Less Invasive Surfactant Administration

A gentle revolution in surfactant therapy

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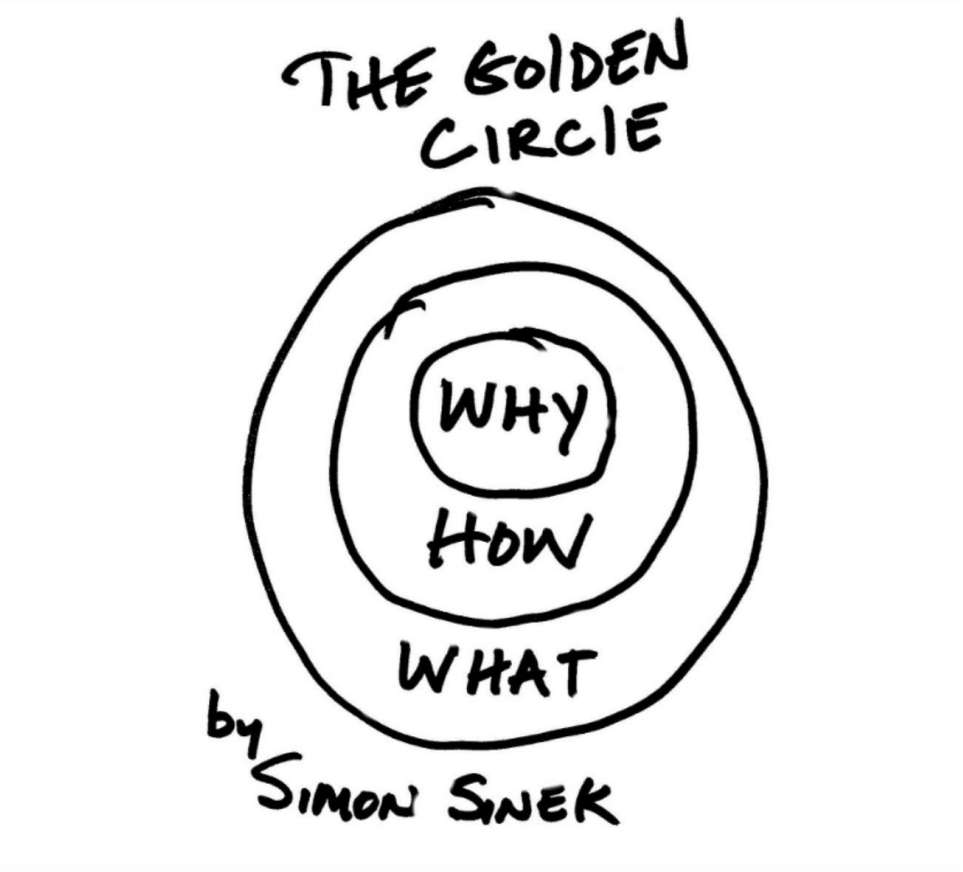
No financial disclosures but some other disclosures:

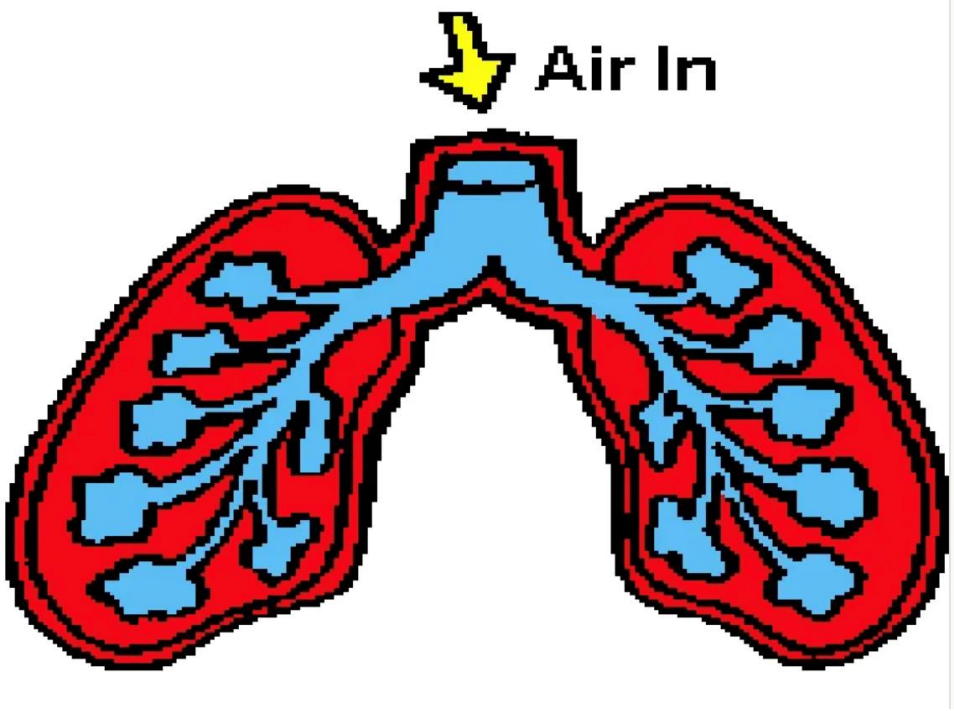
- This is my first meeting at District VIII and I am loving it
- Some of the topics that I will talk about today are from the era before I was born while few folks in audience here had lived and practiced in that era
- I tried to blend in with the locals by ordering a huckleberry latte and pretending I know how to fly fish. Didn’t work. They still spotted me as a Seattleite in 0.2 seconds

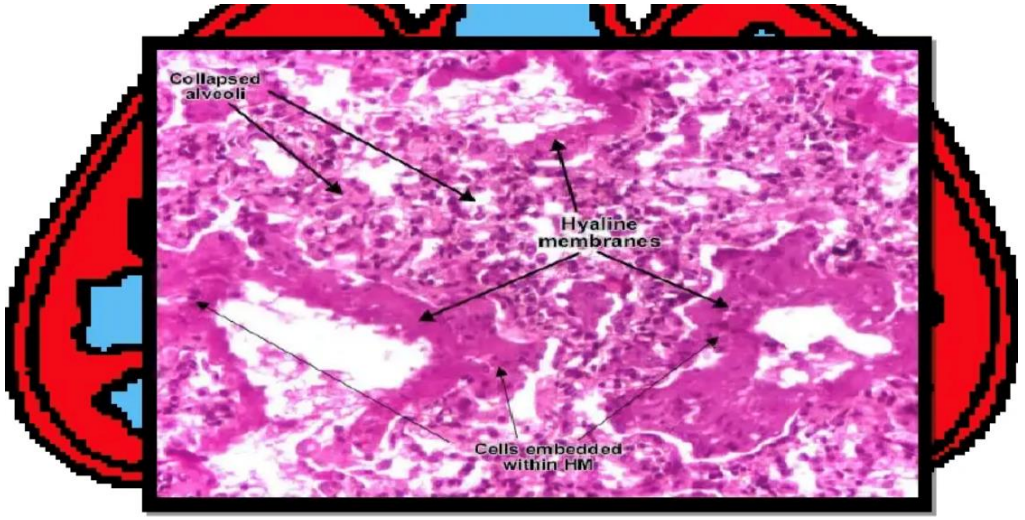
Objectives

- To review and discuss what we know about less invasive surfactant administration (LISA)
- ***Why***
- When
- Where
- Who
- How



100 years of journey





Fibrin elastic substances
Pulmonary aspiration
Aspiration of amniotic fluid
Pulmonary Ischemia
Absence of surface active agents
Idiopathic

The fascinating story of surfactant

Kurt von Neergaard
1887-1947

1929

– Surface tension as a force counteracting the first breath of the newly born baby should be investigated further

Switzerland
Porcine lungs:
Air filled and fluid filled

Peter Gruenwald

1947

– Resistance to aeration is due to surface tension. No idea about von Neergaard´s experiments

Harvard, Boston
Lungs of stillborn infants

1950s

Canada

Charles Macklin
1883-1959

England

Richard Pattle
1918 - 1980

USA

John Clements
1923 - 2024

Effects of nerve gases on lungs

Bubbles covered by a substance from the lining layers in the lung

Chemical warfare study

J Paediatrics Child Health, Volume: 53, Issue: 4, Pages: 327-332, First published: 08 March 2017, DOI: (10.1111/jpc.13500)

A.M.A JOURNAL OF
DISEASES OF CHILDREN

Surface Properties in Relation to Atelectasis and Hyaline Membrane Disease

MARY ELLEN AVERY, M.D., and JERE MEAD, M.D., Boston

Avery and Mead concluded ‘Hyaline membrane disease is associated with absence or late appearance of some substances which in normal subjects render the internal surface capable of attaining a low surface tension when lung volume is decreased’.

