Respiratory Distress Syndrome: Landmarks in Surfactant Replacement Therapy

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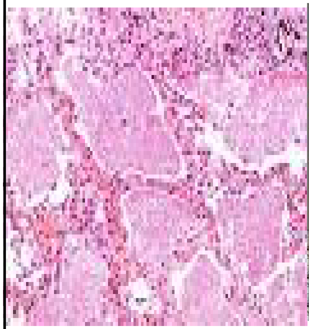
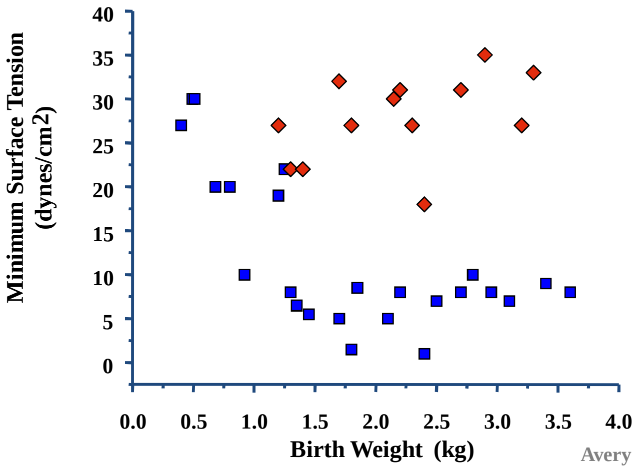


Foundations for Understanding Surfactant Replacement Therapy

In 1929 Kurt von Neergaard,a German physiologist working in Switzerland, evacuated air from an isolated porcine lungs which he then filled with an isotonic gum solution "to eliminate surface tension of the air tissue interfaces" He performed the first pressure-volume during expansion of lungs with both air and liquid.

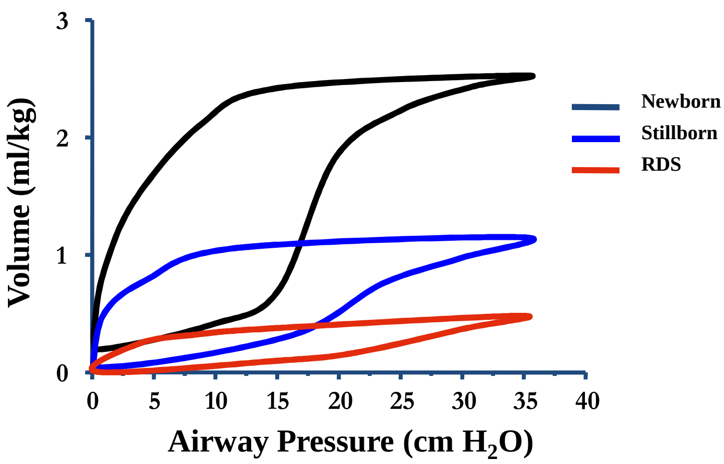
"Surface tension as a force counteracting the first breath of the newly born should be investigated further."

RDS & Defective Surfactant

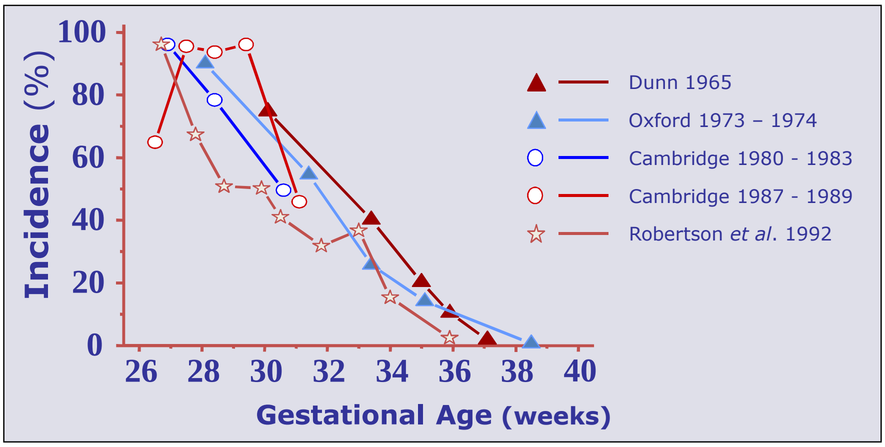


Avery & Mead, AJDC 1959

Pressure - Volume Curves

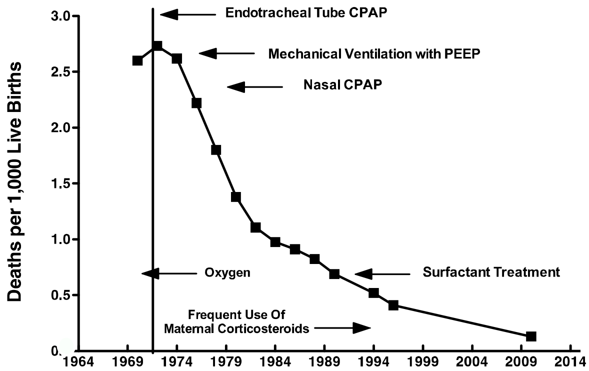


Incidence of RDS by Gestational Age

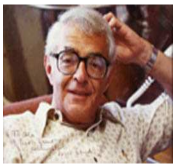


Greenough A, et al. In Greenough A, Milner AO, Robertson NRC, eds. *Neonatal Respiratory Disorders. London, England. Arnold; 1996:238-279*

