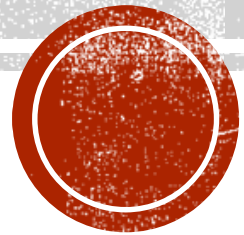
SURFACTANT

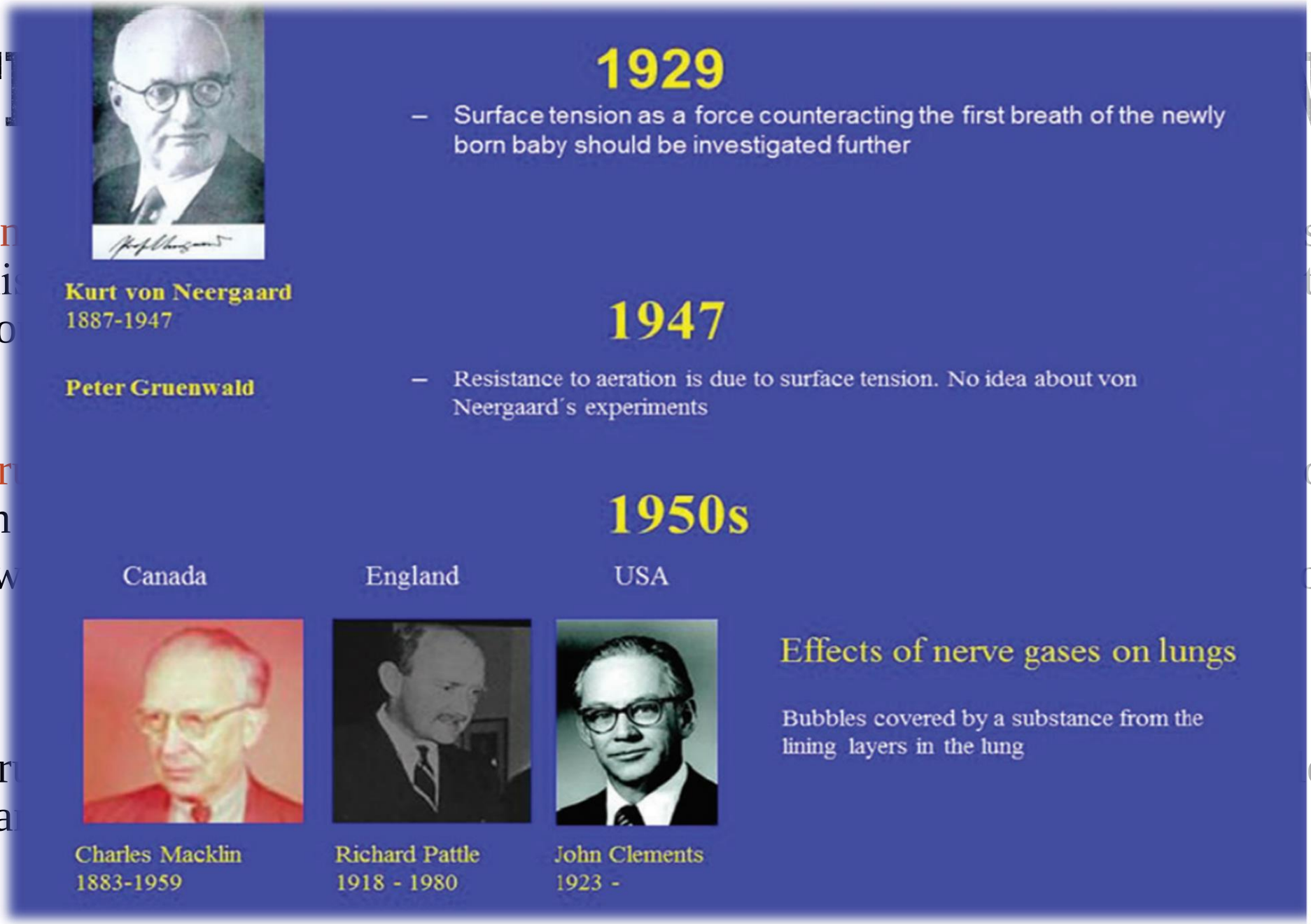


SCOPE

- History
- Life Cycle and composition
- Function of components
- Review of Evidence
  - Role of Surfactant in SDD
  - Surfactant vs CPAP
  - Early vs Delayed
  - Types of surfactant and comparative studies
  - Mode of Delivery-INSURE/InRecSure
  - LISA/MIST/LMA/Nebulization/Pharyngeal
  - Surfactant and Inhaled steroids
- Recommendation/Guidelines

T T

- Kurt von spiratory mechani the newly born sho
- Peter Gr of stillborn Gruenw ounteracts
- Peter Gr e in understa



1959

- Avery and Mead - HMD is associated with absence or late appearance of some substance which in normal subjects renders the surface capable of attaining a low surface tension when lung volume is decreased

7.08.1963

- 3rd child of president and Jackie kennedy was born at 35 weeks and died on day 2 of life due to HMD
- This event helped focus interest on RDS and within a year trials on synthetic surfactant began

1964-1968

- Ist trial on synthetic surfactant –Canada and Singapore- used nebulized DPPC – No Apparent benefit-Marshall Klaus

1969

- Graham Liggins- Obstetrician administered steroids [illegible] event preterm labour
- Found- immature lambs did not die soon after birth
- Published in 1972

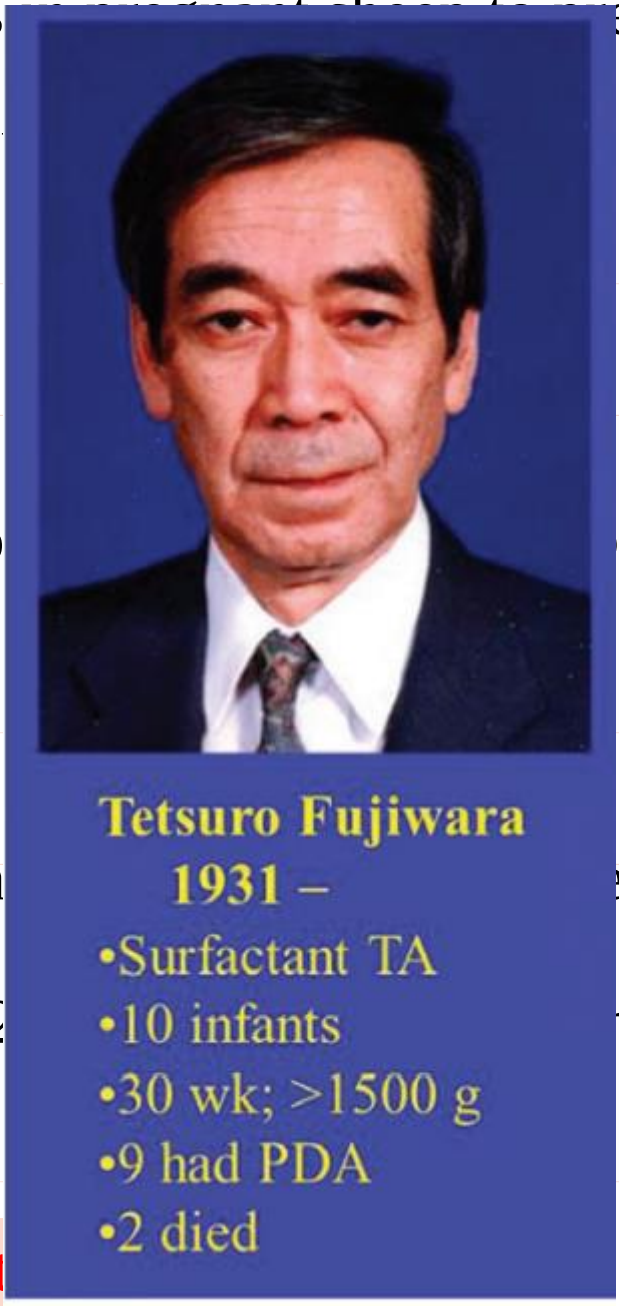
1972

- Goran Enhorning in Stockholm and Bengt Robertso [illegible] its with natural surfactant – did not die soon

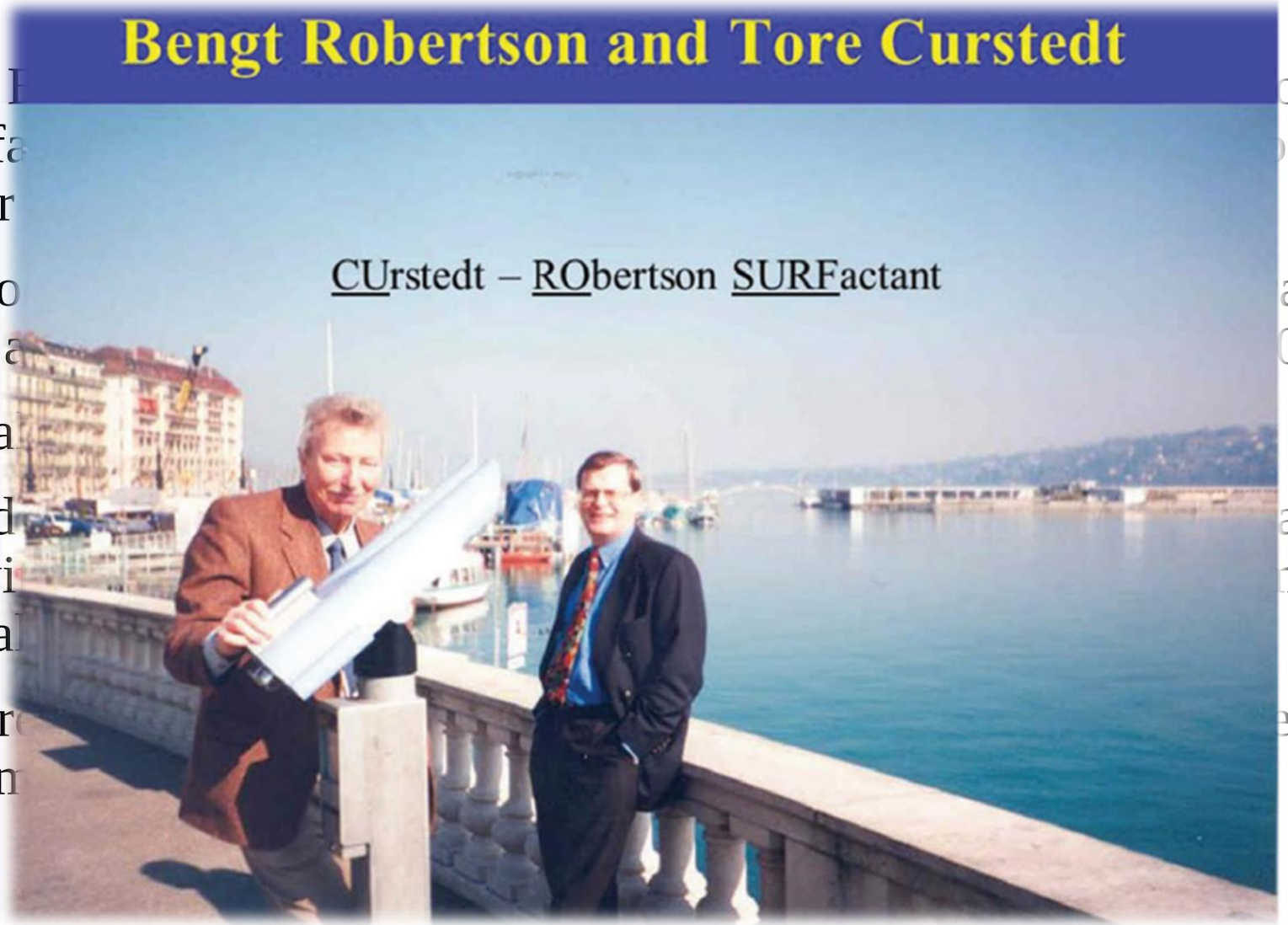
1980

- Tetsuro Fujiwara tested Surfactant TA in 10 preterm [illegible] ean gestational age of 30 weeks with BW >1500 gms
- Mean arterial oxygen tension increased from 45 to 2 [illegible] nest radiograph

This launched the first natural bovine derived surfact [illegible] for RDS in 1980

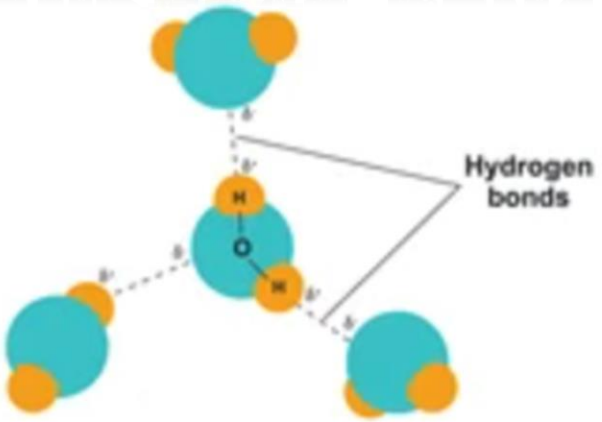


- Stockholm, … ogether produced a porcine surfa… ertson surfactant or Curosurf for…
- Unique - pro… aphy leaving only polar lipids a… 0 mg/mL
- First Clinica… a drug company.
- Randomised … age - 10 hours to treatment wi… nechanical ventilation a…
- Significant r… eath or bronchopuln…

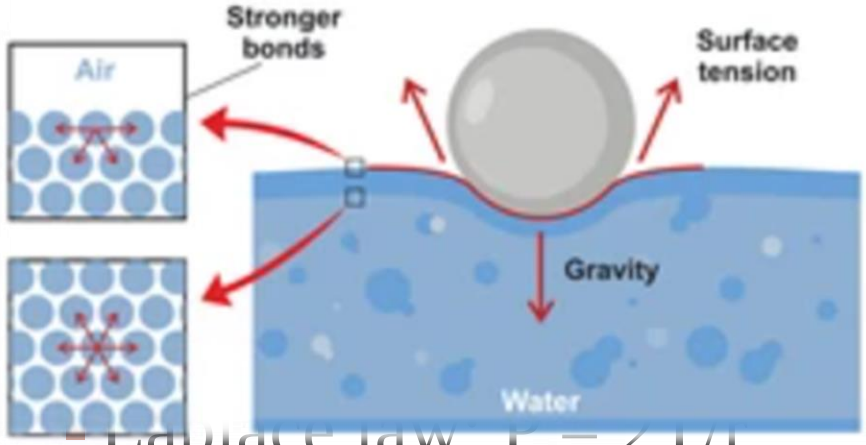


Collaborative European Multicenter Study Group. Surfactant replacement therapy for severe neonatal respiratory distress syndrome: An international randomized clinical trial. Pediatrics 1988