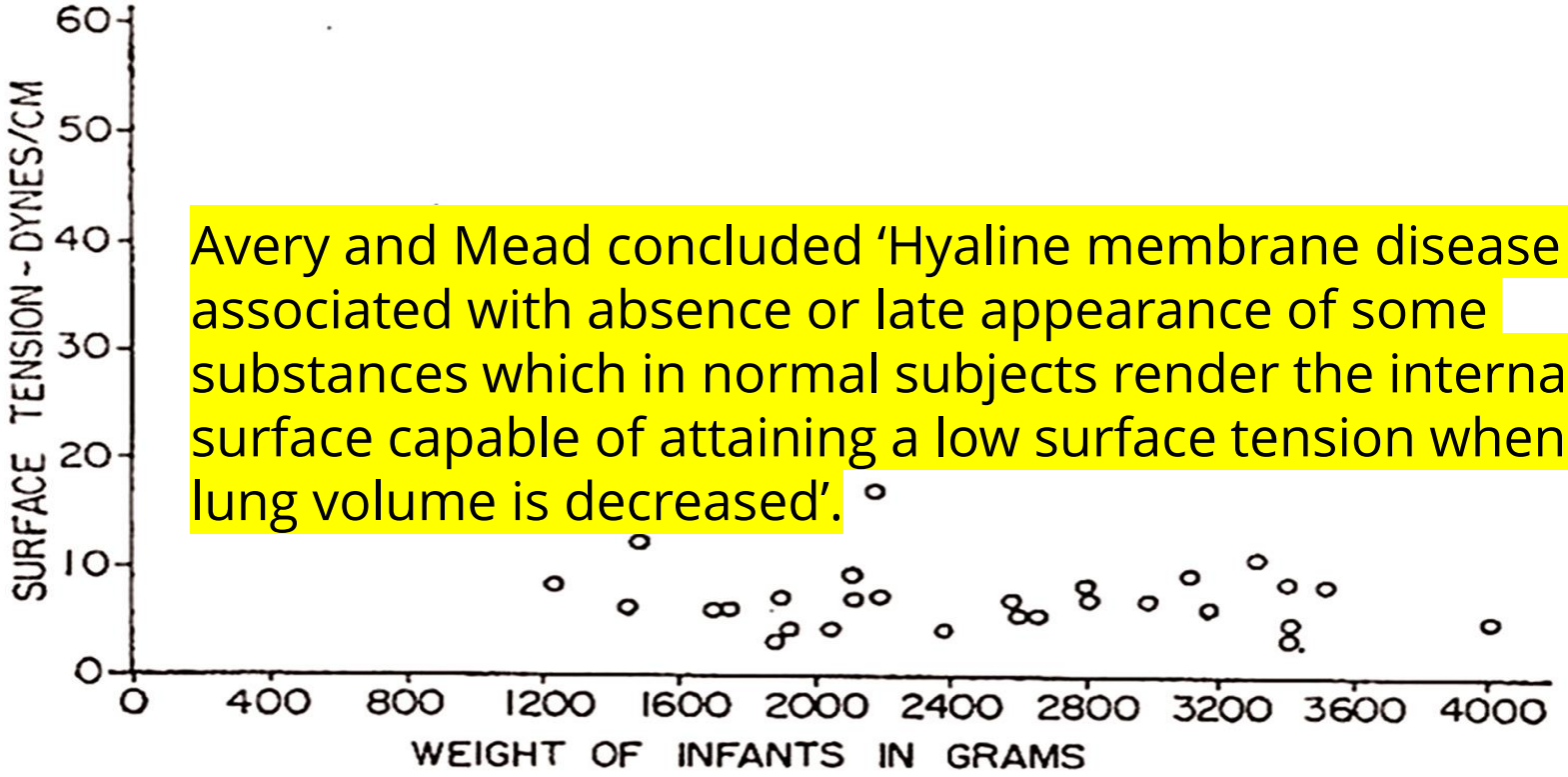


Fig. 3.—Lowest surface tension measured on compression of the surface. Open circles=infants dying from causes other than hyaline membrane disease. Closed circles=infants dying with hyaline membrane disease. Triangle=stillborn infant of a diabetic mother.

Mary Avery

1927 - 2011

Avery ME, Mead J: Am J Dis Child 1959;97:517-523

CONCERN MARKED the face of President Kennedy as he left Otis Air Force Base with his sister, Mrs. Jean Smith. His newly born son had just been rushed to Boston Children's Medical Center. The President had visited Mrs. Kennedy and was on his way to Boston to be with the child.

Invasion

Integration means another race has the right to enjoy the same poor service and bad food the rest have been given all these years.

The Rus

Russell County's Only Daily Paper

VOL. XXXIII — NO. 185

Jackie Gives Birth To Son Prematurely

Wife of President Rushed to Hospital

OTIS AIR FORCE BASE, Mass. (UPI) — Mrs. Jacqueline Kennedy, wife of the President, gave birth today to a four-pound 10½ ounce boy at the Otis Air Force Base Hospital.

THE BABY BOY, five and one-half weeks premature, was born at

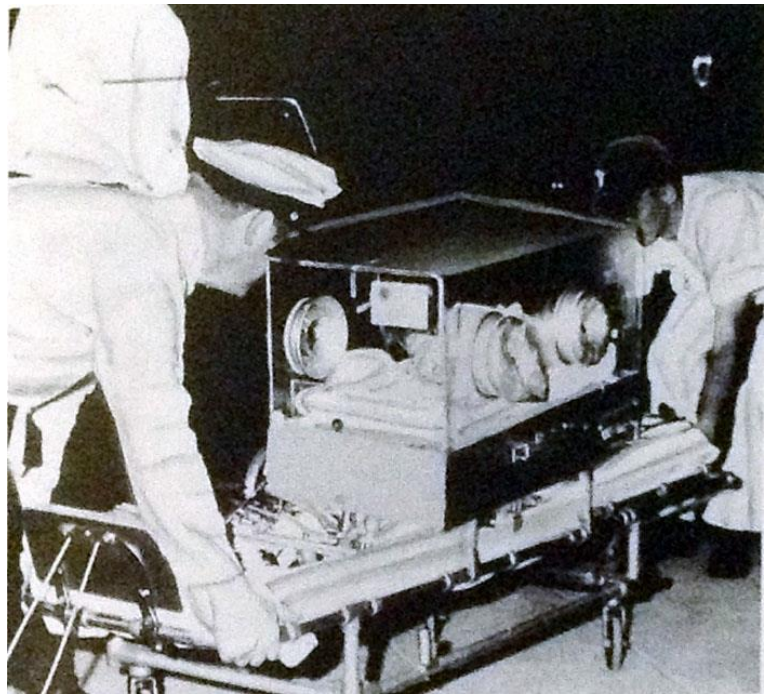
Kennedy was in good condition.

THE CHILD was the third born to President and Mrs. Kennedy and their second boy.

Salinger reported that Mrs. Kennedy had gone from the Kennedy's rented summer home to a stable area owned by the Kennedy family near Osterville about 11 a.m. However, she returned home im-

Dr. John W. Walsh,

Patrick Bouvier Kennedy
August 7, 1963
34.5 weeks and 2100 g
Placental abruption



2d Son Born to Kennedys; Has Lung Illness

Child Transferred to Boston After Birth at Cape Hospital

By WILLIAM M. BLAIR
Special to The New York Times

BOSTON, Aug. 7—A second son, Patrick Bouvier Kennedy, was born to President and Mrs. Kennedy at Otis Air Force Base on Cape Cod today. A few hours later the premature infant was rushed to Boston for treatment of a respiratory ailment.

The President flew from Washington to Cape Cod but arrived 40 minutes after the

An obituary in the New York Times noted the absence of any specific treatment for hyaline membrane disease.

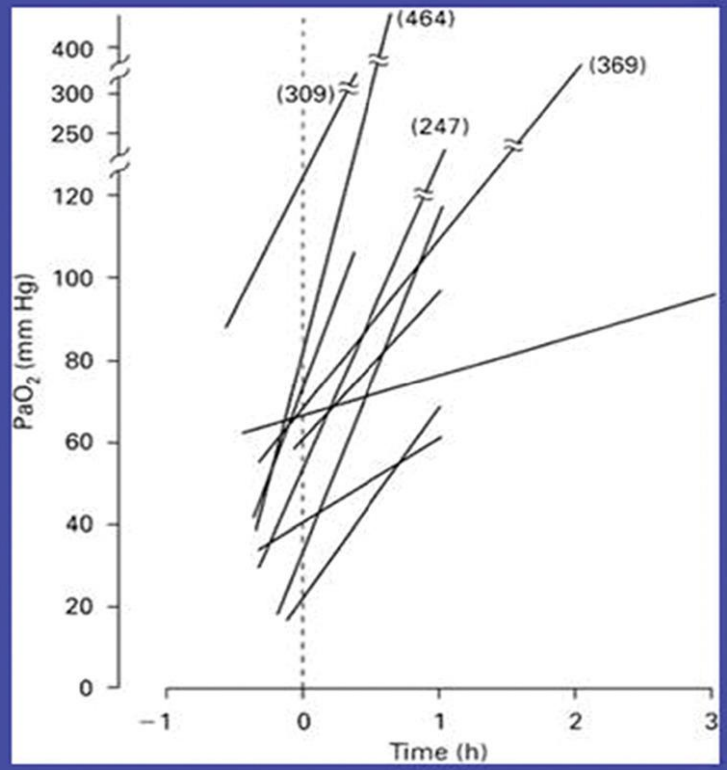
This event helped focus attention on RDS.
Within a year trials with synthetic surfactants had begun.