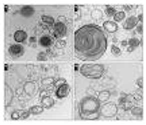
Mortality from RDS – US Population Data



Pathophysiology of RDS



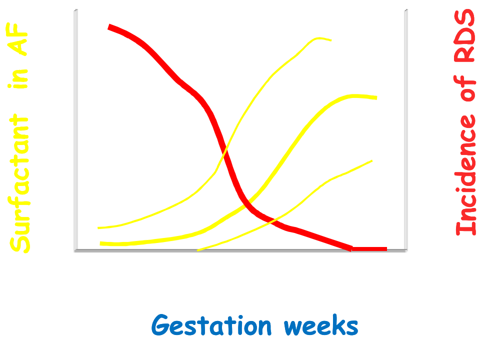
- Surfactant deficiency causes:
- Decreased functional residual capacity
  - Increased chest wall compliance
- Decreased alveolar surface area
- Increased airways compliance
- Gluck et al predicted the probability of RDS based on Lecithin/Sphingomyelin Ratio < 2.0 in Amniotic Fluid



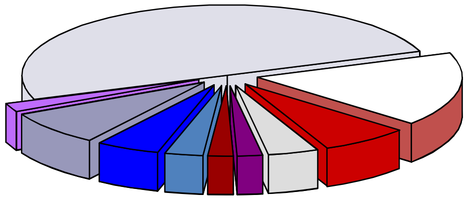
- Hallman et al reported that predominance of phosphatidylinositol in preterm infants and **absence of Phosphatidylglycerol** in Amniotic Fluid also predicted RDS with PPV 98% and regardless of maternal illness e.g. especially diabetes, or "stressed fetuses" that was the basis of the "Lung Profile" for antenatal prediction of RDS

Surfactant and the Risk of RDS

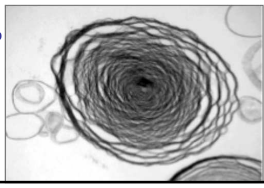
- Surfactant very deficient in immature lung (low pool size)
- Towards term, surfactant secreted into amniotic fluid
- Large variation in surfactant pools for a given gestation
- Surfactant components (L/S and PG) predicts the risk of RDS before birth

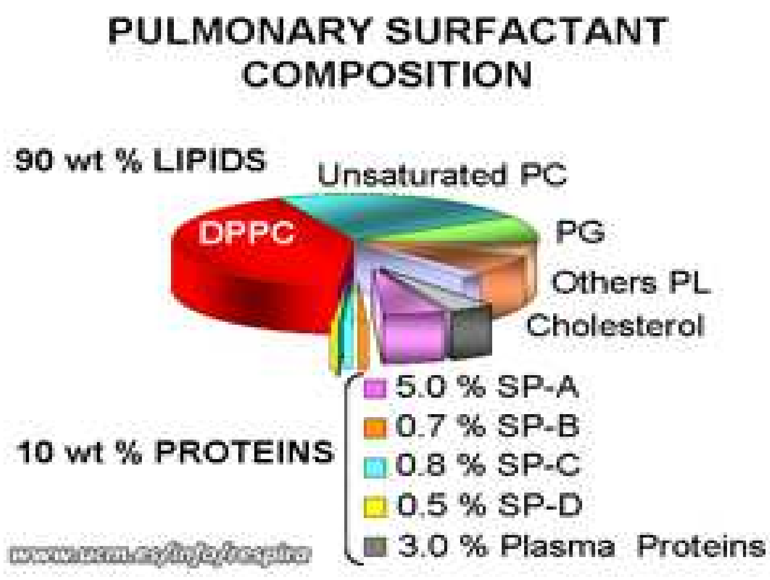


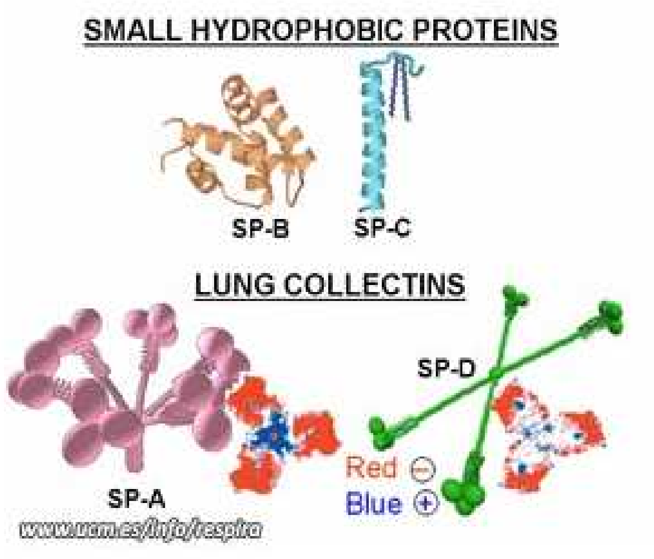
Human Surfactant Composition



- DPPC – dipalmitoylphosphatidylcholine 50%
- Unsaturated phosphatidylcholine 17%
- Phosphatidylglycerol 17%
- Phosphatidylethanolamine 4%
- Syphingomyelin 2%
- Phosphatidylinositol 2%
- Other phospholipids 3%
- Other lipids 5%
- Serum proteins 8%
- Apoproteins or surfactant specific proteins 2%







