	41 (21%)	0.047	1.44 (1.02 to 2.04)
Neonatal temperature at admission >38°C	0 (0%)	7 (4%)	0.02	0.07 (0.01 to 1.19)

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Gaps of knowledge
2015 → 2020

- Algorithm
- **Initial steps (**tempereture, **HR detection)**
- Meconium aspiration syndrome
- Oxygenation
- Ventilation
- Chest compressions
- Ethics
- Cord clamping
- Education

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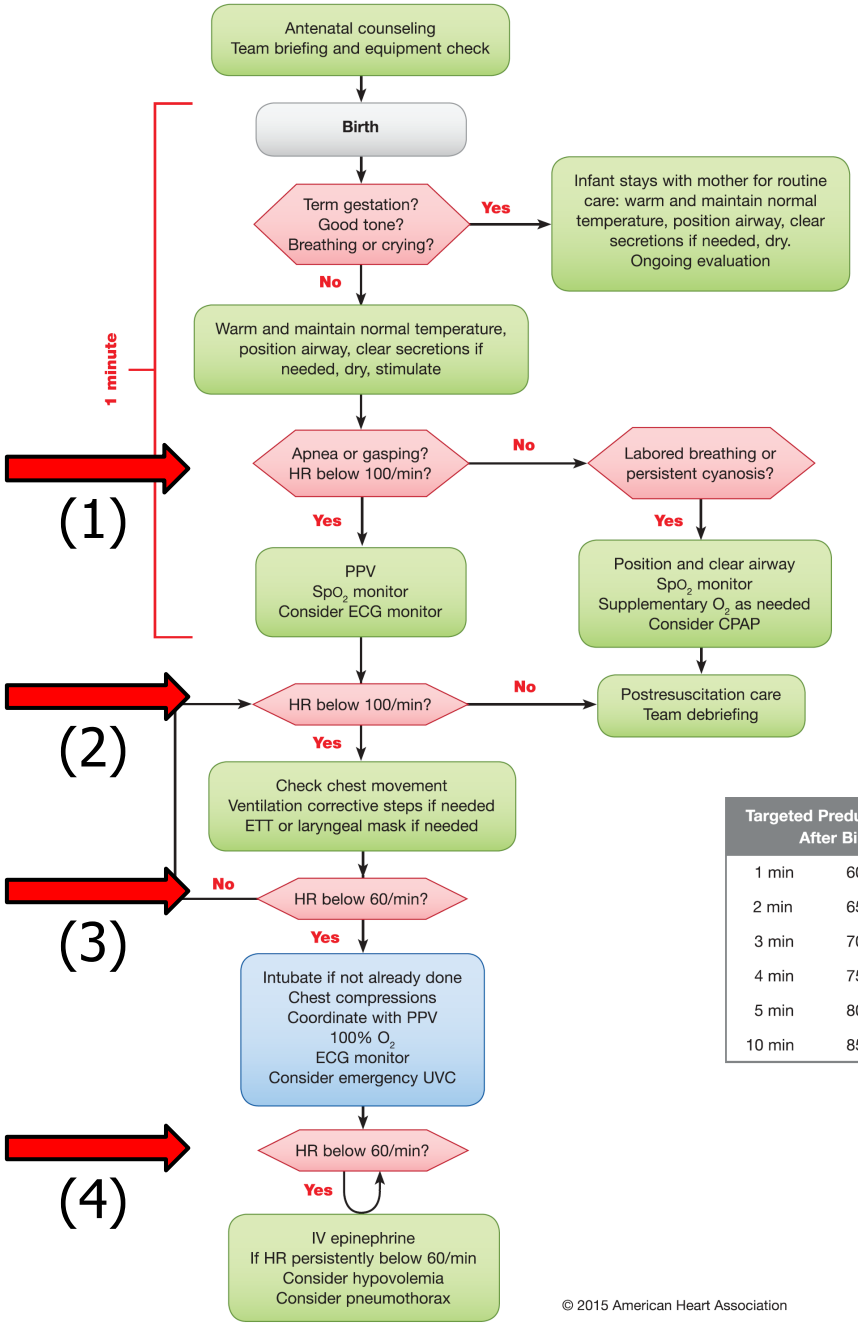
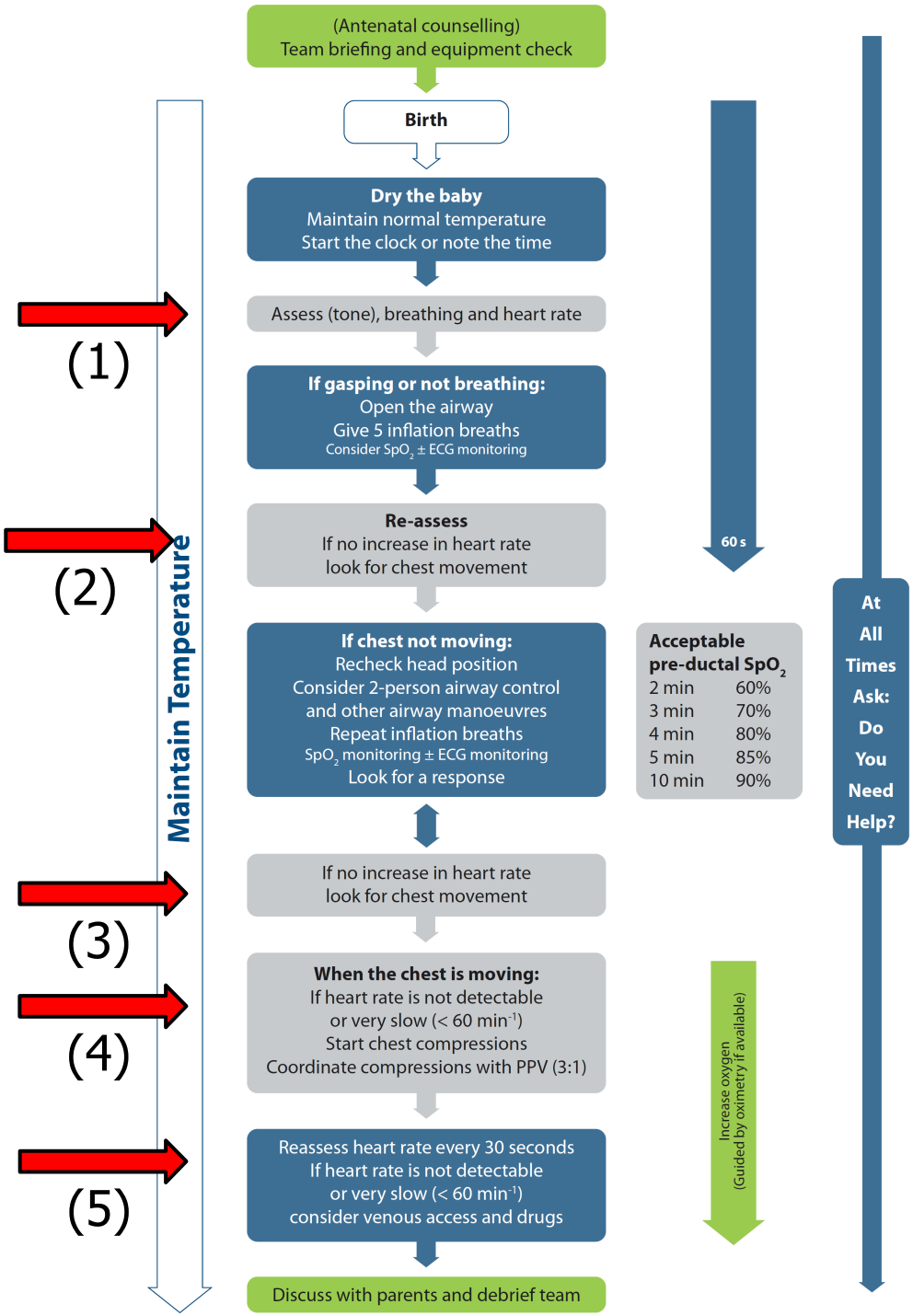
Neonatal Resuscitation Algorithm—2015 Update



Targeted Preductal SpO_2 After Birth	
1 min	60%-65%
2 min	65%-70%
3 min	70%-75%
4 min	75%-80%
5 min	80%-85%
10 min	85%-95%

Wyckoff MH et al. AHA Guidelines, Circulation 2015

Figure 1. Neonatal Resuscitation Algorithm—2015 Update.



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Wyllie J et al. ERC Guidelines, Resuscitation 2015

Heart rate assessment

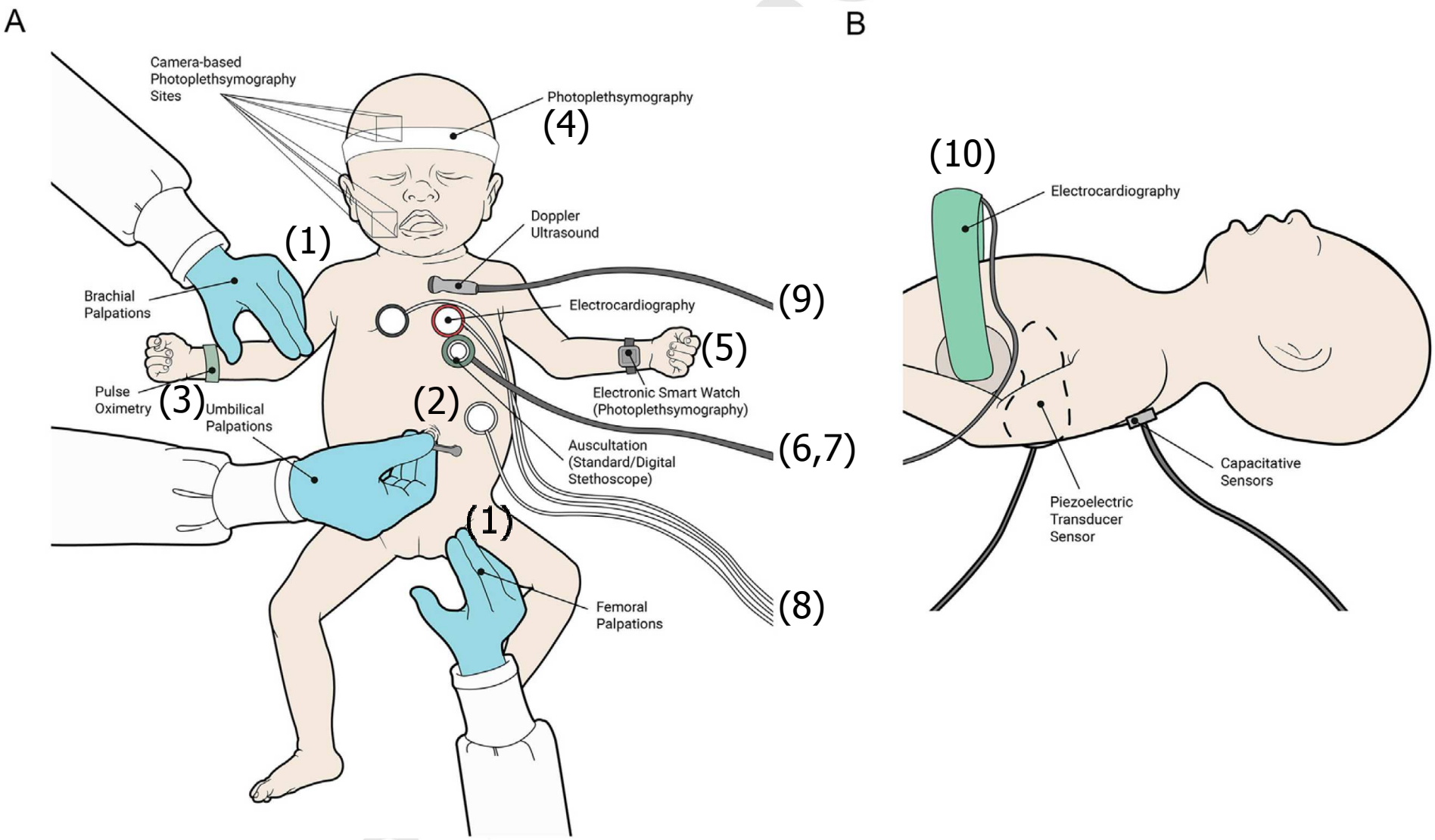

Fig. 2. A and B: Current technologies for heart rate assessment in newborn infants.

Johnson PA et al. Resuscitation 2019

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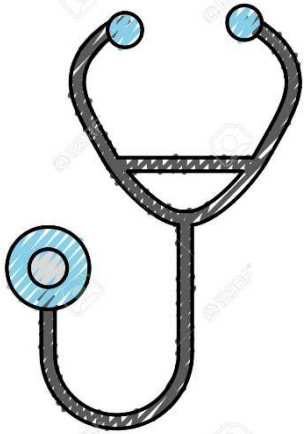
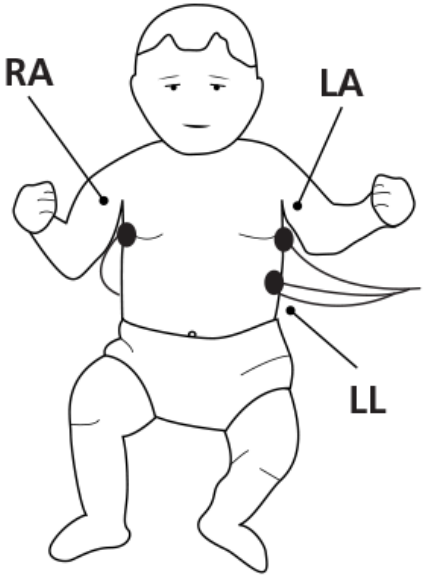
Heart rate assessment

Umbilical cord palpation

Auscultation



3 lead ECG



Guidelines 2010 < 2015

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Table 4 – Adjusted associations of the ECG monitoring with medical practice outcomes.

Practice/outcomes	aOR* (95% CI)	*P* value
Delivery room practice interventions		
Supplemental oxygen	1.51 (.87–2.62)	.138
Continuous positive airway pressure	2.82 (1.77–4.51)	<.001
Face mask ventilation	3.85 (1.61–9.21)	.003
Endotracheal intubation	.65 (.45–.94)	.023
Chest compressions	3.59 (1.36–9.46)	.009
Epinephrine use	>99.99 (<.1–>99.99)	.934
Neonatal outcomes		
Death	1.58 (.83–3.03)	.167
Respiratory distress syndrome	.93 (.62–1.41)	.748
Pneumothorax	.70 (.34–1.46)	.343
Bronchopulmonary dysplasia	.94 (.44–1.99)	.867
Mechanical ventilation	.62 (.43–.89)	.011
Sepsis	.77 (.45-1.32)	.337
Necrotizing enterocolitis	5.85 (1.09–31.26)	.039
Symptomatic patent ductus arteriosus	.78 (.39–1.54)	.481
Intraventricular hemorrhage (grade 3/4)	1.27 (.75–2.17)	.375
Severe retinopathy of prematurity	.32 (.14–.71)	.005

aOR, adjusted odds ratio; *CI*, confidence interval.

* Adjusted association represents the odds of outcome for neonatal heart rate monitoring by ECG compared with auscultation/pulse oximetry in the delivery room. There were no significant interactions between ECG monitoring and covariates.

Shah BA et al. Resuscitation 2019

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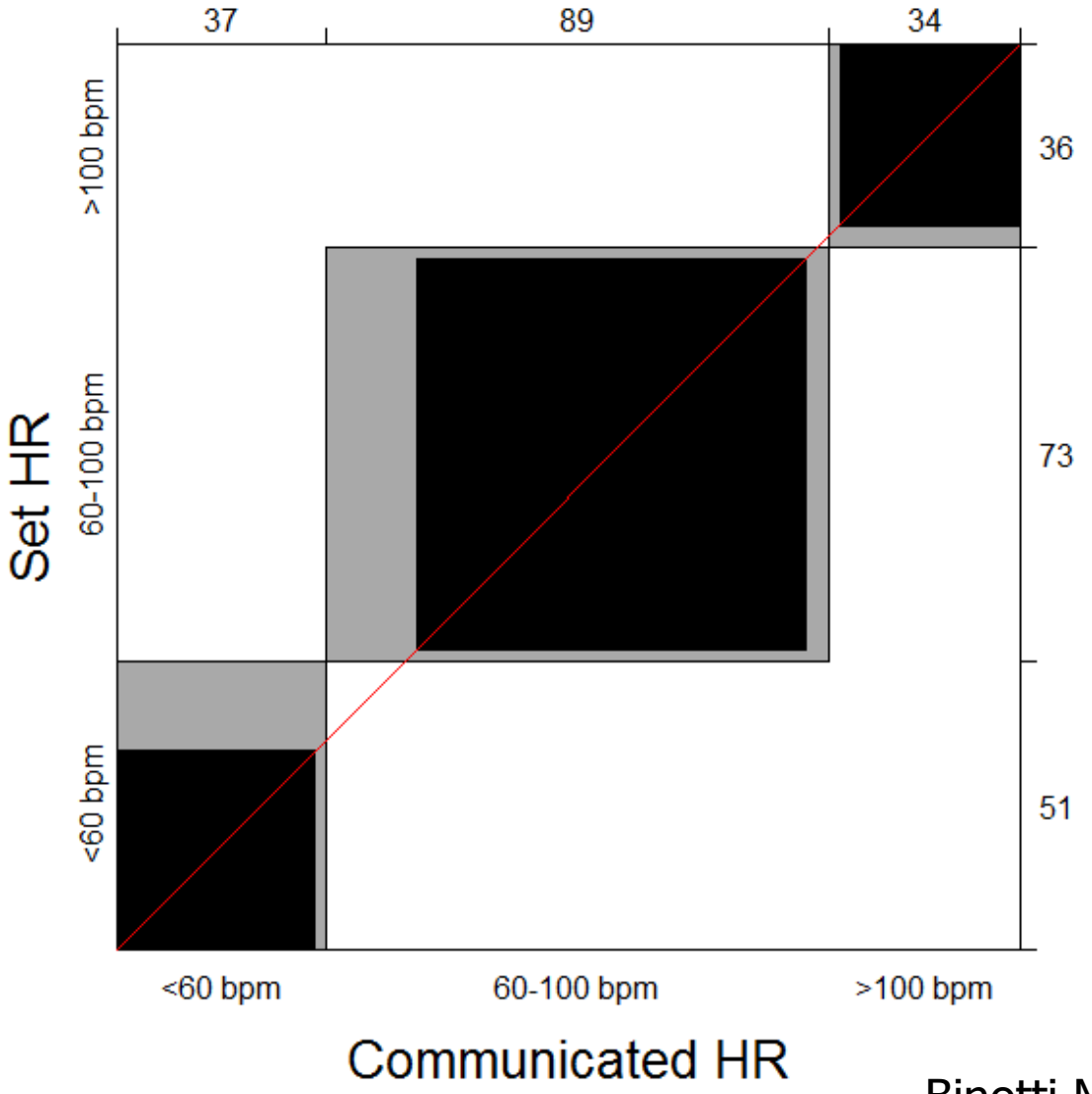
NeoTapAdvancedSupport, NeoTapAS

(free-of-charge mobile application)

http://tap4life.org/

Binotti M et al, ADCF&N Ed 2018

Accuracy in heart rate assessment using NeoTap: a simulation study.



Binotti M et al, ADCF&N Ed 2018

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Aim

To evaluate the impact of NeoTapAS on timing of HR communication and resuscitation interventions.