Nebulized synthetic surfactants: 1964-1968

JFK Baby Death in 1963 Sparked Medical Race to Save Preemies - ABC News

1. Worked in Adams´ laboratory in Los Angeles, California in the 1960s and the 1970s

2. Returned to Japan and treated ten preterm babies with a modified natural surfactant (Surfactant-TA)



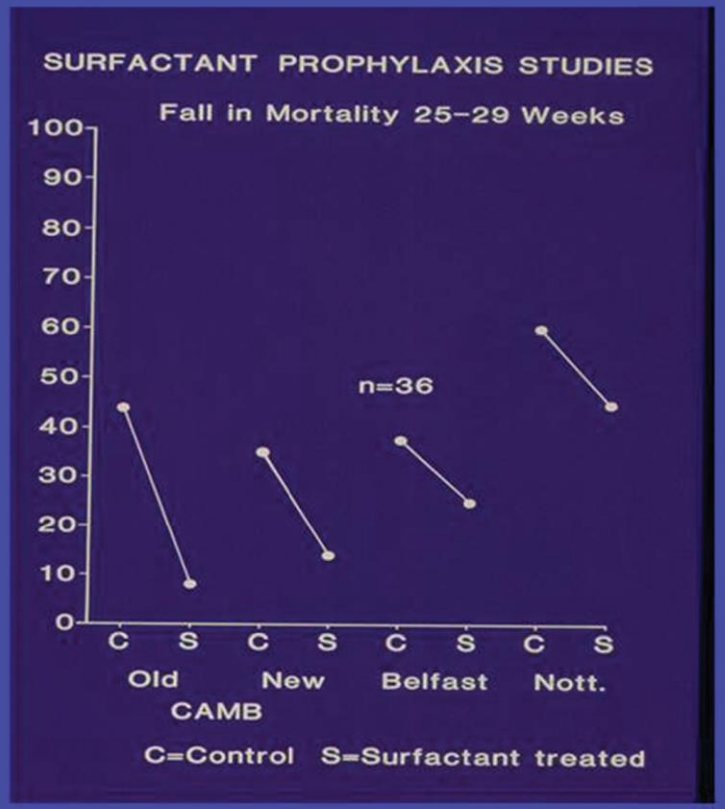
Tetsuro Fujiwara
1931 – 2024

- Surfactant TA
- 10 infants
- 30 wk; >1500 g
- 9 had PDA
- 2 died

Fujiwara et al: Lancet 1980; i:55-59

Colin Morley

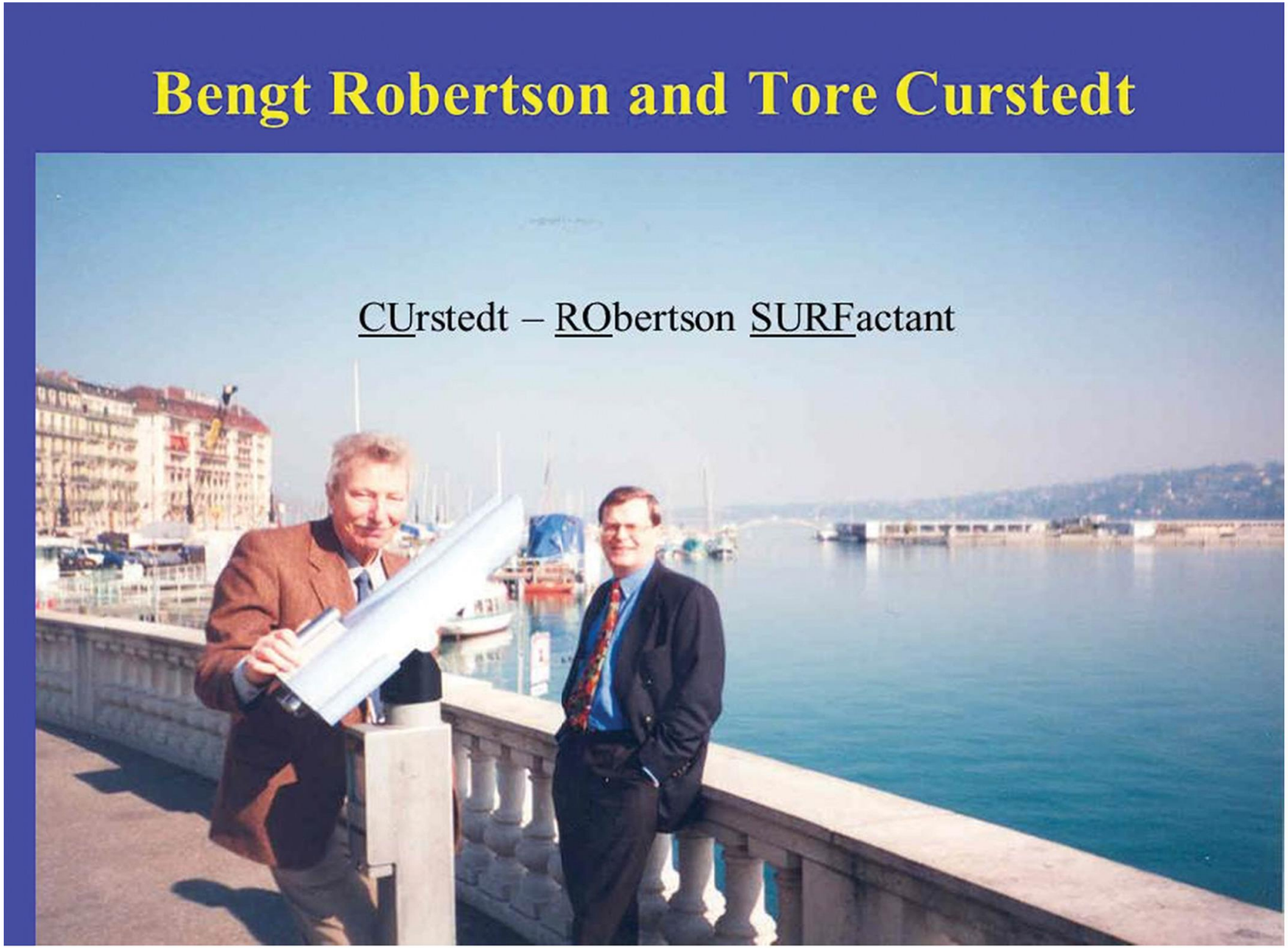
Pumactant or ALEC with Alec Bangham in 1980s – DPPC and PG.
Halliday et al: Lancet; i: 476-8: Turfsurf – DPPC and HDL.



UK trials with DPPC-based surfactants

J Paediatrics Child Health, Volume: 53, Issue: 4, Pages: 327-332, First published: 08 March 2017, DOI: (10.1111/jpc.13500)

Bengt Robertson and Tore Curstedt



J Paediatrics Child Health, Volume: 53, Issue: 4, Pages: 327-332, First published: 08 March 2017, DOI: (10.1111/jpc.13500)

1980-1990

- Multiple RCTs
- Meta-analysis articles suggesting surfactant saves lives

Clinical Trial > Eur J Pediatr. 1990 Mar;149(6):416-23. doi: 10.1007/BF02009663.

A European multicenter randomized controlled trial of single dose surfactant therapy for idiopathic respiratory distress syndrome

J D Horbar [1], R F Soll, H Schachinger, G Kewitz, H T Versmold, O Linderkamp, E P Zilow, et al.

