European RDS Guidelines 2022 Update

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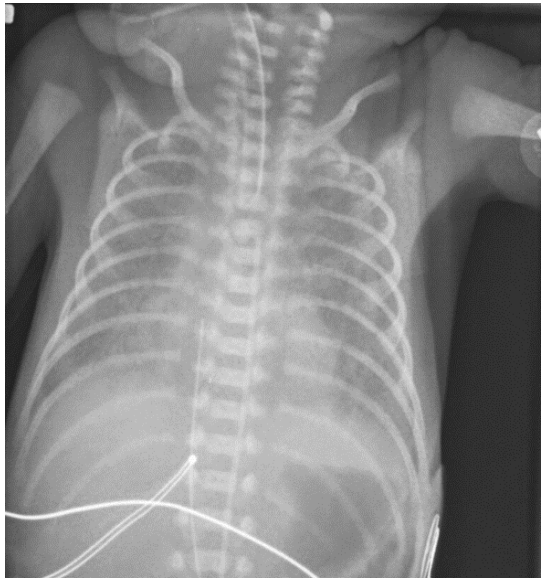
Disclosures

Received Honoraria and expenses for presenting at meetings

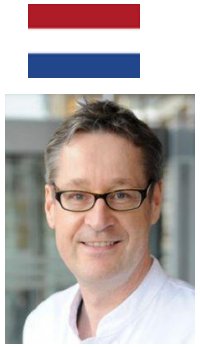
Chiesi
Abbvie
Drager

Objectives

- Discuss approach to management for preterm babies at risk of RDS in the context of European RDS Guidelines 2022
- Understand current controversies
- Highlight where things are changing



RDS Guidelines 2022



RDS - Treatment

- Prenatal Steroids
- Oxygen
- Non-Invasive support
- Mechanical ventilation
- Surfactant replacement
- General supportive Care

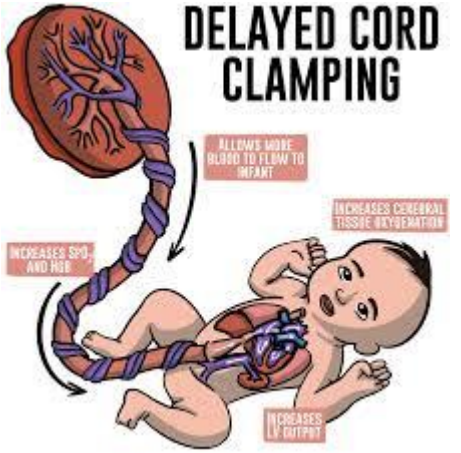
Strength of Evidence
A-D

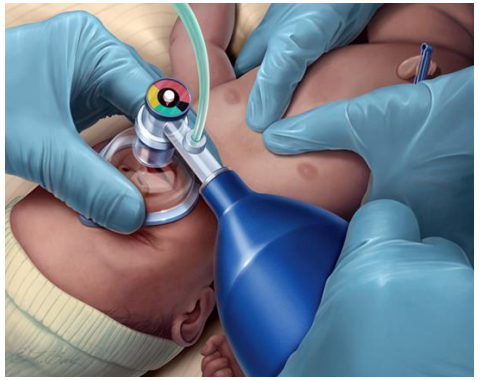
Strength of Recommendation
1 or 2

- Live saving
- May cause BPD/ other harms
- Many interventions subjected to RCTs

Delivery Room Stabilisation – Considerations

- Timing of cord clamping versus resuscitation
  - Resuscitation with cord intact?
  - Cord Milking?
- Devices for monitoring and supporting first breaths
  - CPAP systems and interfaces
  - Devices for monitoring wellbeing
- Temperature control in the delivery room





Delivery Room
Aims/ goals of supported transition

- Aim to delay cord clamping
- Avoid routine intubation if possible
- Stabilise with CPAP
- Avoid excess bag & mask ventilation
- Avoid too long with a face mask
- Avoid hypothermia

During the first minute of DCC what do we do with baby?

Effect of tactile stimulation

RCT 44 infants 27-32 weeks. Repetitive tactile stimulation vs. standard stimulation

Table 3
Effect of tactile stimulation on breathing effort.

	Standard stimulation (n = 23)	Repetitive stimulation (n = 21)	P-value
Minute volume at 1–4 min after birth (ml/kg)[a]	51.5 (5.3–114.2)	69.2 (11.5–153.9)	0.439
Minute volume at 1–7 min after birth (ml/kg)[a]	89.6 (21.4–141.7)	110.5 (42.3–166.8)	0.324
Tidal volume at 1–4 min after birth (ml/kg)[a]	2.7 (1.0–5.7)	3.6 (1.7–6.3)	0.131
Tidal volume at 1–7 min after birth (ml/kg)[a]	2.9 (1.3–5.4)	3.7 (2.1–5.9)	0.134
Rate of rise to maximum tidal volumes at 1–4 min after birth (ml/kg/sec)[a]	7.4 (3.7–13.6)	10.3 (4.5–19.3)	0.213
Rate of rise to maximum tidal volumes at 1–7 min after birth (ml/kg/sec)[a]	8.4 (4.5–14.1)	10.8 (6.0–17.5)	0.219
Respiratory rate/min at 1–4 min after birth[a]	23 (7–36)	24 (8–45)	0.795
Respiratory rate/min at 1–7 min after birth[a]	32 ± 19	35 ± 19	0.627
Oxygen saturation (%)[b]	81.7 ± 8.7	87.6 ± 3.3	0.007
Pulse rate [b]	143 (133–150)	138 (133–151)	0.581
Percentage of tidal volumes > 4 ml/kg (%)[b]	39.7 ± 21.2	47.1 ± 25.0	0.315
Percentage of tidal volumes > 8 ml/kg (%)[b]	5.0 (2.0–14.0)	6.0 (1.5–22.5)	0.673
Time of mask ventilation (sec)[b]	35 (13–131)	16 (0–118)	0.231
Maximum FiO_2 during resuscitation (%)[b]	93.4 (48.9–99.9)	62.0 (35.3–99.3)	0.110
Time at which infant is transported to NICU (min:sec)[b]	15:06 (10:34–19:09)	12:32 (9:24–16:21)	0.258
FiO_2 at start of transport to the NICU (%)[b]	33.6 (29.4–44.1)	28.2 (22.8–35)	0.036
Caffeine administered during stabilization at birth (%)[d]	9/23 (39.1)	2/21 (9.5)	0.036
Time after birth of caffeine administration (minutes)[c]	6:32 (5:25–7:46)	6:00 (4:10–6:00)	0.661
Respiratory support after birth (% CPAP only)[d]	5/23 (21.7)	10/21 (47.6)	0.112
Intraventricular haemorrhage ≥ grade 3[d]	0/23 (0%)	1/21 (5%)	0.477
Surfactant administration at NICU[d]	4/23 (17%)	5/21 (24%)	0.716