ND SURFACTANT

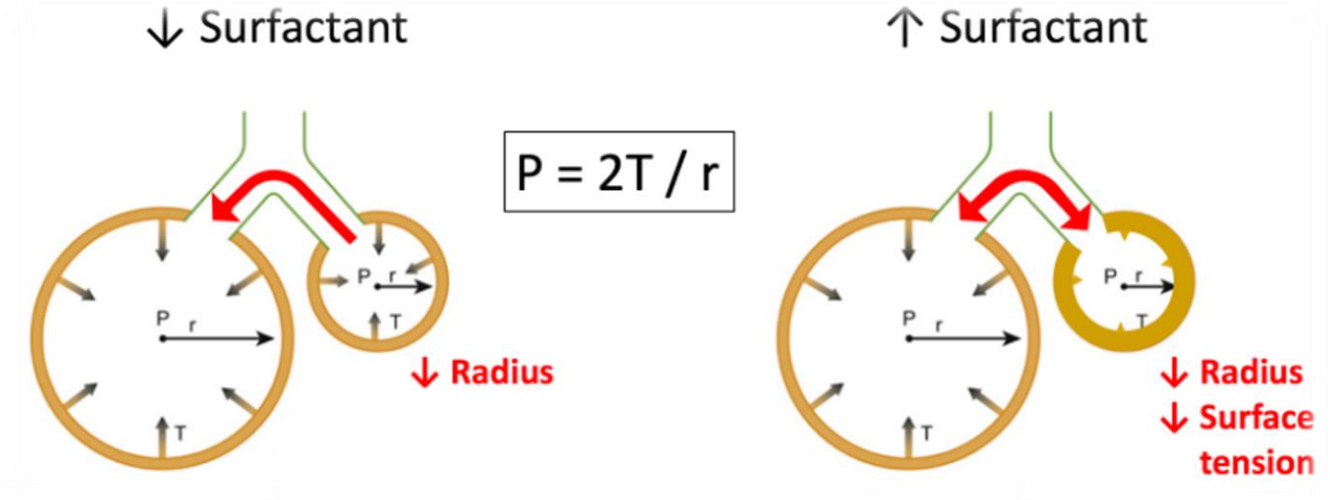


e between the attractive forces on molecules at an

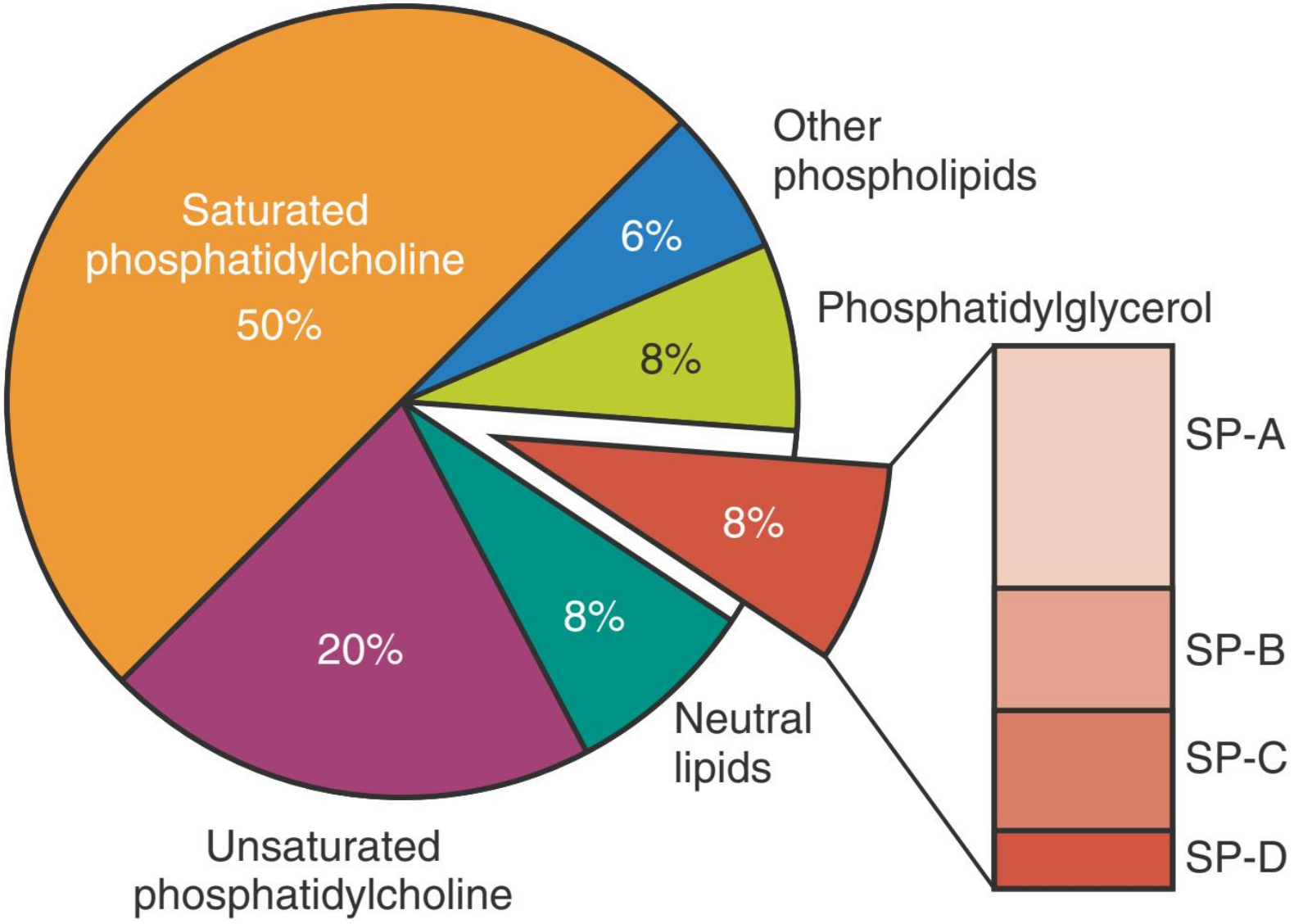


face film that resists expansion of the bubble and
act surface area.

- Laplace law, P = 2T/r



COMPOSITION



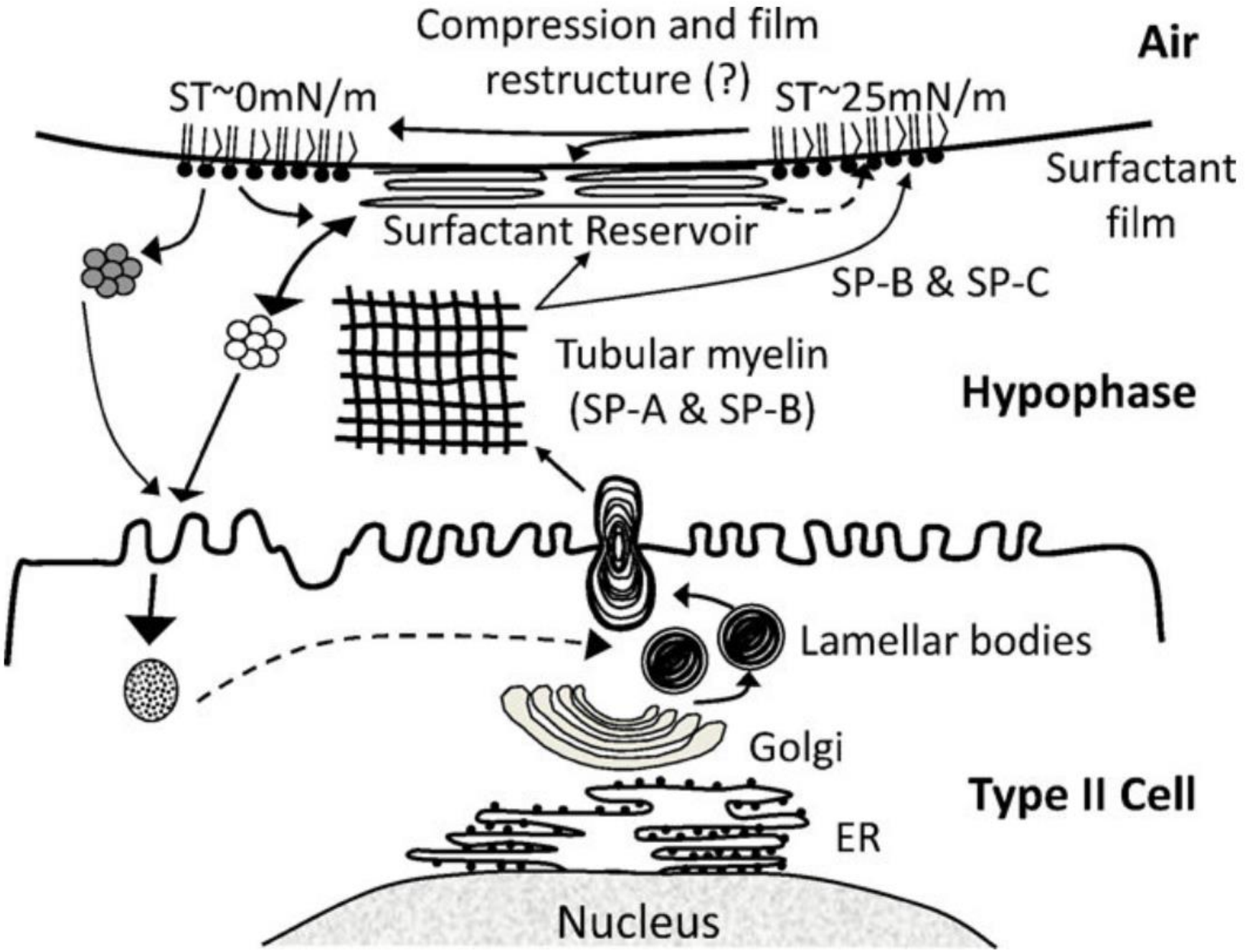
SURFACTANT PROTEINS

PROTEIN	STRUCTURE	FUNCTION
SP-A	• Water-soluble 36-kDa-collectin • Not critical to regulation of surfactant metabolism.	• Innate host defense protein/regulator of inflammation • Binds to multiple pathogens - GBS, Staph aureus, and HSV 1. • Facilitates phagocytosis by macrophages • Patients with a deficiency of SP-A have not been identified • Polymorphisms A/W with increased risk for RDS, BPD/ bronchiolitis.
SP-D	• 43 kDa - collectin with structural similarities to SP-A. • Immune function	• Innate host defense molecule by binding pathogens and facilitating their clearance. • Animal studies- decreased the ventilator-mediated inflammation. • SP-D deficiency in neonates has not been described.

SP-B	• Small hydrophobic proteins • 2%-4% to the surfactant mass. • 8-kDa protein before it enters lamellar bodies for co-secretion with the phospholipids	• Facilitates **surface adsorption of lipids** • Genetic absence - lethal respiratory failure
SP-C	• Hydrophobic 4-kDa protein • Responsible for progressive interstitial lung disease and emphysema later in life.	• Work cooperatively with SP B to optimize rapid adsorption and spreading of phospholipids on a surface and reduce Surface tension.

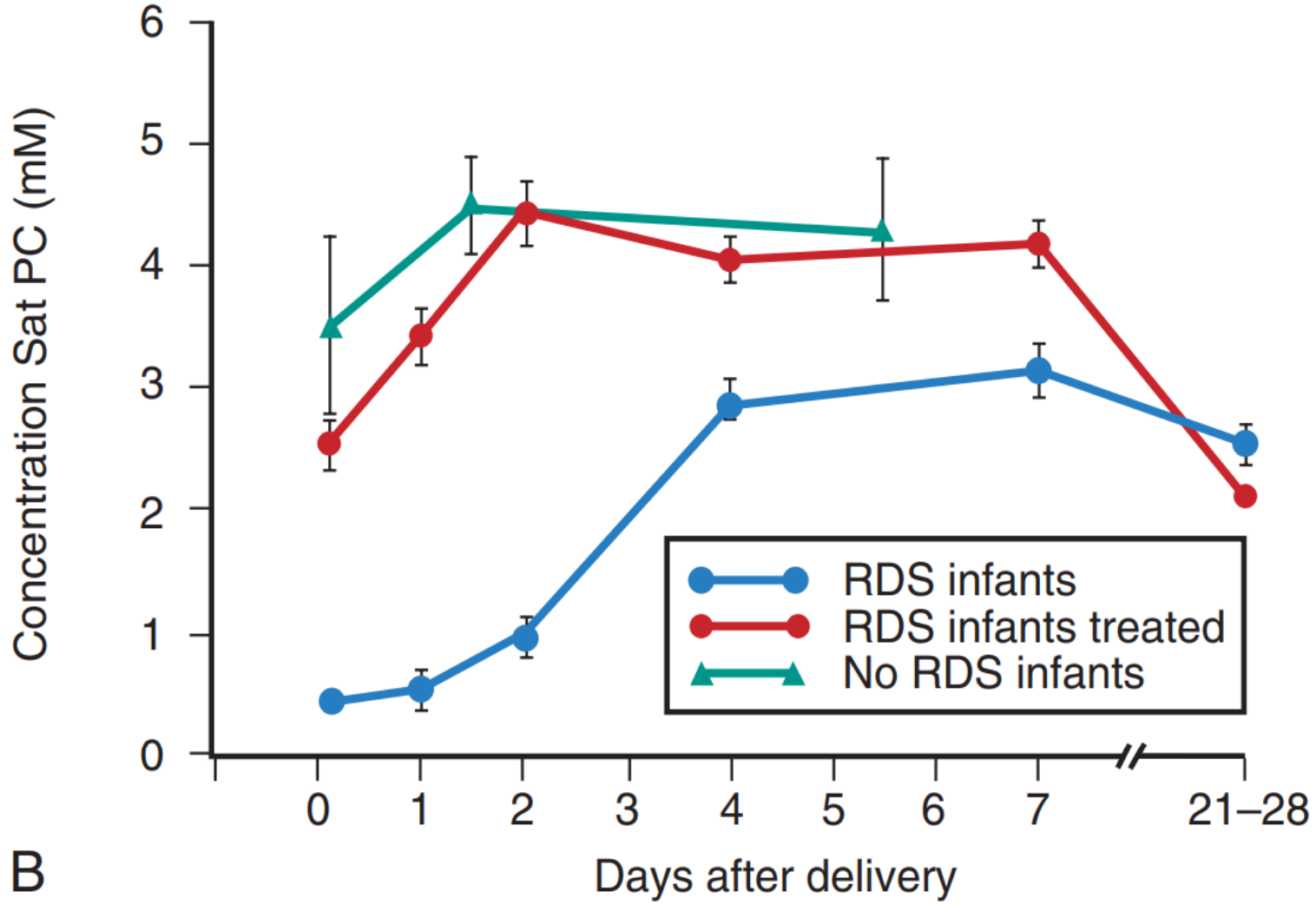
SYNTHESIS AND SECRETION

- Specific enzymes within the ER use glucose, phosphate, and fatty acids as substrates for phospholipid synthesis
- Assembled and stored in the lamellar bodies, (concentric) →extruded into the fluid layer lining the alveoli by exocytosis
- Unravel into Tubular myelin
- Hydrophobic fatty acyl groups of the phospholipids extend into the air, whereas the hydrophilic polar head groups bind water
- New surfactant enters the surface film and “used” surfactant leaves in the form of small vesicles, which is cleared from the airspaces
-


Compression and film
restructure (?)
Air
ST~0mN/m
ST~25mN/m
Surfactant
film
Surfactant Reservoir
SP-B & SP-C
Tubular myelin
(SP-A & SP-B)
Hypophase
Lamellar bodies
Golgi
Type II Cell
ER
Nucleus

SURFACTANT POOL SIZE

- Increasing surfactant pool size – better is the compliance of lung
- Term newborn animals: 100 mg/kg
- Very preterm with severe RDS: <5 mg/kg
- Adult: 4 mg/kg
- Preterm have 5% of amount of surfactant in term


Concentration Sat PC (mM)
6
5
4
3
2
1
0
0
1
2
3
4
5
6
7
21–28
Days after delivery
RDS infants
RDS infants treated
No RDS infants
B

REVIEW OF EVIDENCE

- Role of Surfactant in SDD
- Surfactant vs CPAP
- Early vs Delayed
- Types of surfactant and comparative studies
- Mode of Delivery-INSURE/InRecSure
- LISA/MIST/LMA/Nebulization/Pharyngeal
- Surfactant and Inhaled steroids

- **Proph**

Within 1

- Brie g in
  alve ators
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Mar ffect

- **Hyp** ne
  effe
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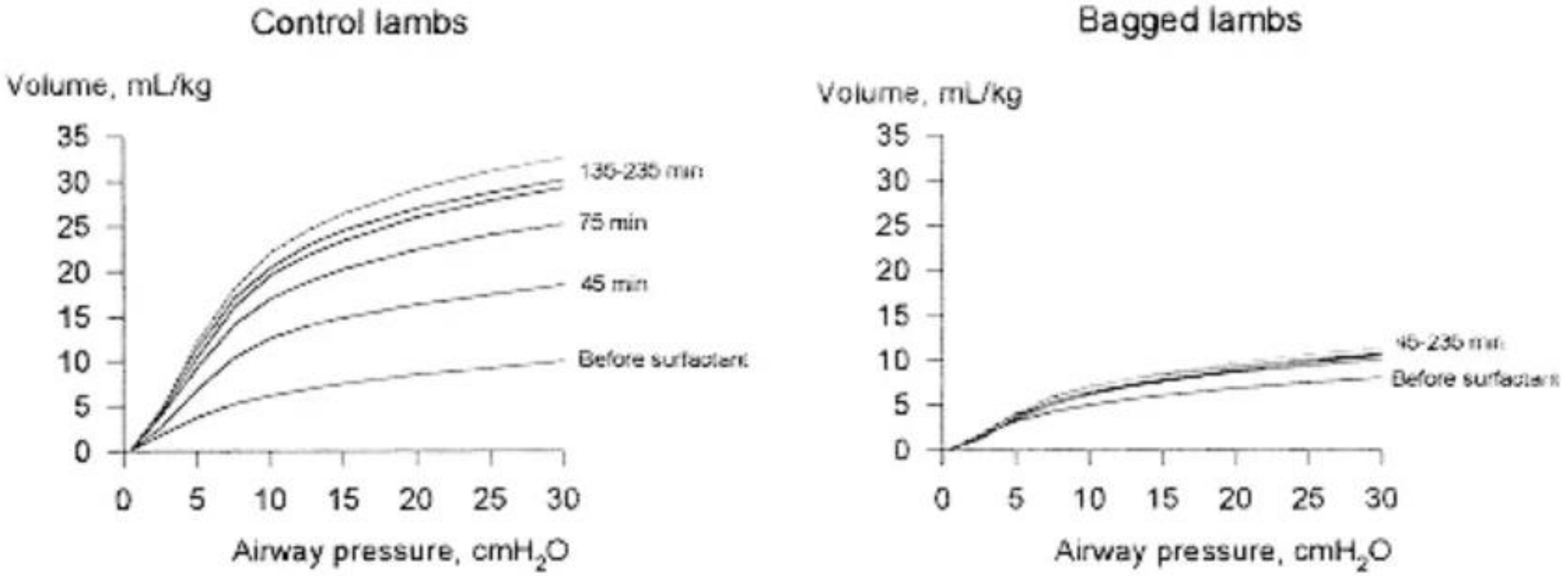
  befo
- **Outcome**: Lung mechanics(Expiratory P-V curves),Histology of lung, Response to Surfactant