Affiliations + expand

PMID: 2185026 DOI: 10.1007/BF02009663

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Volume 85, Issue 6

June 1990

ARTICLES | JUNE 01 1990

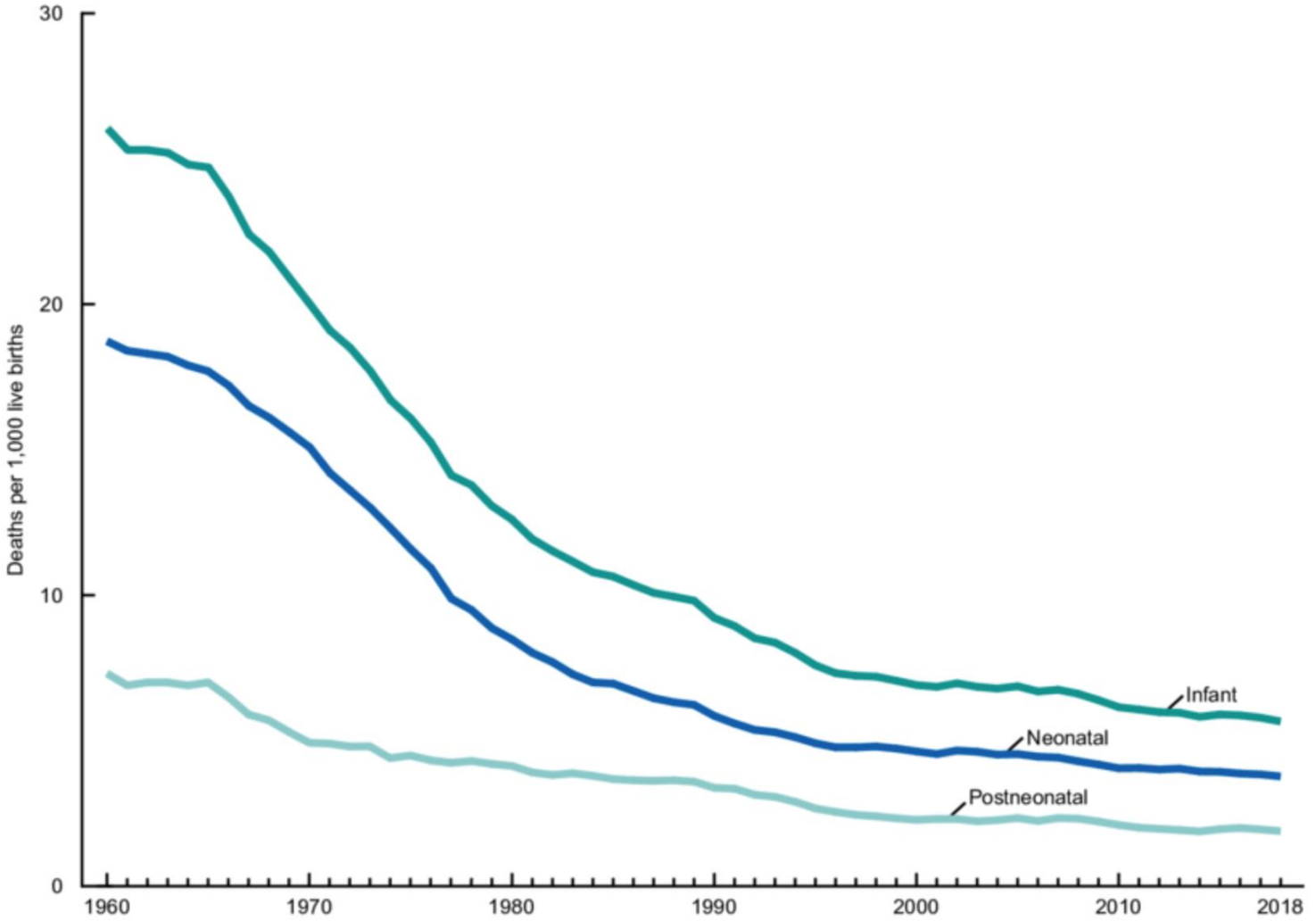
Multicenter Trial of Single-Dose Modified Bovine Surfactant Extract (Survanta) for Prevention of Respiratory Distress Syndrome

Roger F. Soll; Ronald E. Hoekstra; John J. Fangman; Anthony J. Corbet; James M. Adams; L. Stanley James; Karl Schulze; William Oh; Jesse D. Roberts, Jr; John P. Dorst; Sandra S. Kramer; A. Jack Gold; Elizabeth M. Zola; Jeffrey D. Horbar; Timothy L. McAuliffe; Jerold F. Lucey; The Ross Collaborative Surfactant Prevention Study Group

Pediatrics (1990) 85 (6): 1092–1102.

https://doi.org/10.1542/peds.85.6.1092 **Article history**

Infant and Neonatal Mortality Rate



NOTE: Rates are infant (under 1 year), neonatal (under 28 days), and postneonatal (28 days–11 months) deaths per 1,000 live births in specified group.
SOURCE: National Center for Health Statistics, National Vital Statistics System, Mortality.

Cochrane Database of Systematic reviews | Review - Intervention

Prophylactic versus selective use of surfactant in preventing morbidity and mortality in preterm infants

Roger Soll, Colin J Morley Authors' declarations of interest

Version published: 23 April 2001 Version history

Comparison 1. Prophylactic Surfactant vs. Treatment with Surfactant

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Pneumothorax	6	2515	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.42, 0.89]
2 Pulmonary interstitial emphysema	5	2037	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.36, 0.82]
3 Necrotizing enterocolitis	5	2368	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.73, 1.40]
4 Patent ductus arteriosus	6	2515	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.85, 1.09]
5 Intraventricular hemorrhage	7	2508	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.82, 1.03]
6 Severe intraventricular hemor-rhage	7	2508	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.66, 1.06]
7 Bronchopulmonary dysplasia	8	2816	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.82, 1.12]
8 Neonatal mortality	7	2613	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.48, 0.77]

1990-2010

- Antenatal steroid optimization
- PEEP optimization
- Early use of surf; especially for extremely preterm infants
- Ongoing conundrum about resource poor settings : unavailability of the surfactant and mechanical ventilation

The rise of NCPAP, INSURE and non-invasive strategies: 1995-2010

Surfactant Replacement in Spontaneously Breathing Babies with Hyaline Membrane Disease – a Pilot Study

Subject Area: Women's and Children's Health

Lars H. Victorin; L.V. Deverajan; Tore Curstedt; Bengt Robertson

Biology of the Neonate (1990) 58 (3): 121–126.
https://doi.org/10.1159/000243250 Article history

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Abstract

In a neonatal unit which, at that time, had no facilities for artificial ventilation, 14 newborn infants with birth weight ≥ 1,500 g fulfilling the diagnostic criteria for severe hyaline membrane disease (HMD) were treated by tracheal instillation of bovine surfactant (200 mg/kg). Twelve of

ACTA PÆDIATRICA
NURTURING THE CHILD

REVIEW ARTICLE | Full Access

RDS – CPAP or surfactant or both

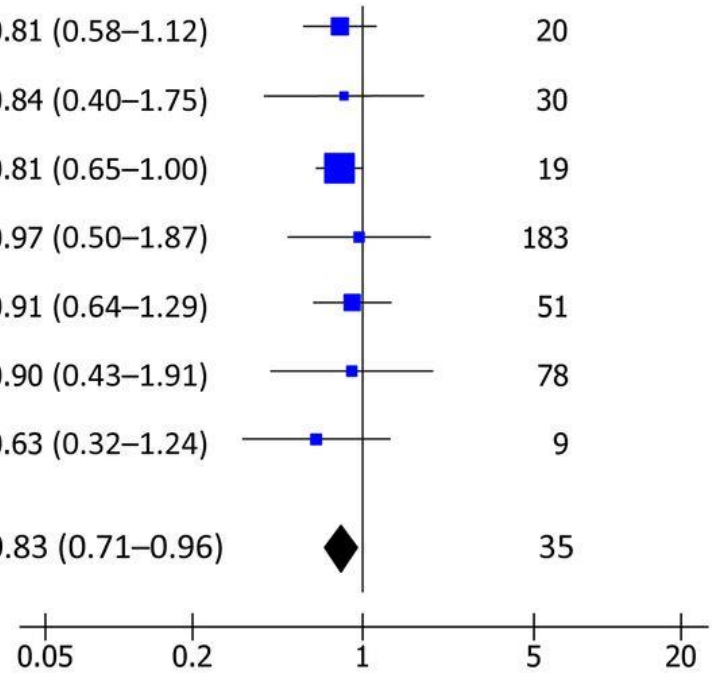
Kajsa Bohlin

To surf or not to surf?

- The initial approach towards the non-invasive ventilation was started out of necessity to optimize care in resource poor settings became critical for the next step of our journey

Because..Effect of avoiding eMV on death or BPD

Study or Subgroup	Avoid ventilation		Control group		Weight, %	Odds Ratio	NNT
	BPD/death	Total	BPD/death	Total		Random effects model (95% CI)	
COIN (2008)	108	307	122	303	19.8	0.81 (0.58–1.12)	20
CNRN (2009)	53	74	54	72	4.0	0.84 (0.40–1.75)	30
SUPPORT (2010)	323	663	353	653	45.5	0.81 (0.65–1.00)	19
CURPAP (2010)	22	103	23	105	4.9	0.97 (0.50–1.87)	183
DRM (2011)	68	223	138	425	17.4	0.91 (0.64–1.29)	51
AMV (2011)	15	108	17	112	3.8	0.90 (0.43–1.91)	78
Take Care (2013)	25	74	30	67	4.6	0.63 (0.32–1.24)	9
Total	614	1552	737	1737	100	0.83 (0.71–0.96)	35



Test for overall effect: $z = 2.55$ ($P = .01$)

Heterogeneity: $Tau^2 = 0.00$; $\chi^2 = 1.27$; df = 6 ($P = .97$); $I^2 = 0\%$

Hendrik S. Fischer, and Christoph Bührer Pediatrics 2013;132:e1351-e1360

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Prophylactic vs Selective surf: Cochrane Review 2012

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Analysis 1.1. Comparison 1 Prophylactic surfactant vs. treatment of established respiratory distress in preterm infants, Outcome 1 Neonatal mortality.