Data is presented as median (IQR) or mean ± SD of the raw data; *p*-values are presented of the linear mixed model (a). Data is presented as median (IQR) or mean ± SD of the raw data; *p*-values are presented of the two-way factorial ANOVA (b). Data is presented as n (%) of the raw data, *p*-values are presented of the two-way factorial ANOVA (c). Data is presented as n (%) of categorical data, *p*-values are presented of the Fisher's exact test (d).

Dekker J et al. Resuscitation 2018

RCT of resuscitation with Cord Intact

8 centre UK pilot study to assess feasibility of resuscitating babies < 32 weeks with cord intact

Table 2 Neonatal care and newborn life support at birth

	Clamp ≥2 min+neonatal care with cord intact (n=135)			Clamp ≤20 s+neonatal care after clamping (n=134)		
	Beside mother	Away from mother	Total	Beside mother	Away from mother	Total
Baby in plastic bag/sheet	100*	15	115 (85%)	41*	67	108 (81%)
Mask ventilation	68	32	100 (74%)	14	89	105† (78%)
Supplemental oxygen	46	38	84 (62%)	9	79	89‡ (66%)
Airway suction	39	36	75 (56%)	10	76	87‡ (65%)
Successful intubation	38	40	78 (58%)	10	77	87 (65%)
Surfactant	28	39	67 (50%)	9	66	75 (56%)
Attempted, unsuccessful intubation	20	15	35 (26%)	5	33	38 (28%)
Continuous positive airway pressure	27	17	44 (33%)	–	34	34 (25%)
Cardiac massage	3	3	6 (4%)	3	7	10 (7%)
Umbilical venous catheterisation	1	2	3 (2%)	–	6	6 (4%)
Other	–	1§	1 (1%)	–	–	–

*Placed in plastic bag beside mother, received all other care at roomside; n=14 clamp ≥2 min, n=26 clamp ≤20 s.
†Location not known for two.
‡Location not known for one.
§Packed cell transfusion.

Duley L, *et al*. *Arch Dis Child Fetal Neonatal Ed* 2018;**103**:F6–F14. doi:10.1136/archdischild-2016-312567

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But do they need this…….. ?

But do they really need all this in the first minutes……?

Crying and breathing by new-born infants after early or delayed cord clamping

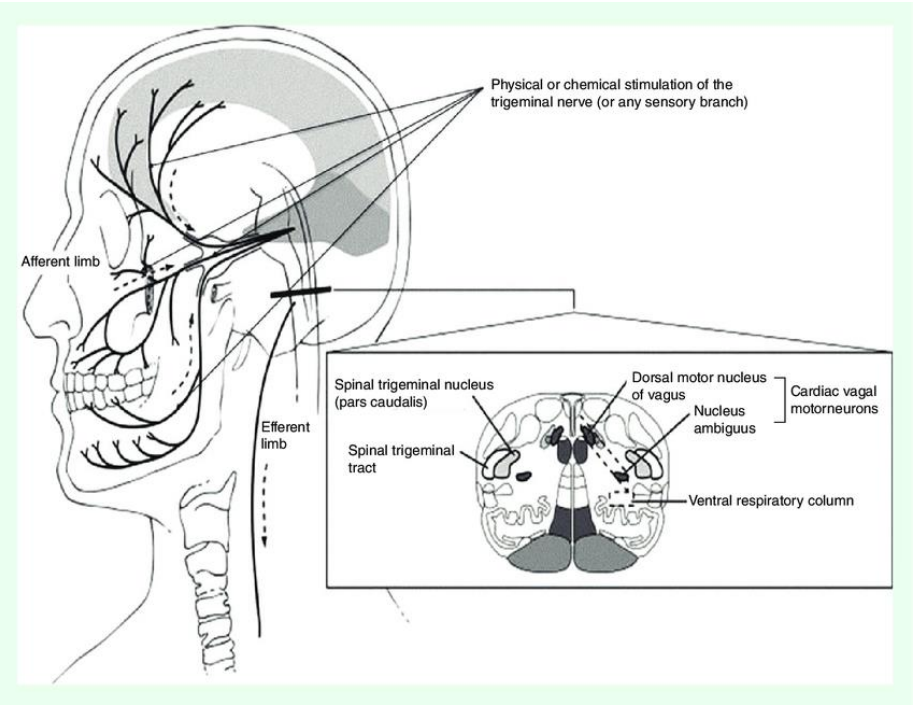
Observation of videos from RCT of early vs. delayed cord clamping

n (%)	Cried	Breathed	Neither breathed nor cried
Arrival ≤60 s			
Total, n=18	10 (56)	16 (89)	2 (11%)
Arrival >60 s			
Total, n=62	47 (76)	57 (92)	5 (8%)

Murphy MC Arch Dis Child 2020

Could applying face mask for CPAP/Ventilation potentially cause problems?

- Applying a mask on the face for respiratory support could induce a trigeminocardiac reflex leading to apnoea and bradycardia.



Available online at www.sciencedirect.com

Resuscitation

journal homepage: www.elsevier.com/locate/resuscitation

Clinical paper

The effect of a face mask for respiratory support on breathing in preterm infants at birth

Kristel L.A.M. Kuypers[a,*], *Tereza Lamberska*[b], *Tessa Martherus*[a], *Janneke Dekker*[a], *Stefan Böhringer*[c], *Stuart B. Hooper*[d,e], *Richard Plavka*[b], *Arjan B. te Pas*[a]

Table 2 – Breathing before and after face mask application.