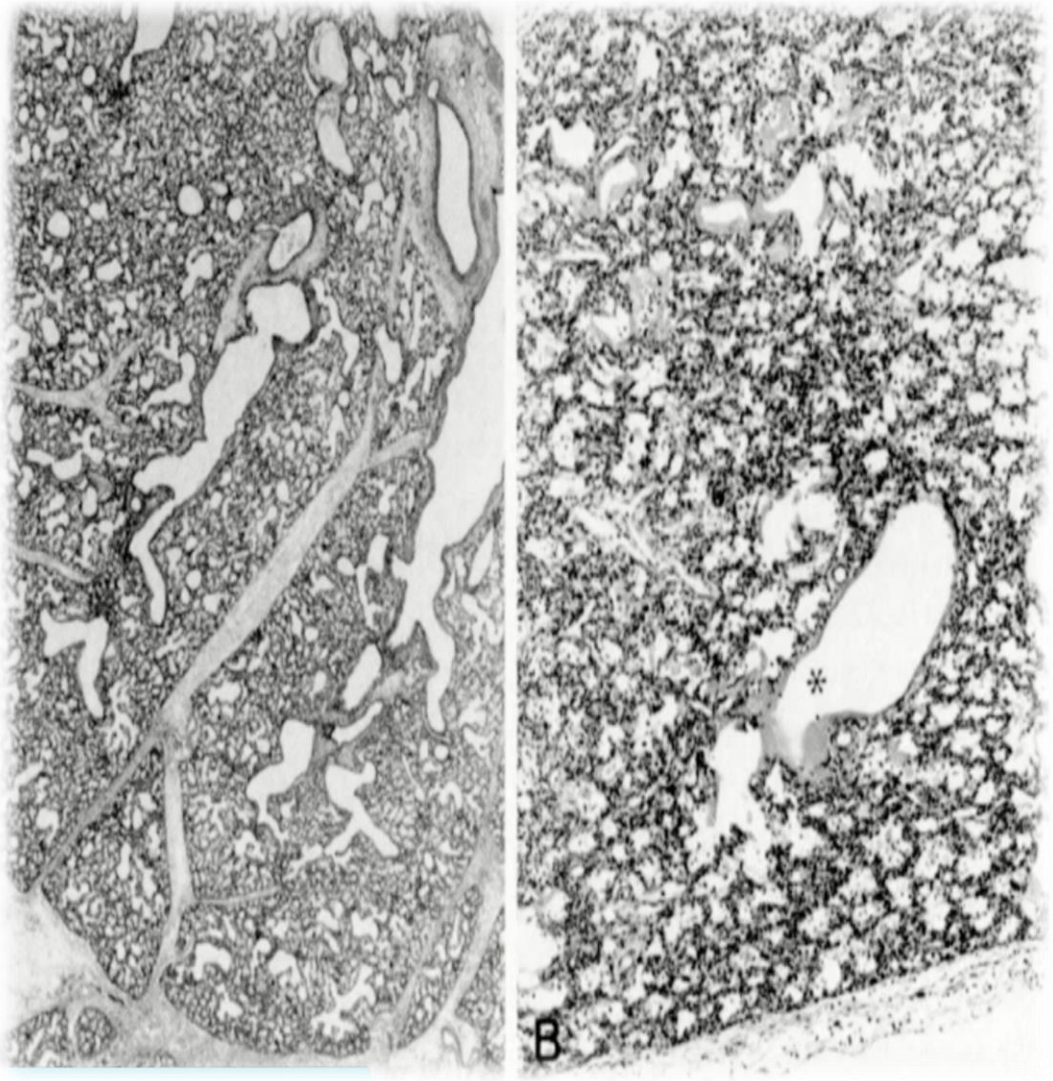


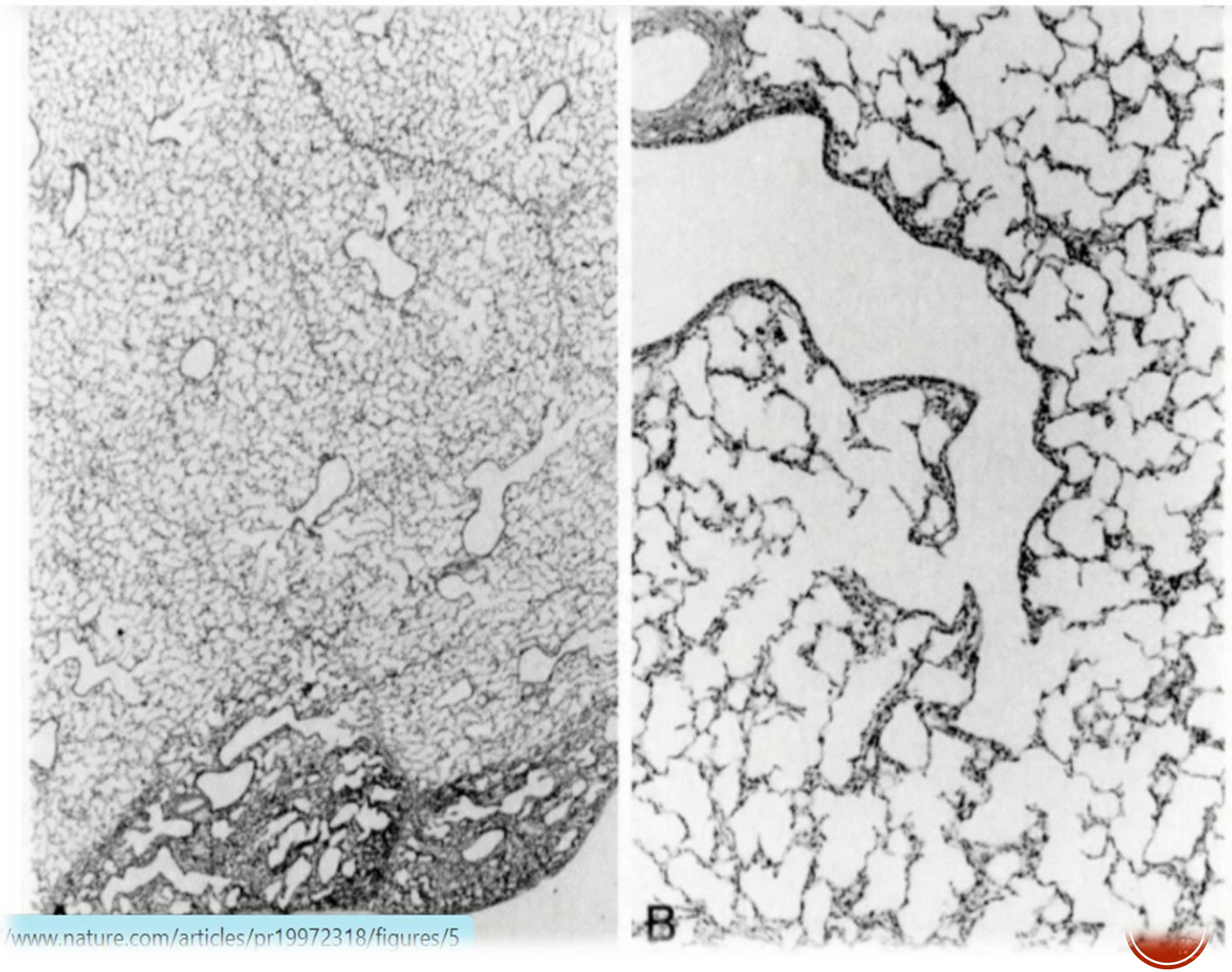
Treatment	Response to surfactant		
	Optimal	Suboptimal	Unsatisfactory
Bagging at birth	0	2	3
Controls	2	2	1

* Values are number of lambs.

Lung with suboptimal response

Lung with optimal response





COCHRANE	Synthetic vs NO Surfactant – 1998 (6 studies)	Prophylactic protein Free surfactant- 2010 (7 studies)	Prophylactic animal derived – 2010 (9 studies)
Pneumothorax	RR 0.64, 95% CI 0.55, 0.76	RR 0.67, 95% CI 0.50, 0.90	RR 0.40, 95% CI 0.29, 0.54
PIE	RR 0.62, 95% CI 0.54, 0.71	RR 0.68, 95% CI 0.50, 0.93)	RR 0.46, 95% CI 0.36, 0.59
Mortality	RR 0.73, 95% CI 0.61, 0.88	RR 0.70, 95% CI 0.58, 0.85	RR 0.60, 95% CI 0.47, 0.77
BPD	**RR 0.75, 95% CI 0.61, 0.92**	**RR 1.06, 95% CI 0.83 1.36**	**RR 0.91, 95% CI 0.79, 1.05**
BPD/ death	RR 0.73, 95% CI 0.65, 0.83	RR 0.90, 95% CI 0.78,1.04;	RR 0.80, 95% CI 0.72, 0.88

- INCREASES the risk of

  - Pulmonary hemorrhage (RR 3.28, 95% CI 1.50, 7.16).
  - Patent ductus arteriosus (RR 1.11, 95% CI 1.00, 1.22), (Protein Free prophylactic surfactant)

  - Apnea of prematurity (RR1.20, 95% CI 1.09, 1.31) (Synthetic prophylactic surfactant)

Prior to 2013, prophylactic surfactant was recommended for the smallest babies as it improved survival in clinical trials from the pre-CPAP era.

Soll RF, Morley CJ. Prophylactic versus selective use of surfactant in preventing morbidity and mortality in preterm infants. Cochrane Database Syst Rev. 2001

- Role of Surfactant in SDD
- Surfactant vs CPAP
- Early vs Delayed
- Types of surfactant and comparative studies
- Mode of Delivery-INSURE/InRecSure
- LISA/MISA/MIST/LMA/Nebulization/Pharyngeal
- Surfactant and Inhaled steroids

Trial	Intervention	N=	Primary Outcome
COIN 2008	CPAP vs Intubation	610[25-28weeks]	Death or BPD RR -0.80 (95%CI, **0.58 to 1.12**)
SUPPORT 2010	Early CPAP f/b selective surfactant vs Early Surfactant f/b MV	1316[24-27+6 weeks]	Death or BPD RR -0.95; (95% **CI 0.85 to 1.05**)
CURPAP 2010	Prophylactic Surfactant vs Early CPAP f/b selective Surfactant	208[25 -28 weeks]	Need for MV on day 5 RR -0.95 [95% **CI: 0.64 –1.41**];
VON DRM 2011	PS vs I-S-X vs CPAP f/b selective surfactant	648[26-29+6]	Death or BPD PS vs ISX- RR 0.78 (95% **CI: 0.59 – 1.03)** PS vs CPAP- RR 0.83 (95% CI: **0.64-1.09)**
NEOCOSUR (2010)	CPAP/INSURE vs oxygen by hood/MV and surfactant	256 [800 to 1500 gms]	Requirement for mechanical ventilation 29.8 vs 59.4% RR- 0.59 (**95%CI 0.43-0.83**

Table 3 – Primary and secondary outcomes.

Name	Primary outcome	Secondary outcomes
SUPPORT	Death or BPD comparable in two groups	No difference in • Need for supplemental oxygen • Need for mechanical ventilation • Air leak • IVH, NEC, ROP or use of postnatal steroids
COIN	Death or BPD comparable in two groups Survivors with oxygen comparable Surfactant usage: 38% in CPAP group	No difference in • Need for supplemental oxygen • Need for mechanical ventilation • IVH, NEC, ROP or use of postnatal steroids ***Air Leak Pneumothorax 9.1% vs 3.0% ($p = 0.001$)***
VON	**PS / INSURE / CPAP** Intubated in 1st hour surfactant 99% / 98.6% / 17.9% 98.6 / 98.2 / 45.1	No difference in • Mortality, BPD • Air leaks, Pulm hemorrhage • PDA, NEC, PVL, Sepsis, ROP
CURPAP	Need for mechanical ventilation within 5 days comparable in two groups Surfactant usage in CPAP group 48.5%	No difference in: • Mortality • BPD • Air Leaks • IVH, PDA or ROP, NEC or PVL • Use of postnatal Steroids
Neocosur	Significantly higher number required mechanical ventilation 29.8% vs 50.4% (p 0.001) Higher surfactant usage 27.5% vs 46.4% ($p = 0.002$)	Comparable • Mortality • BPD • Air leaks • PDA, IVH, NEC, ROP, Sepsis ***Higher nasal damage in CPAP group 8.4% vs 0% ($p = 0.001$)***

Table 2 – Surfactant usage and primary outcomes.

Name	Surfactant usage in CPAP arm (%)	Primary outcome BPD or death, *n*/*N* (%)		Risk ratio (95% CI)
		CPAP	control	
SUPPORT	67	323/663 (49)	333/653 (54)	0.91 (0.83–1.01)
COIN	38	104/307 (34)	118/303 (39)	0.80 (0.58–1.12)
VON	45	68/223 (31)	76/209 (37)	0.83 (0.64–1.09)
CURPAP	74	23/105 (22)	22/103 (21)	1.03 (0.61–1.72)
Neocosur	37	18/131 (14)	24/125 (19)	0.72 (0.41–1.25)
Overall	67	539/1429 (38)	573/1393 (41)	0.92 (0.84–1.00)

- After 2013, with increased use of antenatal steroids and early initiation of CPAP, surfactant was reserved for infants showing clinical signs of RDS
- Early initiation of CPAP in smallest infants may avoid the harmful effects of intubation and mechanical ventilation during the transitional phase.

Rojas-Reyes MX, Morley CJ, Soll R. Prophylactic versus selective use of surfactant in preventing morbidity and mortality in preterm infants. Cochrane Database of Systematic Reviews 2012

The overall aim is to avoid invasive MV if possible whilst endeavouring to give surfactant as early as possible in the course of RDS once it is deemed necessary

- Role of Surfactant in SDD
- Surfactant vs CPAP
- Early vs Delayed
- Types of surfactant and comparative studies
- Mode of Delivery-INSURE/InRecSure
- LISA/MISA/MIST/LMA/Nebulization/Pharyngeal
- Surfactant and Inhaled steroids

EARLY RESCUE VS LATE

- **Early:**
- Within 2- 3 hours of birth.
- Have been defined variably
- Presence of lung fluid in early administration helps in uniform distribution of surfactant.