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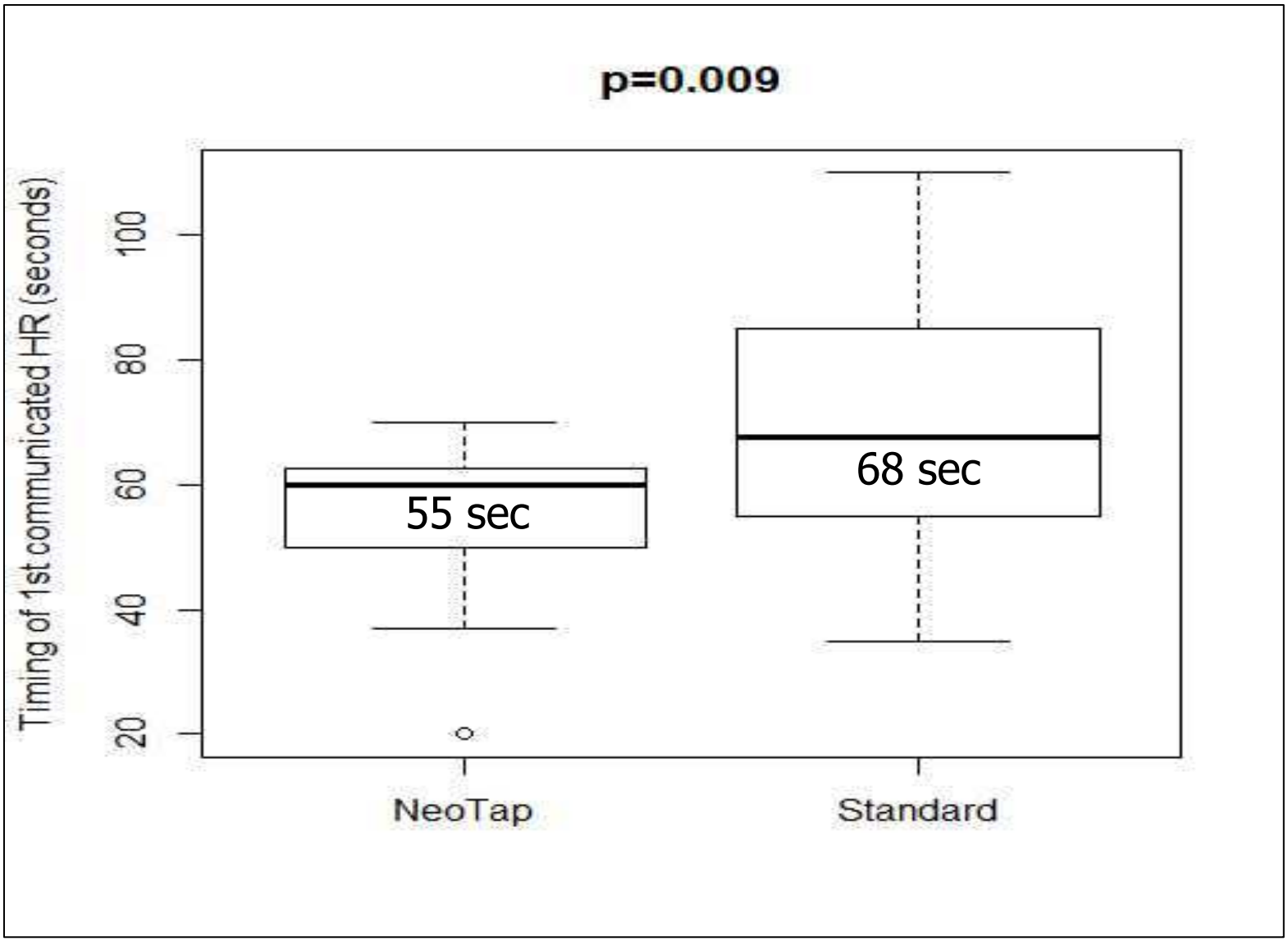
Timing of the first communicated HR



Cavallin F. et al. ADCFN Ed 2019

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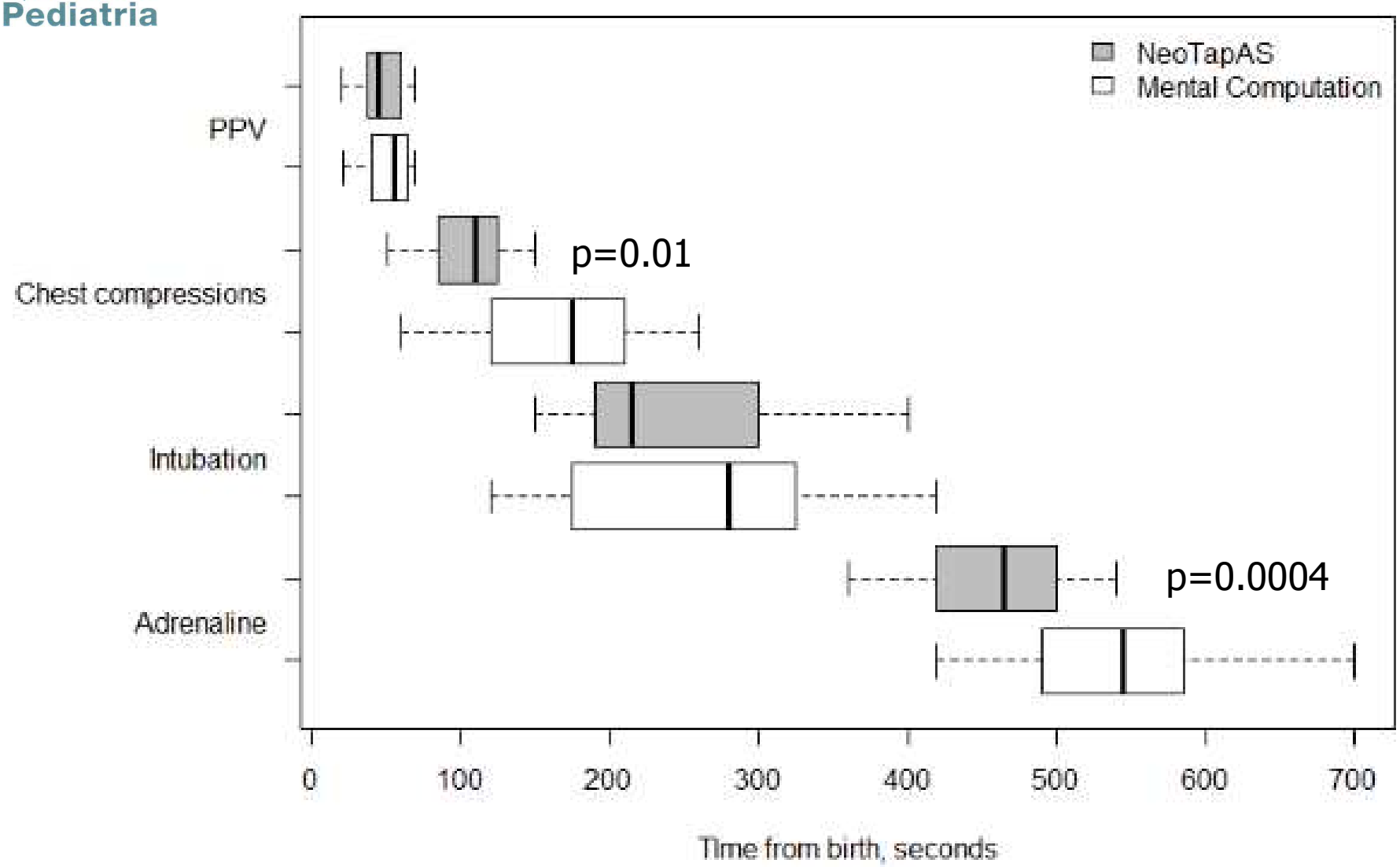

Cavallin F. et al. ADCFN Ed 2019

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Stimulation

Virginia Apgar
(1952)

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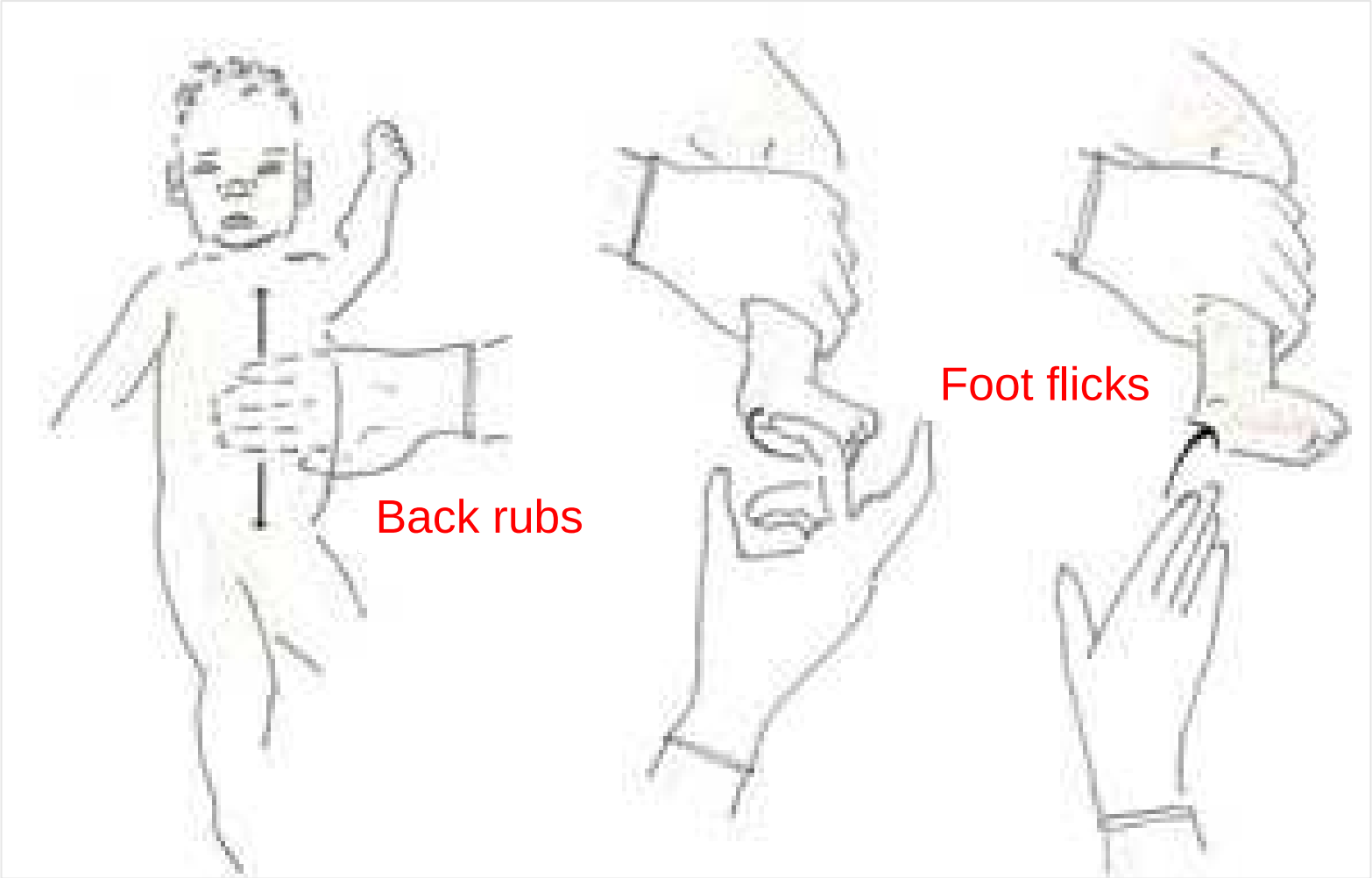
Stimulation



Manual of Neonatal Resuscitation, AHA, Ed 2016

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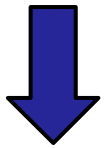
Stimulation

- ✓ **2 observational studies**
- ✓ **High resource settings**

Dekker J et al. Tactile stimulation to stimulate spontaneous breathing during stabilization of preterm infants at birth: A Retrospective Analysis. Front Pediatr. 2017 Apr 3;5:61.

Gaertner VD et al. Physical stimulation of newborn infants in the delivery room. Arch Dis Child Fetal Neonatal Ed. 2018;103:F132-F136.



Back rubs > Foot flicks ?

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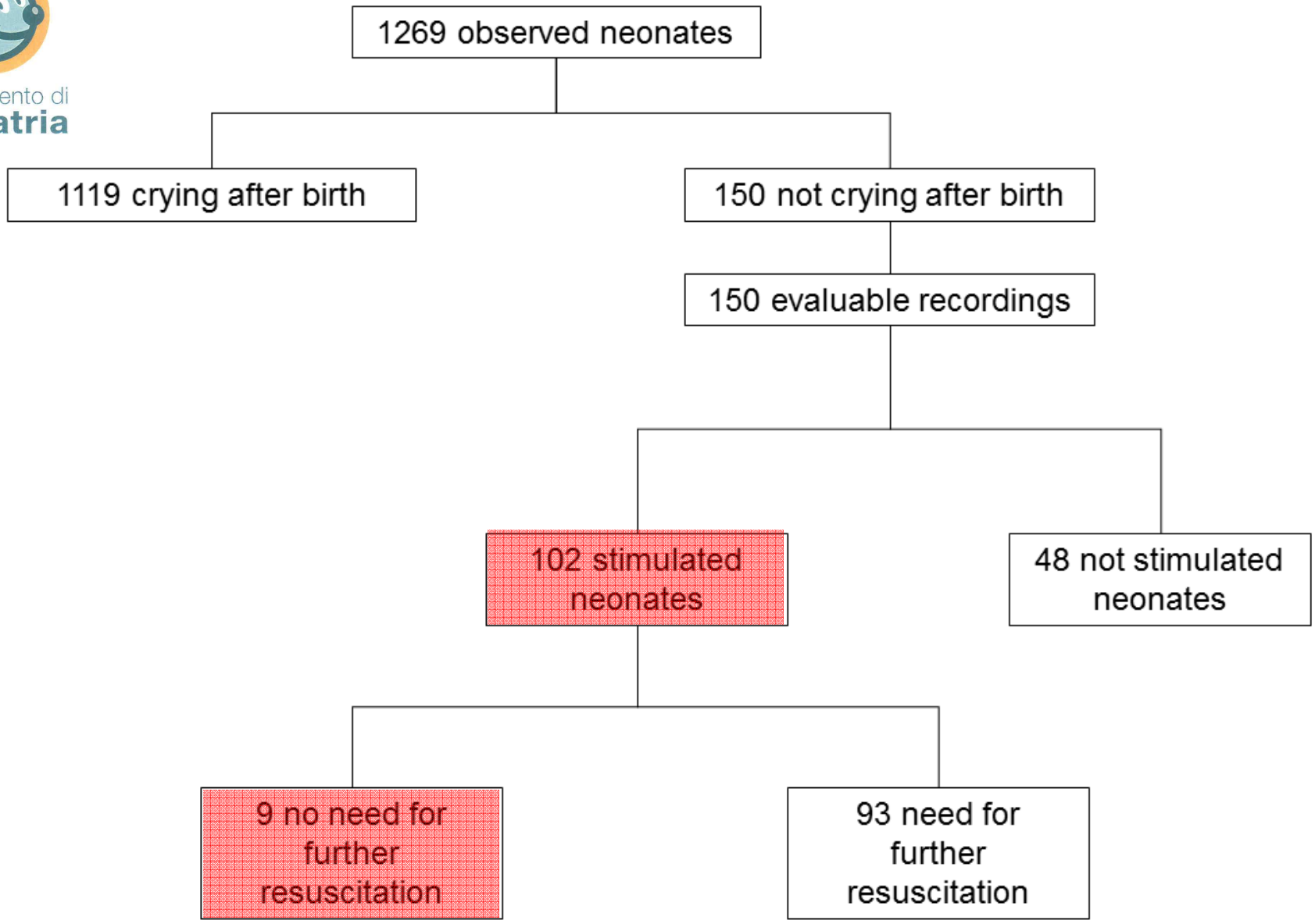

(8.8%)

Pietravalle A, BMC Pediatr 2018

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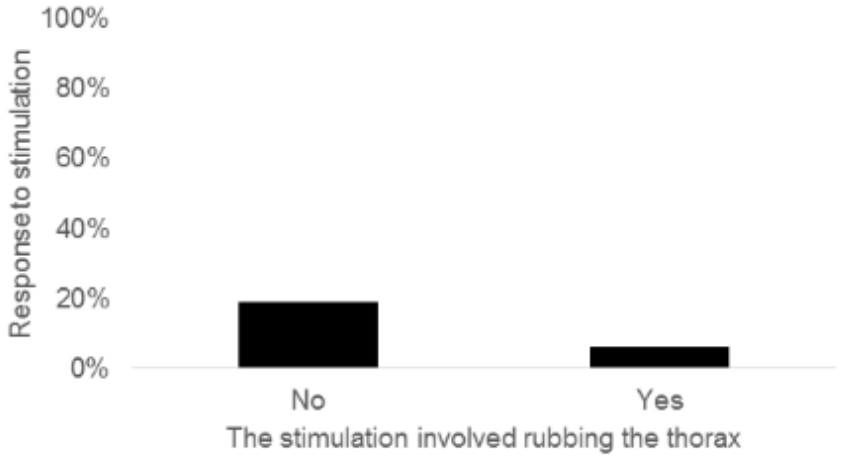

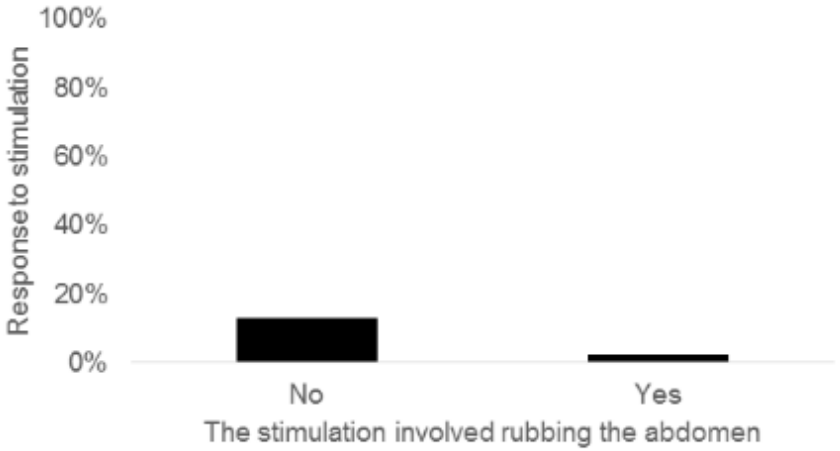

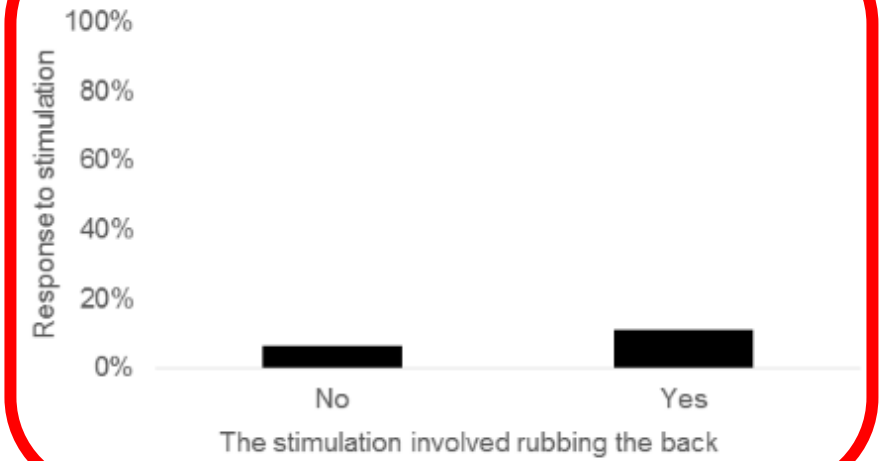

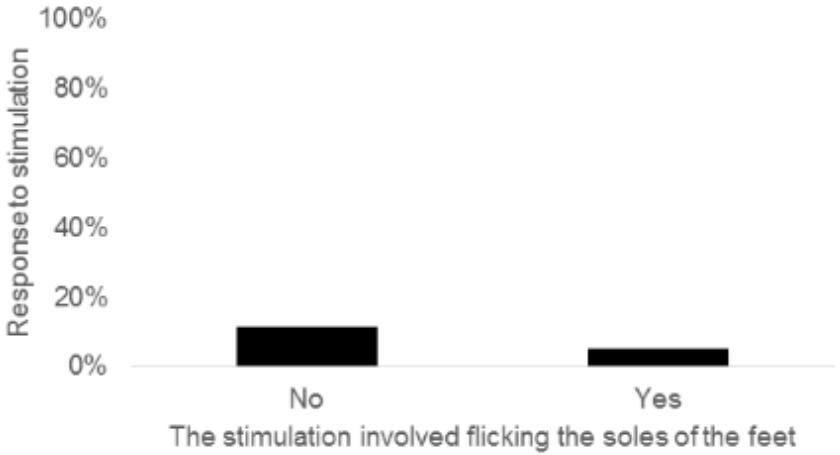

Pietravalle A, BMC Pediatr 2018

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Back rubs or foot flicks for stimulation at birth in a low-resource setting: a randomized controlled trial

Matani Hospital, Uganda

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Gaps of knowledge
2015 → 2020

- Algorithm
- Initial steps (temperature, HR detection)
- Meconium aspiration syndrome
- **Oxygenation**
- Ventilation
- Chest compressions
- Ethics
- Cord clamping
- Education