Surfactant Proteins

Present	Characteristics	Main Effects
SP-B & SP-C	Low molecular weight Hydrophobic, SP-B, SP-C Essential, SP-B null mice die at birth	Adsorption and spreading of phospholipids, Fetal SP-C associated PPROM

Absent	Characteristics	Main Effects
SP-A & SP-D	High molecular weight Hydrophilic, Collectins	Host defense and modulation of inflammatory cytokines in premature labor (from fetal Membranes and Placenta

Van Golde L, *Biol Neonate.* 1995;67(suppl 1):2-17
Jobe A, *N Engl J Med.* 1993;328:861-868
Salminen A, Ph.D. thesis Univ Oulu 2011

Surfactant Protein Function

Protein	Function
SP – A	Tubular myelin, Opsonin, Uptake & secretion of surfactant lipids, Reduces inactivation
SP – B	Tubular myelin, Lipid adsorption, Minimal surface tension, Reduces inactivation
SP – C	Affects lipid order, Synergy with SP – B for surface activity, Reduction of inactivation
SP – D	Opsonin

Surfactant Hydrophobic Proteins-Whitsett and Weaver, NEJM, 2002

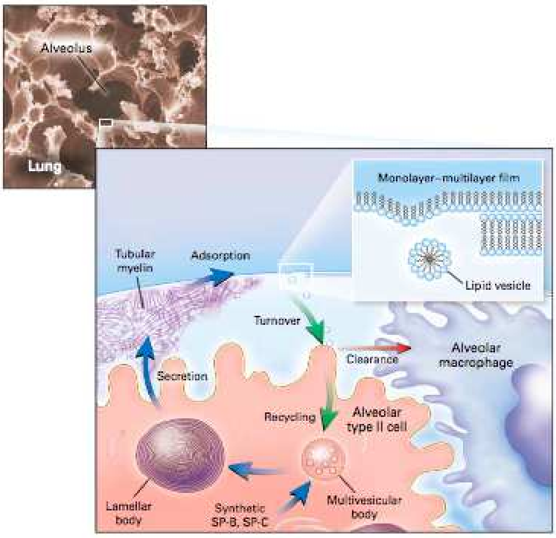
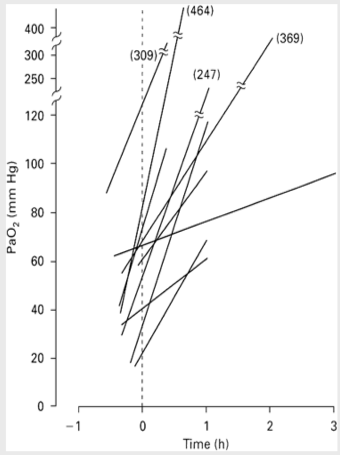


Figure 1. Freeze-Frame View of the Alveolar Space with a Magnified View of the Air–Liquid Interface, with Formation of Pulmonary Surfactant Films.

Tetsuro Fijiwara from Akito,Japan used a bovine lung homogenate (Surfactant TA) (Lancet 1980) give via endotracheal tube in 10 premature infants with RDS average BW <1250 gm and $Fi0_2$ >.8 (2/10 infants died)



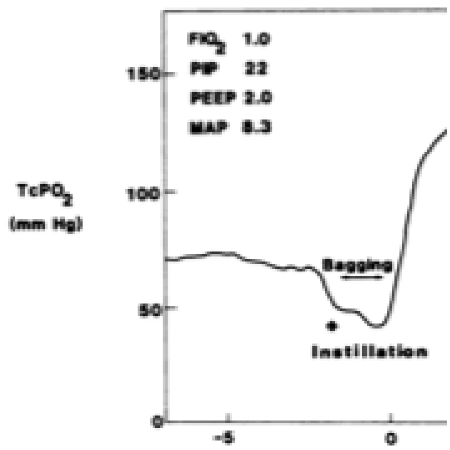
Changes in arterial oxygen tension after surfactant instillation. Fujiwara. Lancet, 1980; i: 55–59.