- **Late:**
- After 2 hours

EARLY VERSUS DELAYED SELECTIVE SURFACTANT TREATMENT FOR NEONATAL RESPIRATORY DISTRESS SYNDROME - COCHRANE 2012

- **Population**:Preterm infants with RDS requiring intubation and assisted ventilation at less than three hours of life

- **Intervention:**Early selective surfactant (via ET tube) within the first three hours of life with delayed selective surfactant when they develop worsening established RDS

- **Primary outcomes**
  1. Neonatal mortality (mortality < 28 days of age) from any cause.
  2. Mortality prior to hospital discharge (from any cause).
  3. BPD-oxygen requirement at 28 to 30 days of age.
  4. BPD or death prior to 28 to 30 days of age.
  5. CLD (use of supplemental oxygen at 36 weeksPMA).
  6. CLD (use of supplemental oxygen at 36 weeks' PMA or death prior to 36 weeks

- Studies included were: European Study 1992; Konishi 1992; OSIRIS 1992; Gortner 1998; Plavka 2002; Lefort 2003

6 RCTs
N=3050

✓Reduction with early treatment in :

- Neonatal mortality (RR 0.84; 95%CI - 0.74 to 0.95)
- CLD (typical RR 0.69; 95% CI 0.55 to 0.86)
- CLD or death at 36 weeks (typical RR 0.83; 95% CI 0.75 to 0.91)

Bahadue FL, Soll R. Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome. Cochrane Database of Systematic Reviews 2012,

- Intubated infants randomized to early selective surfactant administration also

  - **Decreased risk of pneumothorax** (RR 0.69; 95% CI 0.59 to 0.82; RD -0.05; 95% CI -0.08 to -0.03; 5 studies; 3545 infants)

  - **Pulmonary interstitial emphysema** (RR 0.60; 95% CI 0.41 to 0.89; RD -0.06; 95% CI -0.10 to -0.02; 3 studies; 780 infants)

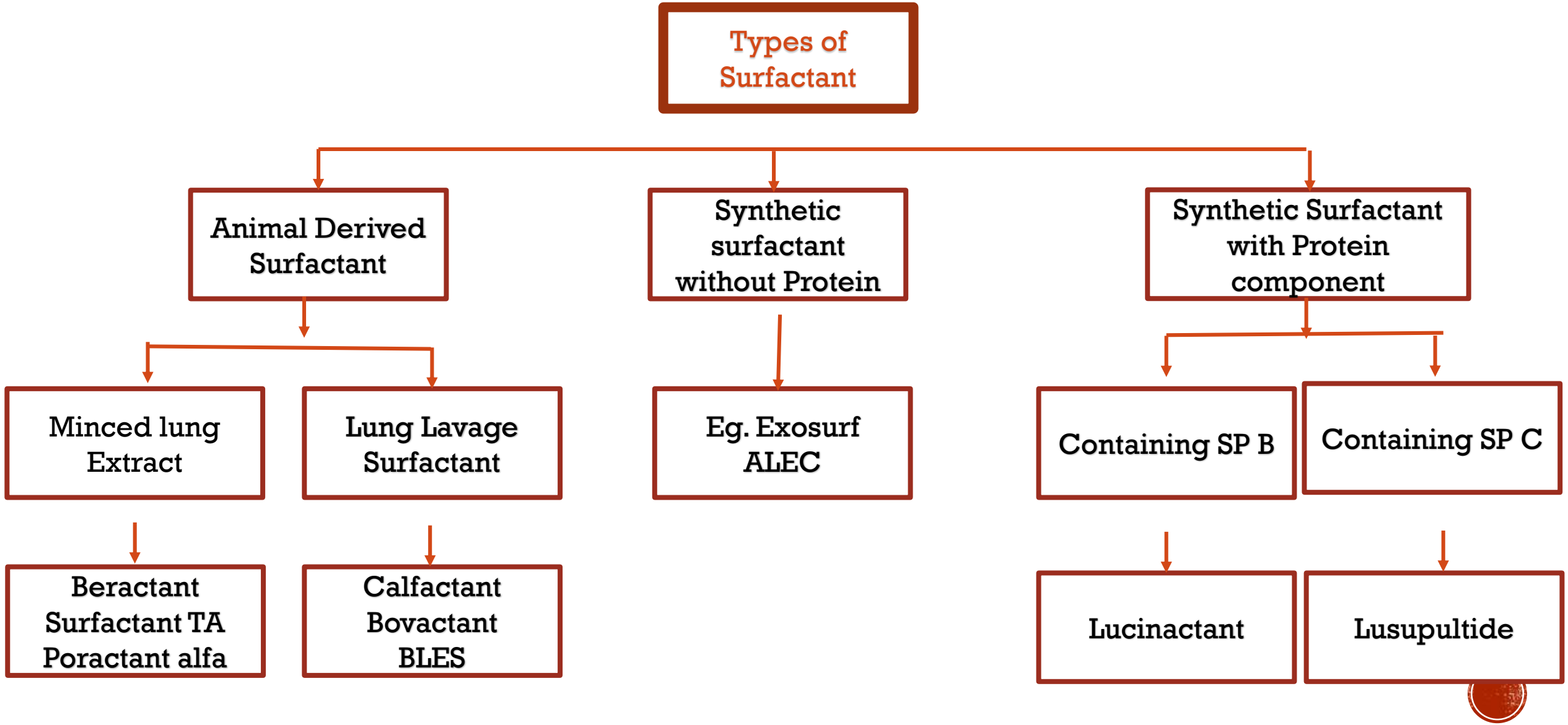
  - **Overall air leak syndromes** (RR 0.61; 95% CI 0.48 to 0.78; RD -0.18; 95% CI -0.26 to -0.09; 2 studies; 463 infants)

  - **BPD or death at 28 days** (RR 0.94; 95% CI 0.88 to 1.00; RD-0.04; 95% CI-0.07 to -0.00; 3 studies; 3039 infants).

- Role of Surfactant in SDD
- Surfactant –Prophylactic/Early vs late
- Types of surfactant and comparative studies
- Mode of Delivery-INSURE/InRecSure
- LISA/MISA/MIST/LMA/Nebulization/Pharyngeal
- Surfactant and Inhaled steroids

TYPES OF SURFACTANT

- The first successful animal model of SRT - Enhorning and Robertson in the 1970s (Enhorning 1972).
- They administered a crude animal derived surfactant extract obtained from lavage of the lungs of mature rabbits directly into the trachea of immature rabbit
- The first successful experience with humans –1980 (Fujiwara 1980)
- 10 preterm infants with severe RDS requiring assisted ventilation
- Improved dramatically with **Surfactant TA,** a **modified bovine surfactant extract, containing SP-B and SP-C.**


Types of Surfactant
Animal Derived Surfactant
Synthetic surfactant without Protein
Synthetic Surfactant with Protein component
Minced lung Extract
Lung Lavage Surfactant
Eg. Exosurf ALEC
Containing SP B
Containing SP C
Beractant
Surfactant TA
Poractant alfa
Calfactant
Bovactant
BLES
Lucinactant
Lusupultide

ANIMAL DERIVED SURFACTANT

- Recovered from alveolar lavages or from saline extracts of minced lungs.
- Contain phospholipids, neutral lipids, and hydrophobic protein (SP)-B and SP-C.
- Organic solvent extraction step removes nonessential proteins
- Extra lipid can be added or removed
- Poractant alfa
  - Liquid chromatography to extract only polar lipids
  - Contains the highest total concentrations of phospholipids and SP-B
  - Highest concentration/Volume

COMPARISON OF ANIMAL DERIVED SURFACTANTS FOR THE PREVENTION AND TREATMENT OF RDS – COCHRANE 2015

❑Objectives

To compare the effect of administration of different animal-derived surfactant extracts

❑Primary outcomes

1. Neonatal mortality (mortality < 28 days of age) from any cause.
2. Mortality prior to hospital discharge (from any cause).
3. Chronic lung disease (in all infants): (a)oxygen requirement at 28 to 30 days of age; (b). oxygen requirement at 36 weeks' postmenstrual age.
4. Death or chronic lung disease: (a). death or oxygen requirement at 28 to 30 days of age; (b). death or oxygen requirement at 36 weeks' postmenstrual age.

- **Bovine lung lavage surfactant extract [calfactant, CLSE (BLES) or SF-RI 1 (bovactant)] vs. modified bovine minced lung surfactant extract (beractant or surfactant TA).**
  - Treatment studies: Seven studies were identified (Attar 2004; Baroutis 2003; Bloom 1997; Bloom 2005; Hammoud 2004; Lam 2005; Yalaz 2004).

- **Bovine lung lavage surfactant extract (calfactant, CLSE (BLES) or SF RI 1 (bovactant)) vs. porcine minced lung surfactant extract (poractant alfa).**
  - Treatment studies: One study was identified (Baroutis 2003).

- **Bovine lung lavage surfactant extract (calfactant, CLSE (BLES) or SF-RI 1 (bovactant)) vs. porcine lung lavage surfactant (Surfacen).**
  - Treatment studies: No studies were identified.

- **Modified bovine minced lung surfactant extract (beractant or surfactant TA) vs. porcine lung lavage surfactant (Surfacen).**
  - Treatment studies: One study was identified (Sanchez-Mendiola 2005).

- **Porcine minced lung surfactant extract (poractant alfa) vs. porcine lung lavage surfactant (Surfacen).**
  - Treatment studies: No studies were identified

❑**Bovine lung lavage surfactant extract vs. modified bovine minced lung surfactant extract**

- Seven treatment studies
- Death or BPD at 36 weeks PMA
  - RR 0.95, 95% CI 0.86 to 1.06;
  - RD −0.02 , 95% CI −0.06 to 0.02;

    (high quality evidence)

❑**Modified bovine minced lung surfactant extract (beractant or surfactant TA) vs. porcine minced lung surfactant extract (poractant alfa).**

- Treatment studies: Nine studies were identified.

(Baroutis 2003; Didzar 2012; Fujii 2010; Gharehbaghi 2010; Halahakoon 1999; Karadag 2014; Malloy 2005; Ramanathan 2004; Speer 1995).

- **Modified bovine minced lung surfactant extract vs Porcine minced lung surfactant extract:**

	RR(95%CI)	RD(95% CI)	No. of Studies	No. Of Babies	Quality of evidence
Risk of mortality prior to hospital discharge	1.44(1.04-2)	0.05(0.01-0.10)	9 studies	901	Moderate
Increase in Death or Oxygen requirement at 36 weeks PMA	1.30(1.04-1.64)	0.11(0.02-0.20)	3 studies	448	Moderate
Receiving more than one dose of surfactant	1.57(1.29-1.92)	0.14(0.08-0.20)	6 studies	786	
PDA requiring treatment	1.86(1.28-2.70)	0.28(0.13-0.43)	3 studies	137	

	Porcine vs bovine (mg/kg)	Result
Neonatal Mortality (<28 days)	100 vs 100[2 studies]	RR 1.20, 95% CI 0.55 to 2.62
Mortality prior to hospital discharge (from any cause)	100 vs 100 [3 studies] >100 vs 100 [7 studies]	RR 1.10, 95% CI 0.61 to 1.96 **RR 1.62, 95% 1.11 to 2.38**
Oxygen requirement at 28 to 30 days of age	100 vs 100 [2 studies] >100 vs 100 [2 studies]	RR 0.96, 95% CI 0.73 to 1.25; RR 1.01, 95% 0.76 to 1.34
Oxygen requirement at 36weeks'postmenstrual age	100 vs 100 [2 studies] >100 vs 100 [6 studies]	RR 0.94, 95% CI 0.65 to 1.37 RR 1.08, 95% CI 0.84 to 1.38;
Death or oxygen requirement at 36 weeks' postmenstrual age	100 vs 100 [1 study] >100 vs 100 [3 studies]	RR 1.04, 95% CI 0.76 to 1.43; **RR 1.39, 95% 1.08 to 1.79**

SYNTHETIC SURFACTANT WITHOUT PROTEIN

- Originally synthesized first commercial products containing only DPPC.
- Newer products have added spreading agents.
- Exosurf consists of 85% DPPC, 9% hexadecanol, and 6% tyloxapol (a spreading agent).
- ALEC (pumactant), (not manufactured) 7:3 mixture of DPPC and phosphatidylglycerol.

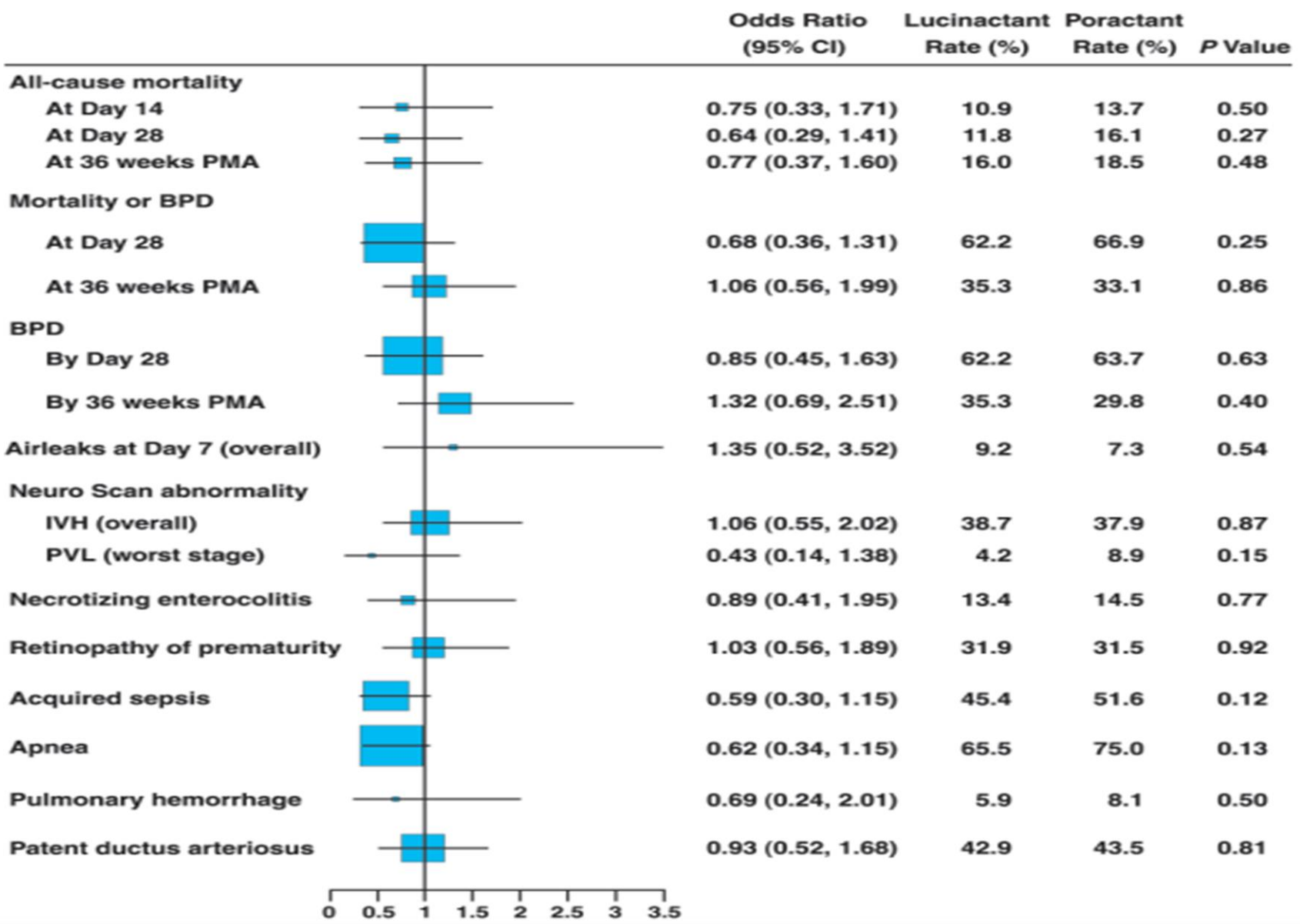
#ALEC: Artificial Lung Expanding Compound

SYNTHETIC SURFACTANT WITH PROTEIN

- **Lucinactant (Surfaxin),** which contains a mimic of SP-B called sinapultide or KL4 peptide(21-amino acid peptide consisting of lysines (K) and leucines (L) arranged in the sequence KLLLLKLLLLKLLLLKLLLLK)
- The drawbacks was
  - Its high viscosity at room temperature and a gel formulation, which required heating, mixing and subsequent cooling to body temperature before administration.
  - Also, the dose-equivalent volume was approximately 2.5 times that of poractant alfa.
- Surfaxin was withdrawn from the European market in 2006, and production was completely stopped by the US manufacturer in 2015
- Lucinactant is currently under development as an aerosolized surfactant (Aerosurf), having reached preclinical testing
- **Lusupultide (Venticute)** contains SP-C analogues, recombinant SP-C .