Outcome	Signs of breathing before face mask (n = 368)	No signs of breathing before face mask (n = 61)	p-Value
Thorax excursions after face mask, n (%)			<0.001*
• Visible (continued breathing)	171 (46)	0 (0)	
• Not visible (stopped breathing[a])	197 (54)	61 (100)	
PPV is given, n (%)	183 (50)	57 (93)	<0.001*

PPV – positive pressure ventilation.

* Chi-square test.

[a] stopped breathing includes also infants with only visible thorax excursions during SI.

Resuscitation 2019

Alternative CPAP strategies already in use

Benvenista Valve CPAP

Benveniste Valve

R-PAP

Corsad Trial (Open trial of R-PAP vs. Mask)

- 246 liveborn infants
- New system: 127 infants | Old system: 123 infants
    - Mean (SD) age: 26 (1.3) weeks
- Infants intubated or died in the delivery room
    - New support system: 33% vs. Standard system: 45%
    - Adjusted Odds Ratio 0.53 (95% CI, 0.30 to 0.94); P=0.03
- There were no differences in 2^0 outcomes or safety variables

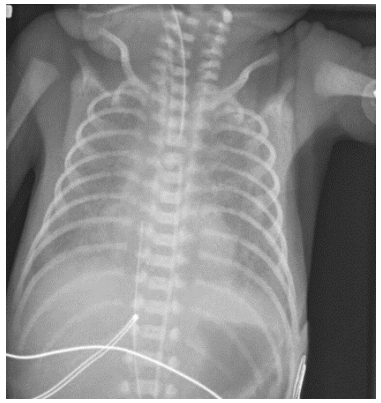
JAMA Paediatrics 2021

Delivery Room Stabilisation – Recommendations

- Delay clamping the umbilical cord for at least 60s (A1). Only if DCC not feasible , consider umbilical cord milking as an alternative when GA> 28 weeks (B2)
- T-piece should be used rather than bag and mask (B1)
- Spontaneously breathing preterm infants should be stabilised using CPAP (A1). If apnoeic give lung inflations. Start with pressure 6/20-25 cm H_2O (D2)
- Oxygen should be controlled using a blender. Use initial FiO_2 of 0.30 for babies < 28 wks' and 0.21 – 0.30 for those 28–31 wks, 0.21 for 32 wks' and above. FiO_2 adjustments up or down should be guided by pulse oximetry (B2). SpO_2 of 80% and HR >100 should be achieved within 5 mins (C2).
- Intubation should be reserved for babies not responding to positive pressure ventilation via face mask or nasal prongs (A1).
- Plastic bags or occlusive wrapping under radiant warmers and humidified gas should be used during stabilisation for babies < 28 weeks' gestation to reduce the risk of hypothermia: Hyperthermia should also be avoided (A1).

Surfactant Therapy - Considerations

- Which surfactant?
- Method of administration?
  - LISA vs. INSURE
  - Laryngeal mask?
  - Nebulisation
- Timing of administration?
  - ?prophylaxis for some
  - Ways to decide if surfactant is needed
  - Role of lung ultrasound
- Repeat dosing



Should we be thinking about surfactant prophylaxis for some babies….. ?

Evolution of RDS Guidelines – Surfactant Prophylaxis

2007

2. Prophylaxis (within 15 min of birth) should be given to almost all babies under 27 weeks' gestation. Prophylaxis should be considered for babies over 26 weeks but <30 weeks' gestation if intubation is required in the delivery suite or if the mother has not received prenatal corticosteroids (**A**).

2010

(2) Prophylaxis (within 15 min of birth) should be given to almost all babies of <26 weeks' gestation. Prophylaxis should also be given to all preterm babies with RDS who require intubation for stabilisation (A).