Study or subgroup	Prophylactic n/N	Selective n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Studies without routine application of CPAP					
Bevilacqua 1996	28/136	46/132		16.94%	0.59[0.39,0.89]
Bevilacqua 1997	9/49	9/41		3.44%	0.84[0.39,1.80]
Dunn 1991	9/62	8/60		2.95%	1.09[0.45,2.63]
Egberts 1993	8/75	14/72		5.18%	0.55[0.24,1.23]
Kattwinkel 1993	3/627	11/621		4.01%	0.27[0.08,0.96]
Kendig 1991	23/235	40/244		14.24%	0.6[0.37,0.97]
Merritt 1991	27/76	21/72		7.83%	1.22[0.76,1.95]
Walti 1995	15/134	23/122		8.74%	0.59[0.33,1.08]
Subtotal (95% CI)	**1394**	**1367**		**63.33%**	**0.69[0.56,0.85]**
Total events: 122 (Prophylactic), 172 (Selective)					
Heterogeneity: Tau^2=0; Chi^2=10.6, df=7(P=0.16); I^2=33.95%					
Test for overall effect: Z=3.54(P=0)					
1.1.2 Studies with routine application of CPAP					
Dunn 2011	10/209	8/221		2.82%	1.32[0.53,3.28]
SUPPORT 2010	114/653	94/663		33.85%	1.23[0.96,1.58]
Subtotal (95% CI)	**862**	**884**		**36.67%**	**1.24[0.97,1.58]**
Total events: 124 (Prophylactic), 102 (Selective)					
Heterogeneity: Tau^2=0; Chi^2=0.02, df=1(P=0.88); I^2=0%					
Test for overall effect: Z=1.73(P=0.08)					
Total (95% CI)	**2256**	**2251**		**100%**	**0.89[0.76,1.04]**
Total events: 246 (Prophylactic), 274 (Selective)					
Heterogeneity: Tau^2=0; Chi^2=22.17, df=9(P=0.01); I^2=59.41%					
Test for overall effect: Z=1.48(P=0.14)					
Test for subgroup differences: Chi^2=13.11, df=1 (P=0), I^2=92.37%					

Favours prophylactic 0.1 0.2 0.5 1 2 5 10 Favours selective

Not all preterm infants would need surfactant replacement therapy but

Early surfactant is better; Cochrane 2011

Analysis 1.6. 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
1.6.1 Synthetic surfactant					
OSIRIS 1992	429/1344	514/1346		94.79%	0.84[0.75,0.93]
Subtotal (95% CI)	**1344**	**1346**		**94.79%**	**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)					
1.6.2 Animal-derived surfactant					
Gortner 1998	12/154	15/163		2.69%	0.85[0.41,1.75]
Plavka 2002	6/21	14/22		2.52%	0.45[0.21,0.95]
Subtotal (95% CI)	**175**	**185**		**5.21%**	**0.65[0.39,1.1]**
Total events: 18 (Early treatment), 29 (Late treatment)					
Heterogeneity: Tau^2=0; Chi^2=1.46, df=1(P=0.23); I^2=31.58%					
Test for overall effect: Z=1.6(P=0.11)					
Total (95% CI)	**1519**	**1531**		**100%**	**0.83[0.75,0.91]**
Total events: 447 (Early treatment), 543 (Late treatment)					
Heterogeneity: Tau^2=0; Chi^2=2.62, df=2(P=0.27); I^2=23.59%					
Test for overall effect: Z=3.68(P=0)					
Test for subgroup differences: Chi^2=0.82, df=1 (P=0.37), I^2=0%					

Favors early 0.1 0.2 0.5 1 2 5 10 Favors delayed

but the one who needs it would benefit if it is given early

Also, unable to recognize the need of surfactant replacement therapy would result in CPAP failure which has worse outcomes

Adjusted Odds Ratios of adverse outcomes for infants with CPAP failure

Outcome	25-28 weeks	29-32 weeks
BPD	1.30 (1.09–1.54)	1.57 (1.23–1.99)
Died	1.40 (0.98–2.01)	3.17 (1.78–5.63)
Died or survived with severe BPD	1.36 (1.15–1.62)	1.77 (1.42–2.21)
Died or survived with major morbidity	1.36 (1.15–1.60)	1.87 (1.54–2.29)

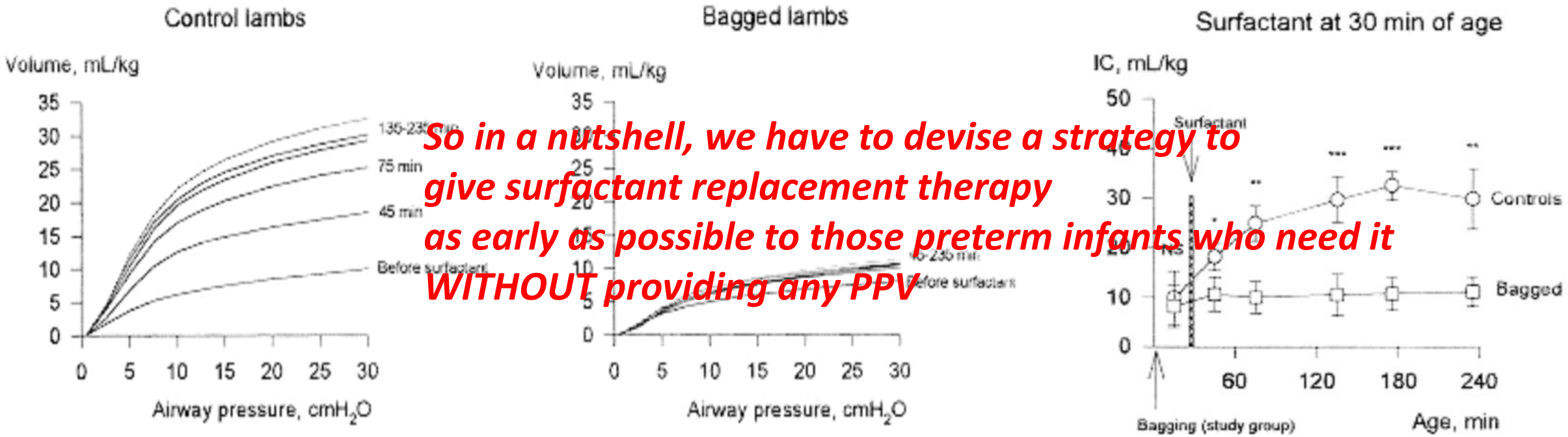
Incidence and Outcome of CPAP Failure in Preterm Infants, Pediatrics, 2016

To recap; thus far; we learned that

- Elective mechanical ventilation is associated with higher death and/or BPD
- CPAP use is not inferior to SRT but CPAP failure rate can be high
- CPAP failure is associated with higher death/BPD
- Therefore----→ Early rescue via INSURE became standard of care across all units by 2012-13

The problem?

Manual Ventilation with a Few Large Breaths at Birth Compromises the Therapeutic Effect of Subsequent Surfactant Replacement in Immature Lambs



So in a nutshell, we have to devise a strategy to give surfactant replacement therapy as early as possible to those preterm infants who need it WITHOUT providing any PPV

Björklund LJ et al; *Pediatr Res*. 1997;42(3):348-355.

What is LISA?

- LISA is an alternative strategy to administer surfactant via a thin endotracheal catheter while providing CPAP in a spontaneously breathing preterm infant with RDS

- Use of LISA allows administration of surfactant while avoiding positive pressure ventilation

- Observational studies have fostered expectations of a positive effect of LISA on mortality, BPD, the need for mechanical ventilation, and the duration of oxygen supplementation (Dargaville PA, Arch Dis 2013; Kribs A *Klin Padiatr*. 2010; Klebermass *Neonatology*. 2013)

- There are four different techniques for less invasive surfactant delivery: surfactant administration via a thin catheter, aerosolized surfactant administration, pharyngeal surfactant administration, and laryngeal mask airway (LMA)-guided surfactant administration

- The most studied method has been surfactant instillation via thin catheter

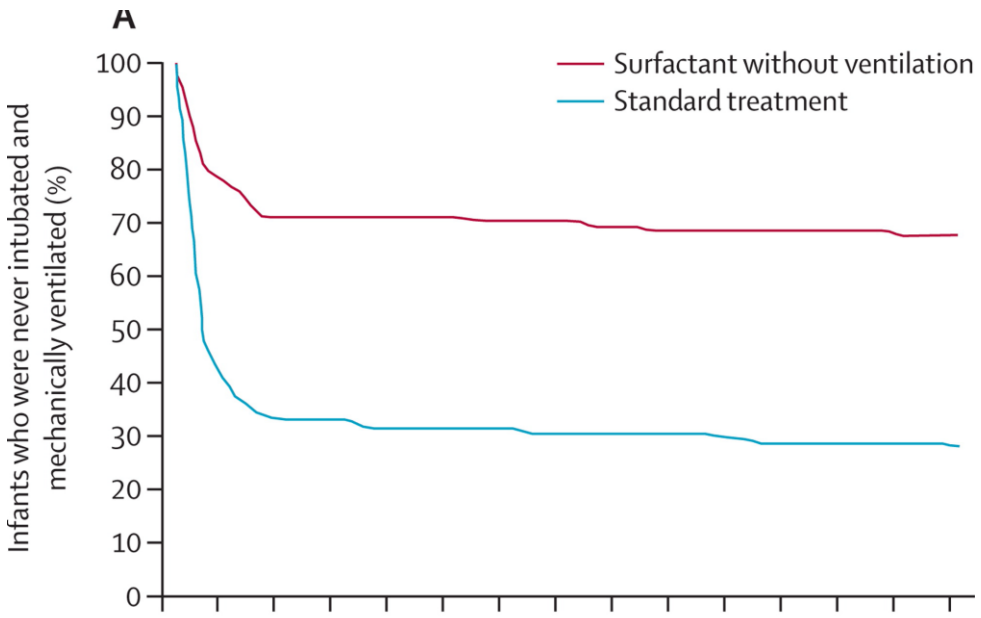
- After few observational studies; 3 major RCTs and meta-analysis have been published