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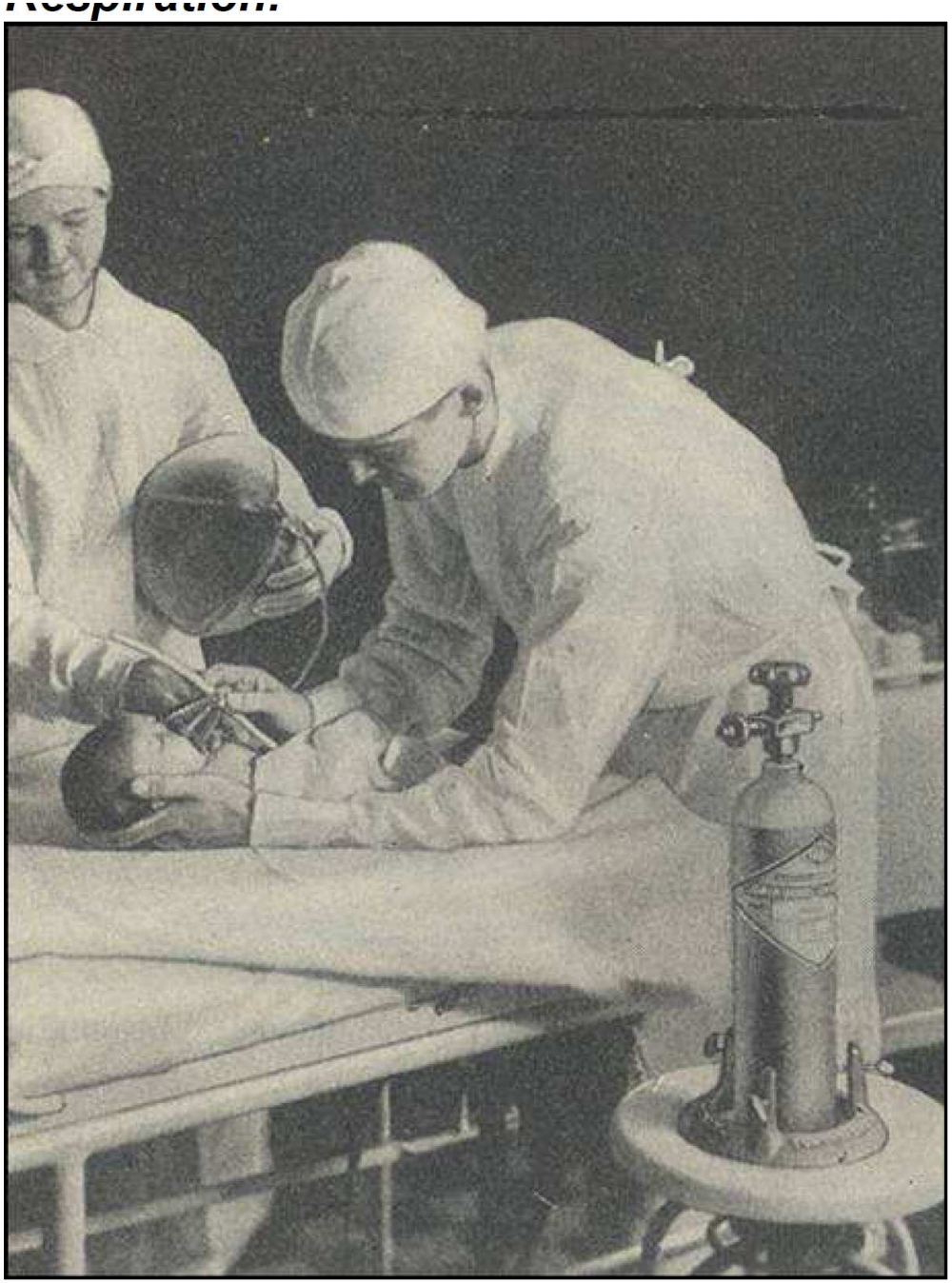

Figure 3. Henderson's Inhalatory Method. Image taken from Henderson (1938) Adventures in Respiration.


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(Oxygen Tank)
MCHRC, Ulaan Bataar - Mongolia, October – November 2008

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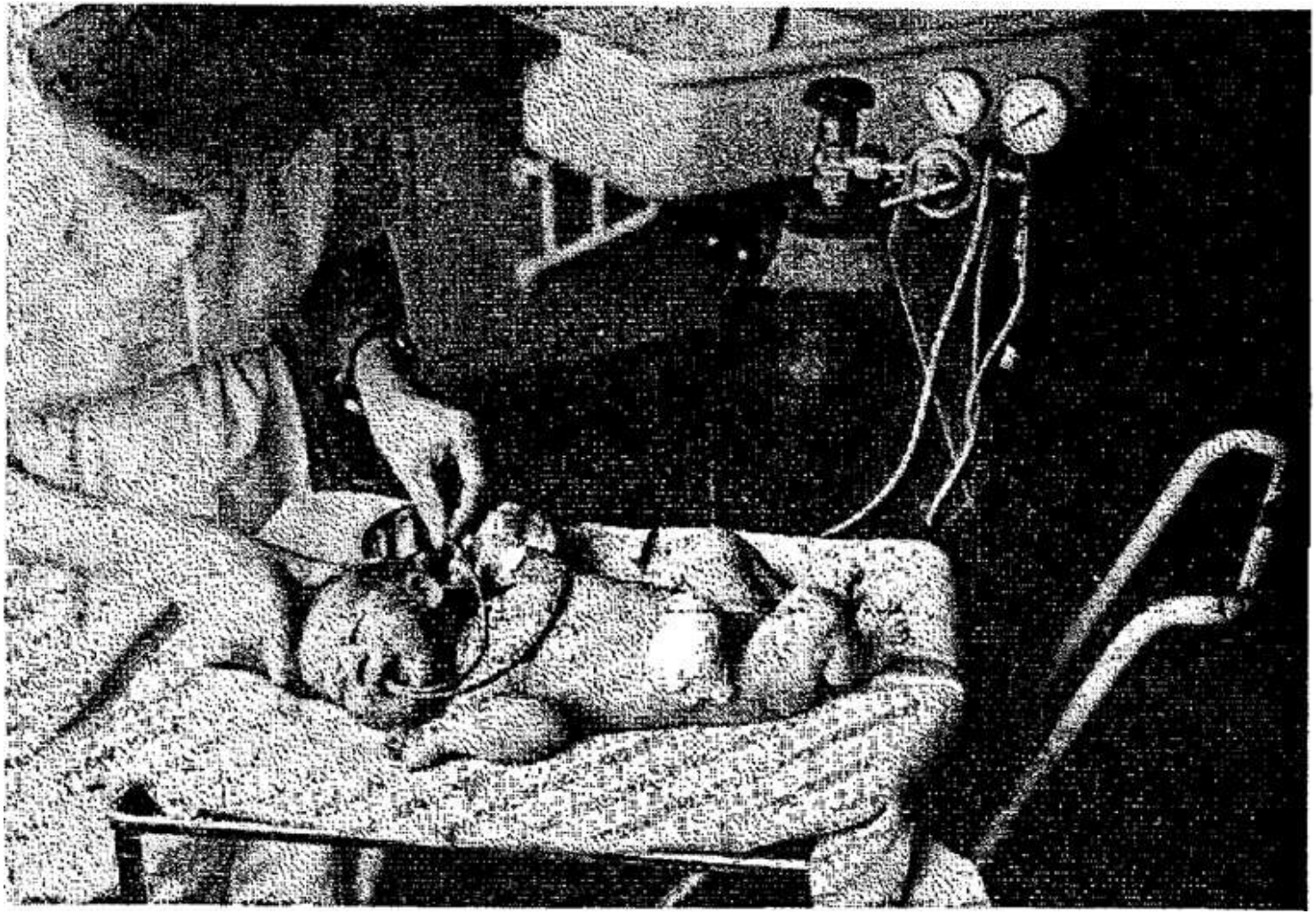
Figure 14. Image of infant being treated with **intragastric oxygen**.

Image is taken from Åkerrén and Fürstenberg (1950) 'Gastro-intestinal administration of oxygen of asphyxia in the newborn', Journal of Obstetrics and Gynaecology of the British Empire, v57(5), p705-713.



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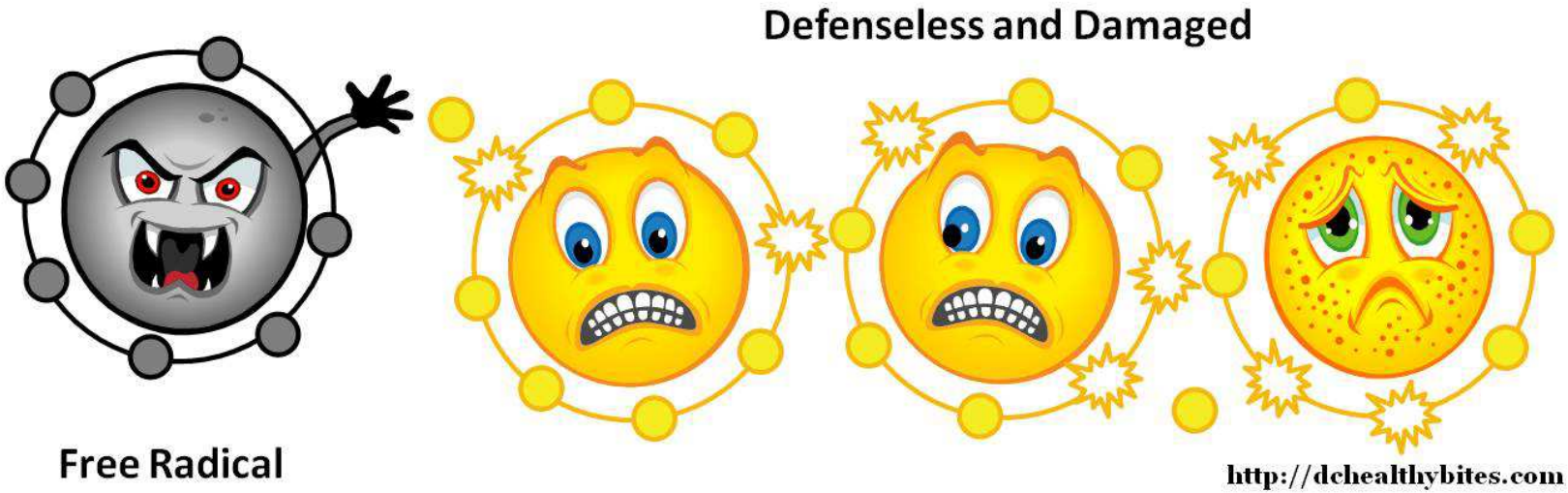
Oxygen as a foe



- Brain
- Lung
- Retina
- Kidney

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Oxygen as a foe

CHILDHOOD CANCER FOLLOWING NEONATAL OXYGEN SUPPLEMENTATION

LOGAN G. SPECTOR, PHD, MARK A. KLEBANOFF, MD, MPH, JAMES H. FEUSNER, MD,
MICHAEL K. GEORGIEFF, MD, AND JULIE A. ROSS, PHD

Objective To evaluate the relationship between neonatal oxygen supplementation (O_2) and childhood cancer in the Collaborative Pe

Study design age 8 years. We used Cox proportiona er (n = 48).

Results The e HR for continuous duration of O_2 was near 1 and not significant. However, the HRs were 0.69 (95% CI = 0.17 to 2.88) and 2.87 (95% CI = 1.46 to 5.66) when comparing 0 to 2 and 3 or more minutes of O_2, respectively, to no O_2. The latter association was weaker (HR = 2.00; 95% CI = 0.88 to 4.54) and not significant (P = .10) when analysis was restricted to cancers diagnosed after age 1 year (n = 41).

Conclusions These findings are consistent with an association between O_2 for 3 minutes or longer and cancer in childhood, and should serve as a basis for further study. *(J Pediatr 2005;147:27-31)*

3 or more minutes of O2

Hazard ratio: 2.87 (95%CI = 1.46-5.66)

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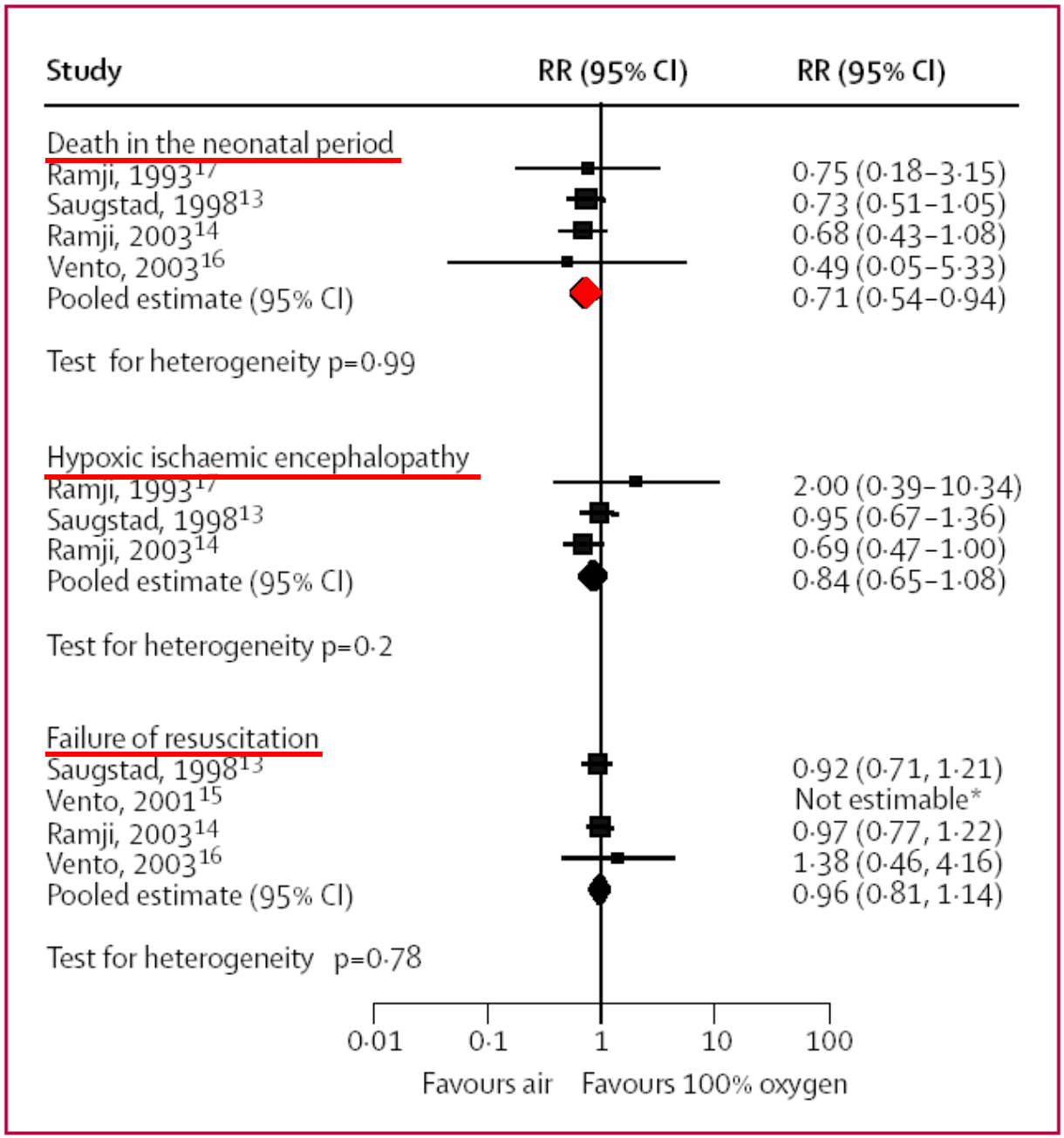

Figure: **Pooled analyses**

Relative risks assessed with fixed-effects model. *No events in either group.

Davis PG, Lancet 2004

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The standard approach to resuscitation is to use 100% oxygen.

AHA, AAP, Pediatrics 2006

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to use 100% oxygen. Some clinicians may begin resuscitation with an oxygen concentration of less than 100%, and some may start with no supplementary oxygen (ie, room air). There is evidence that employing either of these practices during resuscitation of neonates is reasonable.

AHA, AAP, Pediatrics 2006

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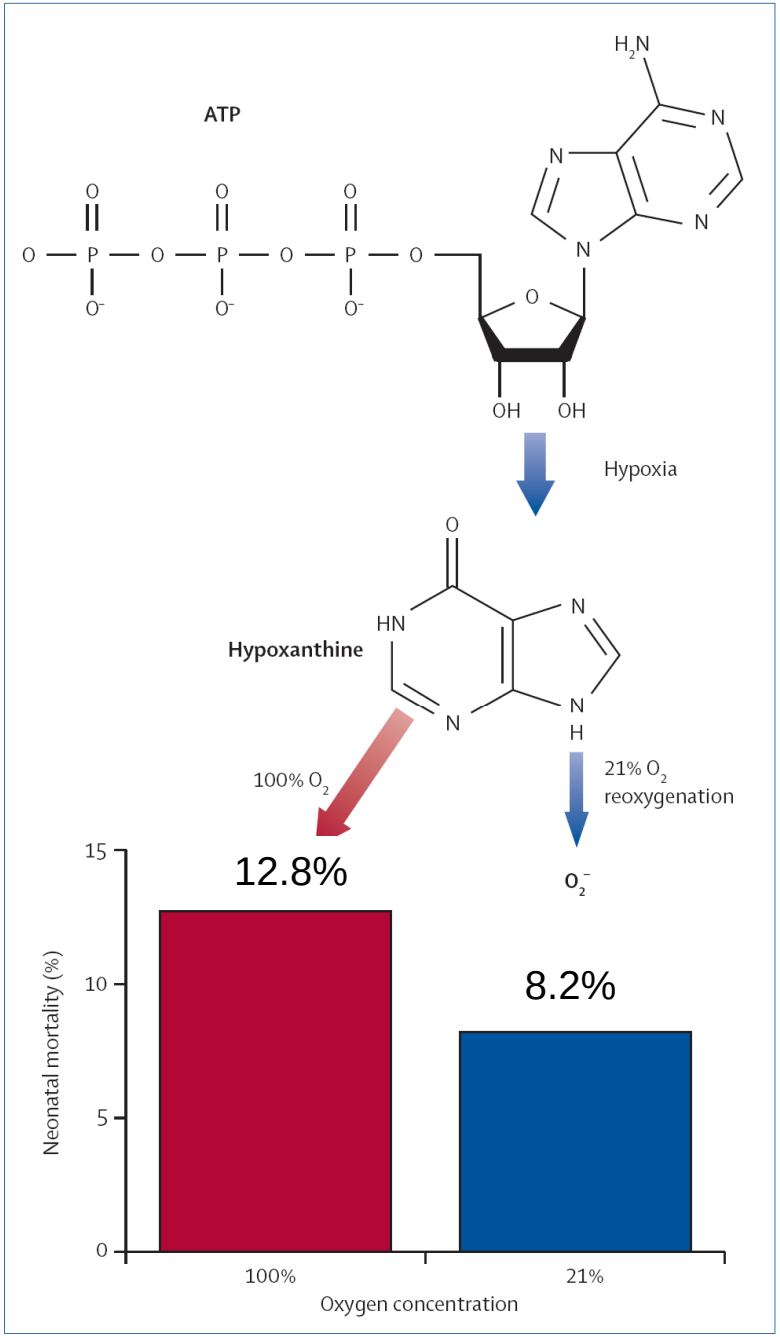

Figure: From molecular understanding to clinical practice in newborn resuscitation

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Mortality rate: relative risk 0·69, (95% CI 0·54–0·88)

"The use of 100% oxygen for newborn resuscitation probably will be remembered as one of the most dangerous therapies inflicted on newborns."

Saugstad OD, Lancet 2010

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For babies born at term it is best to begin resuscitation with air rather than 100% oxygen.