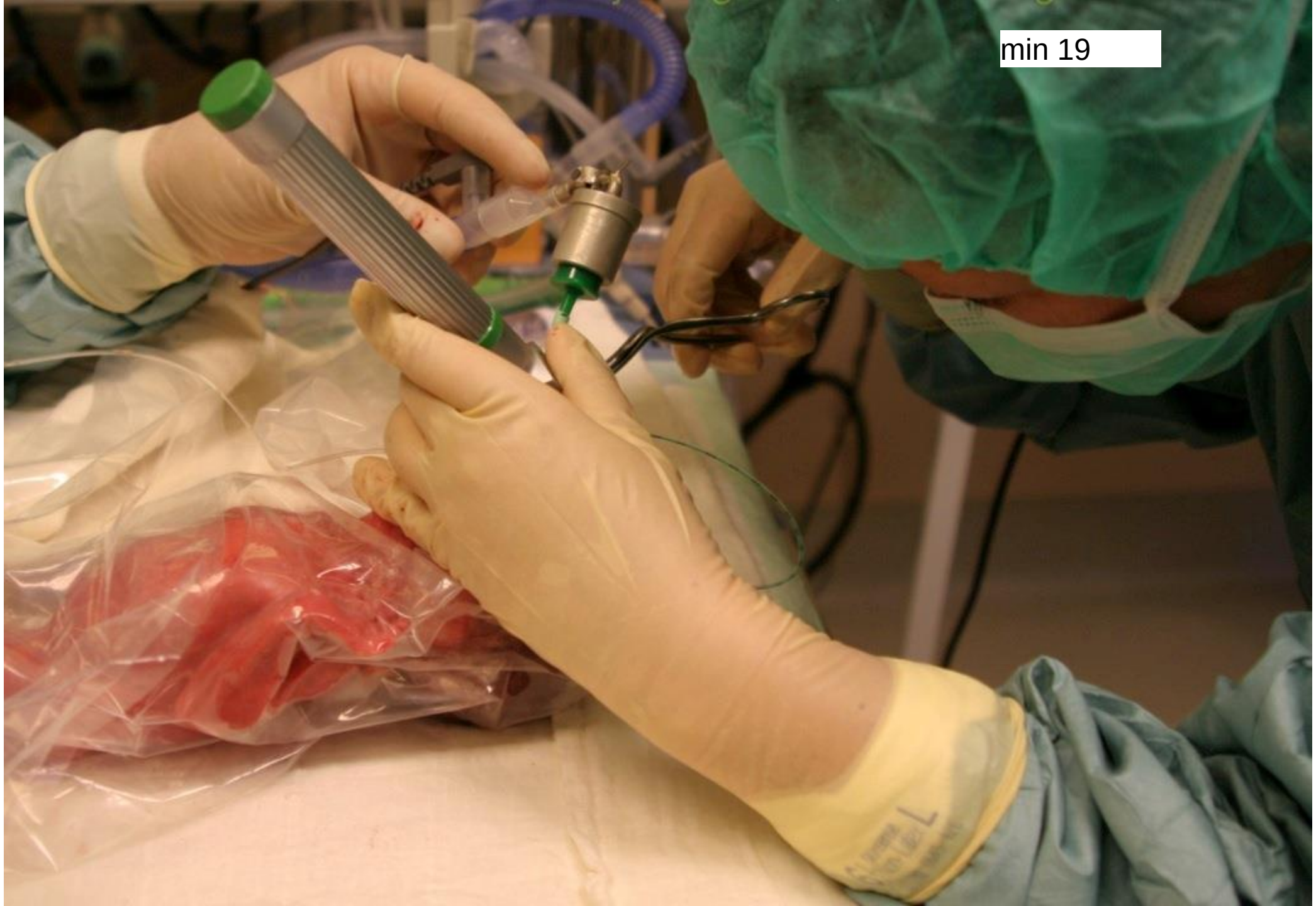
2013

(2) A policy of early rescue surfactant should be standard but there are occasions when surfactant should be administered in the delivery suite, such as extremely preterm infants in whom the mother has not had antenatal steroids or those who require intubation for stabilization (A).

2016

2 A policy of early rescue surfactant should be standard (A1) but there are occasions when surfactant should be administered in the delivery suite, such as those who require intubation for stabilization (B1).

But….. The studies included in these RCTs weren't using LISA surfactant administration


min 19

Association of Administration of Surfactant Using Less Invasive Methods With Outcomes in Extremely Preterm Infants Less Than 27 Weeks of Gestation

Christoph Härtel, MD,[1] Egbert Herting, MD, PhD,[2] Alexander Humberg, MD,[2] Kathrin Hanke, MD,[2] Katrin Mehler, MD,[3] Titus Keller, MD,[3] Isabell Mauer, MD,[1] Eric Frieauff, MD,[1] Sascha Meyer, MD,[4] Ulrich H. Thome, MD,[5] Christian Wieg, MD,[6] Susanne Schmidtke, MD,[7] Angela Kribs, MD,[3] and Wolfgang Göpel, MD[2], for the German Neonatal Network

Short-term Outcomes Among Infants According to LISA Exposure[a]

Outcome	Infants receiving LISA (n = 2534)		Infants not receiving LISA				*P* value, LISA vs no LISA
	No. (%)	95% CI	No surfactant (n = 476)		ETT surfactant (n = 3532)		
			No. (%)	95% CI	No. (%)	95% CI	
Pneumothorax	126 (5.0)	4.2-5.9	6 (1.3)	1.0-2.5	306 (8.7)	8.1-9.8	<.001
Death in hospital, all cause	178 (7.0)	6.1-8.1	31 (6.5)	4.8-8.6	402 (11.4)	10.1-12.7	<.001
BPD	796 (31.4)	29.6-33.3	104 (21.8)	17.5-26.1	1578 (44.7)	43.2-46.2	<.001
BPD or death	944 (37.3)	35.4-39.2	130 (27.3)	23.6-31.1	1907 (54.0)	52.1-56.2	<.001
ICH[b]							
Any	723 (28.5)	26.8-30.3	75 (15.8)	13.0-18.7	1375 (39.0)	37.6-40.5	

Jama Network open 2022

INSURE – CPAP INtubate SURfactant Extubate

	INSURE (surf & CPAP)	RESCUE & VENT	P VALUE
N	355	329	
DEATH	1.5%	3.5%	0.84
Need for Vent	35%	55%	0.009
Use of surfactant	99%	61%	0.001
Airleak	4%	8%	0.03
BPD 28 days	7.5%	15%	0.04

Stevens and Blennow Cochrane 2007

Cochrane Library

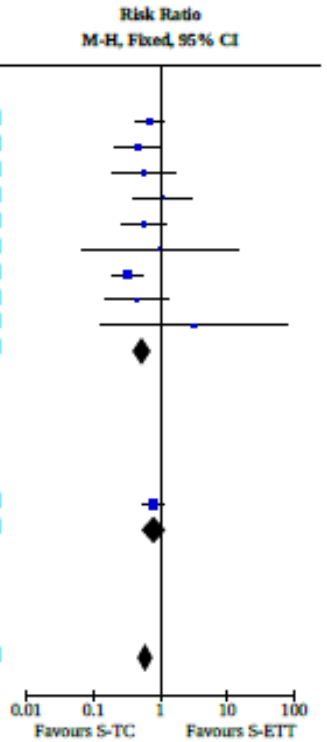
Cochrane Database of Systematic Reviews

Surfactant therapy via thin catheter in preterm infants with or at risk of respiratory distress syndrome (Review)

Abdel-Latif ME, Davis PG, Wheeler KI, De Paoli AG, Dargaville PA

Analysis 1.1. Comparison 1: Trials comparing S-TC with S-ETT - overall analysis, Outcome 1: Death or BPD