Hallman, Merritt et al: Isolation of human surfactant from amniotic fluid and a pilot study of its efficacy in respiratory distress syndrome Pediatrics 1983; (17):473

:diate Effects of Surfactant Supplemen-

A mmediately Before Surfactant	B 5 Min After Surfactant	C 1 Hr After Surfactant
69 ± 11	239 ± 19[a]	73 ± 13
50 ± 3	48 ± 1	44 ± 2[b]
.26 ± 0.04	7.26 ± 0.03	7.32 ± 0.02
.94 ± 0.03	0.95 ± 0.03	0.49 ± 0.03[a]
0.3 ± 1.1	10.2 ± 1.2	9.5 ± 0.7[c]

re defined in Table 5 footnote. [a] P < with A; [b] P < .025 as compared with A; ared with A.



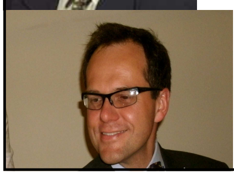
Proof of Principle: Human Surfactant Therapy Collaboration between Helsinki and San Diego

Exogenous human surfactant for treatment of severe respiratory distress syndrome: A randomized prospective clinical trial, J Pediatrics 1985 Mikko Hallman, M.D. T. Allen Merritt, M.D. Anna-Liisa Jarvenpaa, M.D. Bruce Boynton, M.D. Frank Mannino, M.D. Louis Gluck, M.D. Thomas Moore, M.D. David Edwards

PROPHYLACTIC TREATMENT OF VERY PREMATURE INFANTS WITH HUMAN SURFACTANT

T. Allen Merritt, M.D., Mikko Hallman, M.D., Barry T. Bloom, M.D., Charles Berry, Ph.D., Kurt Benirschke, M.D., David Sahn, M.D., Thomas Key, M.D., David Edwards, M.D., Anna-Liisa Jarvenpaa, M.D., Maija Pohjavuori, M.D., Kaisa Kankaanpaa, M.D., Marjatta Kunnas, M.D., Heikki Paatero, M.D., Juhani Rapola, M.D., and Jaakko Jaaskelainen, M.D.

New Engl Journal Medicine, 1986



Era of Surfactant Clinical Trials from 1980-2005 Europe, Canada & USA

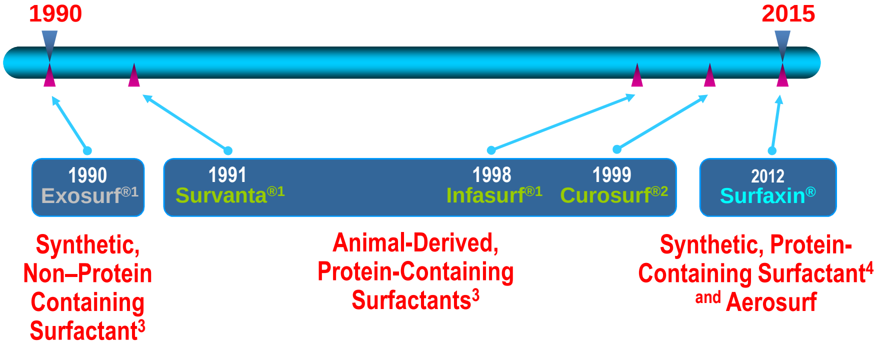
Surfactant treatment trials comprised the most studied "drug(s)" used in Neonatal Medicine that has been evaluated by Randomized Controlled Clinical Trials either versus placebo or a comparative surfactants

Surfactant has reduced infant mortality greater than any treatment for infants since the introduction of PEEP.

Landmark studies on surfactant therapy

1st trial with Detergent Alevaire	Gruenwald 1948
Deficient surface activity in RDS	Avery 1959
1st RTC with Dipalmitoyl PC	Clements 1964
L/S ratio, fetal lung maturity	Gluck 1970-72
Antenetal glucocorticoid	Liggins 1972
Animal studies on surfactant therapy	Robertson, Jobe, Ikegami 1973-83
1st trial with natural surfactant	Fujiwara 1980
1st RTC with synthetic DPPC-PG	Morley 1985
1st RTC with natural surfactant	Hallman,Merritt 1985 Enhörning 1985
Proph vs Rescue surfactant better	Merritt 1986
1st commercial synthetic surfactant	1990 (Exosurf)
1st commercial natural surfactant	1990-2 (Survanta)
1st commercial peptide-surfactant	2007 (Lucinactant)

Evolution of Commerically Available Surfactants in USA/Europe



1. FDA/CDER drug approvals. Available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist. **2.** Doctor's Guide. FDA approves Curosurf for respiratory distress in premature infants. Available at: http://www.pslgroup.com/dg/14a1ea.htm. **3.** Halliday and Robertson. In: Hanson et al, eds. *Breathing*. 1994;269-271. *Fetus and Neonate: Physiology and Clinical Applications;* vol 2. **4.** Data on file, Discovery Laboratories.