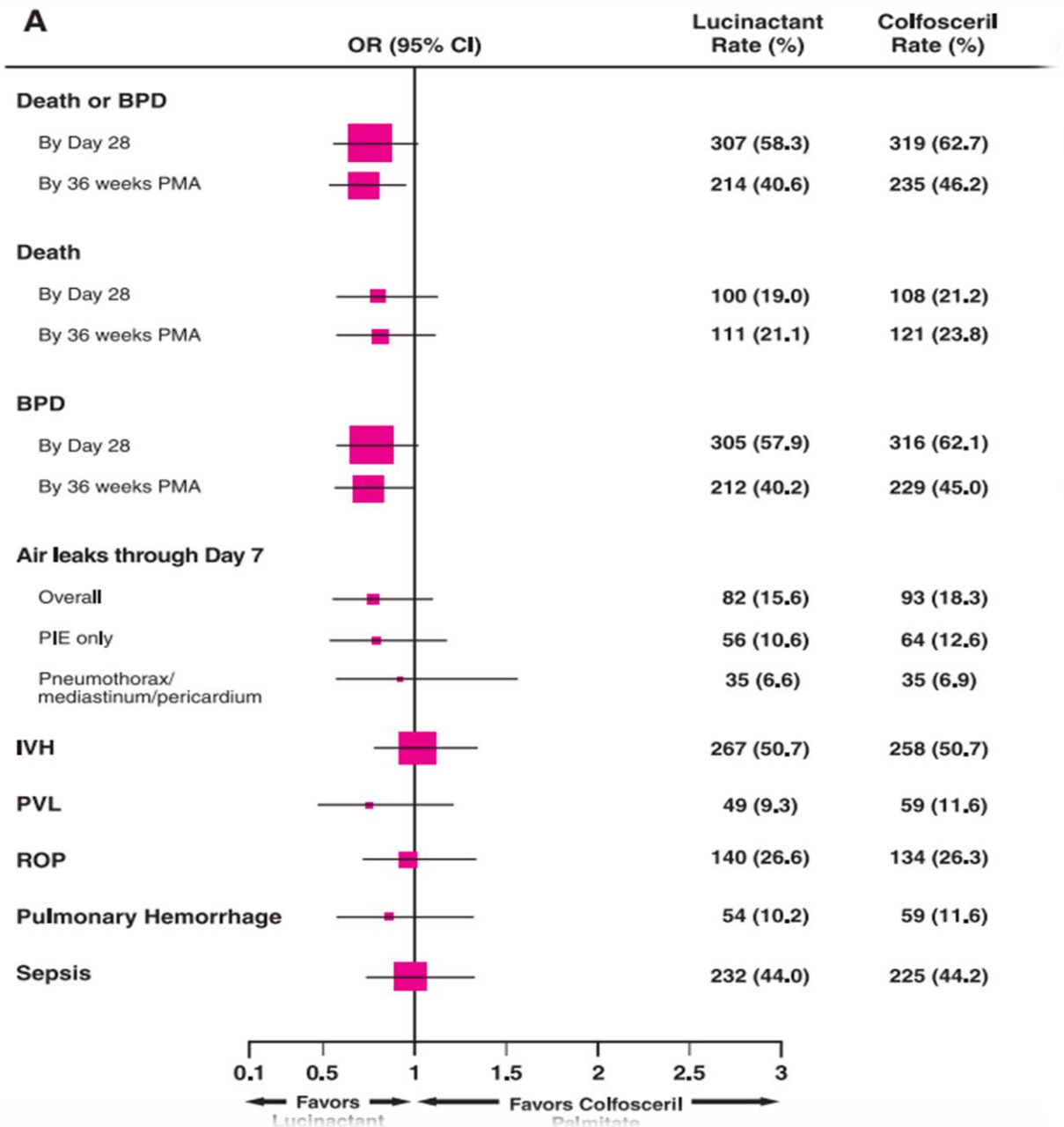
STAR(SURFAXIN THERAPY AGAINST RDS)

- **Hypothesis**: lucinactant is non inferior to an animal-derived surfactant- Poractant alfa
- 22 NICUs in Canada, France, Hungary, Poland, Portugal, Spain, UK and US
- **Population:** GA 24-28 weeks ; 600-1250 gms intubated at birth
- **Intervention**: Double blind trial; Lucinactant - 175 mg/kg (5.8 mL/kg, 30 mg/mL) in 30 mins
- **Control:** Poractant alfa - 175 mg/kg (2.2 mL/kg, 80 mg/mL),
- **Sample size**: 248 in each group; Could not be completed due to slow recruitment
- **Primary Outcome**: Survival without BPD through day 28
- **Statistical analysis**: Lower margin of inferiority **-14.5%**


Odds Ratio (95% CI)
Lucinactant Rate (%)
Poractant Rate (%)
P Value
All-cause mortality
At Day 14 0.75 (0.33, 1.71) 10.9 13.7 0.50
At Day 28 0.64 (0.29, 1.41) 11.8 16.1 0.27
At 36 weeks PMA 0.77 (0.37, 1.60) 16.0 18.5 0.48
Mortality or BPD
At Day 28 0.68 (0.36, 1.31) 62.2 66.9 0.25
At 36 weeks PMA 1.06 (0.56, 1.99) 35.3 33.1 0.86
BPD
By Day 28 0.85 (0.45, 1.63) 62.2 63.7 0.63
By 36 weeks PMA 1.32 (0.69, 2.51) 35.3 29.8 0.40
Airleaks at Day 7 (overall) 1.35 (0.52, 3.52) 9.2 7.3 0.54
Neuro Scan abnormality
IVH (overall) 1.06 (0.55, 2.02) 38.7 37.9 0.87
PVL (worst stage) 0.43 (0.14, 1.38) 4.2 8.9 0.15
Necrotizing enterocolitis 0.89 (0.41, 1.95) 13.4 14.5 0.77
Retinopathy of prematurity 1.03 (0.56, 1.89) 31.9 31.5 0.92
Acquired sepsis 0.59 (0.30, 1.15) 45.4 51.6 0.12
Apnea 0.62 (0.34, 1.15) 65.5 75.0 0.13
Pulmonary hemorrhage 0.69 (0.24, 2.01) 5.9 8.1 0.50
Patent ductus arteriosus 0.93 (0.52, 1.68) 42.9 43.5 0.81
0 0.5 1 1.5 2 2.5 3 3.5

SELECT (SAFETY AND EFFECTIVENESS OF LUCINACTANT VERSUS EXOSURF IN A CLINICAL TRIAL)

- **Hypothesis:** synthetic surfactant – Lucinactant would be superior to colfosceril palmitate.
- **Population:** GA: 24 and 32 weeks,600 and 1250 g, Intubated at birth(N=1294;527/509/258)
- **Intervention:** lucinactant at 175 mg of phospholipid per kg (5.8 mL/kg, 30 mg/mL), colfosceril palmitate at 67.5 mg of phospholipids per kg (5.0 mL/kg, 13.5mg/ml), beractant at 100 mg of phospholipid per kg (4.0 mL/kg, 25 mg/ mL).
- **Primary Outcome**: Development of RDS at 24 hours and the occurrence of death related to RDS through 14 days of age



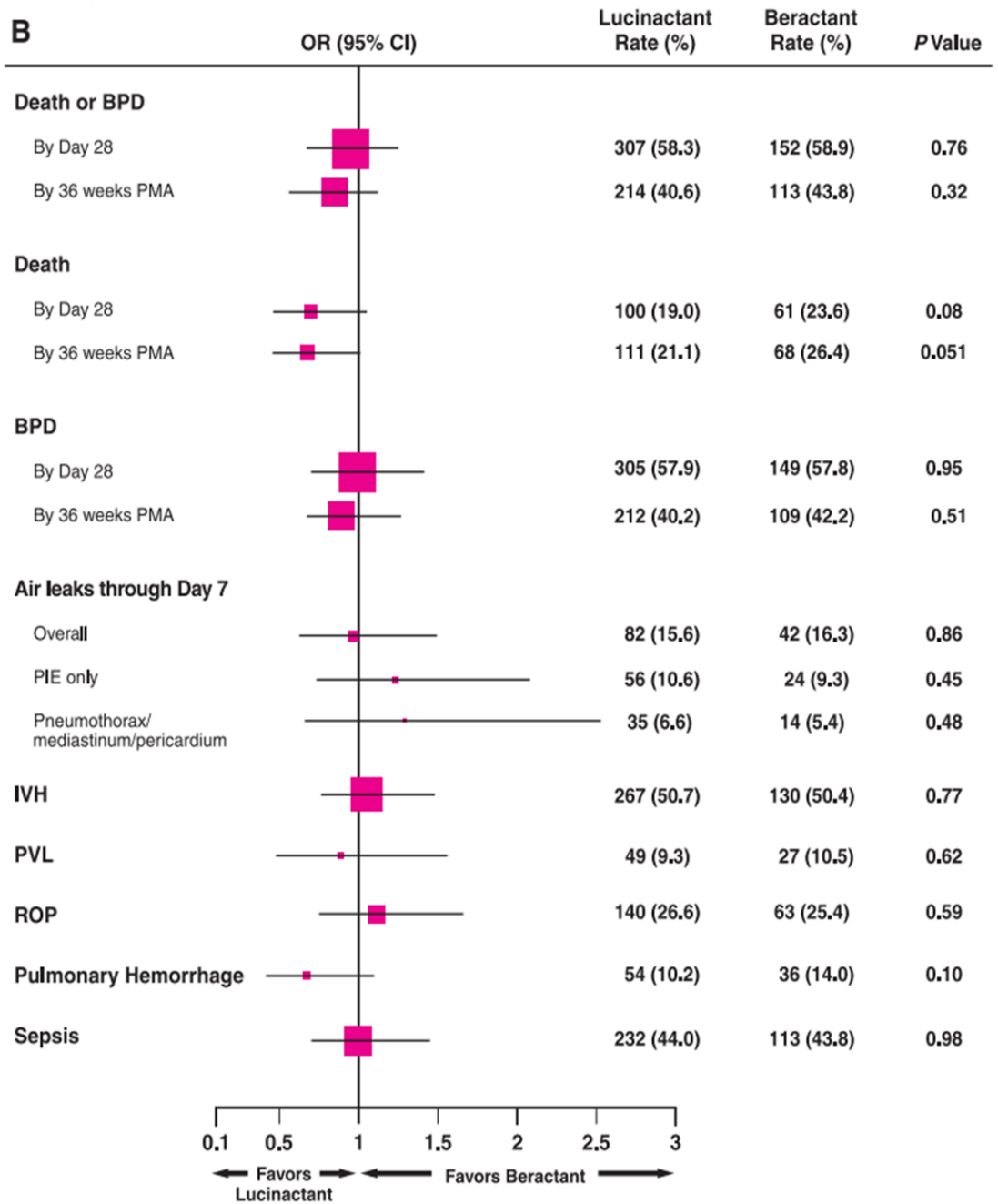


Fig 3. Continued.

THIRD GENERATION - CHF5633

- Compound combining SP-B analog and SP-C analog in a 1:1 DPPC
- Developed by Tore Curstedt and Jan Johansson in collaboration with Chiesi Farmaceutici
- Animal studies -delay in catabolism and enhanced phospholipid recycling compared to poractant alfa.
- Decreased proinflammatory cytokine synthesis in macrophages
- The first phase-I human trial(under the guidance of Christian Speer) in 40 infants with 27–34 weeks GA reports rapid and sustained improvement in oxygen requirement for 98% of the infants, good tolerability and no unexpected adverse events.
- A phase-II multicenter double-blinded clinical trial comparing CHF5633 with poractant alfa is ongoing.-
-

A Double Blind, Randomized, Controlled Study to Evaluate CHF 5633 (Synthetic Surfactant) and Poractant Alfa in Neonates With Respiratory Distress Syndrome

- Population:24 to 29 weeks
- N= 113 analyzed [56 vs 57]
- Primary outcome: Oxygen Requirement and Ventilatory Support -- SpO2/FiO2 Ratio analyzed at Post-treatment Day 1: 30 min, at 1h, 3h, 6h, 12h, 18h, 24 h; Day 2, 3, 5, and 7
- Results: No difference

SURFACTANT - II

- Role of Surfactant in SDD
- Surfactant vs CPAP
- Early vs Delayed
- Types of surfactant and comparative studies
- Mode of Delivery-INSURE/InRecSure
- LISA/MISA/MIST/LMA/Nebulization/Pharyngeal
- Guidelines- NNF/AAP/CPS/European

INSURE

- When Surfactant was given prophylactically – some are treated who do not need it
- While waiting until RDS develops- Treatment is delayed!!
- Mechanical ventilation – definitely harms - volutrauma , barotrauma, biotrauma sets the stage for chronic inflammatory processes leading to BPD
- **Swede Lars Victorin** was the **first to treat infants** with short-time intubation and surfactant instillation in Kuwait, where no neonatal ventilators were available in the 1980s.

Intubate- SURfactant- Bag and Mask ventilation- Extubate

Victorin LH, Deverajan LV, Curstedt T, Robertson B. Surfactant replacement in spontaneously breathing babies with hyaline membrane disease–a pilot study. Neonatology. 1990.

- Six randomized trials, (INSURE vs later, selective administration of surfactant, followed by continued MV and extubation from low respiratory support.
- GA - <35 weeks. And BW <2500.
- INSURE reduced –
  - The need for mechanical ventilation: RR 0.67, 95% CI 0.57-0.79
  - Air-leak syndromes - RR 0.52, 95% CI 0.28-0.96
  - BPD (oxygen at 28 days) - RR 0.51, 95% CI 0.26-0.99.
  - A lower threshold for treatment at study entry (FiO2 <0.45) resulted in a lower incidence of air leak - (RR 0.46, 95% CI 0.23-0.93) and BPD (RR 0.43, 95% CI 0.20-0.92).
  - A higher treatment threshold (FiO2 > 0.45) at study entry was associated with a higher incidence of patent ductus arteriosus requiring treatment (typical RR 2.15, 95% CI 1.09-4.13)

Stevens TP, Harrington EW, Blennow M, et al: Early surfactant administration with brief ventilation vs. selective surfactant and continued mechanical ventilation for preterm infants with or at risk for respiratory distress syndrome. Cochrane Database Syst Rev 2007

IN-REC-SUR-E

- IN-SUR-E might not be successful because of lung de-recruitment during intubation, which impedes surfactant distribution and efficacy

- Animal Models - Lung recruitment before surfactant administration improved gas exchange and lung function

- Studies suggest - volume recruitment manoeuvre improves surfactant distribution as surfactant preferentially distributes into underinflated and aerated alveolar areas while rarely reaching collapsed alveolar areas

- Principle - Optimising end-expiratory lung volume before surfactant administration

Lung recruitment before surfactant administration in extremely preterm neonates with respiratory distress syndrome (IN-REC-SUR-E): a randomised, unblinded, controlled trial