Study or Subgroup	Surfactant via catheter Events	Total	Surfactant via ETT Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 S-TC vs INSURE						
Kanmaz 2013	22	100	32	100	18.2%	0.69 [0.43 , 1.10]
Mirnia 2013a	7	66	16	70	8.8%	0.46 [0.20 , 1.06]
Mohammadizadeh 2015	4	19	7	19	4.0%	0.57 [0.20 , 1.63]
Bao 2015	7	47	6	43	3.6%	1.07 [0.39 , 2.93]
Choupani 2018	8	52	14	52	8.0%	0.57 [0.26 , 1.25]
Boskabadi 2019	1	20	1	20	0.6%	1.00 [0.07 , 14.90]
Jena 2019	15	175	47	175	26.7%	0.32 [0.19 , 0.55]
Gupta 2020	4	29	9	29	5.1%	0.44 [0.15 , 1.28]
Yang 2020	1	47	0	50	0.3%	3.19 [0.13 , 76.36]
Subtotal (95% CI)		**555**		**558**	**75.2%**	**0.52 [0.40 , 0.68]**
Total events:	69		132			
Heterogeneity: Chi² = 8.13, df = 8 (P = 0.42); I² = 2%						
Test for overall effect: Z = 4.81 (P < 0.00001)						
1.1.2 S-TC vs surfactant via ETT with delayed extubation						
Kribs 2015	35	107	43	104	24.8%	0.79 [0.55 , 1.13]
Subtotal (95% CI)		**107**		**104**	**24.8%**	**0.79 [0.55 , 1.13]**
Total events:	35		43			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.29 (P = 0.20)						
Total (95% CI)		**662**		**662**	**100.0%**	**0.59 [0.48 , 0.73]**
Total events:	104		175			
Heterogeneity: Chi² = 11.12, df = 9 (P = 0.27); I² = 19%						
Test for overall effect: Z = 4.86 (P < 0.00001)						
Test for subgroup differences: Chi² = 3.31, df = 1 (P = 0.07), I² = 69.8%						



Cochrane 2021

Laryngeal mask surfactant

100 infants 28 - 35 weeks gestation, >1250 grams and <36 hours old requiring 0.30-0.40 oxygen on CPAP were randomized to:

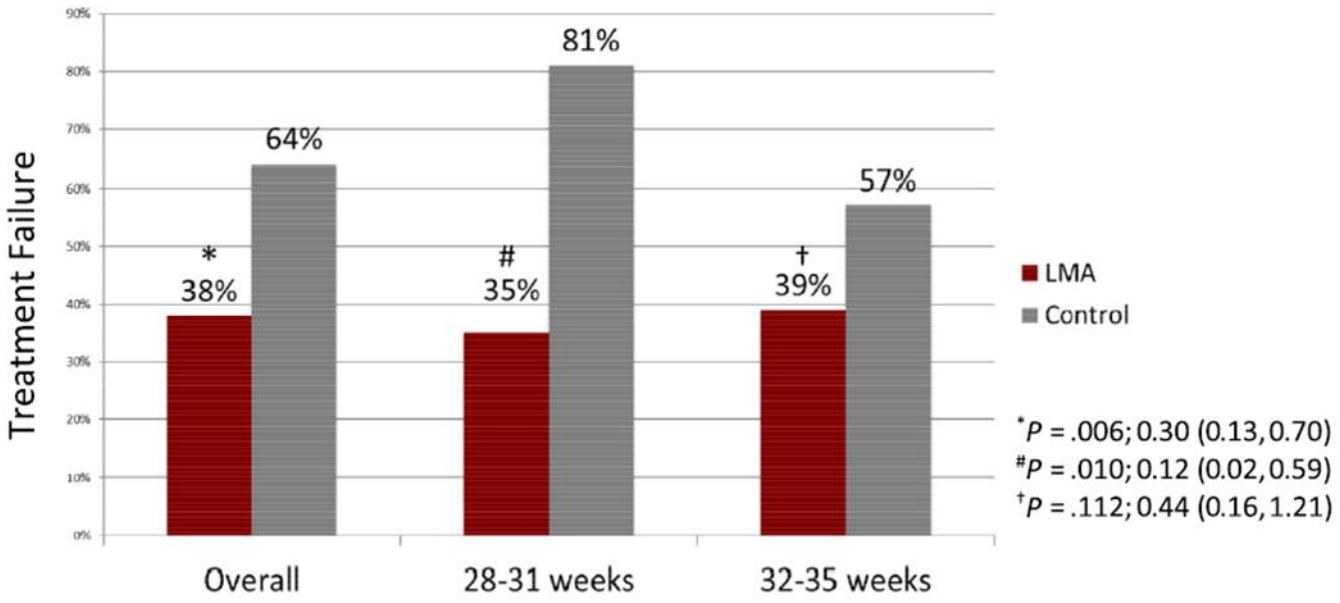
- LMA Surfactant then continue CPAP
- Just continue CPAP

Curosurf 200 mg/kg was administered in 2 ml aliquots. After each aliquot 2 min of hand bag ventilation was performed.
After the procedure the infant was put back on CPAP 6 cm H_2O

Variables	Total (n = 103)	LMA (n = 50)	Control (n = 53)
Birth weight, mean (SD) (range), g	1982 (492) (1250-3305)	1968 (506) (1250-3180)	1995 (483) (1254-3305)
Gestational age, mean (SD) (range), wk	32 5/7 (1 6/7) (28 5/7-35 6/7)	32 5/7 (1 6/7) (29 3/7-35 6/7)	32 6/7 (1 6/7) (28 5/7-35 6/7)
Gestational age 32 0/7-35 6/7 wk, n (%)	70 (68)	33 (66)	37 (70)

Roberts et al, J Pediatr. 2018 Feb;193:40-46.e1

Laryngeal Mask Airway for Surfactant Administration in Neonates: A Randomized, Controlled Trial.



FiO_2 <36%; *P* = .019, 0.25 (0.08, 0.80)
FiO_2 ≥36%; *P* = .103, 0.37 (0.11, 1.23)
Surfactant <6 hours of age; *P* = .012; 0.32 (0.13, 0.77)
Surfactant ≥6 hours of age; *P* = .075, 0.26 (0.06, 1.14)
p-value, OR (95% CI)

Roberts et al, J Pediatr. 2018 Feb;193:40-46.e1

When should we treat with surfactant if baby stable on CPAP?

Earlier versus later surfactant

Analysis 1.6. Comparison 1 Early versus delayed selective surfactant treatment, Outcome 6 CLD or death at 36 weeks' PMA.