Surfactants Used in RCT 1983-2015

- ***Protein-Free***
- Pumactant (ALEC)
- Colfosceril palmitate
- (Exosurf)
- TurfSurf (Belfast)
- ***Peptide Surfactants***
- Lucinactant (KL4)
- (Surfaxin)(Aerosurf)
- rSPC Surf(Venticute)
- SP C/SP-B analogue CHF5633 (Chiesi)

Natural (Amniotic Fluid)

Human AF Surf

Lung Lavage Extracts

Calf lung surfactant (BLES), (Infasurf)

SF-R11 (Alveofact)

Minced Lung Extracts

Beractant (Suvanta)

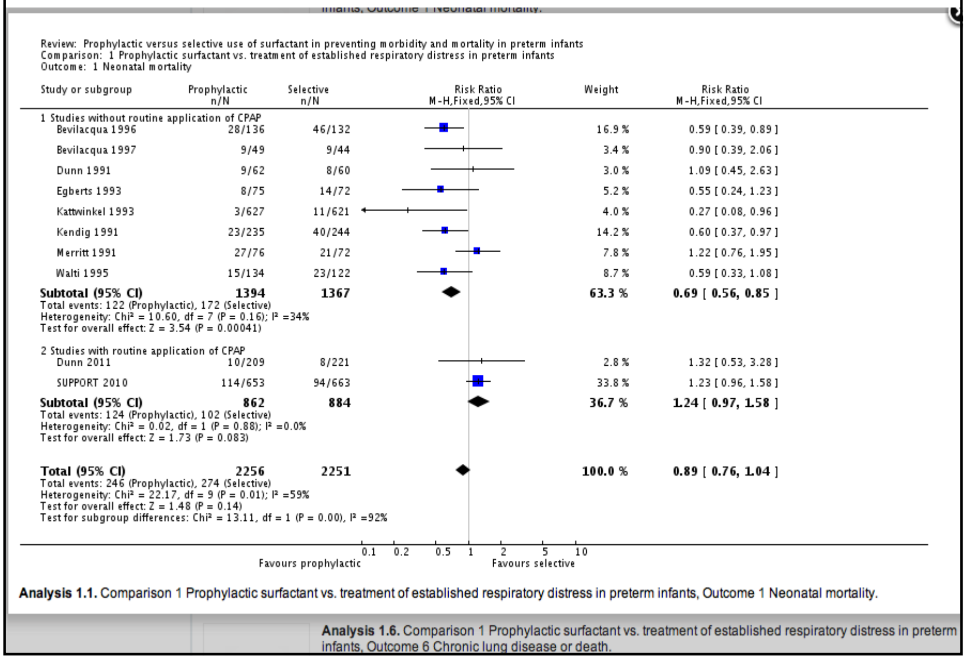
Poractant Alfa (Curosurf)

Comparative Trials of Animal Derived Surfactants:

Speer et al	Curosurf v Survanta
Halahakoon	Curosurf v Survanta
Baroutta et al	Curosurf v Survanta v Alveofact
Ramanathan et al	Curosurf v Survant
Malloy et al	Curosurf v Survanta
Bloom et al	Infasurf v Survanta
Van Overmeire et al	Alveofact v Survanta

Subtle Differences between animal derived surfactants

Curosurf having overall improved survival (but comparisons involved infants of differing GA and Birth Weights)



infants, Outcome 1 Neonatal mortality.

Review: Prophylactic versus selective use of surfactant in preventing morbidity and mortality in preterm infants
Comparison: 1 Prophylactic surfactant vs. treatment of established respiratory distress in preterm infants
Outcome: 1 Neonatal mortality

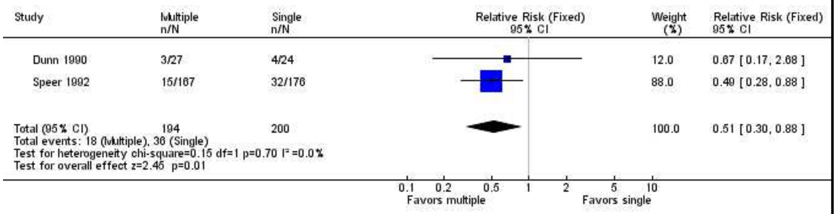
Study or subgroup	Prophylactic n/N	Selective n/N	Weight	Risk Ratio M-H,Fixed,95% CI
1 Studies without routine application of CPAP				
Bevilacqua 1996	28/136	46/132	16.9 %	0.59 [0.39, 0.89]
Bevilacqua 1997	9/49	9/44	3.4 %	0.90 [0.39, 2.06]
Dunn 1991	9/62	8/60	3.0 %	1.09 [0.45, 2.63]
Egberts 1993	8/75	14/72	5.2 %	0.55 [0.24, 1.23]
Kattwinkel 1993	3/627	11/621	4.0 %	0.27 [0.08, 0.96]
Kendig 1991	23/235	40/244	14.2 %	0.60 [0.37, 0.97]
Merritt 1991	27/76	21/72	7.8 %	1.22 [0.76, 1.95]
Walti 1995	15/134	23/122	8.7 %	0.59 [0.33, 1.08]
Subtotal (95% CI)	**1394**	**1367**	**63.3 %**	**0.69 [0.56, 0.85]**
Total events: 122 (Prophylactic), 172 (Selective)				
Heterogeneity: Chi² = 10.60, df = 7 (P = 0.16); I² =34%				
Test for overall effect: Z = 3.54 (P = 0.00041)				
2 Studies with routine application of CPAP				
Dunn 2011	10/209	8/221	2.8 %	1.32 [0.53, 3.28]
SUPPORT 2010	114/653	94/663	33.8 %	1.23 [0.96, 1.58]
Subtotal (95% CI)	**862**	**884**	**36.7 %**	**1.24 [0.97, 1.58]**
Total events: 124 (Prophylactic), 102 (Selective)				
Heterogeneity: Chi² = 0.02, df = 1 (P = 0.88); I² =0.0%				
Test for overall effect: Z = 1.73 (P = 0.083)				
Total (95% CI)	**2256**	**2251**	**100.0 %**	**0.89 [0.76, 1.04]**
Total events: 246 (Prophylactic), 274 (Selective)				
Heterogeneity: Chi² = 22.17, df = 9 (P = 0.01); I² =59%				
Test for overall effect: Z = 1.48 (P = 0.14)				
Test for subgroup differences: Chi² = 13.11, df = 1 (P = 0.00), I² =92%				