Perlman JM et al. Pediatrics, 2010

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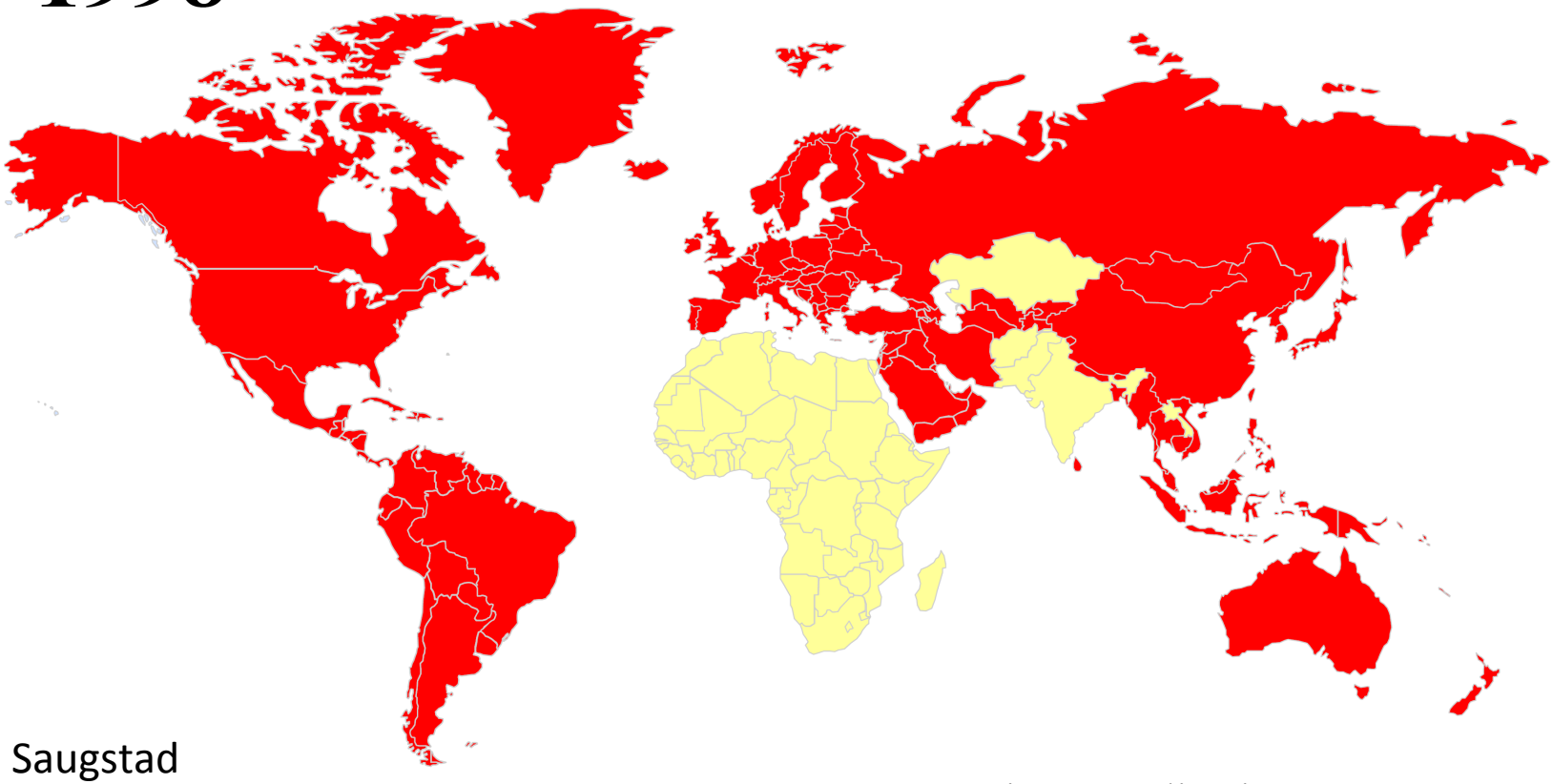
Before
1998

World Map Before 1998
Resuscitation of Newborn Infants



Courtesy Dr. Saugstad

100% O2

1998: Resair 2 . Pediatrics 1998
WHO Basic Newborn Resuscitation:
Use air

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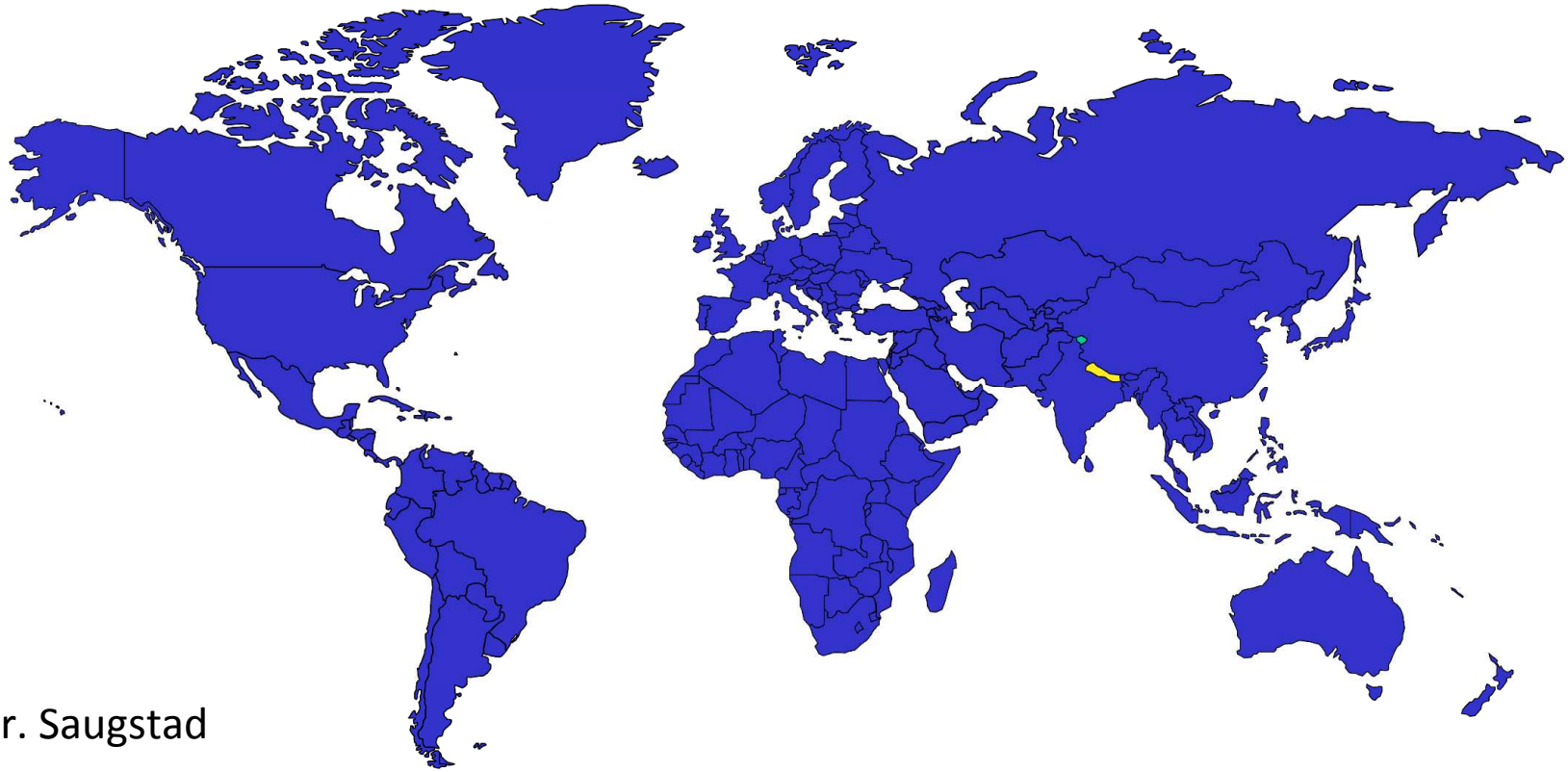
Ressucitation World Map 2010-11?
Term or Near term Infants



Courtesy Dr. Saugstad

ILCOR October 18th 2010

Low oxygen approach

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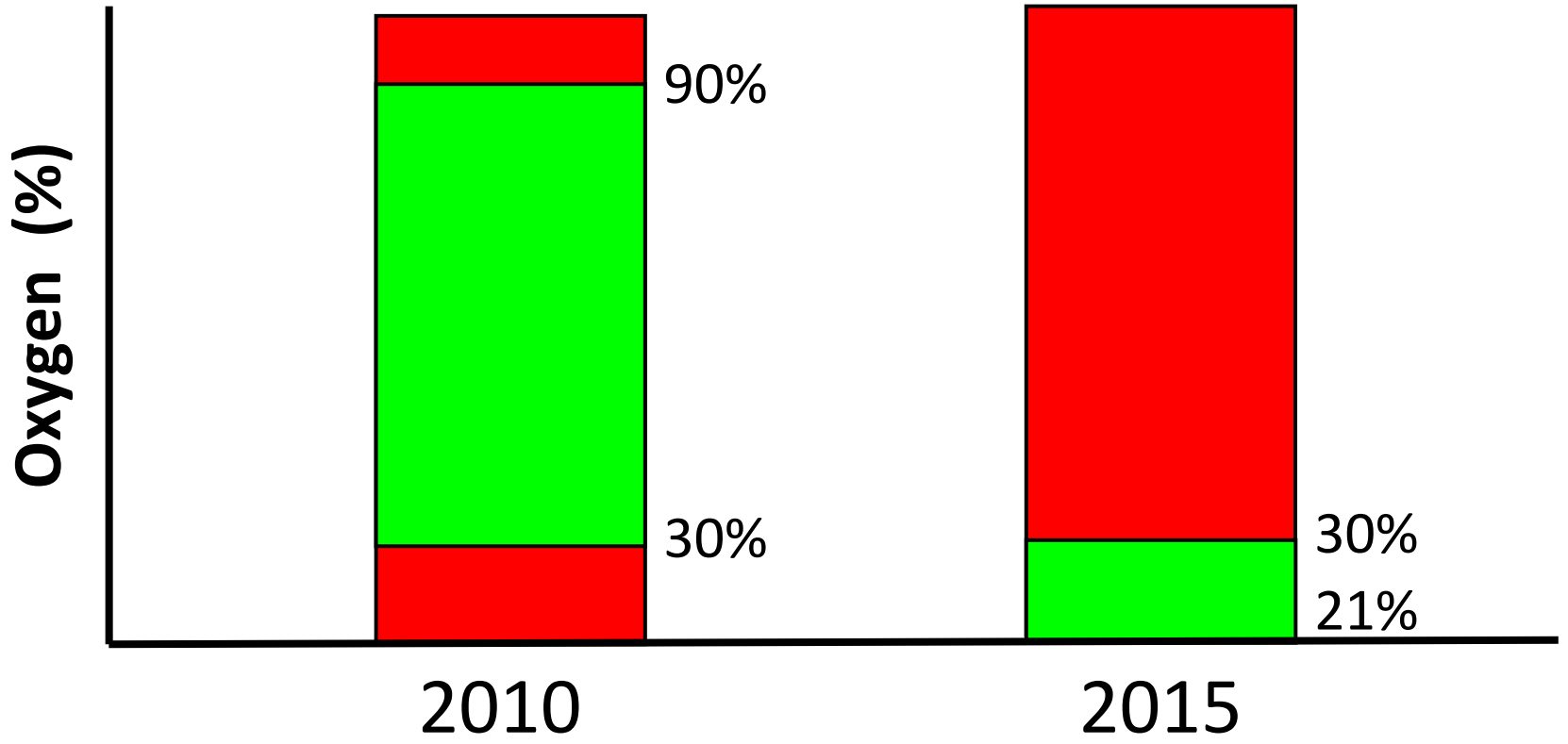
Oxygen to initiate resuscitation in preterm infants (<35 wks)



Wyckoff MH et al. 2015 AHA Guidelines

Wyllie J et al. 2015 ERC Guidelines

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High O_2 (50%–100%) versus Low O_2 (21%-30%)

Outcome	n. subjects	RR (95%CI)
mortality before discharge	607	1.48 (0.8–2.73)
bronchopulmonary dysplasia	502	1.08 (0.59–1.98)
intraventricular hemorrhage	400	0.90 (0.47–1.72)
retinopathy of prematurity	359	1.28 (0.59–2.77)

Perlman J et al. Circulation 2015

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Torpido Study

- Study design: RCT
- GA: <32 weeks' gestation
- Treatment: RA versus 100% oxygen
- SpO2 targets: 65-95% up to 5 min and 85-95% until admission

J.L. Oei et al. Pediatrics 2017

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TABLE 4 Mortality

Variable	All Infants		
	RA, $n = 144$	100% O_2, $n = 143$	RR (95% CI)
All deaths	14 (10)	6 (4)	2.3 (0.9–5.7), $P = .10$
Neonatal death (death <28 d)	12 (8)	5 (3)	3.1 (0.9–11.1), $P = .08$
Death before hospital discharge	14 (10)	5 (3)	2.6 (0.9–7.1), $P = .06$
Age of death, d	12 (2–95)	4 (1–11)	$P = .24$
Causes of death[c]			

J.L. Oei et al. Pediatrics 2017

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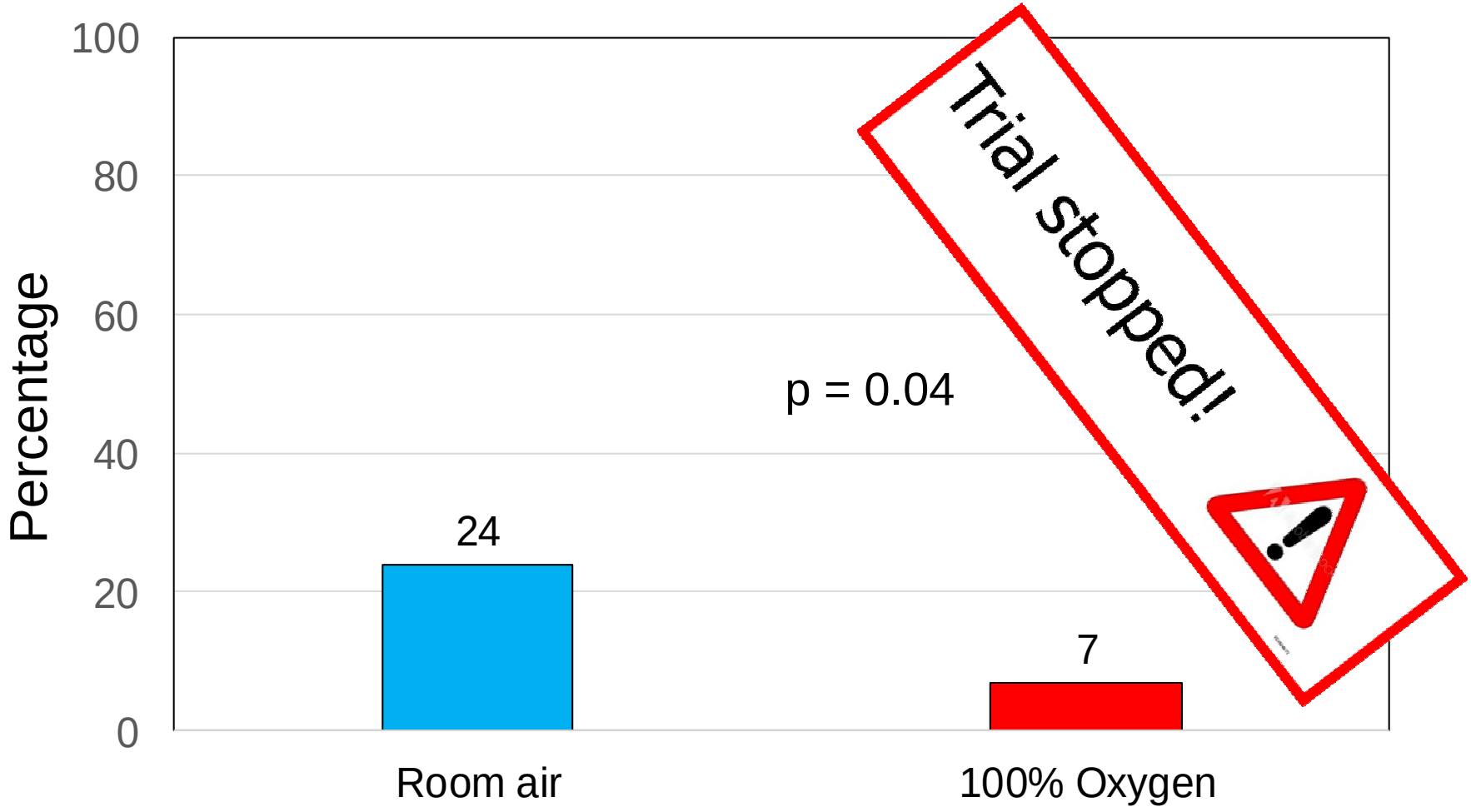
Mortality rate

[subgroup of babies <28 weeks' gestation]



J.L. Oei et al. Pediatrics 2017

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Adjusted OR for Outcome - Room Air as reference

Outcome	Intermediate	100% O_2
Primary		
Death or NDI	**1.01 (0 .77-1.34)**	**1.03 (0.78-1.35)**
Death or severe NDI	**1.14 (0.82-1.58)**	**1.22 (0.90- 1.67)**
Secondary		
Death	**1.03 (0.68 -1.56)**	**0.93 (0.63-1.37)**
NDI	**1.00 (0.74- 1.35)**	**1.08 (0.81-1.45)**
Severe NDI	**1.22 (0.78-1.91)**	**1.57 (1.05-2.35)**
Language score < 70	**1.54 (0.89-2.67**	**1.73 (1.02-2.91)**

No significant differences: CP, Cognitive score < 85, Cogntive score < 70, Visual impairmen , Hearing impariment

Soraisham AS et al. J Perinatol 2017

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Initial Oxygen Concentration for Preterm Neonatal Resuscitation

CONCLUSIONS: The ideal initial F_{IO_2} for preterm newborns is still unknown, although the majority of newborns ≤32 weeks' gestation will require oxygen supplementation.

Welsford M et al. Pediatrics 2019

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Recommendation of FiO2 and newborn resuscitation

- Term and near term infants

OR for mortality: 0.69 (95%CI 0.54-0.88) in favour of air

➡ Start with room air – adjust according to SpO2

- Preterm infants 28-31 weeks GA

OR for mortality: 1.9 (95%CI 0.33-11.1)

➡ Start with 21-30% – adjust according to SpO2

- Preterm infants <28 weeks GA

OR for mortality: 5.3 (95% CI 1.35-20)

➡ Don't start with 21%

➡ Start with 30% – adjust according to SpO2

Until more data are available from randomized studies aim at a SpO2 of 80-85% within 5 minutes

Saugstad OD, 2017

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Table 1. Suggestions on how to supply oxygen in the delivery room to newly born infants.

Gestational Age	Initial FiO_2	Target SpO_2 at 5 min
<37 weeks	0.21	85–90%
33^{+0} to 36^{+6} weeks	0.21	85%
29^{+0} to 32^{+6} weeks	0.21-0.30*	80–85%
≤28 weeks	0.3	80%

Lara-Cantón I. et al. Children 2019

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Gaps of knowledge
2015 → 2020

- Flow-chart
- Initial steps (temperature, HR detection)
- Meconium aspiration syndrome
- Oxygenation
- **Ventilation**
- Chest compressions
- Ethics
- Cord clamping
- Education

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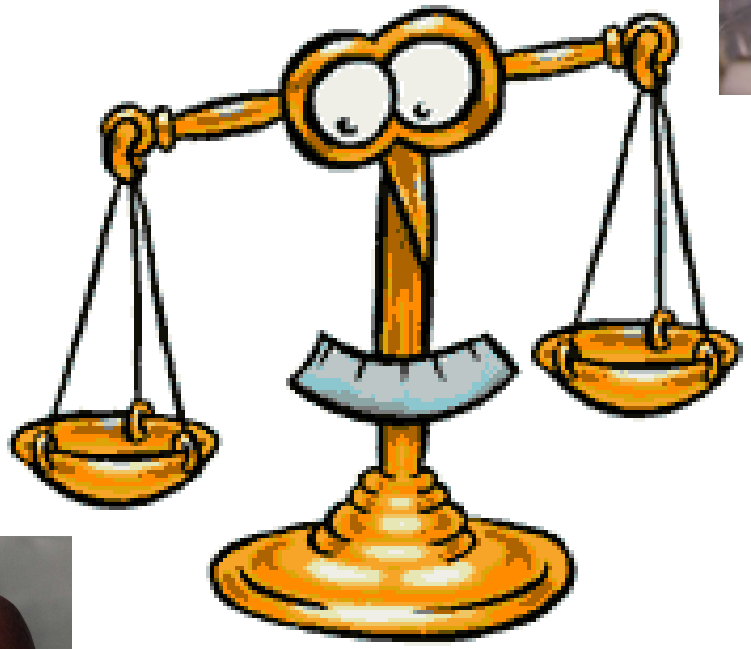
Nasal-CPAP



Intubation
+/-
surfactant

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Guidelines 2015

CPAP

- **We suggest…** ⟶ in favor…

Wyckoff MH et al. 2015 AHA Guidelines

Wyllie J et al. 2015 ERC Guidelines

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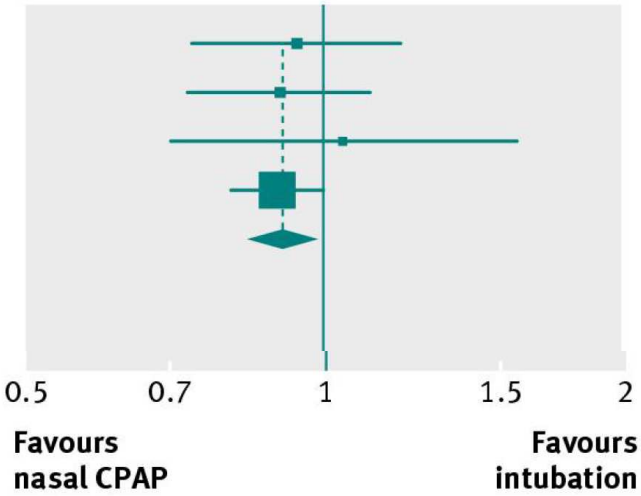
[NNT: 25]

Study or subgroup	No of events/total: Nasal CPAP	No of events/total: Intubation	Weight (%)	Risk ratio (Mantel-Haenszel) random (95% CI)
Death or BPD				
Dunn 2011[9]	68/223	138/425	12.6	0.94 (0.74 to 1.19)
Morley 2008[7]	108/307	118/303	17.0	0.90 (0.73 to 1.11)
Sandri[10]	33/103	32/105	4.5	1.05 (0.70 to 1.57)
SUPPORT[8]	323/663	353/653	65.9	0.90 (0.81 to 1.00)
Total (95% CI)	532/1296	641/1486	100.0	0.91 (0.84 to 0.99)

Test for heterogeneity: τ^2=0.00, χ^2=0.60, df=3, P=0.90, I^2=0%

Test for overall effect: z=2.10, P=0.04



Schmolzer GM, BMJ 2013


Gestational age: 24 wks
Birth weight: 410 g

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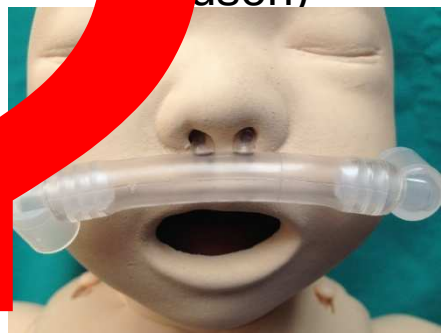
Single NF prong

Double NF prong

Short …sal prongs …dson)



Short binasal cannulae (Fisher&Paykel / RAM)

?