Review: Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome

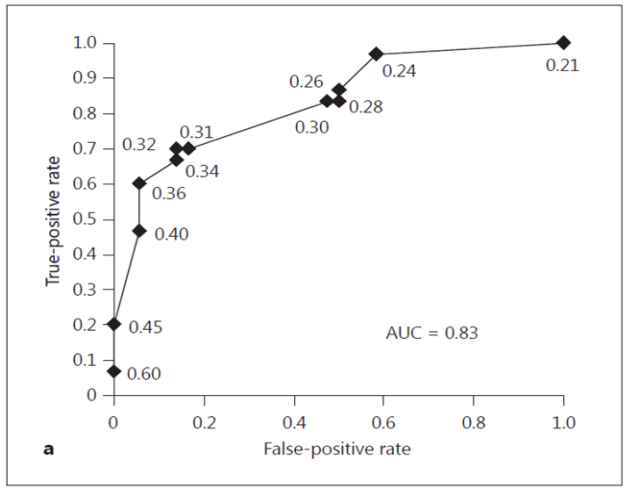
Comparison: 1 Early versus delayed selective surfactant treatment

Outcome: 6 CLD or death at 36 weeks' PMA

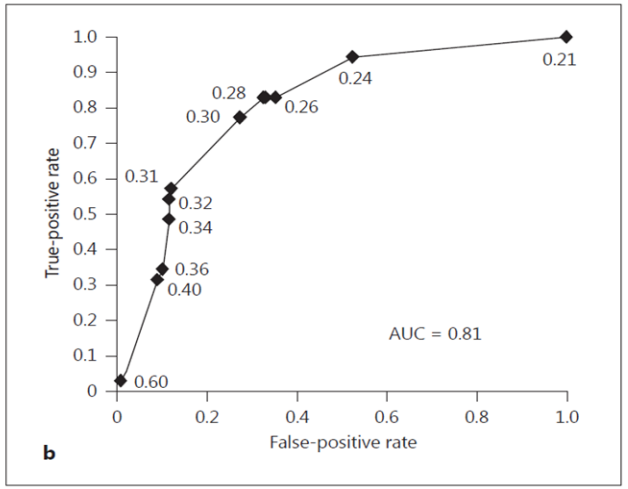
Study or subgroup	Early treatment n/N	Late treatment n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Synthetic surfactant					
OSIRIS 1992	429/1344	514/1346		94.8 %	0.84 [0.75, 0.93]
Subtotal (95% CI)	**1344**	**1346**		**94.8 %**	**0.84 [0.75, 0.93]**
Total events: 429 (Early treatment), 514 (Late treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.39 (P = 0.00069)					
2 Animal-derived surfactant					
Gortner 1998	12/154	15/163		2.7 %	0.85 [0.41, 1.75]
Plavka 2002	6/21	14/22		2.5 %	0.45 [0.21, 0.95]
Subtotal (95% CI)	**175**	**185**		**5.2 %**	**0.65 [0.39, 1.10]**
Total events: 18 (Early treatment), 29 (Late treatment)					
Heterogeneity: Chi^2 = 1.46, df = 1 (P = 0.23); I^2 =32%					
Test for overall effect: Z = 1.60 (P = 0.11)					
Total (95% CI)	**1519**	**1531**		**100.0 %**	**0.83 [0.75, 0.91]**
Total events: 447 (Early treatment), 543 (Late treatment)					
Heterogeneity: Chi^2 = 2.62, df = 2 (P = 0.27); I^2 =24%					
Test for overall effect: Z = 3.68 (P = 0.00023)					
Test for subgroup differences: Chi^2 = 0.82, df = 1 (P = 0.37), I^2 =0.0%					

Badahue FL Cochrane 2012

CPAP failure may be predictable with $FiO_2 \geq 30\%$



Infants 25–28 weeks' gestation, 2 hrs post-birth



Infants 29–32 weeks' gestation, 6 hrs post birth

- CPAP failure can be predicted at:
  - $FiO_2 \geq 30\%$ at 2 hrs at 25-28 weeks' gestation
  - $FiO_2 \geq 30\%$ at 6 hrs at 29-32 weeks' gestation

AUC: Area Under Curve

Dargaville et al. Neonatology 2013; 104: 8-14

Also Gulczyńska E, Neonatology 2019

Clinical trials of surfactant therapy via thin catheter

All studies

Surfactant via thin catheter compared with…	**Gestation range (weeks)**	**FiO_2 entry threshold**
…continuation of CPAP		
• **Göpel** *Lancet* 2011;378:1627-34. (**N=220**)	26-28	0.30
• **Dargaville** *JAMA* 2021;326:2478-87. (**N=485**)	25-28	0.30
…surfactant via ETT		
• **Bao** *BMC Pediatr* 2015;15:21. (**N=90**)	28-32	0.30 (28-29 w); 0.35 (30-32) w
• **Boskabadi** *J Clin Neonatol* 2019;8:227-31. (**N=40**)	<32	0.40
• **Choupani** *Iranian Journal of Neonatology* 2018;9:33-40. (**N=104**)	28-37	0.40
• **Gupta** *Eur J Pediatr* 2020;179:1287–1293. (**N=58**)	28-34	None, FiO_2 0.45-0.50 at entry
• **Halim** *J College Physicians Surgeons Pakistan* 2019;29:226-230. (**N=100**)	<35	0.40
• **Han** *Front Pediatr* 2020;8:1-12. (**N=298**)	<32	0.40
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• **Kribs** *JAMA Pediatr* 2015;169:723-30. (**N=211**)	23-26.8	0.30
• **Mirnia** *Med J Islamic World Acad Sci* 2013;21:143-48. (**N=136**)	27-32	0.30
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• **Olivier** *Paediatrics Child Health* 2017;22:120-4. (**N=45**)	32-36	0.35
• **Yang** *Medicine (Baltimore)* 2020;99:e19216. (**N=97**)	32-36	0.40