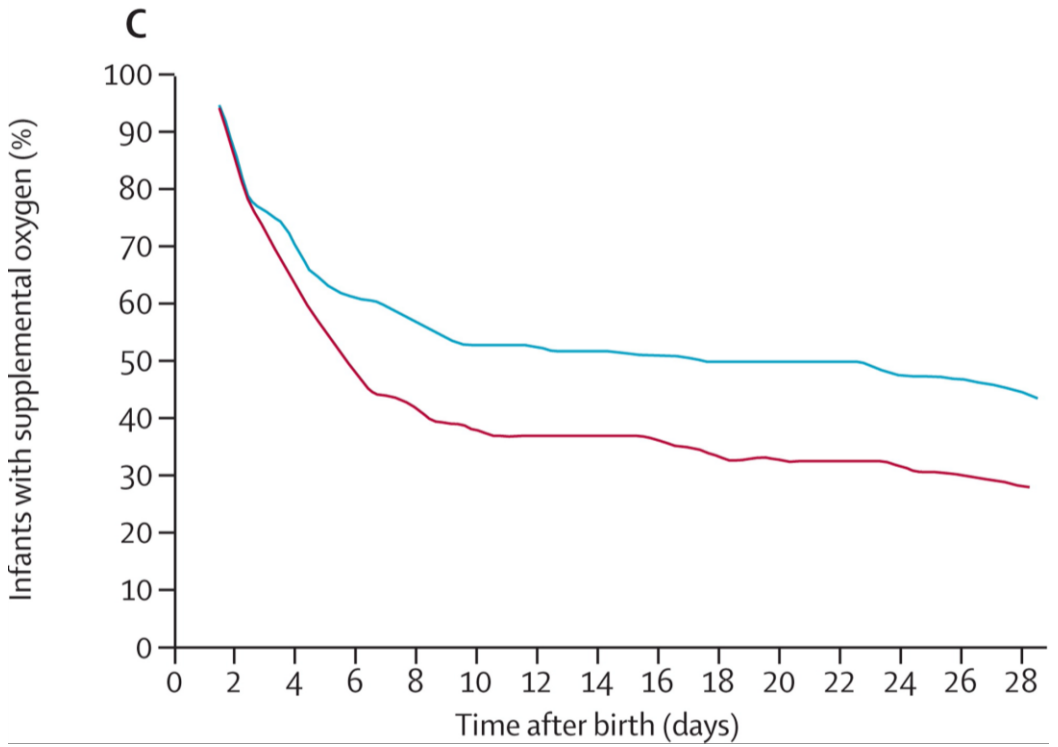
Avoidance of mechanical ventilation (AMV): an open-label, randomized, controlled trial; Lancet, 2011

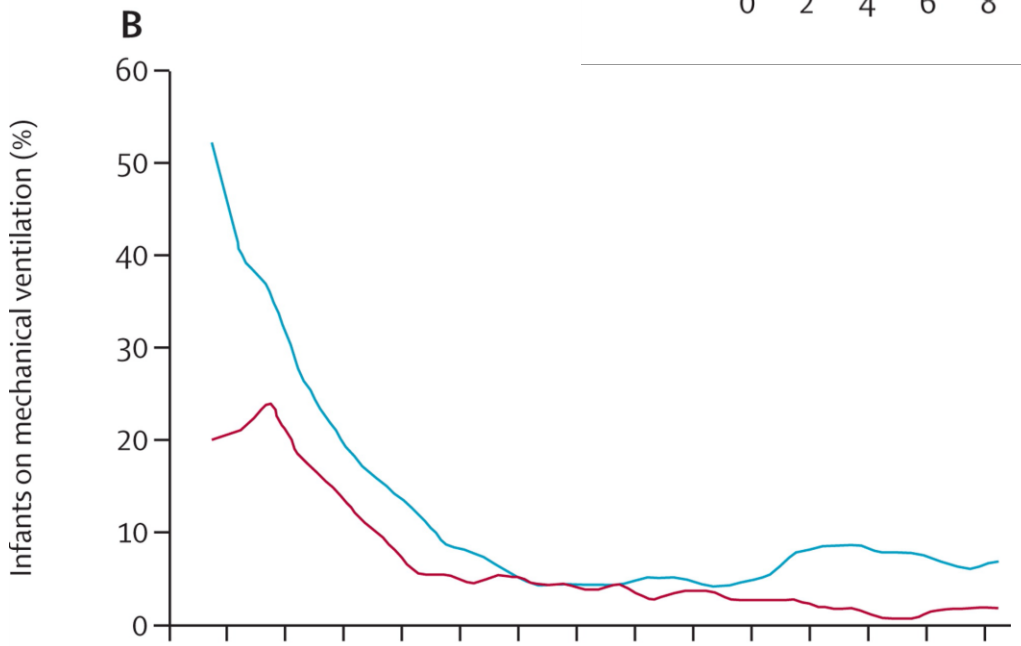
	Intervention group (n=108)	Standard treatment group (n=112)	Absolute risk reduction (95% CI)	Number needed to treat (95% CI)	p value*
All infants (%)	30 (28%)	51 (46%)	−0·18 (−0·30 to −0·05)	6 (3 to 20)	0·008
26 weeks' gestation (%)	11/26 (42%)	11/26 (42%)	0·00 (−0·27 to 0·27)	..	1·000
27 weeks' gestation (%)	12/41 (29%)	21/44 (48%)	−0·18 (−0·39 to 0·03)	..	0·119
28 weeks' gestation (%)	7/41 (17%)	19/42 (45%)	−0·28 (−0·47 to −0·08)	4 (2 to 13)	0·009

26-28 weeks
< 1500 g BW:
12 centers across Germany

Primary endpoint: Need for any mechanical ventilation for the first 72 HOL







Infants who received LISA were

A. **less frequently intubated,**
B. **had fewer days of mechanical ventilation,**
C. **needed less oxygen at 28 days**

AMV, Lancet, 2011

Primary Outcome	Take Care *n* = 100	InSurE *n* = 100	*P*	RR	95% CI	NNT	*P**
All infants							
Early MV, %	30	45	.02	−0.52	−0.94 to −0.29	6	.02
Any MV, %	40	49	.12	−0.56	−1 to −0.29		.08
BPD, *n* (%)	9 (10.3)	17 (20.2)	.009	−0.27	−0.72 to −0.1	10	.005
≤28 wk	*n* = 59	*n* = 55					
Early MV, %	32	52	.02	−0.43	−0.91 to −0.19		.02
Any MV, %	45	59	.09	−0.42	−0.94 to −0.47		.03
BPD, *n* (%)	6 (13.6)	16 (26.2)	.008	−0.21	−0.65 to −0.07	7	.004

Take Care, Pediatrics, 2013
<32 weeks
LISA vs INSURE
Primary outcome:
Need for MV in the first 72 HOL

LISA in Extremely Preterm Infants (23-26 weeks)

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

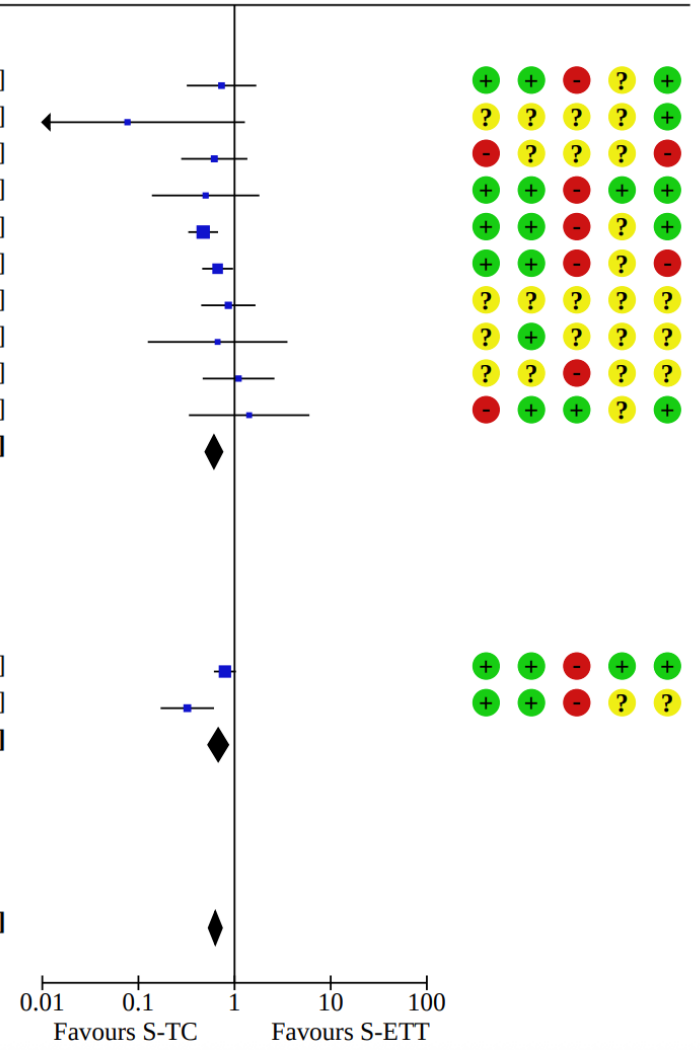
OPTIMIST TRIAL; JAMA 2021

	No./total (%)		Risk difference, % (95% CI)[a]	Relative risk (95% CI)[a]	*P* value
	Minimally invasive surfactant therapy	Control treatment			
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