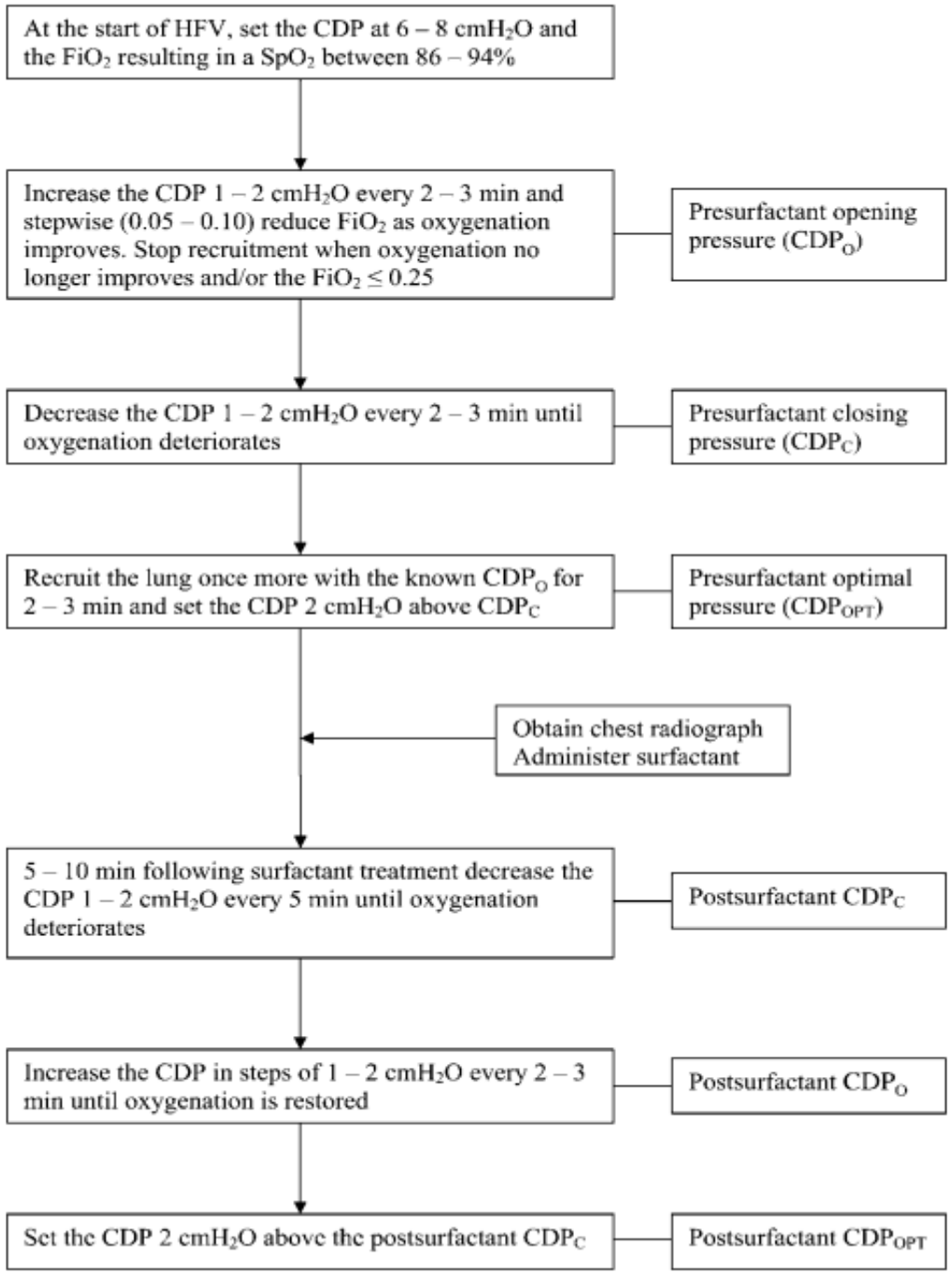
Population: GA- 24 to 27+6 in 36 NICU in ITALY; who failed CPAP

Intervention: IN-REC-SUR-E via HFOV using **de Jaegere method**

Control: IN-SUR-E

Outcome: Need for mechanical ventilation in first 72 hours of life

Number: 218 infants were recruited from Nov 12, 2015, to Sept 23, 2018


At the start of HFV, set the CDP at 6 – 8 cmH_2O and the FiO_2 resulting in a SpO_2 between 86 – 94%
Increase the CDP 1 – 2 cmH_2O every 2 – 3 min and stepwise (0.05 – 0.10) reduce FiO_2 as oxygenation improves. Stop recruitment when oxygenation no longer improves and/or the $FiO_2 \leq 0.25$
Presurfactant opening pressure (CDP_O)
Decrease the CDP 1 – 2 cmH_2O every 2 – 3 min until oxygenation deteriorates
Presurfactant closing pressure (CDP_C)
Recruit the lung once more with the known CDP_O for 2 – 3 min and set the CDP 2 cmH_2O above CDP_C
Presurfactant optimal pressure (CDP_{OPT})
Obtain chest radiograph
Administer surfactant
5 – 10 min following surfactant treatment decrease the CDP 1 – 2 cmH_2O every 5 min until oxygenation deteriorates
Postsurfactant CDP_C
Increase the CDP in steps of 1 – 2 cmH_2O every 2 – 3 min until oxygenation is restored
Postsurfactant CDP_O
Set the CDP 2 cmH_2O above the postsurfactant CDP_C
Postsurfactant CDP_{OPT}

	IN-SUR-E group (n=111)	IN-REC-SUR-E group (n=107)	Relative risk (95% CI)	p value
Primary outcome				
Mechanical ventilation in the first 72 h of life	60 (54%)	43 (40%)	..	..
Crude analysis	..	..	0·74 (0·56–0·99)	0·044
Adjusted analysis	..	..	0·75 (0·57–0·98)	0·037
Secondary outcomes				
Two doses of surfactant	58 (52%)	44 (41%)	0·79 (0·59–1·05)	0·10
In-hospital mortality*	37 (33%)	23 (21%)	0·64 (0·41–1·01)	0·055
Invasive respiratory support, days	6 (1–20)	6 (0–20)	..	0·56
Non-invasive respiratory support, days	35 (8–49)	40 (25–53)	..	0·46
Oxygen therapy, days	25 (9–52)	30 (5–63)	..	0·78
Moderate to severe bronchopulmonary dysplasia†	23/75 (31%)	29/86 (34%)	1·09 (0·69–1·71)	0·72
In-hospital stay, days	80 (19–108)	87 (60–107)	..	0·44
Pneumothorax*	7 (6%)	4 (4%)	0·59 (0·18–1·97)	0·39
Pulmonary interstitial emphysema	8 (7%)	4 (4%)	0·52 (0·16–1·67)	0·27
PDAhs	46 (41%)	56 (52%)	1·26 (0·95–1·68)	0·11
Pulmonary haemorrhage	9 (8%)	8 (7%)	0·92 (0·37–2·30)	0·86
Intraventricular haemorrhage worse than grade 2*	17 (15%)	12 (11%)	0·73 (0·37–1·46)	0·38
Periventricular leukomalacia	4 (4%)	10 (9%)	2·59 (0·84–8·02)	0·10
Sepsis‡	63 (57%)	59 (55%)	0·97 (0·77–1·23)	0·80
Necrotising enterocolitis	10 (9%)	11 (10%)	1·13 (0·50–2·55)	0·77
Retinopathy of prematurity worse than grade 2	12 (11%)	15 (14%)	1·30 (0·64–2·64)	0·47
Postnatal steroids	39 (35%)	40 (37%)	1·06 (0·75–1·51)	0·73

Need for mechanical ventilation within the first 72 h of life occurred in

43 (40%) of 107 infants in the IN-REC-SUR-E group

VS

60 (54%) of 111 infants in the IN-SUR-E group

Adjusted RR 0·75 (95% CI 0·57–0·98; p=0·037)

Absolute risk reduction - 14% (95% CI 1–27)

NNT - 7·2 (3·7–135·0)

- Role of Surfactant in SDD
- Surfactant vs CPAP
- Early vs Delayed
- Types of surfactant and comparative studies
- Mode of Delivery-INSURE/InRecSure
- LISA/MISA/MIST/LMA/Nebulization/Pharyngeal
- Guidelines- NNF/AAP/CPS/European

LESS INVASIVE METHODS OF SURFACTANT ADMINISTRATION

1. Thin catheter administration- also called
   MIST (minimally invasive surfactant therapy);
   LISA (less invasive surfactant administration)- cologne/Take care/Hobart method
   SurE (surfactant without endotracheal tube);
   MISA (minimally invasive surfactant administration);
   NISA (non-invasive surfactant administration).
2. Aerosolized or nebulized route
3. LMA-guided administration
4. Pharyngeal route

LISA

- 1992 - **Danish neonatologist Henrik Verder** - was the first to use a small-diameter gastric tube during spontaneous breathing- advantage of - unlike an endotracheal tube *no neonatologist would be tempted to leave a thin catheter longer than needed in the trachea*
-]
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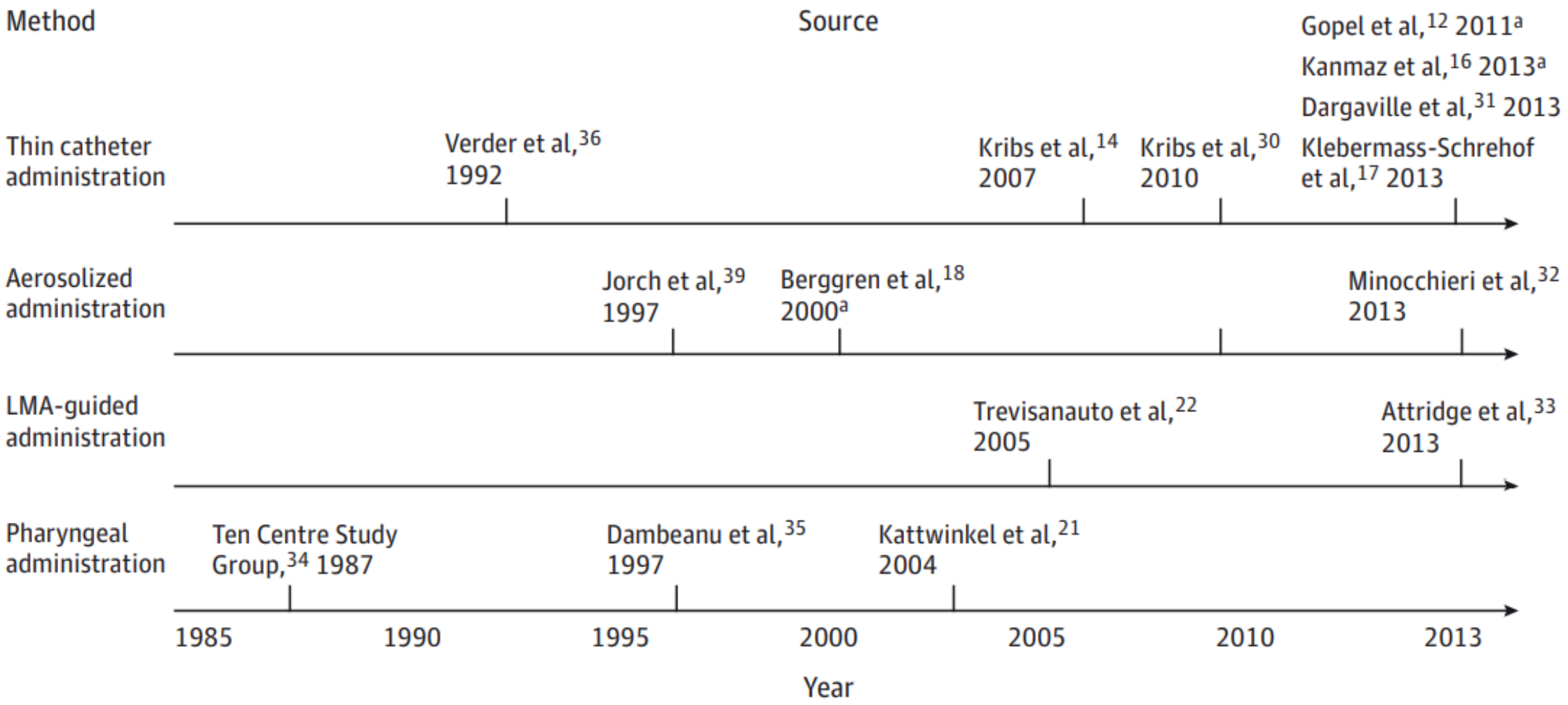
- 2011- The first RCT- **AMV study** of the German Neonatal Network, which included preterm infants - 26–29 weeks - statistically significant risk reduction in the need for mechanical ventilation during the first 72 h

Avoidance of mechanical ventilation by surfactant treatment of spontaneously breathing preterm infants (AMV): an open-label, randomised, controlled trial

Wolfgang Göpel, Angela Kribs*, Andreas Ziegler, Reinhard Laux, Thomas Hoehn, Christian Wieg, Jens Siegel, Stefan Avenarius, Axel von der Wense, Matthias Vochem, Peter Groneck, Ursula Weller, Jens Möller, Christoph Härtel, Sebastian Haller, Bernhard Roth, Egbert Herting, on behalf of the German Neonatal Network*

TILL 2014


Method
Source
Thin catheter administration
Verder et al,[36] 1992
Kribs et al,[14] 2007
Kribs et al,[30] 2010
Gopel et al,[12] 2011[a]
Kanmaz et al,[16] 2013[a]
Dargaville et al,[31] 2013
Klebermass-Schrehof et al,[17] 2013
Aerosolized administration
Jorch et al,[39] 1997
Berggren et al,[18] 2000[a]
Minocchieri et al,[32] 2013
LMA-guided administration
Trevisanauto et al,[22] 2005
Attridge et al,[33] 2013
Pharyngeal administration
Ten Centre Study Group,[34] 1987
Dambeanu et al,[35] 1997
Kattwinkel et al,[21] 2004
1985
1990
1995
2000
2005
2010
2013
Year

MIST(MINIMALLY INVASIVE SURFACTANT THERAPY)

- 2011- the procedure was modified by Dargaville et al. - who used a rigid adult vascular catheter (16-G Angiocath) to avoid use of the Magill forceps.

This method was named MIST and was evaluated in trials showing similar results

- Key benefits of LISA in RCTS – MV/Death/BPD/Pneumothorax/IVH
- Issues
  - Sedation
  - Which catheter/Surfactant
  - Need for more than one attempt - 5 – 30 %
  - Apnea
  - Need for PPV 12 - 44%

LISA vs INSURE

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

Cochrane Library

STUDIES: 16 studies (N= 2164 neonates)-

12 studies: LISA VS INSURE

2 studies : LISA vs delayed extubation

1 study: LISA vs CPAP and rescue surfactant administration at pre-specified criteria

1 Study : Compared different strategies of surfactant administration via thin catheter.

- Population: less than 37 weeks with or at risk of RDS
- **Primary outcome**:
  - Death/BPD
  - Need for MV within 72 hours
  - Air leak
  - Severe IVH
  - BPD
  - Death or survival with disability
- **Secondary Outcome**
  - Catheter/ETT placement unsuccessful at first attempt (during trial-related intervention)
  - Bradycardia
  - Hypoxemia during procedure

Figure 2. Primary and follow-up studies included in the review categorised by comparison group.