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

Analysis 1.6. Comparison 1 Prophylactic surfactant vs. treatment of established respiratory distress in preterm infants, Outcome 6 Chronic lung disease or death.

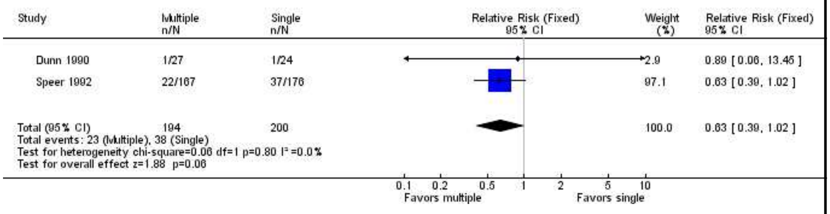
Multiple vs single dose of natural surfactant in preventing severe RDS and mortality in preterm infants

Pneumothorax



Study	Multiple n/N	Single n/N	Weight (%)	Relative Risk (Fixed) 95% CI
Dunn 1990	3/27	4/24	12.0	0.67 [0.17, 2.68]
Speer 1992	15/167	32/176	88.0	0.49 [0.28, 0.88]
Total (95% CI)	194	200	100.0	0.51 [0.30, 0.88]
Total events: 18 (Multiple), 36 (Single)				
Test for heterogeneity chi-square=0.15 df=1 p=0.70 I² =0.0%				
Test for overall effect z=2.45 p=0.01				

Death



Study	Multiple n/N	Single n/N	Weight (%)	Relative Risk (Fixed) 95% CI
Dunn 1990	1/27	1/24	2.9	0.89 [0.06, 13.45]
Speer 1992	22/167	37/176	97.1	0.63 [0.39, 1.02]
Total (95% CI)	194	200	100.0	0.63 [0.39, 1.02]
Total events: 23 (Multiple), 38 (Single)				
Test for heterogeneity chi-square=0.06 df=1 p=0.80 I² =0.0%				
Test for overall effect z=1.88 p=0.06				

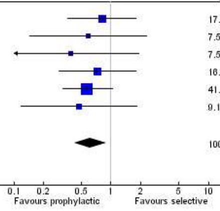
Soll: The Cochrane Library, Volume (4).2006

Prophylactic (< 1-2 hours) vs selective use of surfactant in preterm infants

Pneumothorax

Study	Prophylactic n/N	Selective n/N	Weight (%)	Relative Risk (Fixed) 95% CI
Bevilacqua 1996	10/136	12/132	17.9	0.81 [0.36, 1.81]
Dunn 1991	3/62	5/60	7.5	0.58 [0.15, 2.32]
Egberts 1993	2/75	5/72	7.5	0.38 [0.08, 1.92]
Kattwinkel 1993	8/627	11/621	16.2	0.72 [0.29, 1.78]
Kendig 1991	16/235	29/244	41.8	0.57 [0.32, 1.03]
Walti 1995	3/130	6/121	9.1	0.47 [0.12, 1.82]
Total (95% CI)	1265	1250	100.0	0.62 [0.42, 0.89]

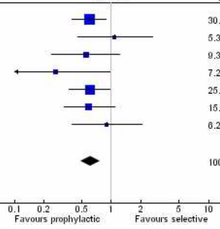
Total events: 42 (Prophylactic), 68 (Selective)
Test for heterogeneity chi-square=1.12 df=5 p=0.95 I^2 =0.0%
Test for overall effect z=2.55 p=0.01



Death

Study	Prophylactic n/N	Selective n/N	Weight (%)	Relative Risk (Fixed) 95% CI
Bevilacqua 1996	28/136	46/132	30.5	0.59 [0.39, 0.89]
Dunn 1991	9/62	8/60	5.3	1.09 [0.45, 2.63]
Egberts 1993	8/75	14/72	9.3	0.55 [0.24, 1.23]
Kattwinkel 1993	3/627	11/621	7.2	0.27 [0.08, 0.96]
Kendig 1991	23/235	40/244	25.7	0.60 [0.37, 0.97]
Walti 1995	15/134	23/122	15.7	0.59 [0.33, 1.08]
Bevilacqua 1997	9/49	9/44	6.2	0.90 [0.39, 2.06]
Total (95% CI)	1318	1295	100.0	0.61 [0.48, 0.77]