Key Points

Question What is the best noninvasive ventilation strategy for preventing death or bronchopulmonary dysplasia in the first 24 hours of life in spontaneously breathing preterm infants with or at risk of respiratory distress syndrome?

Findings In this meta-analysis, less invasive surfactant administration was the strategy associated with the lowest odds of the composite outcome of death or bronchopulmonary dysplasia compared with either nasal continuous positive airway pressure or mechanical ventilation.

Meaning Less invasive surfactant administration should be considered as a first-line ventilation strategy for spontaneously breathing preterm infants with respiratory distress syndrome.

Isayama T et al. JAMA 2016

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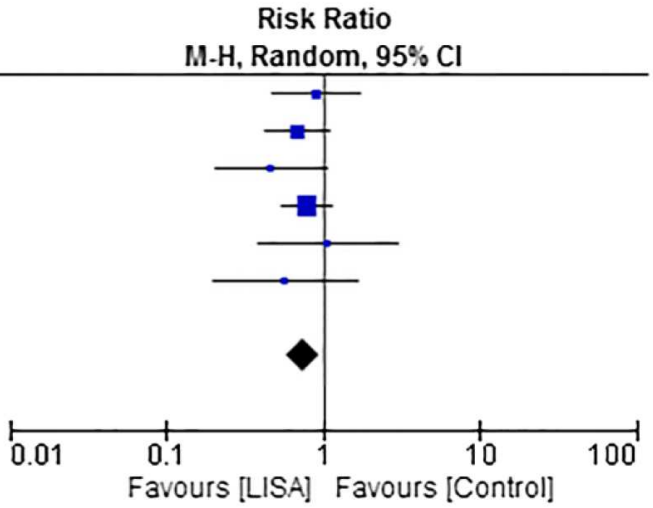
Figure 2 Composite outcome of **death or bronchopulmonary dysplasia at 36 weeks**. LISA, less invasive surfactant administration.

Study or Subgroup	LISA Events	LISA Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Gopel 2011	15	108	17	112	13.3%	0.92 [0.48, 1.74]
Kanmaz 2013	22	100	32	100	25.1%	0.69 [0.43, 1.10]
Mirnia 2013	7	66	16	70	8.1%	0.46 [0.20, 1.06]
Kribs 2015	35	107	43	104	43.3%	0.79 [0.55, 1.13]
Bao 2015	7	47	6	43	5.4%	1.07 [0.39, 2.93]
Mohammadizadeh 2015	4	19	7	19	4.9%	0.57 [0.20, 1.63]
Total (95% CI)		**447**		**448**	**100.0%**	**0.75 [0.59, 0.94]**
Total events	90		121			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.63$, $df = 5$ ($P = 0.76$); $I^2 = 0\%$
Test for overall effect: $Z = 2.46$ ($P = 0.01$)



Aldana-Aguirre JC, et al. Arch Dis Child Fetal Neonatal Ed 2017

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LISA/INSURE vs CPAP

- **P:** In spontaneous breathing preterm infants with distress requiring respiratory support in DR or during stabilization shortly after birth
- **I:** does surfactant administration avoiding prolonged mechanical ventilation via INSURE or LISA
- **C:** compared with CPAP alone
- **O:** change outcome?

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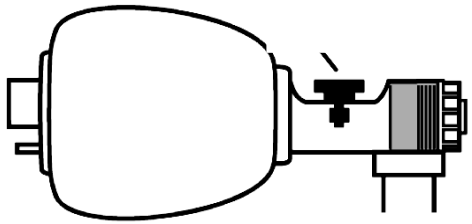
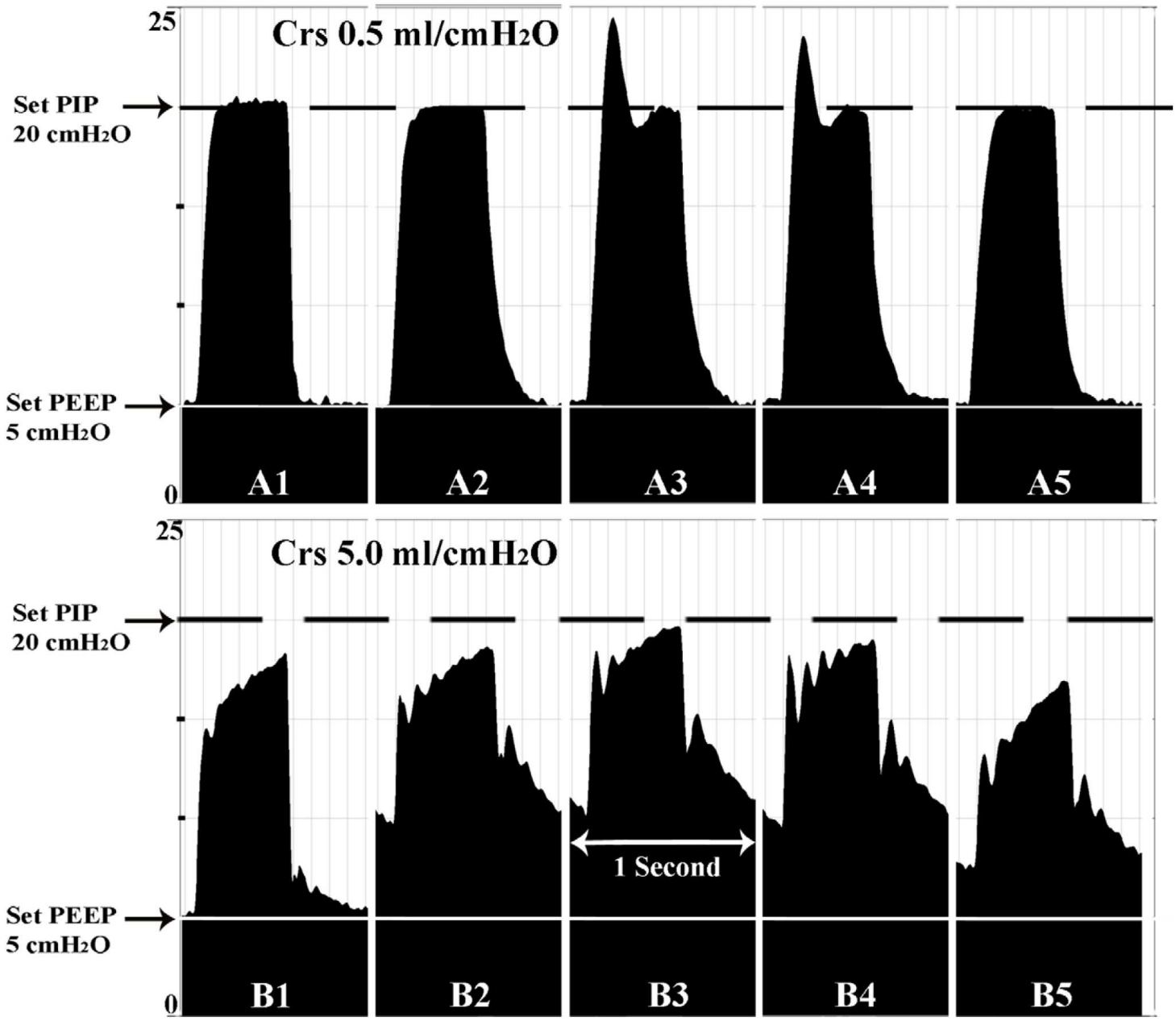


T-piece > **Self-inflating bag**

Szyld E et al. J Pediatr 2014

Giunburg R et al. ADCF&N Ed 2018



Which T-piece?

Hinder M, ADC 2019

Figure 4 Examples of recorded pressure waveforms for each TPR device tested: 1: rPAP; 2: Neopuff; 3: GE Panda; 4: Draeger Resuscitaire; and 5: Atom at test lung compliances: A: 0.5 mL/cmH_2O and B: 5.0 mL/cmH_2O. Time scale 1 s per segment. PEEP, positive-end expiratory pressure; PIP, peak inflation pressure; TPR, T-piece resuscitator.

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Sustained Lung Inflation

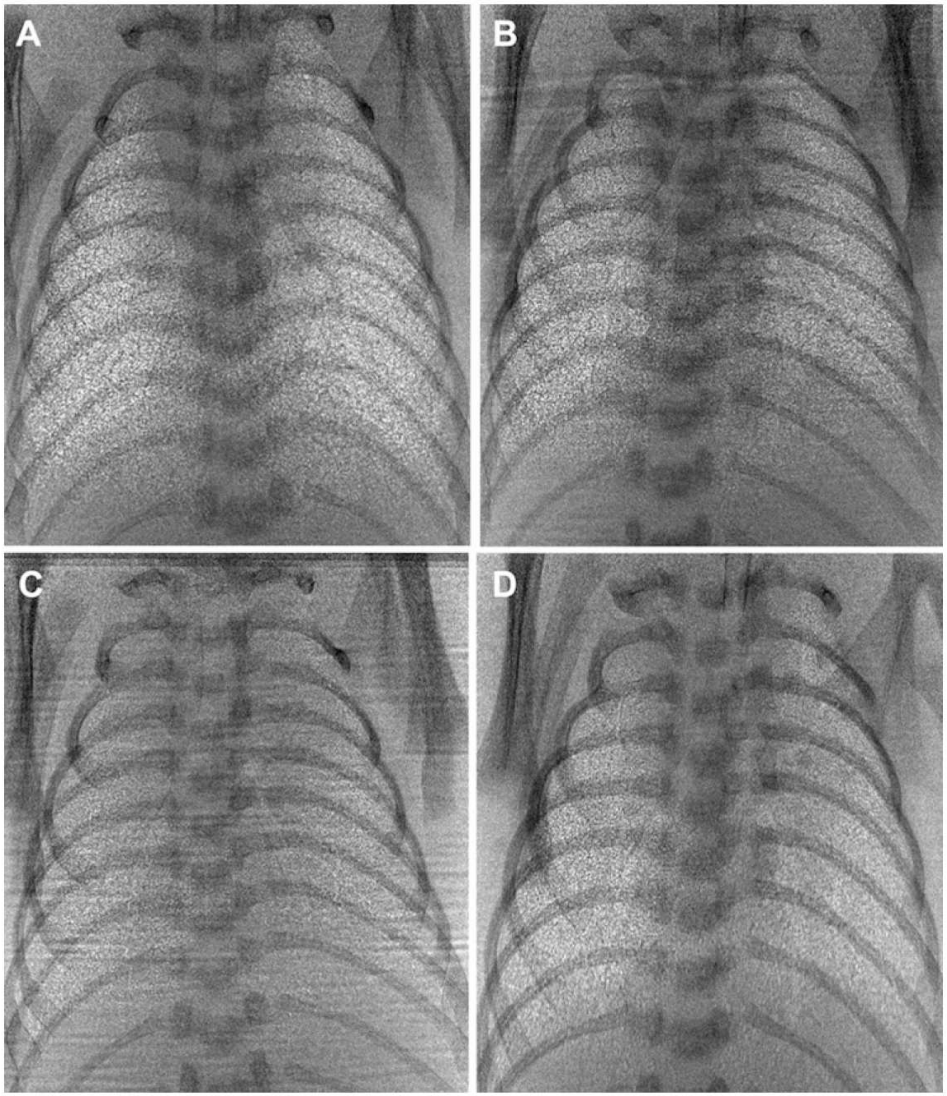

Figure 2. Representative examples of phase contrast x-ray images from each group. Images were acquired at end expiration (FRC) 20 s after birth in anesthetized preterm rabbit pups in which an initial SI of 20 s or not was given and ventilated in the presence/absence of PEEP (5 cm H_2O). SI + PEEP (*A*), no SI + PEEP (*B*), no SI + no PEEP (*C*), SI + no PEEP (*D*).

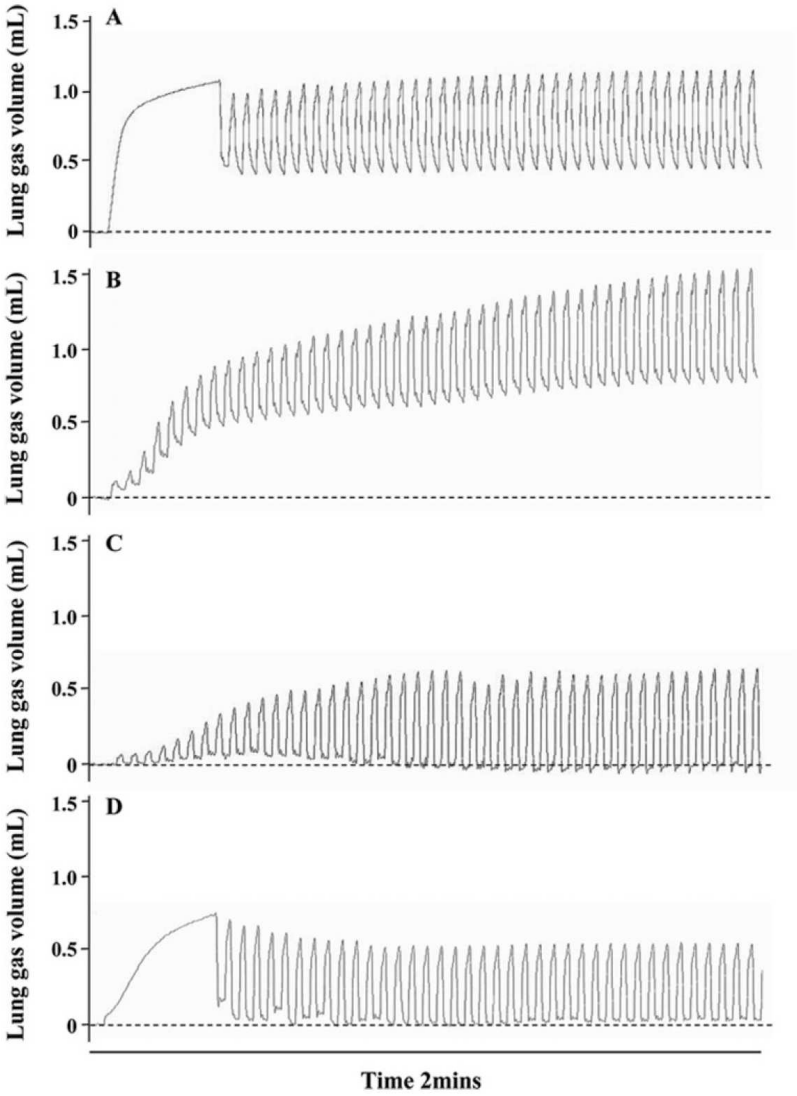

Figure 1. Representative examples of recordings from each group. Change in lung gas volume from birth in anesthetized ventilated preterm rabbit pups using plethysmography. With PEEP (*A* and *B*), an end-expiratory gas volume (FRC) was rapidly formed whereas in the absence of PEEP a significant FRC was not formed (*C* and *D*).

Te Pas et al. Pediatr Research 2009

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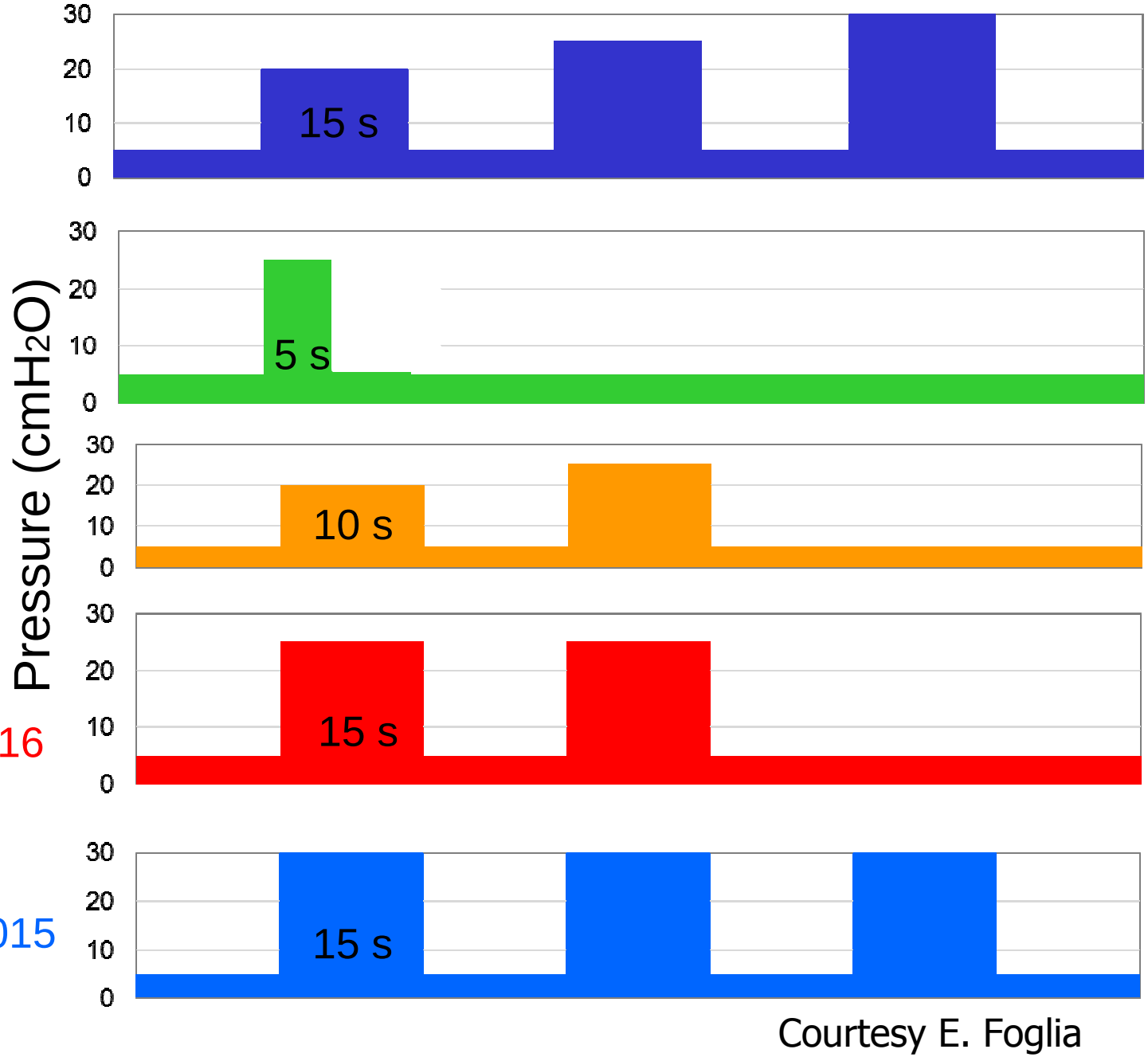
What is a Sustained Inflation?