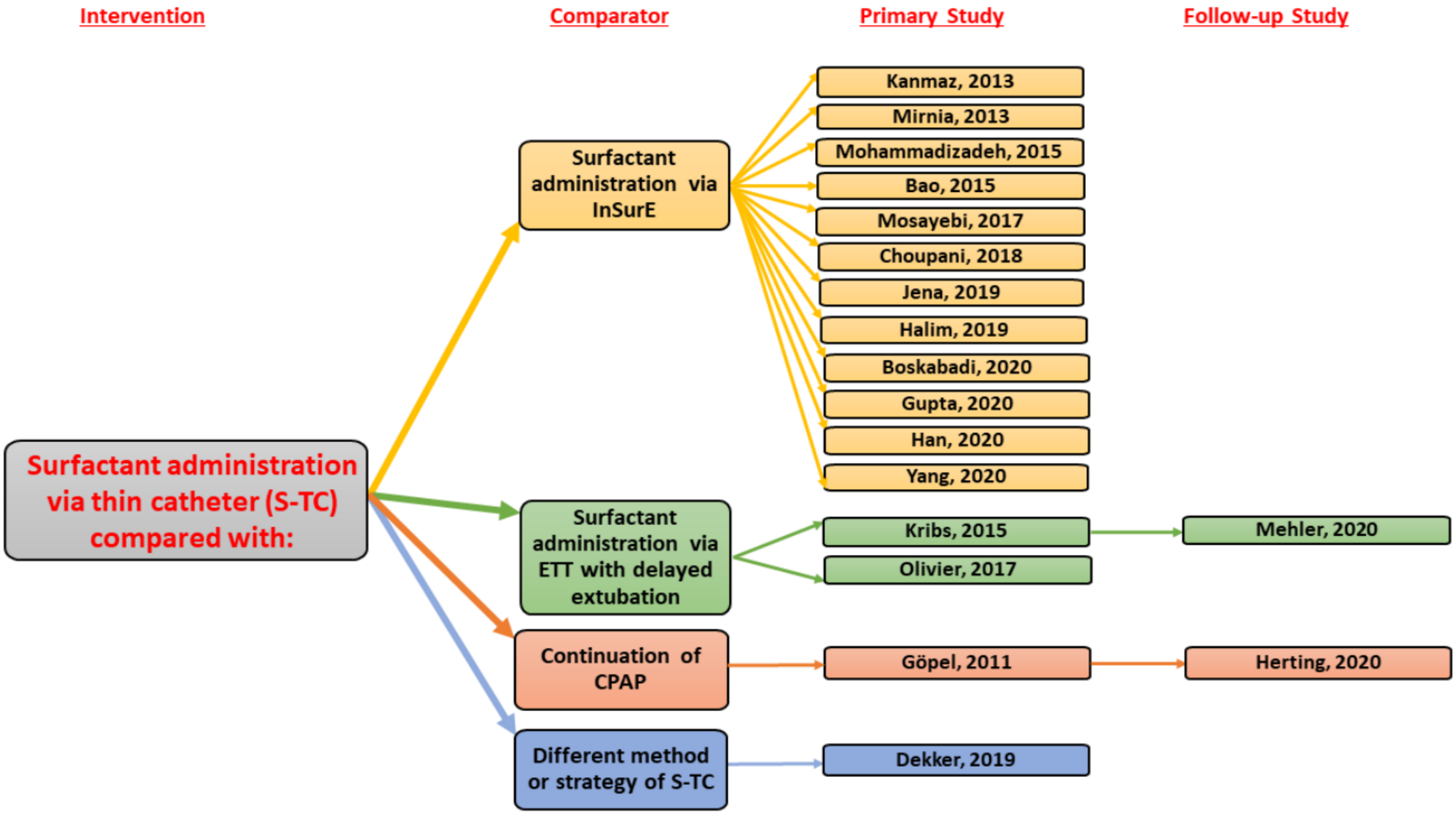
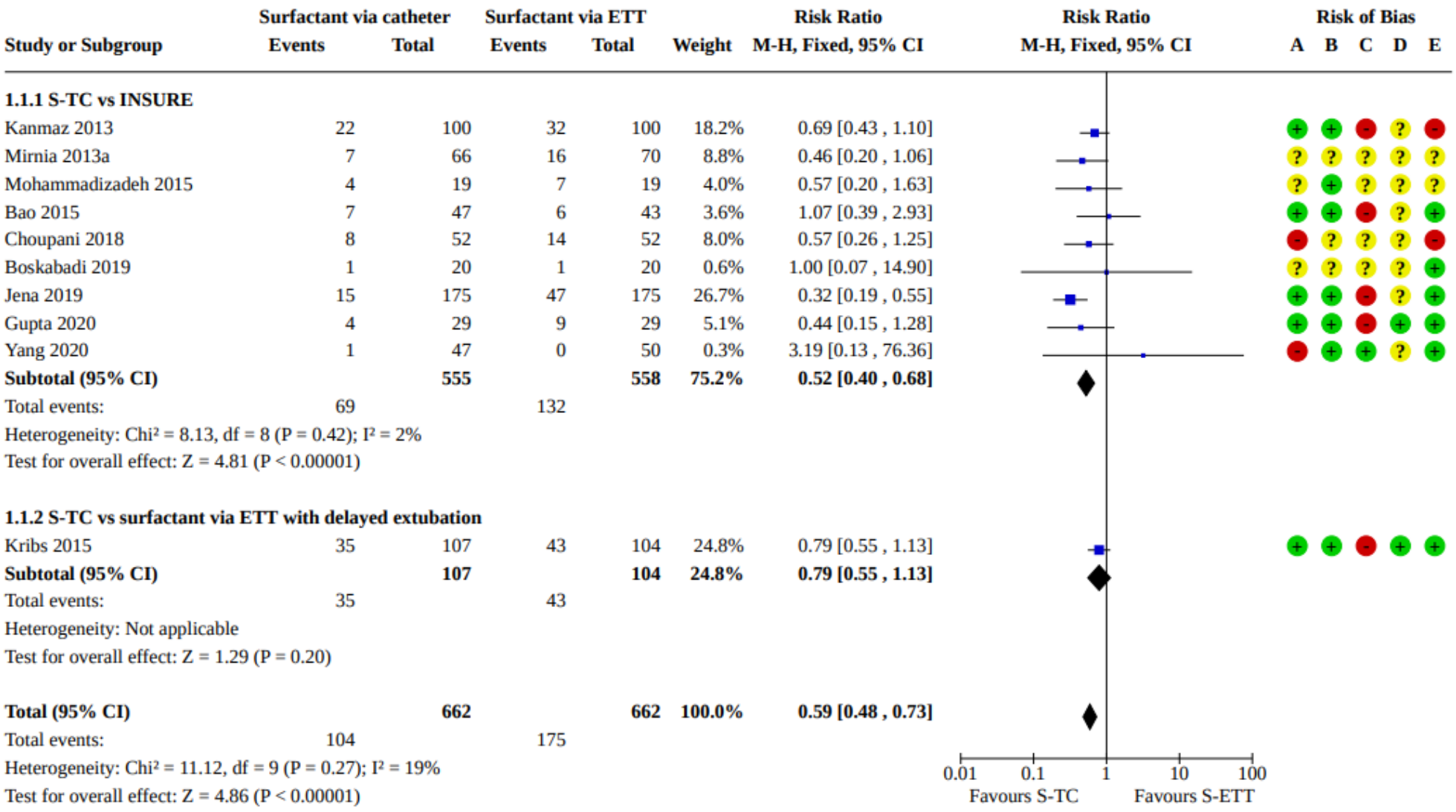
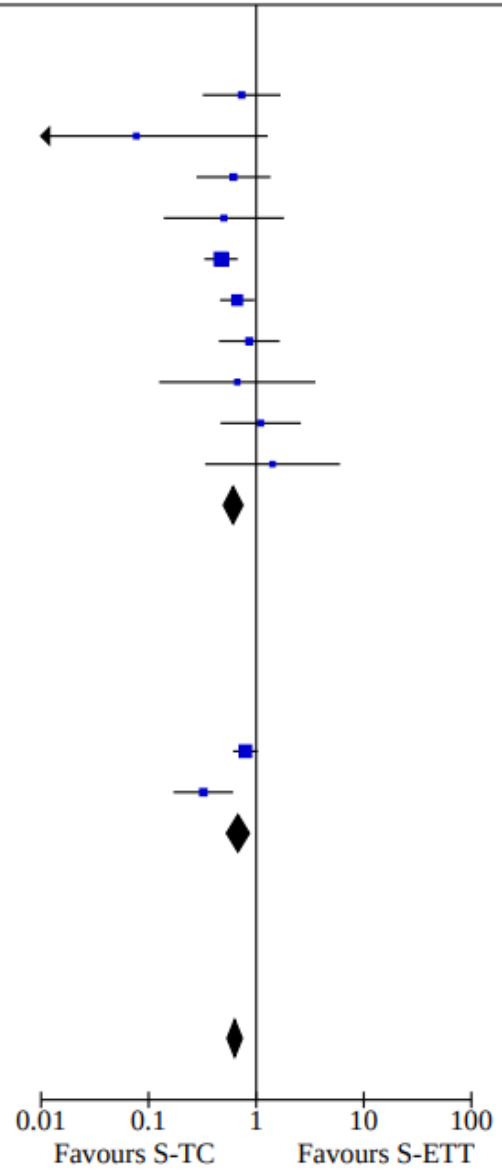


Figure 5. Forest plot of comparison: 1 Trials comparing S-TC with S-ETT - overall analysis, outcome: 1.1 Death or BPD.



Study or Subgroup	Surfactant via catheter Events	Total	Surfactant via ETT Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A	B	C	D	E
1.2.1 S-TC vs INSURE												
Bao 2015	8	47	10	43	4.0%	0.73 [0.32 , 1.68]		+	+	-	?	+
Boskabadi 2019	0	20	6	20	2.5%	0.08 [0.00 , 1.28]		?	?	?	?	+
Choupani 2018	8	52	13	52	5.0%	0.62 [0.28 , 1.36]		-	?	?	?	-
Gupta 2020	3	29	6	29	2.3%	0.50 [0.14 , 1.81]		+	+	-	+	+
Jena 2019	33	175	70	175	26.9%	0.47 [0.33 , 0.67]		+	+	-	?	+
Kanmaz 2013	30	100	45	100	17.3%	0.67 [0.46 , 0.96]		+	+	-	?	-
Mirnia 2013a	13	66	16	70	6.0%	0.86 [0.45 , 1.65]		?	?	?	?	?
Mohammadizadeh 2015	2	19	3	19	1.2%	0.67 [0.13 , 3.55]		?	+	?	?	?
Mosayebi 2017	8	27	7	26	2.7%	1.10 [0.47 , 2.60]		?	?	-	?	?
Yang 2020	4	47	3	50	1.1%	1.42 [0.34 , 6.00]		-	+	+	?	+
Subtotal (95% CI)		**582**		**584**	**68.9%**	**0.61 [0.50 , 0.75]**						
Total events:	109		179									
Heterogeneity: Chi² = 8.80, df = 9 (P = 0.46); I² = 0%												
Test for overall effect: Z = 4.73 (P < 0.00001)												
1.2.2 S-TC vs surfactant via ETT with delayed extubation												
Kribs 2015	49	107	60	104	23.3%	0.79 [0.61 , 1.03]		+	+	-	+	+
Olivier 2017	7	24	19	21	7.8%	0.32 [0.17 , 0.61]		+	+	-	?	?
Subtotal (95% CI)		**131**		**125**	**31.1%**	**0.68 [0.53 , 0.86]**						
Total events:	56		79									
Heterogeneity: Chi² = 6.59, df = 1 (P = 0.01); I² = 85%												
Test for overall effect: Z = 3.18 (P = 0.001)												
Total (95% CI)		**713**		**709**	**100.0%**	**0.63 [0.54 , 0.74]**						
Total events:	165		258									
Heterogeneity: Chi² = 15.92, df = 11 (P = 0.14); I² = 31%												
Test for overall effect: Z = 5.68 (P < 0.00001)												
Test for subgroup differences: Chi² = 0.41, df = 1 (P = 0.52), I² = 0%												



- Meta-analyses of 14 studies - significant decrease in
- **Composite outcome of death or bronchopulmonary dysplasia (BPD)** at 36 weeks' PMA- RR- 0.59, 95% CI 0.48 to 0.73; NNT-9 95% CI 7 to 16; 10 studies; 1324 infants; (moderate-certainty evidence);
- **The need for intubation within 72 hours -** (RR 0.63, 95% CI 0.54 to 0.74; NNTB 8, 95% CI; 6 to 12; 12 studies, 1422 infants; moderate-certainty evidence);
- **Severe intraventricular haemorrhage** (RR 0.63, 95% CI 0.42 to 0.96; NNTB 22, 95% CI 12 to 193; 5 studies, 857 infants; low-certainty evidence);
- **Death during first hospitalisation** (RR 0.63, 95% CI 0.47 to 0.84;NNTB 20, 95% CI 12 to 58; 11 studies, 1424 infants; low-certainty evidence); and
- **BPD among survivors** (RR 0.57, 95% CI 0.45 to 0.74; RD -0.08, 95% CI -0.11 to -0.04; NNTB 13, 95% CI 9 to 24; 11 studies, 1567 infants; moderate-certainty evidence).

- No difference: in risk of air leak requiring drainage (RR 0.58, 95% CI 0.33 to 1.02; RD -0.03, 95% CI -0.05 to 0.00; 6 studies, 1036 infants; low-certainty evidence

UPCOMING STUDIES

- **OPTIMIST B trial**: MIST Vs Sham treatment in 29-32 weeks
- **LPPSA**: less invasive surfactant administration versus endotracheal surfactant instillation followed by limited peak pressure ventilation in preterm infants with respiratory distress syndrome in China
- **MISurf:** MISurF versus InSurE. A comparison of minimally invasive surfactant application techniques in preterm infants
- **ECALMIST**(Early CPAP And Large Volume Minimal Invasive Surfactant Therapy): ECALMIST versus InSurE in preterm infant < 32 weeks, multi-centre, multi-national RCT
- **LISPAP**: RCT to compare LISA VS InSURE for Poractant Alfa
- **MOLISAN:** modified intubation-surfactant-extubation (InSurE) technique in preterm neonates with RDS-
  - To compare surfactant application via 2 techniques
  - LISA combined with synchronised nasal intermittent positive-pressure ventilation (SNIPPV) technique (LISA + SNIPPV group): this group receives surfactant by way of SNLISA followed by nasal SNIPPV vs INSURE
- **PROLISA**: propofol versus placebo (with rescue with ketamine) before LISA
- **StrAAS**: stress assessment in preterms with RDS treated or not with an analgesic drug during traditional or LISA

LARYNGEAL MASK AIRWAY

- Preterm lungs are at risk of volutrauma by mechanical ventilation; laryngoscopy is still traumatic.
- LMA achieved effective ventilation during neonatal resuscitation.
- Compared with bag and mask ventilation- more effective in terms of shorter resuscitation and ventilation time and resulted in less need for endotracheal intubation.
- In 2004, surfactant administration using a LMA was first described in a case report by Brimacombe et al

Laryngeal mask airway for surfactant administration versus standard treatment methods in preterm neonates with respiratory distress syndrome: A systematic review and meta-analysis- 2021

- Six RCTs , 357 infants.
- Studies included: Attridge et al (2013), Sadeghnia et al (2014), Roberts et al(2018), Pinheiro et al(2016), Gharebaghi et al(2018), Barbosa et al (2017)

Table 1 Baseline characteristics of included studies

Study (year)	Population, settings, surfactant	Criteria for surfactant	LMA group	Control group	Comments
Attridge et al (2013)[14]	BW > 1,200 g USA Calfactant 3 mL/kg	< 72 h with radiograph and clinical diagnosis of RDS on nCPAP for at least 30 min, FiO_2 between 0.30 and 0.60	$n = 13$ GA: 32 wk[a] BW: 2,130 g[a] LMA North America, San Diego Catheter followed by nCPAPAS: 54%	$n = 13$ GA: 33.5 wk[a] BW: 2,001 g[a] CPAP, no surfactant AS: 46%	
Sadeghnia et al (2014)[15]	GA: 33–36 wk Iran Survanta 100 mg/kg	RDS symptoms within 48 h of birth, treated with CPAP with CDP equal to 5 cm H_2O, required FiO_2 ≥0.3 for more than 30 min	$n = 35$ GA: 34.9 wk BW: 2,352 g I-gel, 5 French catheter AS: 51%	$n = 35$ GA: 35 wk BW: 2,374 g InSurE protocol: yes AS: 65%	No data on premedication
Pinheiro et al (2016)[12]	GA: 29–36.6 wk USA Calfactant 3 mL/kg	RDS between 4 and 48 h of age, nCPAP >5 cm H_2O plus FiO_2 0.30–0.60	$n = 30$ GA: 37% <33 wk BW: 2,118 g LMA (classic), 5 French catheter Followed by nCPAP AS: 50%	$n = 30$ GA: 60% <33 wk BW: 1,945 g InSurE protocol: yes AS: 53%	Atropine for LMA group Atropine and morphine for premedication in InSurE group
Barbosa et al (2017)[13]	GA: 28–35 wk Brazil Poractant alfa 200 mg/kg	Subjects on nCPAP, silverman score ≥4 and/or RR >60 bpm and/or (FiO_2) ≥0.40 clinical/radiological diagnosis of RDS	$n = 28$ GA: 31.1 wk BW:1,515 g[a] LMA (ProSeal), 6 French silicon catheter followed by nCPAP AS: 53.8%	$n = 22$ GA: 31.4 wk BW: 1,495 g[a] InSurE protocol: yes AS: 77.2%	Remifentanyl and midazolam for premedication in InSure group
Roberts et al (2018)[11]	GA: 28 to <36 wk USA Poractant alfa 200 mg/kg	≤36 h, on nCPAP or NIPPV, FiO_2 0.30–0.40 for ≥30 min and chest radiograph and clinical presentation consistent with RDS	$n = 50$ GA: 32.5 wk BW: 1,968 g LMA North America, San Diego Suction catheter, followed by nCPAP AS: 72%.	$n = 53$ GA: 32.6 wk BW: 1,995 g CPAP, no surfactant AS: 64%	Atropine and sucrose for LMA insertion
Gharehbaghi et al (2018)[16]	GA: 33–37 wk BW: >1,800 g Iran Survanta 100 mg/kg	RDS based on clinical signs and radiologic findings	$n = 25$ GA: 32.88 wk BW: 2,078 g LMA (classic) size 1, thin catheter then nCPAP applied	$n = 25$ GA: 33.76 wk BW: 2,198 g InSurE protocol: yes	Fentanyl for premedication

Laryngeal mask airway for surfactant administration versus standard treatment methods in preterm neonates with respiratory distress syndrome: A systematic review and meta-analysis- 2021

- Six RCTs , 357 infants.
- **Primary Outcome:** Surfactant dose repeats and Fio2 requirement,
  - Data on surfactant dosing repeats - four studies – RR - 1.64, 95% CI: 1.08–2.49
  - Fio2 - pre- and post-surfactant administration (3 studies) – MD - 10.55, 95% CI: 5.66–15.44, n=105, p< 0.001.
- **Secondary Outcome** :
  - Need for MV (6 RCT) - LMA vs control - RR - 0.49, 95% CI: 0.38–0.63, NNT= 4
  - Need for intubation – LMA vs Control - RR - 0.28, 95% CI: 0.14–0.58, NNT = 1.8;