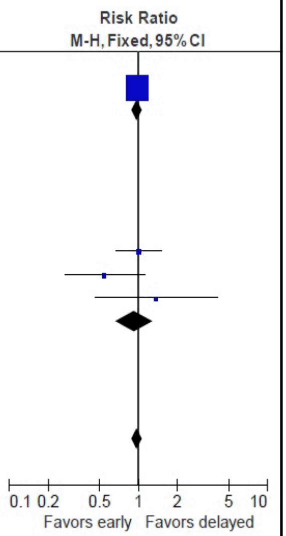
Total events: 95 (Prophylactic), 151 (Selective)
Test for heterogeneity chi-square=4.16 df=6 p=0.65 I^2 =0.0%
Test for overall effect z=4.12 p=0.00004



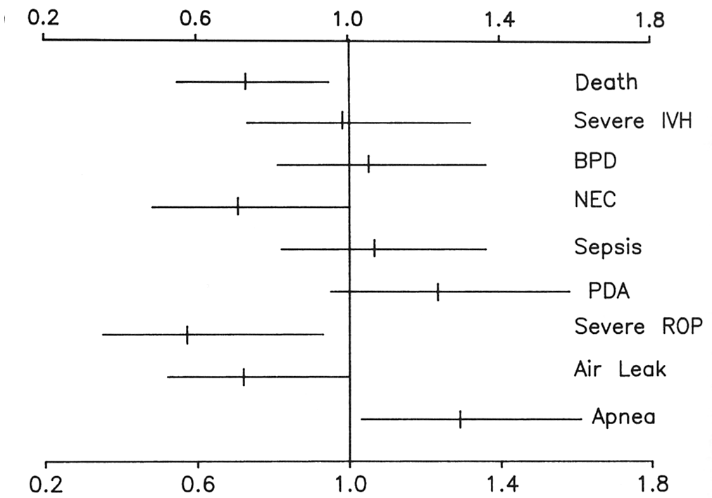
From: Soll: The Cochrane Library, Volume (4).2006

1.3 Bronchopulmonary dysplasia

Study or Subgroup	Early treatment Events	Early treatment Total	Late treatment Events	Late treatment Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.3.1 Synthetic surfactant						
OSIRIS 1992	483	1344	497	1346	90.4%	0.97 [0.88, 1.08]
Subtotal (95% CI)		**1344**		**1346**	**90.4%**	**0.97 [0.88, 1.08]**
Total events	483		497			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.53 (P = 0.59)						
1.3.2 Animal-derived surfactant						
Gortner 1998	36	154	38	163	6.7%	1.00 [0.67, 1.49]
Konishi 1992	6	16	11	16	2.0%	0.55 [0.27, 1.11]
Lefort 2003	6	35	5	40	0.8%	1.37 [0.46, 4.11]
Subtotal (95% CI)		**205**		**219**	**9.6%**	**0.94 [0.67, 1.31]**
Total events	48		54			
Heterogeneity: Chi² = 2.79, df = 2 (P = 0.25); I² = 28%						
Test for overall effect: Z = 0.37 (P = 0.71)						
Total (95% CI)		**1549**		**1565**	**100.0%**	**0.97 [0.88, 1.07]**
Total events	531		551			
Heterogeneity: Chi² = 2.91, df = 3 (P = 0.41); I² = 0%						
Test for overall effect: Z = 0.62 (P = 0.53)						
Test for subgroup differences: Chi² = 0.04, df = 1 (P = 0.84), I² = 0%						



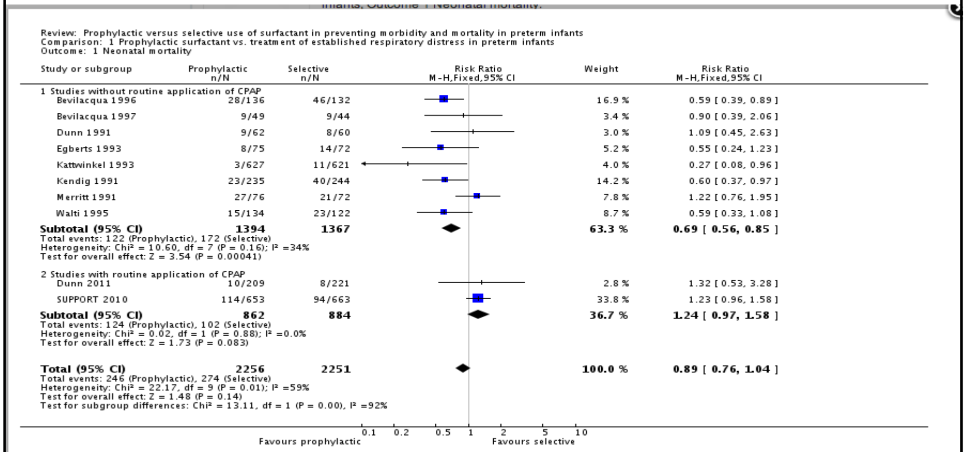
Outcomes associated with surfactant use in clinical practice. Compilation of 5629 VLBW infants from 14 centers