25-28 weeks
33 centers across the world
MIST vs SHAM
Death or BPD: 43% vs 49%

Avoidance of early MV in the first 72 HOL

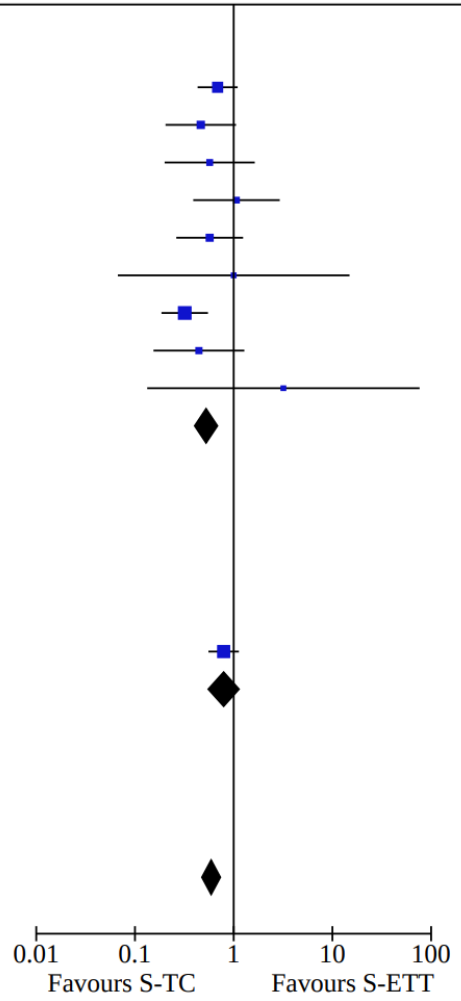
Study or Subgroup	Surfactant via catheter Events	Total	Surfactant via ETT Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 S-TC vs INSURE						
Bao 2015	8	47	10	43	4.0%	0.73 [0.32 , 1.68]
Boskabadi 2019	0	20	6	20	2.5%	0.08 [0.00 , 1.28]
Choupani 2018	8	52	13	52	5.0%	0.62 [0.28 , 1.36]
Gupta 2020	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)						



Cochrane Analysis, 2021

Death or BPD at 36 weeks

Study or Subgroup	Surfactant via catheter Events	Total	Surfactant via ETT Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A	B	C	D	E
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 Analysis, 2021

Volume 120, Issue 1
March 2023

120 | 1 | 23
Neonatology
Fetal and Neonatal Research

GUIDELINES | MARCH 07 2023

European Consensus Guidelines on the Management of Respiratory Distress Syndrome: 2022 Update

Government of Western Australia
Child and Adolescent Health Service

Child and Adolescent Health Service
Neonatology

GUIDELINE

Surfactant Therapy

Scope (Staff):	Nursing and Medical Staff
Scope (Area):	NICU KEMH, NICU PCH, NETS WA

POSITION STATEMENT

828 Shares

Guidelines for surfactant replacement therapy in neonates

Test Your Knowledge

Posted: Feb 1, 2021

The preferred method of surfactant administration has now become LISA

Of the 472 neonatologists who answered the survey, 15% used LISA either as a part of routine care (8%) or as part of research (7%).

D.Kurepa, J Perinat 2019

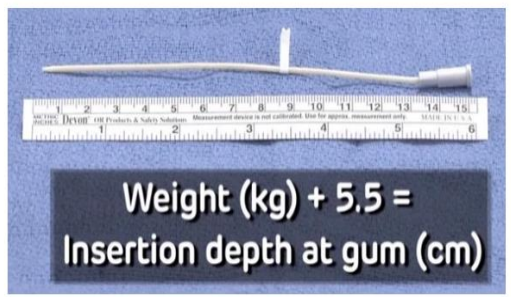
Types of catheter

Name	Device type	Procedure/instruments
Cologne method	Flexible suction catheter	Laryngoscope + Magill forceps
SONSURE	Flexible nasogastric tube	Laryngoscope + Magill forceps
Take Care method	Flexible nasogastric tube	Laryngoscope, no forceps
Hobart method	Semi-rigid vascular catheter Device name: for example, Lisacath	Laryngoscope, no forceps
QuickSF	Soft catheter Device name: Neofact	Laryngoscope + intrapharyngeal guidance device
INSURE	Endotracheal tube	Laryngoscope

Implementation of LISA at UW/SCH Regional Network

Pre-Procedure:

- Provider:
  - Order medications & equipment (STAT)
    - *Curosurf (2.5 ml/kg)*
    - IV atropine (0.02 mg/kg)
    - Optional: IV fentanyl (0.5 mcg/kg)
    - Pre-medications for possible intubation and appropriate equipment should be immediately available in the case of need for traditional intubation with ETT
  - Prepare Catheter (*BD Angiocath* – 16GA 5.25IN, 1.7 x 133 mm)
    - With sterile gloved hands, **REMOVE STYLET FROM ANGIOCATH**
    - If desired, bend tip of Angiocath gently
    - Mark circumferentially with a piece of tape at the location determined by the following equation:

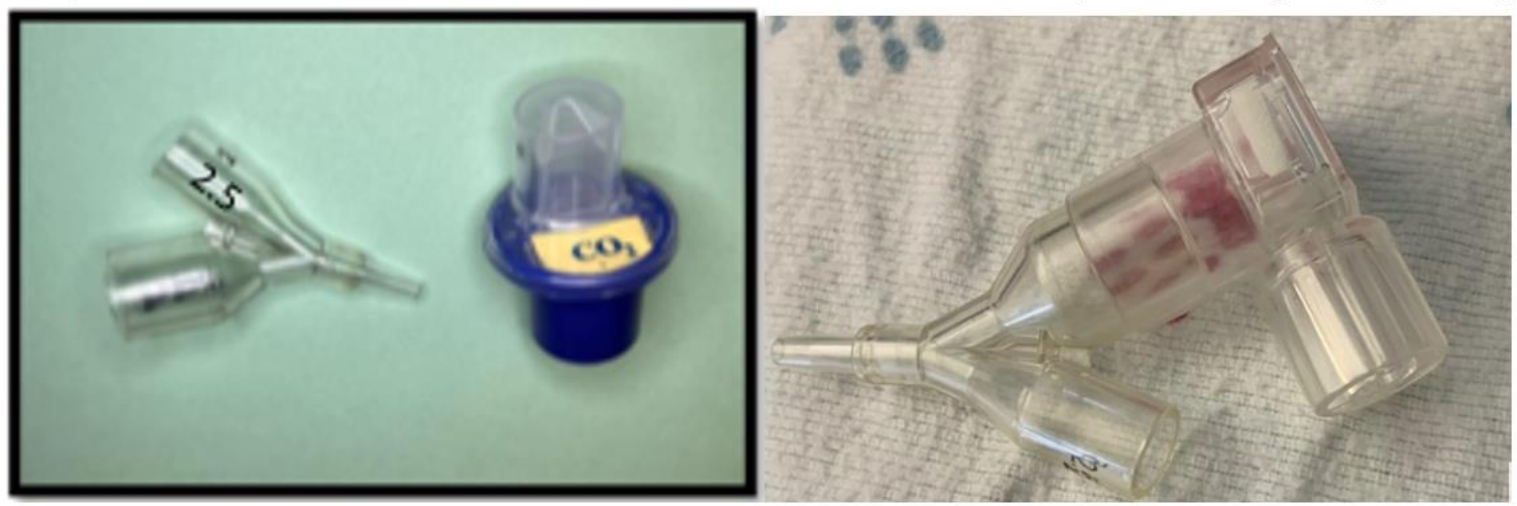


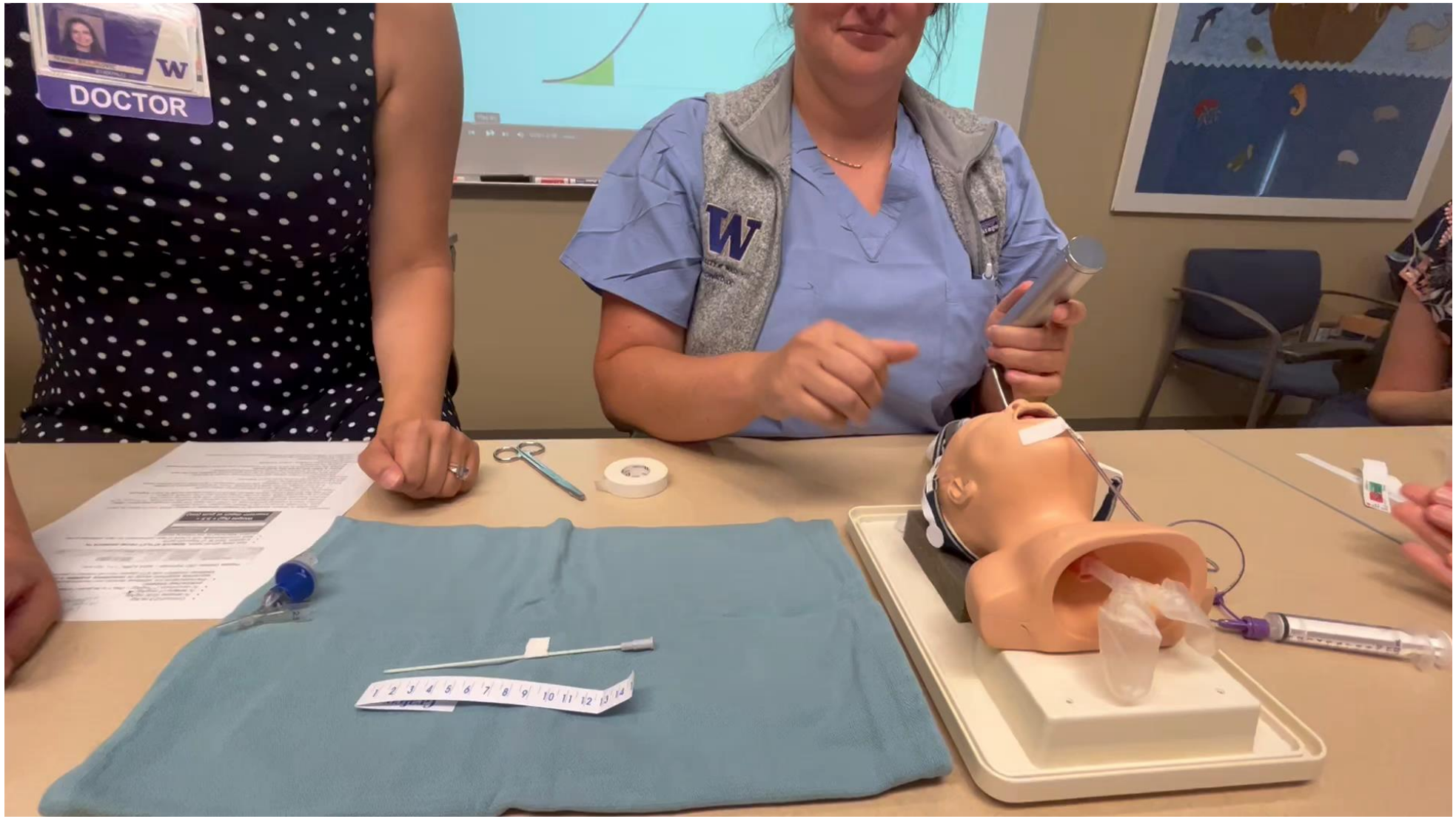
- Nurse:
  - Place OG tube prior to procedure; aspirate stomach contents
  - Have suction catheter available, 8 or 10 fr.
  - Swaddle infant if vigorous, leaving feet exposed for flicking

RT:

- Obtain surfactant and intubation tray

- Prepare laryngoscope or Video Glideslope with appropriately sized blade
- Prepare end-tidal CO_2 detector and 2.5 or 3.0 ETT Y-piece adaptor (below)




DOCTOR

Implementation of LISA at UW/SCH

- Four level III-IV NICUs within the UW/Seattle Children's Hospital Neonatology Regional Network participated in this QI project
- Each local site established a multidisciplinary team and providers from all four sites participated in monthly regional meetings
- A protocol for LISA was crafted and adapted at each individual site
- The process was refined through shared experience across sites, including use of premedication, interface for delivery of positive pressure during the procedure, type of laryngoscope, type of catheter, process for catheter depth estimation, methods for confirming catheter placement, and rate of surfactant administration. Providers participated in education and simulations
- Frequent simulation sessions
- Information regarding each LISA encounter was entered into a REDCap database and data were analyzed across sites using descriptive statistical tools
- ***Threshold for use of surfactant replacement therapy: FiO2 0.3% and max NCPAP 6 cm of H20***

UW experience

- Out of 2019 total NICU admissions of infants <37 weeks across all four hospital sites, **273 (13.5%)** received surfactant administration during the implementation periods at all sites

- There were a total of **183** (9%) LISA encounters across all four sites

- Out of 343 VLBW infants, 163 infants (47%) received surfactant replacement therapy. Out of which **89** (26%) had LISA.

UW/SCH experience

Patient/procedure	N=183
Gestational age, median (IQR)	28 (25-36)
Birthweight, mean (SD)	1542 (715)
Male n (%)	102 (56%)
First attempt success, n (%)	131 (72%)
Number of attempts, median (range)	2 (1-4)
Final procedure success, (%)	160 (92%)
Unsuccessful procedure due to inability to place cath	9 (4.8%)
Unsuccessful procedure due to patient decompensation	4 (2.4%)

Characteristics among VLBW infants	Pre LISA N-321	Post LISA N=343
Use of any surfactant	45%	53%
BPD	12%	9.2%
Death or BPD	23%	17%
Home oxygen	12%	8.5%
CPAP failure	29%	18%

No difference in IVH, NEC, length of mechanical ventilation, ROP and sepsis rates

Future steps

- DR-LISA with NCPAP
- Optimal timing of LISA (sooner is better- <2 HOL)- use of POCUS LUS
- Video vs Direct laryngoscopy
- LISA failure
- Long term outcomes

DR-LISA

NEJM Evidence

CURRENT ISSU

ORIGINAL ARTICLE

Caffeine and Less Invasive Surfactant Administration for Respiratory Distress Syndrome of the Newborn

Authors: Anup Katheria, M.D., Felix Ines, R.C.P., Anamika Banerji, M.D., Andrew Hopper, M.D., Cherry Uy, M.D., Anupama Chundu, M.D., Katherine Coughlin, M.D., +6, and Neil Finer, M.D. Author Info & Affiliations

Published November 21, 2023 | NEJM Evid 2023;2(12) | DOI: 10.1056/EVIDoa2300183 | VOL. 2 NO. 12

2 years outcomes

JAMA

QUESTION For preterm infants with respiratory distress syndrome supported with continuous positive airway pressure, does administration of surfactant via a thin catheter improve survival without moderate to severe neurodevelopmental disability at 2 years of age?

CONCLUSION This follow-up of a randomized clinical trial found that compared with sham treatment, surfactant therapy did not lead to a reduction in the composite outcome of death or neurodevelopmental disability at 2 years of age.

POPULATION

228 Females
225 Males

Infants with a gestational age of 25 to 28 weeks supported with continuous positive airway pressure

Median gestation:
27.3 weeks

LOCATION

33 Neonatal intensive care units worldwide

INTERVENTION

486 Infants randomized
453 Infants analyzed

224
Minimally invasive surfactant
Exogenous surfactant (200 mg/kg poractant alfa) via a thin catheter

229
Control
Sham treatment consisting only of transient repositioning without airway instrumentation

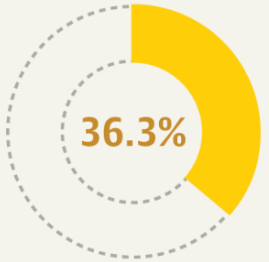
PRIMARY OUTCOME

Death or moderate to severe neurodevelopmental disability at 2 years

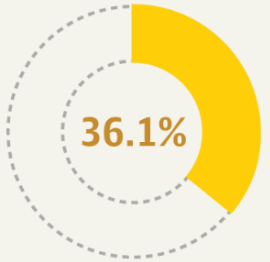
FINDINGS

Death or moderate to severe neurodevelopmental disability

Minimally invasive surfactant
78 of 215 infants



Control
79 of 219 infants



Risk difference, **0%** (95% CI, −7.6% to 7.7%)

Relative risk, **1.00** (95% CI, 0.81 to 1.24)

Dargaville PA, Kamlin COF, Orsini F, et al; OPTIMIST-A Trial Investigators. Two-year outcomes after minimally invasive surfactant therapy in preterm infants: follow-up of the OPTMIST-A randomized clinical trial. *JAMA*. Published September 11, 2023. doi:10.1001/jama.2023.15694

Summary

- Our century-long journey to understand Respiratory Distress Syndrome has been challenging, yet immensely rewarding

- In preterm infants with worsening RDS after initial CPAP stabilization, LISA offers potential advantages over INSURE or continued mechanical ventilation

- Given the current evidence, U.S.-based clinicians are well-justified in routinely adopting LISA as an alternative to intubation and traditional surfactant delivery

- Ongoing research aims to refine the optimal timing, catheter selection, insertion techniques, and the role of pharmacologic and non-pharmacologic support during LISA

- LISA should be integrated into a comprehensive NICU strategy to advance non-invasive respiratory care and improve outcomes in preterm infants.

Thank you!!

“People don’t buy what you do; they buy why you do it.”