Clinical trials of surfactant therapy via thin catheter

All infants in study <30 weeks' gestation

Surfactant via thin catheter compared with…	**Gestation range (weeks)**	**FiO_2 entry threshold**
…continuation of CPAP		
• **Göpel** *Lancet* 2011;378:1627-34. (**N=220**)	26-28	0.30
• **Dargaville** *JAMA* 2021;326:2478-87. (**N=485**)	25-28	0.30
…surfactant via ETT		
• **Bao** *BMC Pediatr* 2015;15:21. (**N=90**)	28-32	0.30 (28-29 w); 0.35 (30-32) w
• **Boskabadi** *J Clin Neonatol* 2019;8:227-31. (**N=40**)	<32	0.40
• **Choupani** *Iranian Journal of Neonatology* 2018;9:33-40. (**N=104**)	28-37	0.40
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Nonintubated Surfactant Application vs Conventional Therapy in Extremely Preterm Infants
A Randomized Clinical Trial

Angela Kribs, MD; Claudia Roll, MD; Wolfgang Göpel, MD; Christian Wieg, MD; Peter Groneck, MD; Reinhard Laux, MD; Norbert Teig, MD; Thomas Hoehn, MD; Wolfgang Böhm, MD; Lars Welzing, MD; Matthias Vochem, MD; Marc Hoppenz, MD; Christoph Bührer, MD; Katrin Mehler, MD; Hartmut Stützer, PhD; Jeremy Franklin, PhD; Andreas Stöhr, PhD; Egbert Herting, MD; Bernhard Roth, MD; for the NINSAPP Trial Investigators

- Preterm babies 23^{+0} to 26^{+6} weeks on CPAP $FiO_2 > 0.3$
- Randomised to LISA surfactant or ventilation with ET surfactant
- Ventilation mandated if $FiO_2 > 0.45$. PH < 7.15 or apnoeic
- Primary outcome death/BPD at 36 weeks
- Secondary outcome was survival without complications
  - BPD, IVH/PVL, NEC, ROP

JAMA Pediatr. 2015;169(8):723-730

NINSAPP Trial (LISA or vent at FiO_2 > 0.3)

Table 2. Primary Outcome and Predefined Secondary Outcomes

Characteristic	Group, No. (%)		Absolute Risk Reduction (95% CI)	*P* Value[a]
	Intervention (n = 107)	Control (n = 104)		
Survival without BPD[b]	72 (67.3)	61 (58.7)	8.6 (−5.0 to 21.9)	.20
Death	10 (9.3)	12 (11.5)	2.2 (−11.5 to 15.6)	.59
Surviving infants with BPD	25 (23.4)	31 (29.8)	7.9 (−6.6 to 22.1)	.19
Survival without major complications[c]	54 (50.5)	37 (35.6)	14.9 (1.4 to 28.2)	.02[a]
Mechanical ventilation[d]				
All infants	80 (74.8)	103 (99.0)[e]	24.3 (16.2 to 33.8)	<.001
Gestation, wk				
23	14/15 (93.3)	9/9 (100.0)	6.7 (−26.6 to 33.5)	>.99
24	24/26 (92.3)	30/31 (96.8)	4.5 (−9.9 to 22.3)	.59
25	24/31 (77.4)	41/41 (100.0)	22.6 (9.4 to 41.1)	.002
26	18/35 (51.4)	23/23 (100.0)	48.6 (30.3 to 66.0)	<.001

JAMA Pediatr. 2015;169(8):723-730

Effect of Minimally Invasive Surfactant Therapy vs Sham Treatment on Death or Bronchopulmonary Dysplasia in Preterm Infants With Respiratory Distress Syndrome

The OPTIMIST-A Randomized Clinical Trial

- Infants 25^{+0} to 28^{+6} weeks
- Infants were eligible if supported with a CPAP level of 5 cm H_2O to 8 cm H_2O and requiring FiO_2 of 0.30 or greater within the first 6 hours of life.
- Randomized to MIST or Sham procedure (Blinded)
- Both groups intubated if FiO_2 > 0.45 or greater
- The primary outcome was the composite of death or physiological BPD assessed at 36 weeks' postmenstrual age.

The OPTIMIST-A Randomized Clinical Trial. JAMA. 2021 Dec 28;326(24):2478-2487.

OPTIMIST – 485 babies

Table 2. Primary Outcome Analysis

	No./total (%)				
	Minimally invasive surfactant therapy	Control treatment	Risk difference, % (95% CI)[a]	Relative risk (95% CI)[a]	*P* value
Death or bronchopulmonary dysplasia[b]	105/241 (43.6)	121/244 (49.6)	−6.3 (−14.2 to 1.6)	0.87 (0.74 to 1.03)	.10
Death prior to 36 weeks' postmenstrual age	24/241 (10.0)	19/244 (7.8)	2.1 (−3.6 to 7.8)	1.27 (0.63 to 2.57)	.51
Bronchopulmonary dysplasia in survivors to 36 weeks' postmenstrual age[b]	81/217 (37.3)	102/225 (45.3)	−7.8 (−14.9 to −0.7)	0.83 (0.70 to 0.98)	.03

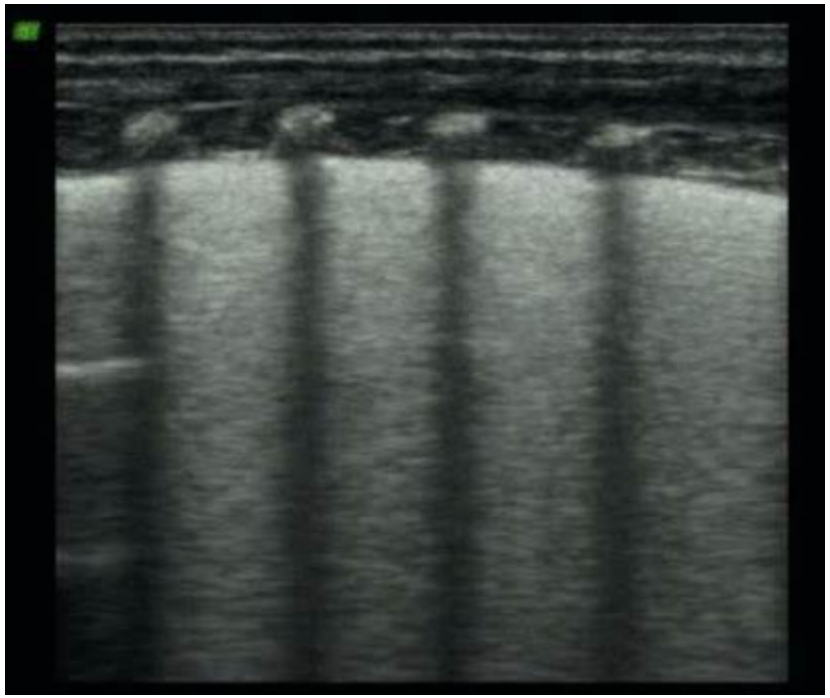
Table 3. Prespecified Key Clinical and Safety Outcomes