Courtesy E. Foglia

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Guidelines 2015

Sustained lung inflation

- **We suggest…** ⟶ against…

Wyckoff MH et al. 2015 AHA Guidelines

Wyllie J et al. 2015 ERC Guidelines

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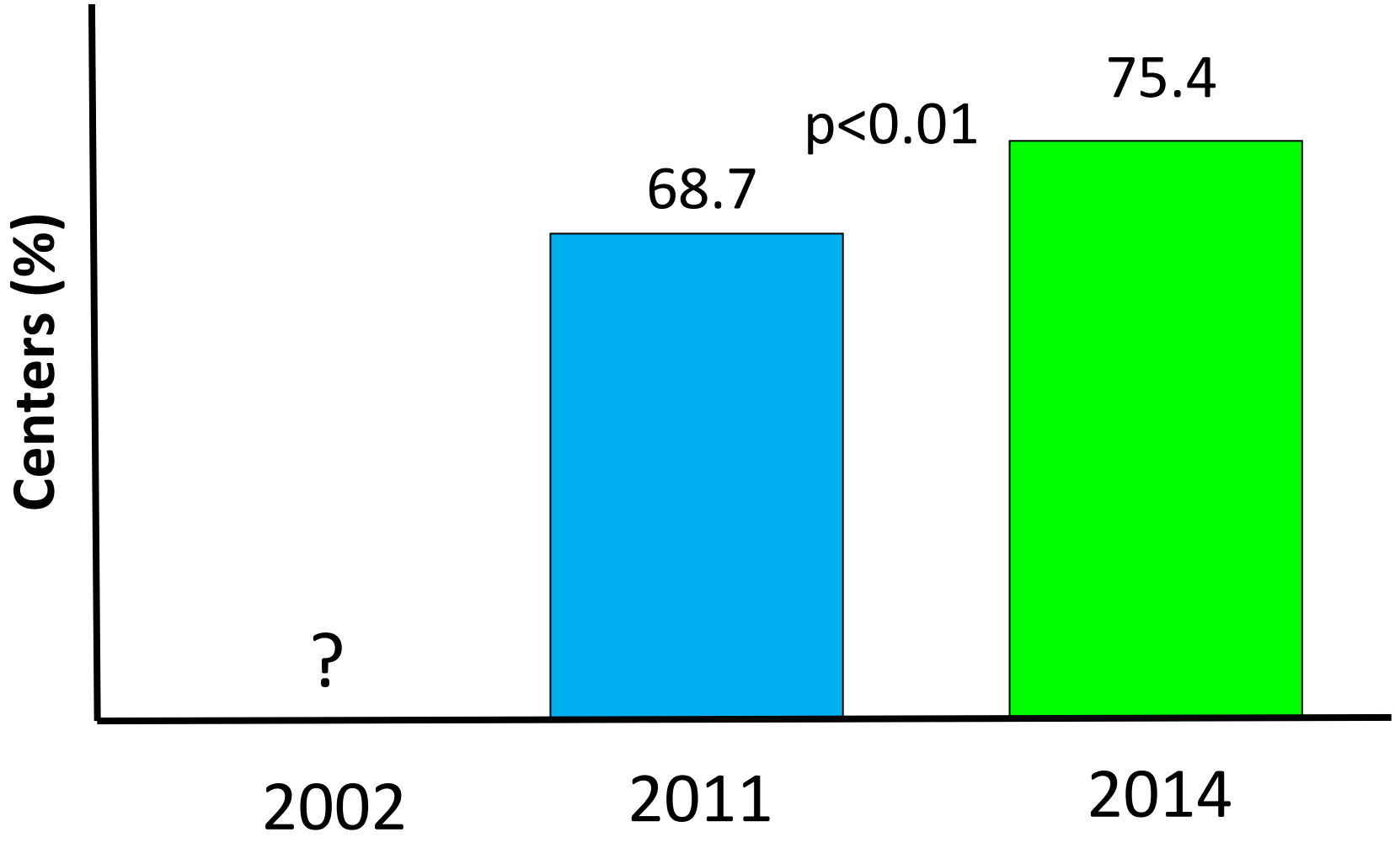
Use of sustained lung inflation in Italian level III centres



Petrillo F.

Trevisanuto et al. Resuscitation 2014

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Foglia *et al. Trials* (2015) 16:95
DOI 10.1186/s13063-015-0601-9

TRIALS

STUDY PROTOCOL Open Access

Sustained Aeration of Infant Lungs (SAIL) trial: study protocol for a randomized controlled trial

Elizabeth E Foglia[1,2], Louise S Owen[3,4,5], Marta Thio[3,4,5], Sarah J Ratcliffe[6], Gianluca Lista[7], Arjan te Pas[8], Helmut Hummler[9], Vinay Nadkarni[10], Anne Ades[1,2], Michael Posencheg[1,2], Martin Keszler[11,12], Peter Davis[3,4,5] and Haresh Kirpalani[1,2*]

Foglia e et al. Trials 2015

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[23-26 wks]

Table 2. Primary Composite Outcome and Component Secondary Outcomes at 36 Weeks' Postmenstrual Age

Outcome	Resuscitation, No. (%)		Adjusted Risk Difference, % (95% CI)[a]	Adjusted Relative Risk (95% CI)	*P* Value[b]
	Sustained Inflation (n = 215)	Standard (n = 211)			
Death or bronchopulmonary dysplasia	137 (63.7)	125 (59.2)	4.7 (−3.8 to 13.1)	1.1 (0.9 to 1.2)	.29
Death	45 (20.9)	33 (15.6)	5.2 (−2.3 to 12.7)	1.3 (0.9 to 1.9)	.17
Bronchopulmonary dysplasia	92 (42.8)	92 (43.6)	0.5 (−8.5 to 9.4)	1.0 (0.8 to 1.2)	.92

Kirpalani H et al. JAMA 2019

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[23-26 wks]

Event	Event Rate, No. (%) Sustained Inflation (n = 215)	Standard Resuscitation (n = 211)	Adjusted Risk Difference, % (95% CI)
Within first 2 days of life			
FIO_2 ≥0.4 for ≥2 h	50 (23.3)	52 (24.6)	-1.9 (-9.8 to 5.9)
Epinephrine	5 (2.3)	2 (1.0)	1.5 (-0.9 to 3.9)
Chest compressions	6 (2.8)	8 (3.8)	-1.4 (-4.7 to 1.9)
Death	16 (7.4)	3 (1.4)	5.6 (2.1 to 9.1)
Within first 10 days of life			
de I/II	51 (23.7)	44 (20.9)	3.2 (-5.0 to 11.4)
/IV	21 (9.8)	22 (10.4)	-0.3 (-6.2 to 5.5)
	11 (5.1)	19 (9.0)	-4.0 (-9.0 to 1.0)
mphysema	7 (3.3)	6 (2.8)	0.0 (-3.1 to 3.2)
	0	0	
At 2			
>30% O	0.7)	76 (36.0)	-4.5 (-14 to 4.6)
Mechanical su		91 (43.1)	-3.1 (-12 to 5.5)

Kirpalani H et al. JAMA 2019

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Gaps of knowledge
2015 → 2020

- Algorithm
- Initial steps (temperature, HR detection)
- Meconium aspiration syndrome
- Oxygenation
- Ventilation
- Chest compressions
- Ethics
- **Cord clamping**
- Education

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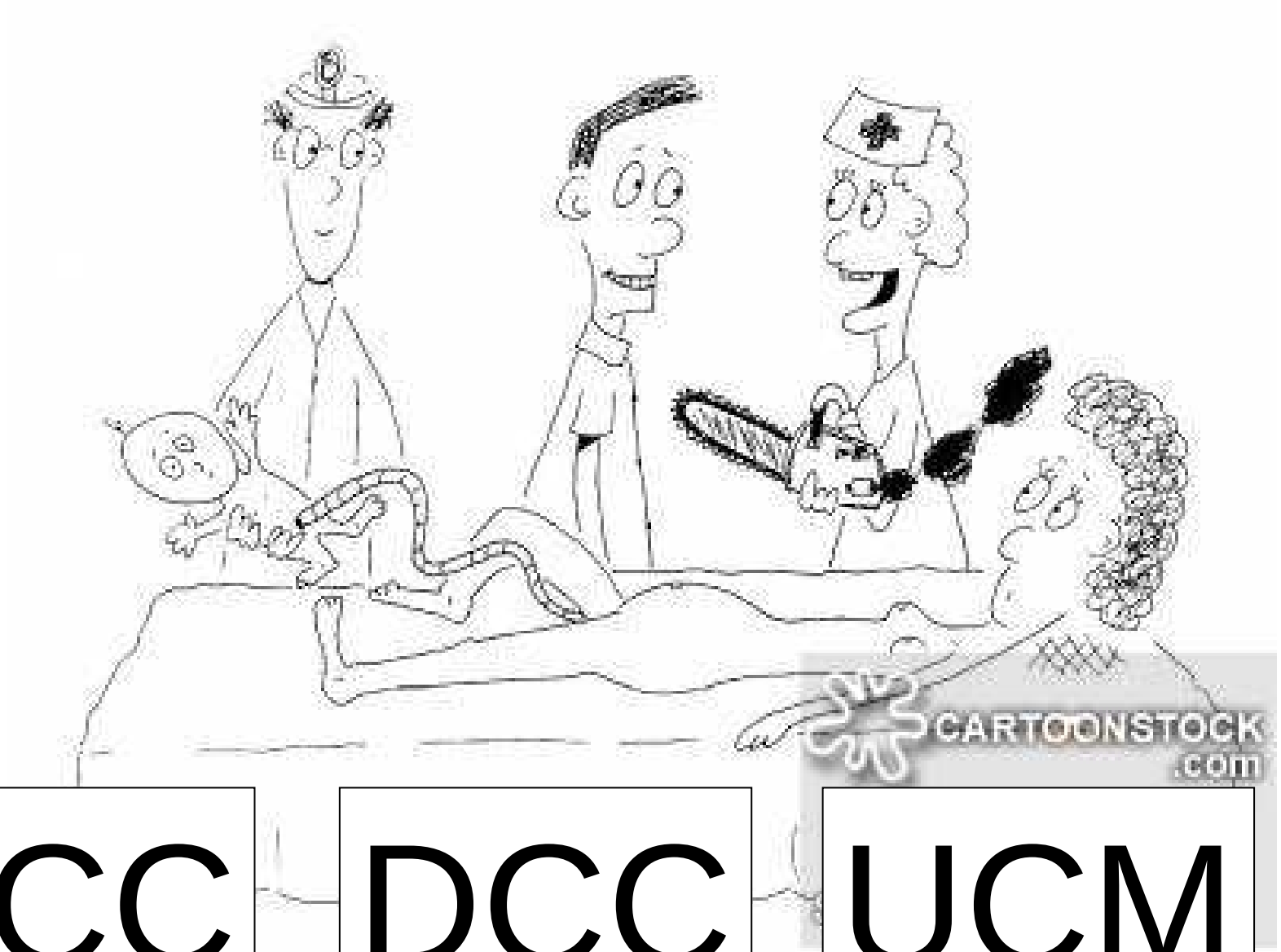

ICC DCC UCM

"Would you like to cut the cord?"

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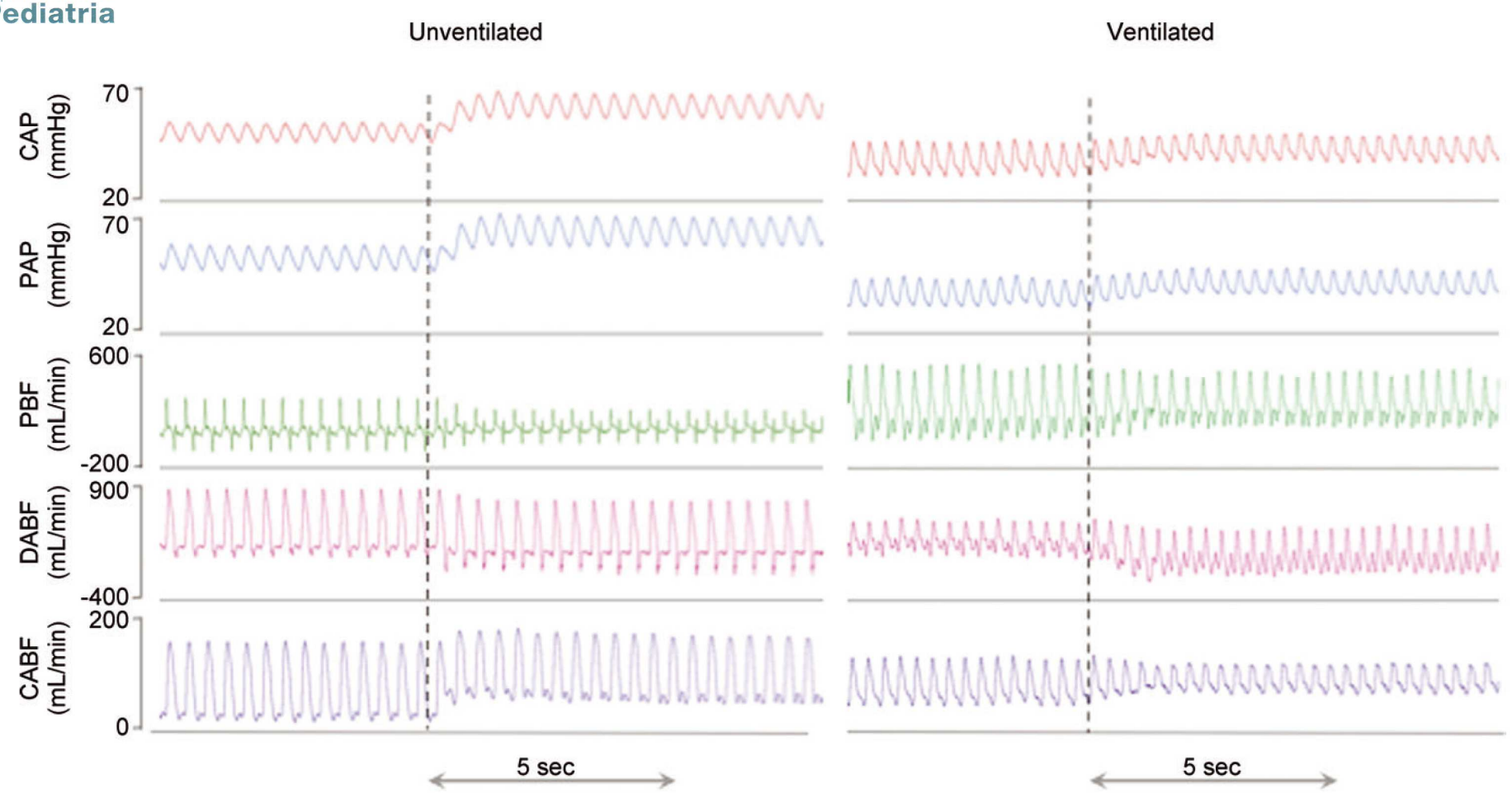

Figure 1. Recordings in unventilated and ventilated lambs before and after umbilical cord occlusion
Carotid arterial pressure (P_{CA}), pulmonary arterial pressure (P_{PA}), pulmonary blood flow (PBF), blood flow through the ductus arteriosus (DABF) and carotid arterial blood flow (CaBF) in unventilated (left) and ventilated (right) lambs before and after umbilical cord occlusion (indicated by dotted line).

Bhatt S et al. J Physiol 2013

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Effect of Delayed Cord Clamping on Neurodevelopment at 4 Years of Age: A Randomized Clinical Trial.

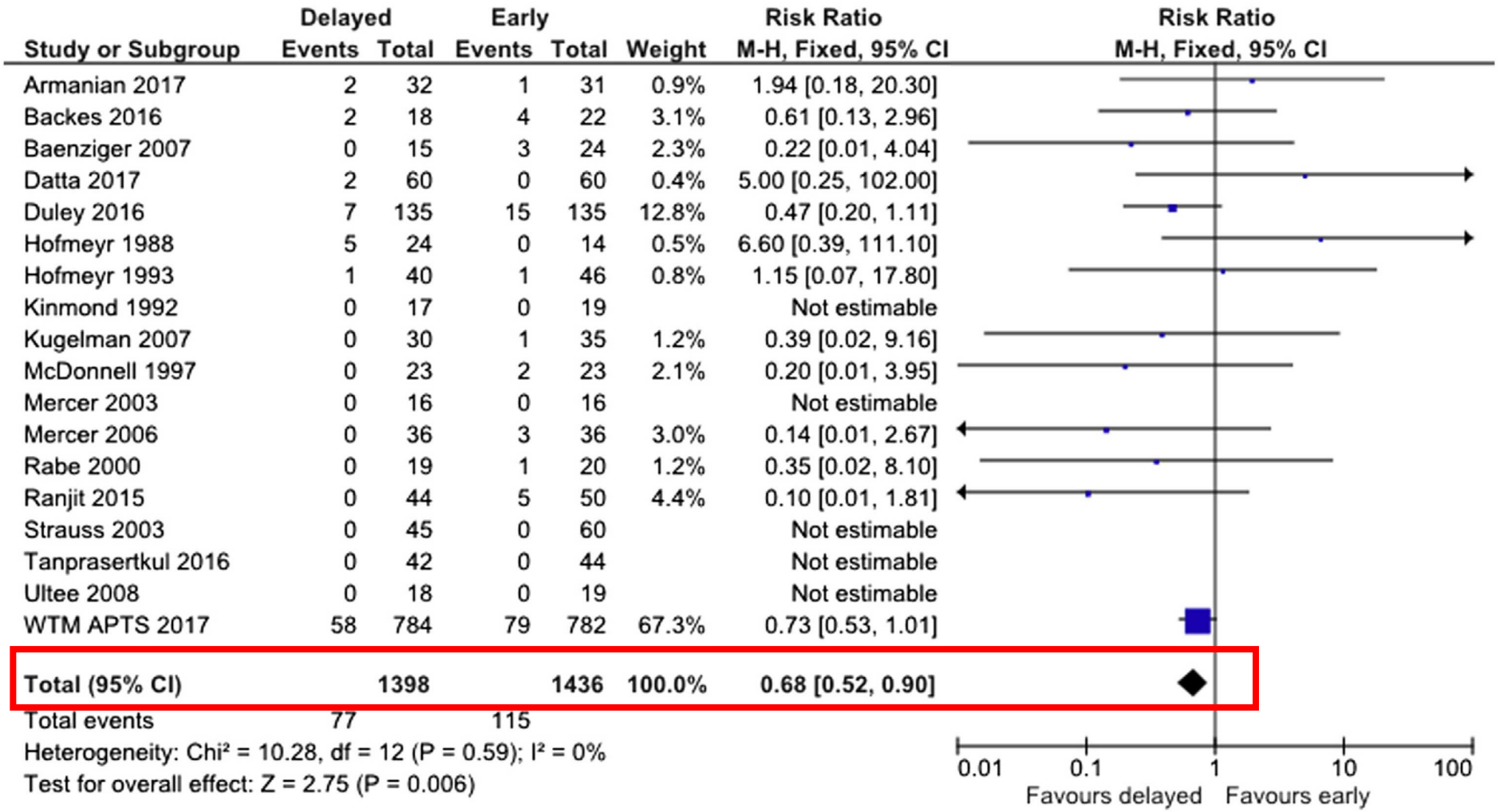
CONCLUSIONS AND RELEVANCE:

Delayed CC compared with early CC improved scores in the fine-motor and social domains at 4 years of age, especially in boys, indicating that optimizing the time to CC may affect neurodevelopment in a low-risk population of children born in a high-income country.

Andersson O et al. JAMA Pediatr 2015

FIGURE 3

Meta-analyses showing effect of delayed clamping on mortality



Study or Subgroup	Delayed Events	Delayed Total	Early Events	Early Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Armanian 2017	2	32	1	31	0.9%	1.94 [0.18, 20.30]
Backes 2016	2	18	4	22	3.1%	0.61 [0.13, 2.96]
Baenziger 2007	0	15	3	24	2.3%	0.22 [0.01, 4.04]
Datta 2017	2	60	0	60	0.4%	5.00 [0.25, 102.00]
Duley 2016	7	135	15	135	12.8%	0.47 [0.20, 1.11]
Hofmeyr 1988	5	24	0	14	0.5%	6.60 [0.39, 111.10]
Hofmeyr 1993	1	40	1	46	0.8%	1.15 [0.07, 17.80]
Kinmond 1992	0	17	0	19		Not estimable
Kugelman 2007	0	30	1	35	1.2%	0.39 [0.02, 9.16]
McDonnell 1997	0	23	2	23	2.1%	0.20 [0.01, 3.95]
Mercer 2003	0	16	0	16		Not estimable
Mercer 2006	0	36	3	36	3.0%	0.14 [0.01, 2.67]
Rabe 2000	0	19	1	20	1.2%	0.35 [0.02, 8.10]
Ranjit 2015	0	44	5	50	4.4%	0.10 [0.01, 1.81]
Strauss 2003	0	45	0	60		Not estimable
Tanprasertkul 2016	0	42	0	44		Not estimable
Ultee 2008	0	18	0	19		Not estimable
WTM APTS 2017	58	784	79	782	67.3%	0.73 [0.53, 1.01]
Total (95% CI)		**1398**		**1436**	**100.0%**	**0.68 [0.52, 0.90]**
Total events	77		115			

Heterogeneity: Chi² = 10.28, df = 12 (P = 0.59); I² = 0%

Test for overall effect: Z = 2.75 (P = 0.006)

Meta-analyses showing effect of delayed vs early cord clamping on risk ratio for hospital mortality in 18 trials in 2834 infants <37 weeks' gestation (top) and 3 trials in 996 infants ≤28 weeks' gestation (bottom).