Attridge et al (2013), Sadeghnia et al (2014), Roberts et al(2018), Pinheiro et al(2016), Gharebaghi et al(2018), Barbosa et al (2017)

NEBULIZED SURFACTANT ADMINISTRATION

- The first attempts of an aerosolized surfactant came in a preliminary study in 1964 by Robillard et al., who attempted to administer an aerosol of the synthetic surfactant beta-gamma-dipalmitoyl-L-alpha-lecithin (DPL) to 11 infants with RDS
- **Dilemmas**
  - Device to deliver- Jet/Ultrasonic/Vibrating/ The capillary aerosol generating (CAG) technology
  - Homogeneity of delivery
  - Duration of treatment – 20 mins to 2 hours
  - ELB- Small-caliber airways - obstruction, small tidal volumes, rapid and irregular respiratory rates
  - Rate of deposition- 2 mg/kg

LISA vs OTHER STRATEGIES

JAMA | Original Investigation

Association of Noninvasive Ventilation Strategies With Mortality and Bronchopulmonary Dysplasia Among Preterm Infants

A Systematic Review and Meta-analysis

Tetsuya Isayama, MD, MSc; Hiroko Iwami, MD; Sarah McDonald, MD, FRCSC, MSc; Joseph Beyene, PhD

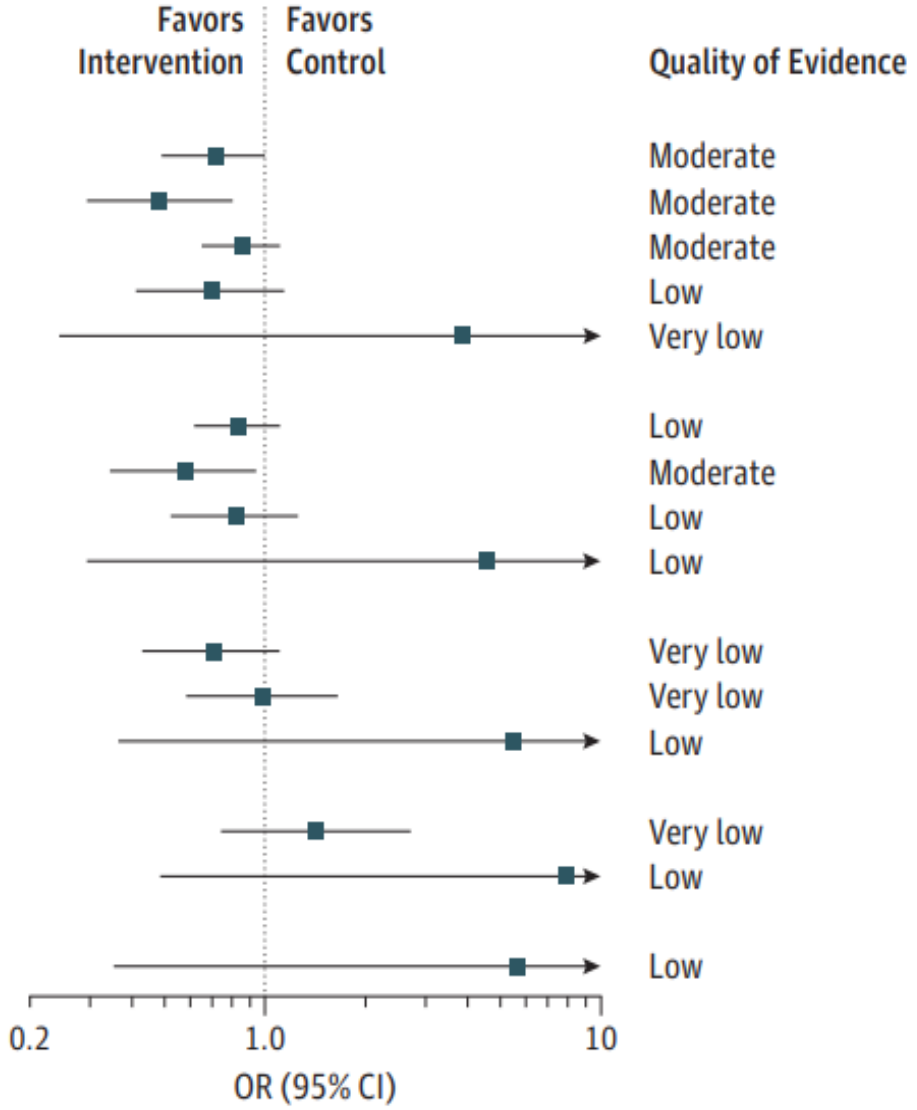
NETWORK METANALYSIS – comparing CPAP vs INSURE vs LISA vs IPPV vs MV vs LMA vs Nebulized surfactant

- Objective : To compare 7 ventilation strategies for preterm infants
- Methods: RCT comparing ventilation strategies < 33 weeks GA within 24 hours of birth who had not been intubated.
- Primary Outcome: A composite of death or BPD at 36 weeks' PMA
- Secondary outcome - Death, BPD, severe IVH and air leak by discharge
- N= 5598 infants; 30 trials
- **RESULTS**: →

Figure 3. Primary Outcome of Bronchopulmonary Dysplasia or Death in Preterm Infants

A Death or bronchopulmonary dysplasia (composite outcome)

Source	No. of Infants	No. of Trials	Network Absolute RD per 1000 (95% CI)	Network OR (95% CI)
MV (control)				
INSURE	419	2	83 Fewer (5 fewer-160 fewer)[a]	0.71 (0.50-0.98)
LISA	189	1	164 Fewer (57 fewer-253 fewer)[a]	0.49 (0.30-0.79)
Nasal CPAP	2085	3	40 Fewer (24 more-99 fewer)	0.85 (0.66-1.10)
NPPV			86 Fewer (30 more-194 fewer)	0.70 (0.42-1.13)
LMA			311 More (280 fewer-539 more)	3.90 (0.25-119.88)
Nasal CPAP (control)				
INSURE	1186	7	41 Fewer (22 more-96 fewer)	0.83 (0.63-1.10)
LISA			112 Fewer (16 fewer-190 fewer)[a]	0.58 (0.35-0.93)[a]
NPPV	775	5	44 Fewer (50 more-127 fewer)	0.82 (0.53-1.24)
LMA			362 More (210 fewer-639 fewer)	4.58 (0.30-141.08)
INSURE (control)				
LISA	381	3	65 Fewer (17 more-131 fewer)	0.70 (0.44-1.09)
NPPV			4 Fewer (91 fewer-105 more)	0.98 (0.59-1.62)
LMA	24	1	402 More (150 fewer-713 more)	5.53 (0.37-167.35)
LISA (control)				
NPPV			62 More (43 fewer-205 more)	1.41 (0.75-2.69)
LMA			467 More (94 fewer-778 more)	7.91 (0.49-244.67)
NPPV (control)				
LMA			348 More (89 fewer-821 more)	5.68 (0.36-177.56)



B Bronchopulmonary dysplasia

Figure 5. Ranking Probability of Strategies and Surface Under the Cumulative Ranking Curve in the Network Meta-analysis of Noninvasive Ventilation Strategies for Preventing Bronchopulmonary Dysplasia or Death in Preterm Infants

A Death or chronic lung disease

	Ranking, median (95% CI)	Surface under the cumulative ranking curve
INSURE	3 (2-4)	0.66
LISA	1 (1-3)	0.94
Nasal CPAP	4 (3-5)	0.41
NPPV	2 (1-5)	0.66
MV	5 (3-6)	0.20
LMA	6 (1-6)	0.13

B Bronchopulmonary dysplasia

	Ranking, median (95% CI)	Surface under the cumulative ranking curve
INSURE	2 (1-5)	0.69
LISA	1 (1-4)	0.89
Nasal CPAP	4 (2-5)	0.42
NPPV	3 (1-6)	0.62
MV	5 (3-6)	0.23
LMA	6 (1-6)	0.14

SURFACTANT AND STEROIDS – WHY ??

- Inflammation – BPD
- Systemic corticosteroids - correlated with serious short-term/ long-term adverse outcomes.
- Early administration of Inhaled corticosteroids by airway - fewer side effects
- Airway administration of budesonide – decreases BPD but increase mortality
- When combining budesonide with surfactant, the risk of BPD was demonstrated 43% reduction without increased mortality or adverse physical or neurologic outcomes.
- Several studies - conflicting results.

Early intratracheal administration of corticosteroid and pulmonary surfactant for preventing bronchopulmonary dysplasia in preterm infants with neonatal respiratory distress syndrome: A meta-analysis

- 8 RCTS;
- **N**= 792 preterm infants - 414 receiving airway administration (inhalation or instillation) of corticosteroid and PS (ICS group) and 378 given placebo plus PS (placebo control group).
- **Inclusion Criteria**: (1) GA < 36 weeks, and the diagnosis of RDS was confirmed; (2) Infants were randomized to receive treatment with airway administration (inhalation or instillation) of corticosteroid and PS (ICS group) or placebo plus PS (placebo control group); (3) interventions started within 1 day after birth; (4) more than one of the outcomes was reported.
- **Primary Outcome**: BPD incidence
- **Secondary Outcome**: Mortality, % of infants using PS more than one time, infection (sepsis) incidence, incidence of ROP, incidence of neurological lesions

Study	Enrollment criteria	Time to start intervention	Treatment		*n*	
			ICS group	Placebo control group	ICS	Control
Kuo, 2010[16] Yeh, 2008[17]	BW <1500 g, RDS	6 h after birth	BUD 0.25 mg/kg + PS 100mg /kg ia	PS 100 mg/kg ia	60	60
Sadeghnia, 2018[18]	GA <28 w, RDS	2 h after birth	BUD 0.5 mg (NEB, bid until day 7) + PS ia	PS ia	35	35
Yeh, 2016[19]	BW <1500 g, RDS	6 h after birth	BUD 0.25 mg/kg + PS 100 mg/kg ia	PS 100 mg/kg ia	131	134
Zimmeman, 2000[20]	BW <1300 g, RDS	3 h after birth	BDP (pMDI 1–4/day for 12 days + PS ia)	Placebo pMDI + PS ia	23	24
Cao, 2018[21]	GA <32 w, RDS needing ventilator support	Day of ICU administration	BUD 0.25 mg/kg + PS 100 mg/kg (NEB, q8h)	PS 100 mg/kg ia, Q8h	40	40
Ke, 2016[22]	GA <32 w, BW<1500 g, RDS	4 h after birth	G1: BUD (pMDI 0.25 mg/kg every day until ventilator withdraw + PS 200 mg/kg ia) G2: BUD (0.25 mg/kg) + PS 200 mg/kg ia	PS 200 mg/kg ia	G1: 46 G2: 46	46
Pan, 2017[23]	GA <32 w, BW <1500 g, RDS with II history	4 h after birth	BUD 0.2 mg/kg + PS 70 mg/kg ia	PS 70 mg/kg ia	15	15
Dg, 2017[24]	GA<37 w, BW <1500 g, RDS	8 h after birth	GA<37 w, BUD 0.25 mg/kg + PS 150 mg/kg ia	PS 150 mg/kg ia	18	28

GA: gestational age; BW: birth weight; RDS: respiratory distress syndrome; BUD: budesonide; BDP: beclomethasone propionate; PS: pulmonary surfactant; ia: via intratracheal administration; NEB: via nebulizer; pMDI: via pressure metered dose inhaler; G1: group 1; G2: group 2; II: intrauterine infection

SUMMARY OF RESULTS

Number of trials	Effect (95% CI)	
	Outcome	Estimate effect
8	BPD incidence	RR=0.56 (95% CI: 0.42–0.76)
6	Mortality	RR=0.67 (95% CI: 0.45–0.99)
5	Percentage of infants using PS more than one time	RR=0.55 (95% CI: 0.45–0.67)
2	Incidence of infection	RR=0.95 (95% CI: 0.59–1.52)
3	Incidence of retinopathy	RR=0.92 (95% CI: 0.62–1.38)
6	Incidence of neuro-motor system impairment	RR=1.13 (95% CI: 0.92–1.39)

GUIDELINES

E 19

Recommendations

1 Babies with RDS should be given an animal-derived surfactant preparation (**A1**).

2 A policy of early rescue surfactant should be standard (**A1**), but there are occasions when surfactant should be given in the delivery suite, such as when intubation is needed for stabilisation (**A1**).

3 Babies with RDS should be given rescue surfactant early in the course of the disease. A suggested protocol would be to treat babies who are worsening when FiO_2 >0.30 on CPAP pressure of at least 6 cm H_2O (**B2**).

4 Poractant alfa at an initial dose of 200 mg/kg is better than 100 mg/kg of poractant alfa or 100 mg/kg of beractant for rescue therapy (**A1**).

5 LISA is the preferred mode of surfactant administration for spontaneously breathing babies on CPAP, provided that clinicians are experienced with this technique (**B2**).

6 A second and occasionally a third dose of surfactant should be given if there is ongoing evidence of RDS such as persistent high oxygen requirement and other problems have been excluded (**A1**).

CANADIAN PEDIATRIC SOCIETY(2021)

1. In settings, where CPAP is routinely used to stabilize, and when the rate of ANS administration has been high (>50%), **prophylactic surfactant is no longer recommended** (Grade A).
2. **Noninvasive respiratory support** (e.g., CPAP) - from birth.
3. Early surfactant should be provided for newborns with increasing severity of RDS, demonstrated by escalating or sustained levels of oxygen requirement and other clinical or radiological indications (Grade B).
4. Infants with RDS whose oxygen requirements exceed FiO2 of 0.5 should receive SRT (Grade A)

CPS

4. Intubated infants with RDS should **receive surfactant before transport** (Grade B).
5. **Repeated dosing** - Only when there is evidence of ongoing moderate to severe RDS (Grade A).
6. For spontaneously breathing infants on CPAP with RDS, - noninvasive methods - LISA or MIST, are preferable. Factors such as clinician experience, optimal dosage, volume, and the types of surfactant available must be considered to optimize delivery method (Grade B).

NNF CPG DEC 2021

1. Prophylactic surfactant **should NOT** be administered to preterm neonates <28 weeks gestation with RDS. They should be stabilized on CPAP and if indicated **selective surfactant replacement** therapy - administered.

   Sub-group considerations: Clinicians may consider delivery room surfactant in <28 weeks gestation who are intubated in the delivery room for severe RDS . [SR,LCOE]

2. **Early INSURE (within 2 hours**) in < 34 weeks' gestation with established RDS and who satisfy the criteria for surfactant administration[WR,LCOE]

3. Surfactant may be given to preterm neonates < 34 weeks' gestation with RDS stabilized on CPAP, who require a **PEEP of ≥ 6 cm H2O and a FiO2 > 0.30 to maintain SpO2 > 91**% [WR, Expert consensus]

4. **LISA may be preferred over INSURE** for surfactant administration in preterm neonates < 34 weeks' gestation with RDS
5. **LMA should NOT be used** for surfactant instillation outside research context in preterm neonates < 37 weeks' gestation with RDS
6. **Poractant-α (200 mg/kg) may be used** for treating preterm neonates < 34 weeks' gestation with RDS and who satisfy the criterion for surfactant administration
7. **Early intra-tracheal corticosteroids may NOT be used** as an adjunct to surfactant in the treatment of preterm neonates < 34 weeks' gestation with RDS.

AAP (2014)

1. Preterm infants born at <30 weeks gestation who need **mechanical ventilation** because of severe RDS should be given (Strong Recommendation).

2. Using CPAP immediately after birth with **subsequent selective surfactant administration** considered as an alternative to routine intubation with prophylactic or early surfactant administration in preterm infants (Strong Recommendation).

3. **Rescue surfactant** may be considered for infants with hypoxic respiratory failure attributable to secondary surfactant deficiency (eg, pulmonary hemorrhage, meconium aspiration syndrome, or sepsis/pneumonia)

4. Preterm and term neonates who are receiving surfactant - managed by nursery and transport personnel with the **technical and clinical expertise** to administer surfactant safely and deal with multisystem illness.

KEY MESSAGES

- Role of Surfactant in SDD
- Surfactant vs CPAP
- Early vs Delayed
- Types of surfactant and comparative studies
- Mode of Delivery-INSURE/InRecSure
- LISA/MISA/MIST/LMA/Nebulization/Pharyngeal

THANK YOU