	No./total (%)				
Outcome[a]	Minimally invasive surfactant therapy	Control treatment	Risk difference, % (95% CI)[b]	Relative risk (95% CI)[b]	*P* value
Pneumothorax requiring drainage	11/241 (4.6)	25/244 (10.2)	−5.8 (−10.2 to −1.4)	0.44 (0.25 to 0.78)	.005
Need for intubation within 72 h of birth	88/241 (36.5)	176/244 (72.1)	−35.8 (−47.2 to −24.4)	0.50 (0.40 to 0.64)	<.001
Intraventricular hemorrhage grade III or IV	18/241 (7.5)	24/244 (9.8)	−2.4 (−6.3 to 1.5)	0.75 (0.48 to 1.19)	.23
Death or major morbidity during first hospitalization[c]	116/241 (48.1)	136/244 (55.7)	−7.9 (−18.6 to 2.7)	0.86 (0.70 to 1.05)	.14
Death during first hospitalization	28/241 (11.6)	20/244 (8.2)	3.3 (−2.2 to 8.9)	1.41 (0.73 to 2.69)	.30
Major morbidity during first hospitalization in survivors[c]	88/213 (41.3)	116/224 (51.8)	−10.3 (−20.8 to 0.2)	0.80 (0.64 to 1.00)	.05

The OPTIMIST-A Randomized Clinical Trial. JAMA. 2021 Dec 28;326(24):2478-2487.

RDS Prediction

- Bedside clinical test for surfactant in gastric aspirate
- Lung ultrasound – potentially identifies same population earlier
- Forced Oscillation technique



Surfactant Therapy - Recommendations

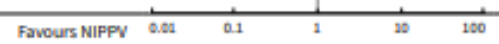
- If a preterm baby < 30 wk's requires intubation they should be given surfactant (**A2**)
- Babies needing treatment should be given an animal-derived surfactant (**A1**).
- LISA is the preferred method of surfactant administration for babies on CPAP (**A1**).
- Laryngeal mask surfactant may be used for more mature infants > 1.0 kg (**B2**)
- An initial dose of 200 mg/kg of poractant alfa is better than 100 mg/kg of poractant alfa or 100mg/kg beractant for rescue therapy (**A1**).
- Rescue surfactant should be given early in the course of the disease (**A1**). Suggested protocol would be to treat worsening babies with RDS when FiO_2 > 0.30 on CPAP pressure ≥ 6 cm H_2O or if lung ultrasound suggests RDS (**B2**).
- A 2nd and occasionally 3rd dose of surfactant should be given if there is ongoing evidence of RDS such as persistent high FiO_2 requirement and other problems have been excluded (**A1**).

Non Invasive Respiratory Support - Considerations

- CPAP, Hiflo, NIPPV, BIPAP – which mode is best?

Analysis 1.2. Comparison 1 NIPPV versus NCPAP to prevent extubation failure, Outcome 2 Endotracheal re-intubation.

Study or subgroup	NIPPV n/N	NCPAP n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Barrington 2001	3/27	3/27		1.17%	1[0.22,4.52]
Friedlich 1999	1/22	1/19		0.42%	0.86[0.06,12.89]
Gao 2010	6/25	15/25		5.84%	0.4[0.19,0.86]
Khalaf 2001	2/34	10/30		4.14%	0.18[0.04,0.74]
Khorana 2008	2/24	4/24		1.56%	0.5[0.1,2.48]
Kirpalani 2013	156/423	182/422		70.99%	0.86[0.72,1.01]
Moretti 2008	2/32	12/31		4.75%	0.16[0.04,0.66]
O'Brien 2012	22/67	29/69		11.13%	0.78[0.5,1.21]
Total (95% CI)	**654**	**647**		**100%**	**0.76[0.65,0.88]**
Total events: 194 (NIPPV), 256 (NCPAP)					
Heterogeneity: Tau^2=0; Chi^2=13.71, df=7(P=0.06); I^2=48.96%					
Test for overall effect: Z=3.7(P=0)					



Cochrane 2017

NIPPV resulted in lesser incidence of bronchopulmonary dysplasia or mortality when compared to CPAP (0.74 [0.52, 0.98]). Nasal injury was lesser with HFNC compared to CPAP (0.15 [0.01, 0.60]).

Ramaswamy 2020

Mechanical Ventilation Strategies - Considerations

- Which mode of ventilation is most lung protective
  - Volume targeting versus time cycled pressure limited
  - HFOV versus time cycled pressure limited
  - Newer modes
- Strategies for minimising ventilation
  - Caffeine
  - Permissive Hypercarbia
  - Use of postnatal steroids
  - Sedation

Caffeine for Apnoea of Prematurity Trial

2006 babies 500 – 1250g < 10 d old randomised to Caffeine or Placebo to treat apnoea or facilitate extubation. Outcome at 36 w

	Caffeine n = 963	Placebo n = 954	OR (95% CI)
Age extubated	29 wk (28-31)	30wk (29-32)	P < 0.001
Age off CPAP	30 wk (29-33)	31 wk (30 -34)	P < 0.001
Age off Oxygen	34 wk (31-37)	35 wk (32-38)	P < 0.001
BPD	36%	47%	0.63 (0.52– 0.76)
Steroids for BPD	14%	20%	P < 0.001

Schmidt – NEJM 2006; 354: 2112 - 2121

Thank You