APTS, Australian Placental Transfusion Study; *CI*, confidence interval; *M-H*, Mantel-Haenszel.

Fogarty M et al. AJOG 2018

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Treatment Recommendation

Delay in umbilical cord clamping for at least 1 minute is recommended for newborn infants not requiring resuscitation.

Perlman JM et al. Pediatrics 2010

Resuscitation with intact umbilical cord ?

Weeks AD, et al. BMJ Innov 2015

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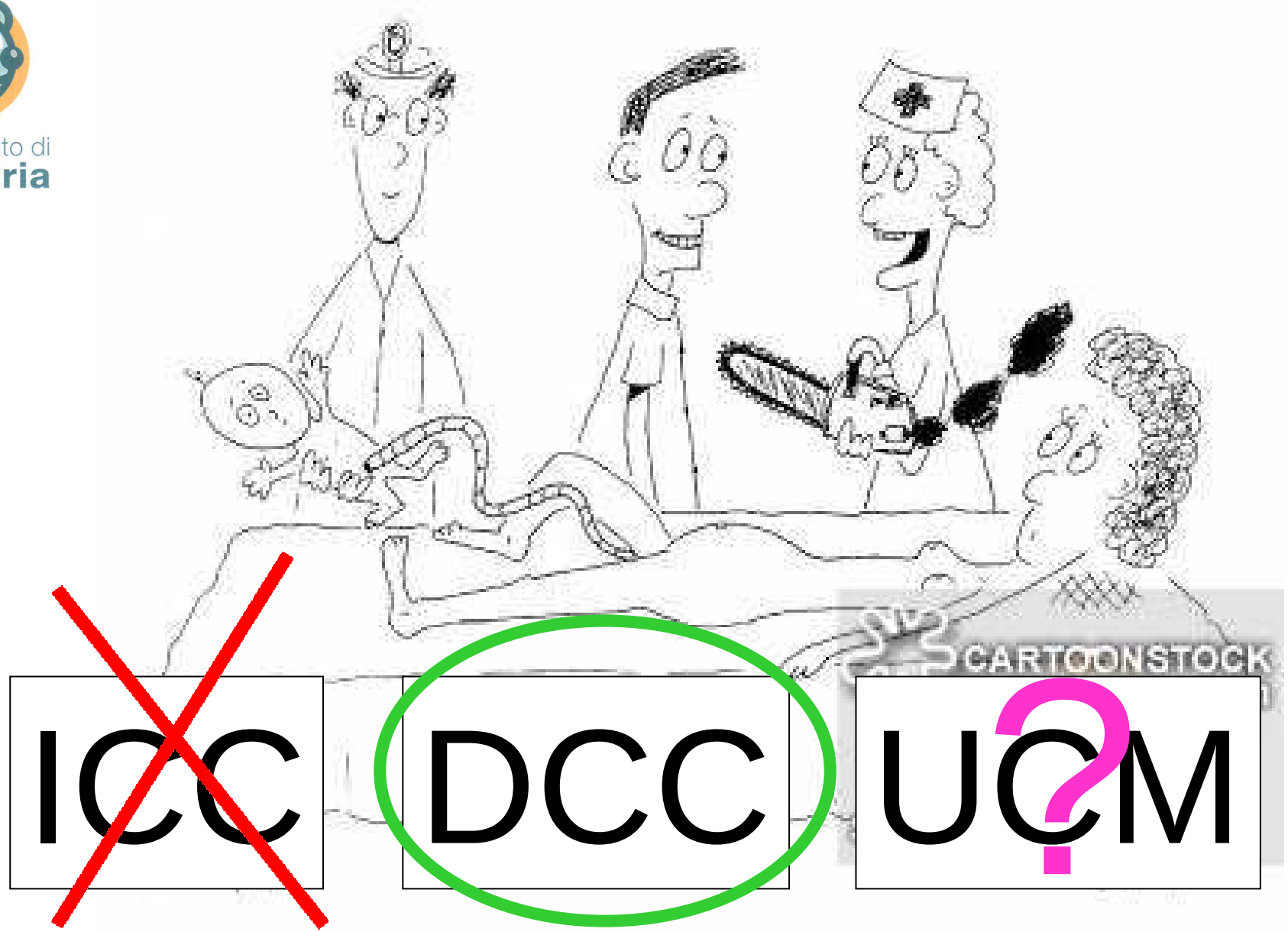


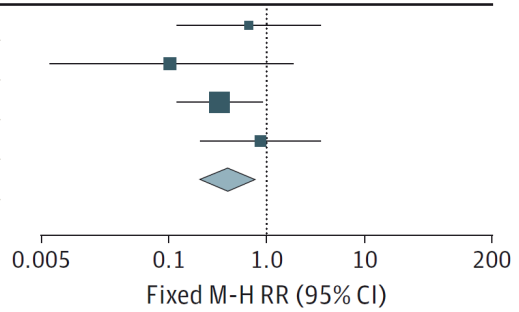
Original Investigation

Efficacy and Safety of Umbilical Cord Milking at Birth

A Systematic Review and Meta-analysis

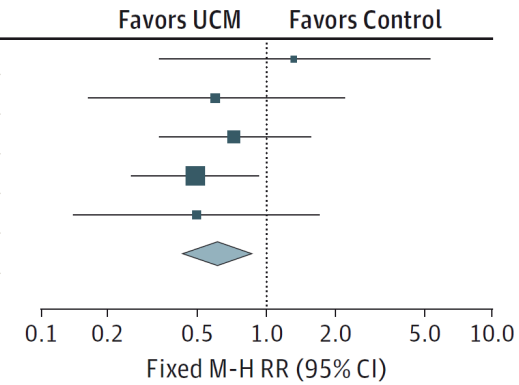
B Oxygen requirement at 36 wk, postmenstrual age in preterm infants[a]

Source	UCM Group No. of Events	UCM Group Total	Control Group No. of Events	Control Group Total	Weight, %	Fixed M-H RR (95% CI)
Alan et al,[16] 2014	2	19	3	19	12.9	0.67 (0.13-3.55)
Hosono et al,[11] 2008	0	18	4	17	19.8	0.11 (0.01-1.82)
Katheria et al,[15] 2014	4	30	12	30	51.4	0.33 (0.12-0.92)
Rabe et al,[14] 2011	3	27	4	31	16.0	0.86 (0.21-3.51)
Total	9	94	23	97	100.0	0.42 (0.21-0.83)
Heterogeneity $x^2_3 = 2.41$ ($P = .49$); $I^2 = 0\%$						
Test for overall effect: $z = 2.50$ ($P = .01$)						



C IVH of all grades[a]

Source	UCM Group No. of Events	UCM Group Total	Control Group No. of Events	Control Group Total	Weight, %	Fixed M-H RR (95% CI)
Alan et al,[16] 2014	4	22	3	22	6.7	1.33 (0.34-5.28)
Hosono et al,[11] 2008	3	20	5	20	11.2	0.60 (0.17-2.18)
Katheria et al,[15] 2014	8	30	11	30	24.6	0.73 (0.34-1.55)
March et al,[12] 2013	9	36	20	39	42.9	0.49 (0.26-0.93)
Rabe et al,[14] 2011	3	27	7	31	14.6	0.49 (0.14-1.72)
Total	27	135	46	142	100.0	0.62 (0.41-0.93)
Heterogeneity $x^2_4 = 2.03$ ($P = .73$); $I^2 = 0\%$						
Test for overall effect: $z = 2.32$ ($P = .02$)						



Al-Wassia H et al. JAMA Pediatr 2015

Benefits of umbilical cord milking versus delayed cord clamping on neonatal outcomes in preterm infants: A systematic review and meta-analysis

Conclusions

UCM wasn't reduced in-hospital mortality and need for transfusion compared to DCC. But our study suggests that UCM may lower the risk of IVH and improve certain neurodevelopmental outcomes compared to DCC in preterm infants.

Nagano N et al. PLOS One 2018

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Guidelines 2015

Cord milking

Treatment Recommendation

"We **suggest against** the routine use of cord milking for infants born at less than 29 weeks of gestation because there is insufficient published human evidence of benefit."

"Cord milking may be considered on an individualized basis or in a research setting as it may improve initial mean blood pressure, hematological indices and intracranial hemorrhage. There is no evidence for improvement or safety in long-term outcomes. (Weak recommendation, low level of evidence)."

Perlman J et al. Circulation 2015

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Premature Infants Receiving Cord Milking Or Delayed Cord Clamping: A Randomized Controlled Non-inferiority Trial

P: In infants with GA 23-31 weeks

I: does Umbilical Cord Milking

C: Delayed Cord Clamping

O: resuce Intraventricular hemorrhage (IVH) or Death

Katheria AC et al. JAMA 2019

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Premature Infants Receiving Cord Milking Or Delayed Cord Clamping: A Randomized Controlled Non-inferiority Trial

Primary outcome

Intraventricular hemorrhage (IVH) or death

DDC	UCM	p-value
19/238 (8%)	28/236 (12%)	0.16

Katheria AC et al. JAMA 2019

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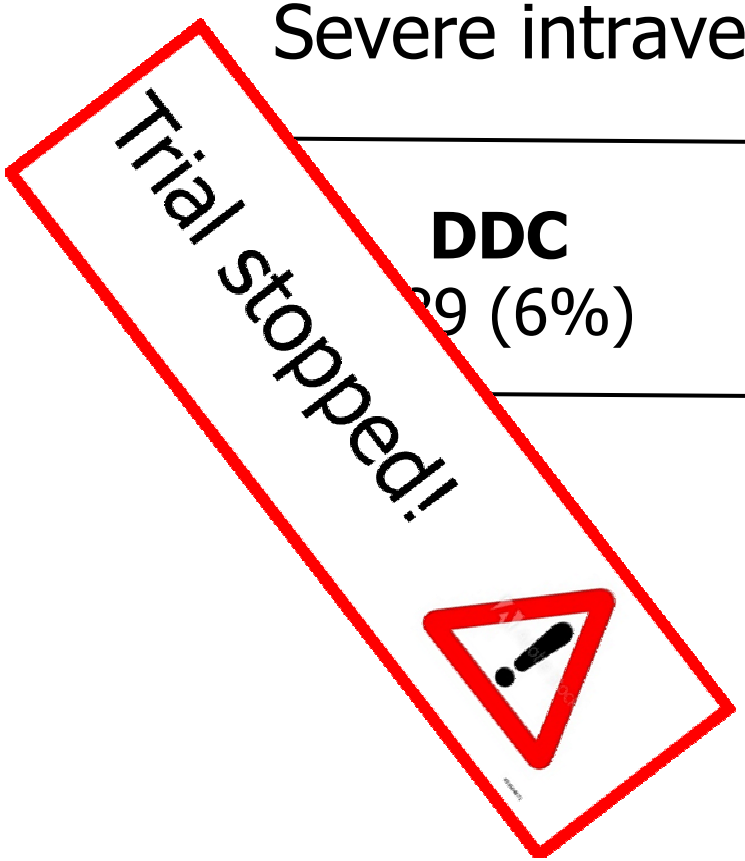
Premature Infants Receiving Cord Milking Or Delayed Cord Clamping: A Randomized Controlled Non-inferiority Trial

[23-27 wks]

Severe intraventricular hemorrhage (IVH)

	DDC	UCM	p-value
	9 (6%)	20/93 (22%)	0.0019



Katheria AC et al. JAMA 2019

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Gaps of knowledge
2015 → 2020

- Flow-chart
- Initial steps (temperature, HR detection)
- Meconium aspiration syndrome
- Oxygenation
- Ventilation
- Chest compressions
- Ethics
- Cord clamping
- **Education**

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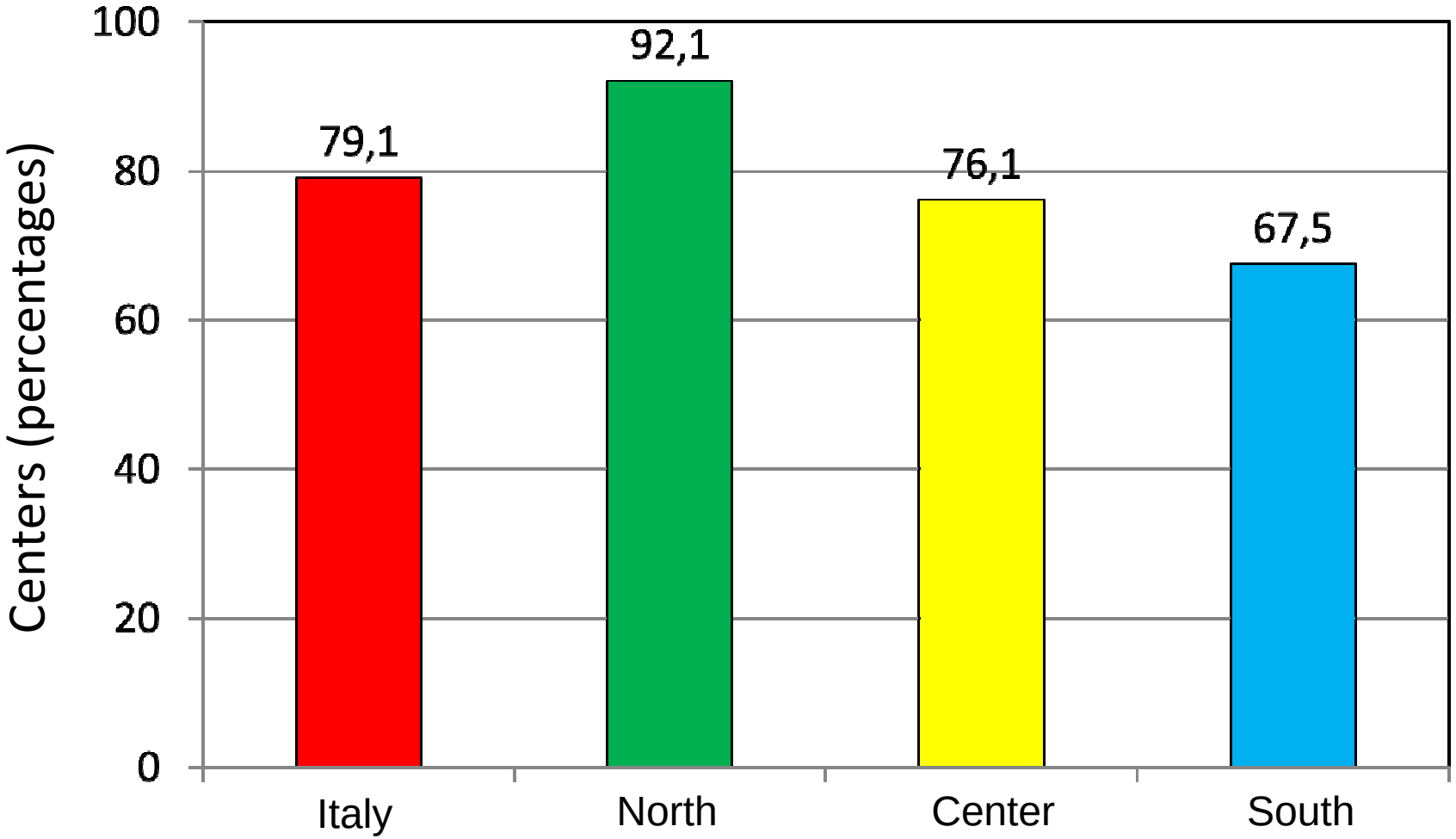
NRP (NLS) courses



Trevisanuto et al. Acta Paediatr 2014

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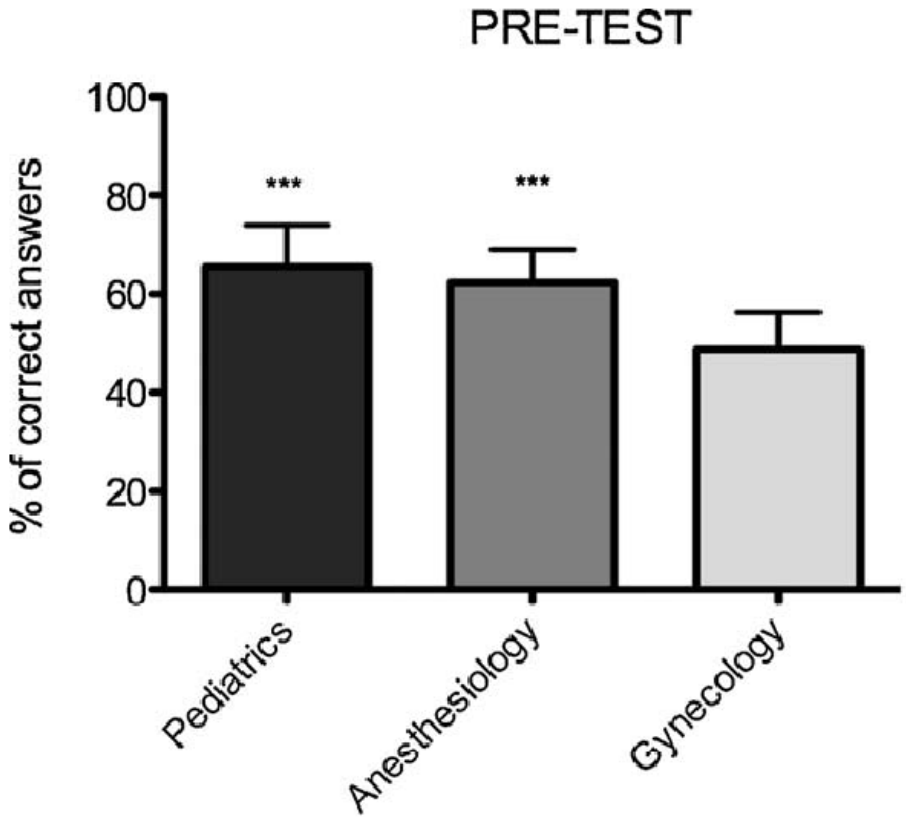
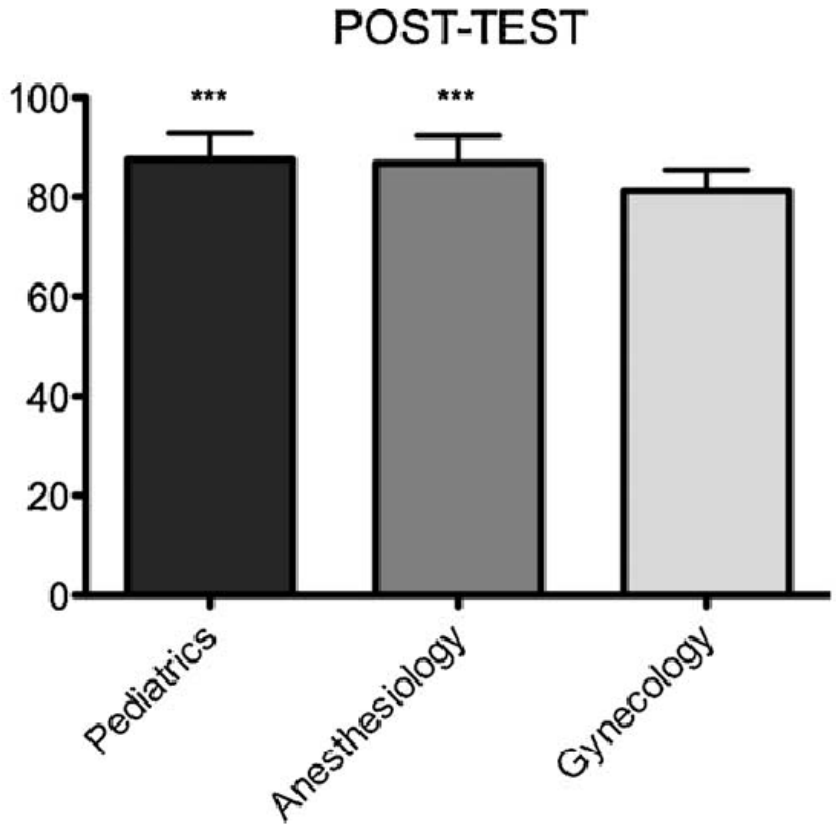
Knowledge





Parotto M et al. Resuscitation 2010

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Manual skills

Table. Percentage of items performed correctly on the performance evaluation (skills evaluation) immediately after course participation (post-test)

	Carlo et al[1]	Trevisanuto et al
Overall performance evaluation	88 (9)	78 (35)
A. Initial steps	87 (11)	75 (21)
1. Indicates use of (universal) standard precautions	78 (42)	25 (41)
2. Prepares for warming	98 (12)	84 (33)
3. Prepares for positioning or for clearing airway	93 (26)	74 (39)
4. Prepares for ventilation	98 (15)	84 (31)
5. Prepares medications	72 (45)	79 (35)
6. Determines need for the initial steps of resuscitation	76 (43)	90 (28)
7. Places baby on preheated radiant warmer or on mother with neck slightly extended	90 (30)	96 (18)
8. Clears mouth and nose	94 (23)	100 (0)
9. Dries the baby	98 (15)	71 (46)
10. Removes wet linen	84 (37)	61 (49)
11. Slaps foot, flicks heel, or rubs back briefly	72 (45)	61 (49)
B. Ventilation	88 (12)	83 (11)
12. Chooses correct size mask or positions the bag	92 (27)	89 (31)
13. Checks the seal	86 (35)	75 (47)
14. Positions the head and applies the face mask	96 (20)	93 (26)
15. Checks for and removes secretions	92 (27)	89 (31)
16. Ventilates with mouth slightly open	79 (41)	68 (47)
17. Increases ventilation pressure	75 (44)	61 (49)
18. Ventilates 30 seconds at a rate of 40-60 times/min	87 (34)	96 (18)
19. Achieves visible rise and fall of the chest	90 (30)	79 (41)
20. Asks for help to administer chest compressions	94 (24)	75 (44)
21. Continues positive pressure ventilation	95 (21)	82 (39)
22. Checks the heart rate by palpation or stethoscope	85 (36)	93 (26)
23. Checks to ensure adequate chest movement	87 (34)	86 (36)
24. Coordinates ventilations and chest compressions appropriately	81 (39)	93 (26)
C. Chest compressions	93 (14)	71 (19)
25. Locates appropriate position on lower one-third of baby's sternum	95 (21)	89 (31)
26. Provides firm support for baby's back	93 (26)	79 (42)
27. Uses fingertips or ring fingers or distal portion of both thumbs	94 (24)	39 (50)
28. Compresses sternum approximately one-third of the anterior-posterior diameter of the chest	92 (27)	75 (44)
29. Maintains cadence of "one- and two- and three- and breathe- and..".	92 (27)	75 (44)

Data are expressed as means (SD).

Trevisanuto D et al. J Pediatr 2010

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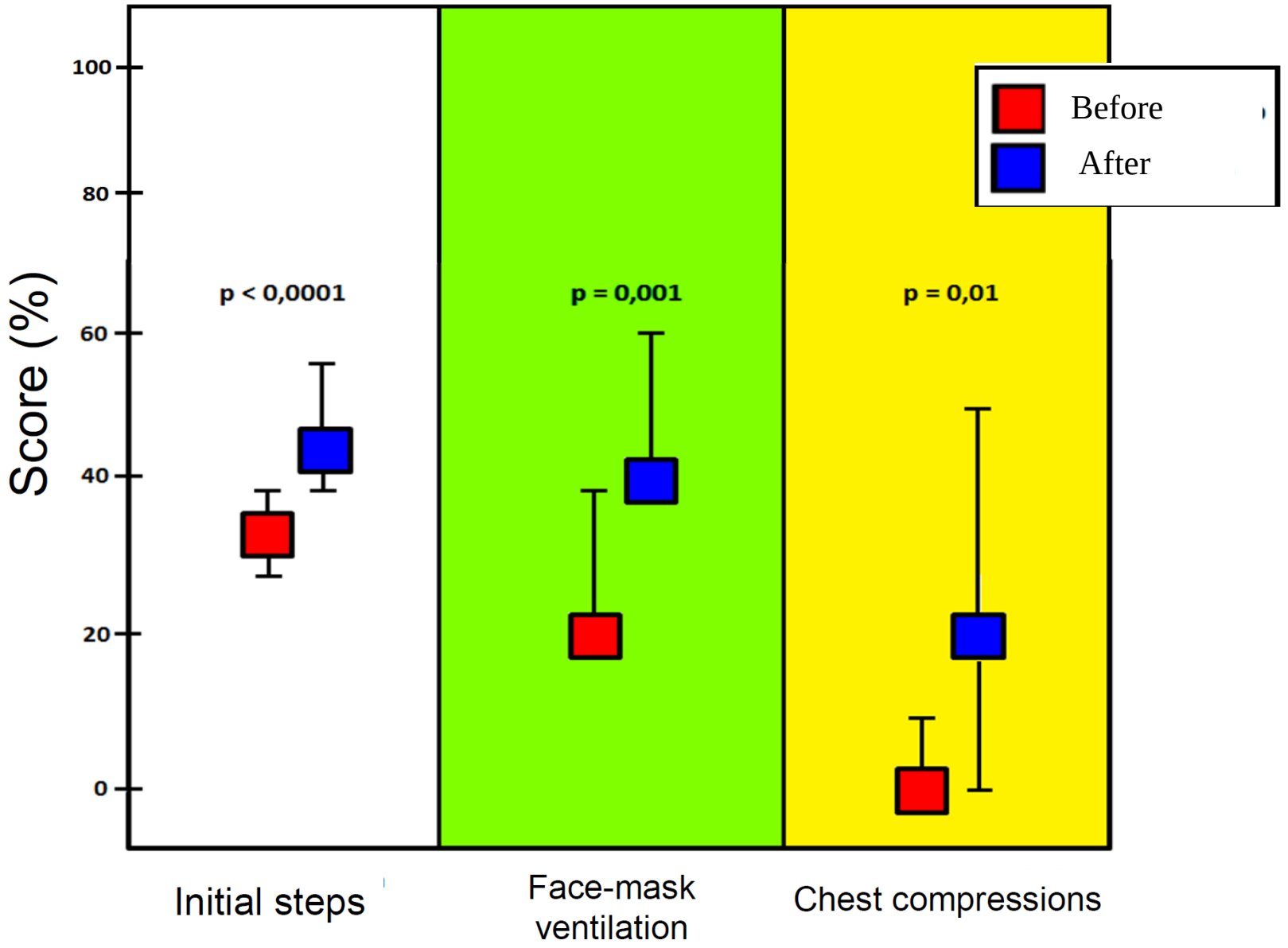
Clinical practice



Trevisanuto D, et al. PlosOne 2015

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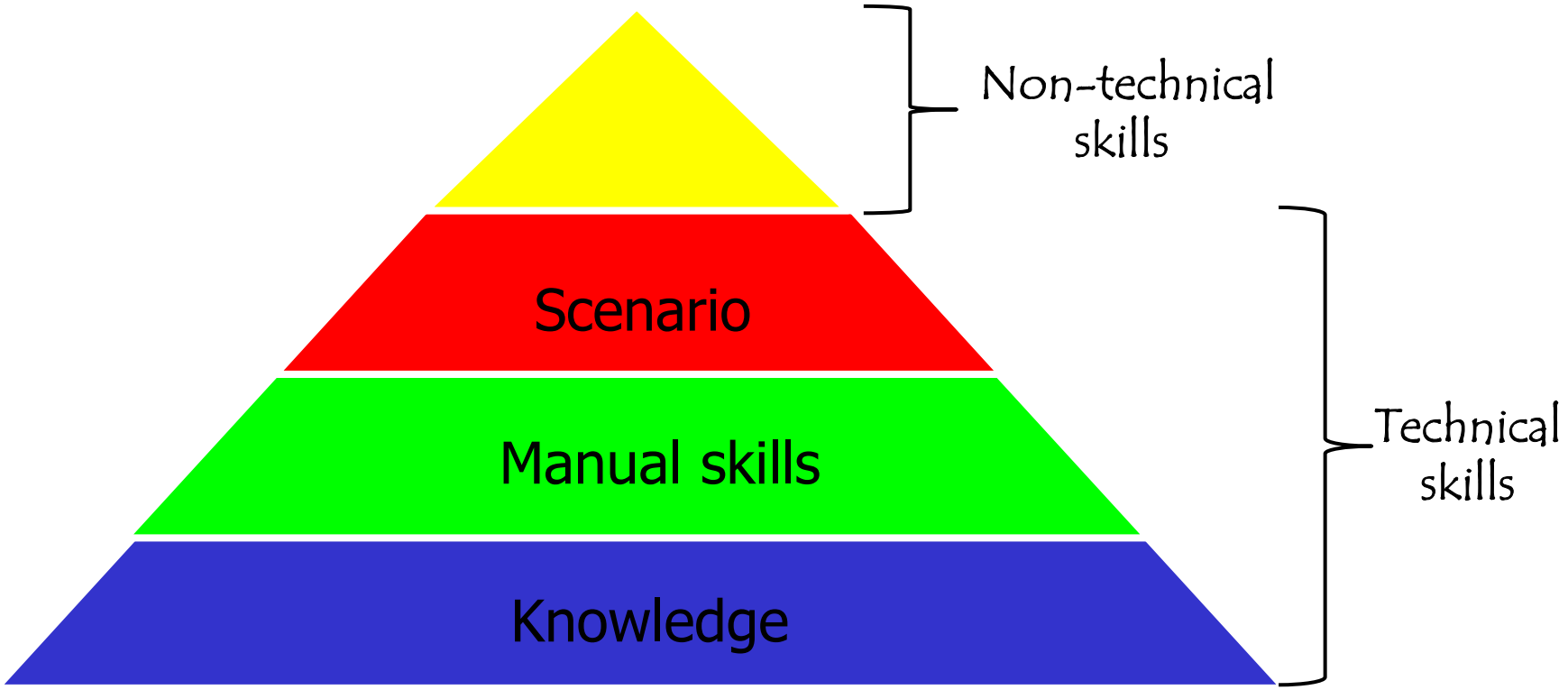
Education



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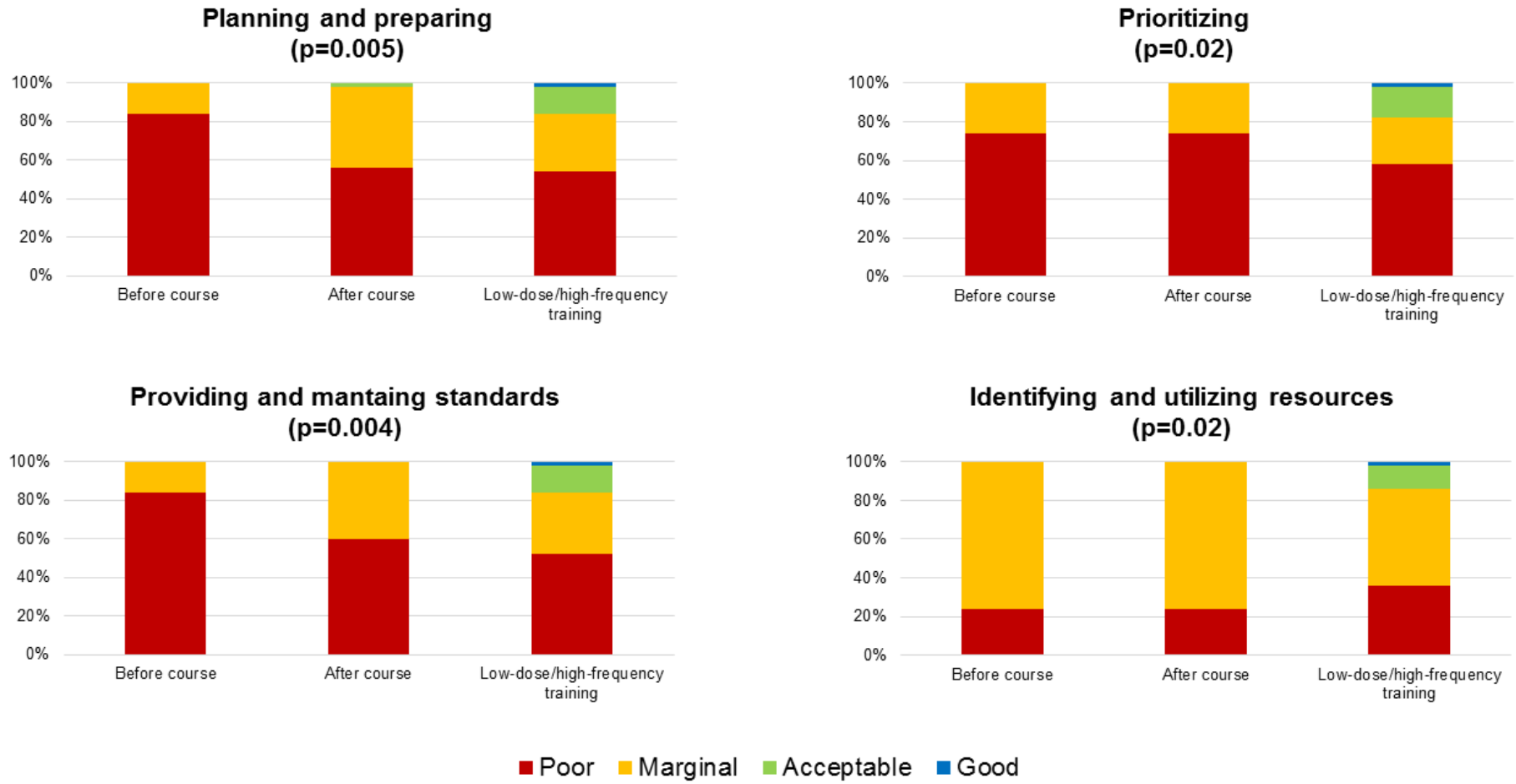
Education

Task management



Cavicchiolo ME et al. Resuscitation 2018

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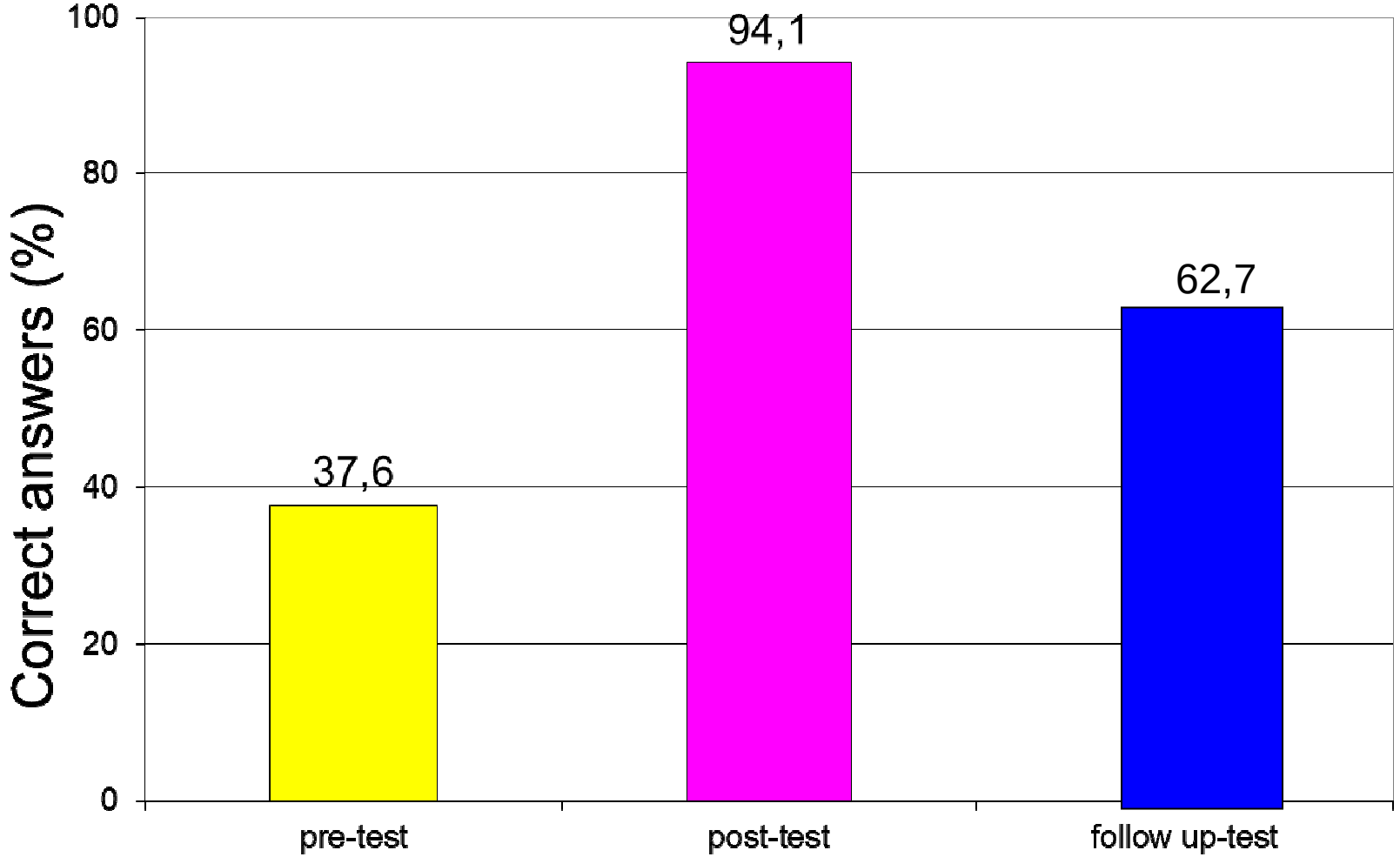
Neonatal resuscitation course for Pediatric Residents (CORRECT ANSWERS)



Trevisanuto et at, Pediatr Anesth 2005

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Conclusions

- ILCOR task-force evaluation is a standardized and continuous process
- Guidelines are based on the ILCOR Consensus on Science
- Hypothermia/hyperthermia are associated with mortality and morbidity
- Low Oxygen concentrations (21-30%) seem reasonable (saturation target a 5 min is the goal)
- CPAP instead of intubation is suggested
- CPAP vs LISA/INSURE needs to be assessed
- SLI is not recommended
- Delayed cord clamping (after breathing) seems to be the best choice
- Milking does not seem to be recommended
- Optimal frequency and contents of training remain to be established

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Thanks…

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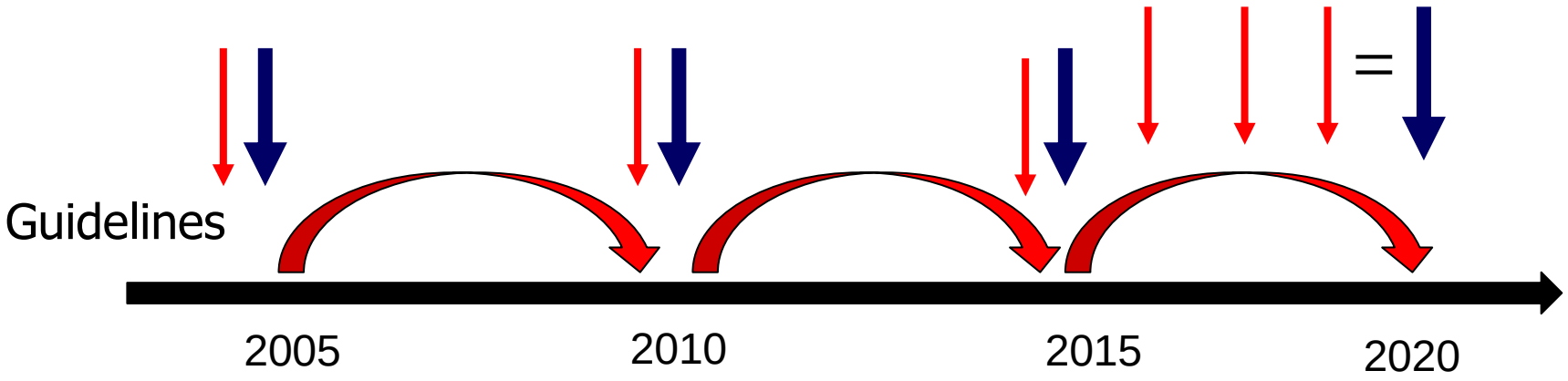
Guidelines 2020

- initial O2 for term and preterm infants
- management of infants born through MSAF



= Consensus on Science

= Guidelines

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[23-26 wks]

Meaning These findings do not support the use of a ventilation strategy involving sustained inflations among extremely preterm infants, although early termination of the trial limits definitive conclusions.

Kirpalani H et al. JAMA 2019

Bertuola F et al. PlosOne 2015
Cavicchiolo ME et al. Neonatology 2018
Cavicchiolo ME et al. Resuscitation 2018

Table II. Neurodevelopmental outcomes and morbidities after discharge

Outcome	Cord milking (n = 70)	DCC (n = 65)	*P* value
Cognitive composite score	100 ± 13	95 ± 12	.031
<85	3 (4)	10 (15)	.040
Language composite score	93 ± 15	87 ± 13	.013
<85	16 (23)	25 (38)	.061
Motor composite score	99 ± 12	97 ± 12	.349
<85	6 (9)	12 (18)	.128
GMFCS level of ≥2	1	0	.999
Vision impairment	8 (11)	10 (15)	.614
Hearing impairment	0	0	.999
Mild neurodevelopmental impairment	4 (6)	10 (15)	.093
Moderate to severe neurodevelopmental impairment	2 (3)	0	.500
Weight (kg)	12.4 ± 3.1	11.9 ± 1.8	.252
Height (cm)	88 ± 5	86 ± 4	.037
Head circumference (cm)	48 ± 2	48 ± 2	.540
Rehospitalized after discharge	15 (21)	12 (18)	.830

Katheria AC et al. J Pediatr 2018