Adjusted Odds ratios

Schwartz et al. NEJM 1994

Comparison of Prophylaxis versus Selective [e.g. Rescue] treatment (Soll, 2006)



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Merritt 1991	27/76	21/72	7.8 %	1.22 [0.76, 1.95]
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Subtotal (95% CI)	**862**	**884**	**36.7 %**	**1.24 [0.97, 1.58]**
Total (95% CI)	**2256**	**2251**	**100.0 %**	**0.89 [0.76, 1.04]**

Subgroup 1: Total events: 122 (Prophylactic), 172 (Selective); Heterogeneity: Chi² = 10.60, df = 7 (P = 0.16); I² =34%; Test for overall effect: Z = 3.54 (P = 0.00041)

Subgroup 2: Total events: 124 (Prophylactic), 102 (Selective); Heterogeneity: Chi² = 0.02, df = 1 (P = 0.88); I² =0.0%; Test for overall effect: Z = 1.73 (P = 0.083)

Total: Total events: 246 (Prophylactic), 274 (Selective); Heterogeneity: Chi² = 22.17, df = 9 (P = 0.01); I² =59%; Test for overall effect: Z = 1.48 (P = 0.14); Test for subgroup differences: Chi² = 13.11, df = 1 (P = 0.00), I² =92%

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

Analysis 1.6. Comparison 1 Prophylactic surfactant vs. treatment of established respiratory distress in preterm infants, Outcome 6 Chronic lung disease or death.

Results of Systematic Reviews from Multiple Surfactants: Natural Protein Containing Surfactants Superior to Non-protein containing surfactants Meta-Analysis 2014

Multiple trials using both protein-free synthetic surfactant Exosurf, and "natural" minced lung (Beractant, Poractant alfa (Curosurf) or lung wash surfactants (Calfactant, Alveofact, in one or multiple doses.
Trials of single versus multiple doses, early surfactant (Prophylaxis) versus later (Rescue surfactant).

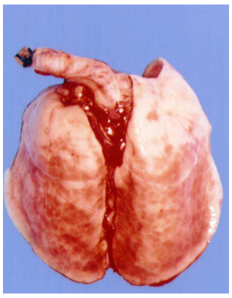
Mortality	*Relative Risk*	*95% CI*	*Number Needed to Treat*
Multiple Doses	*0.63*	*0.39-1.02*	*14 (7-1000)*
Natural Surfactant	*0.86*	*0.76-0.98*	*50 (20-1000)*
Prophylaxis	*0.61*	*0.48-0.77*	*20 (14-50)*
Early INSURE	*0.38*	*0.08-1.81*	*---*

Lessons learned regarding effectiveness and distribution surfactant during administration

• Property of Surfactant	Clinical Effects
• Surface Activity	Causes rapid adsorption & spreading in airways/lung
• Volume	Higher volumes result in Improved distribution
• Rate of admin.	Bolus administration Improves Distribution
• Ventilator settings	PIP and PEEP help clear airways of fluid
• Fluid vol in lung	Higher volumes of fetal lung fluid surfactant distribution (e.g. earlier is better)

Effect of Volume on Bolus Surfactant Distribution

Low volume administered: substantial atelectasis persists

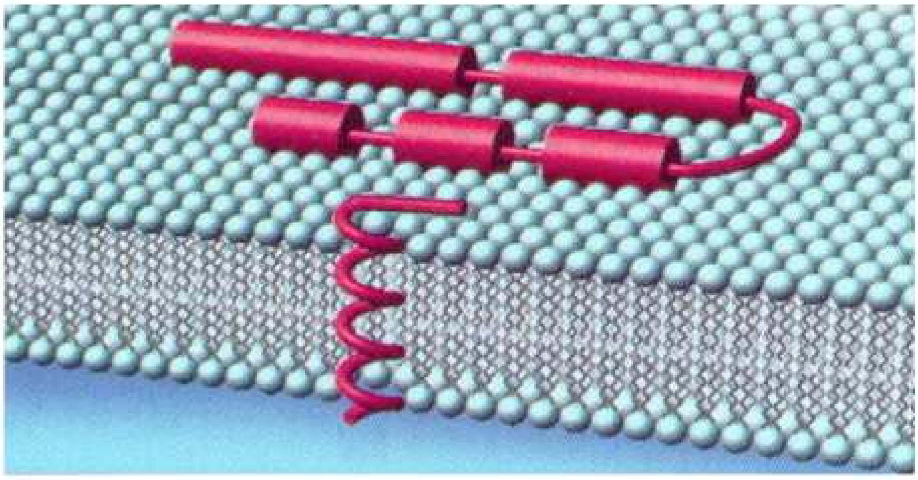


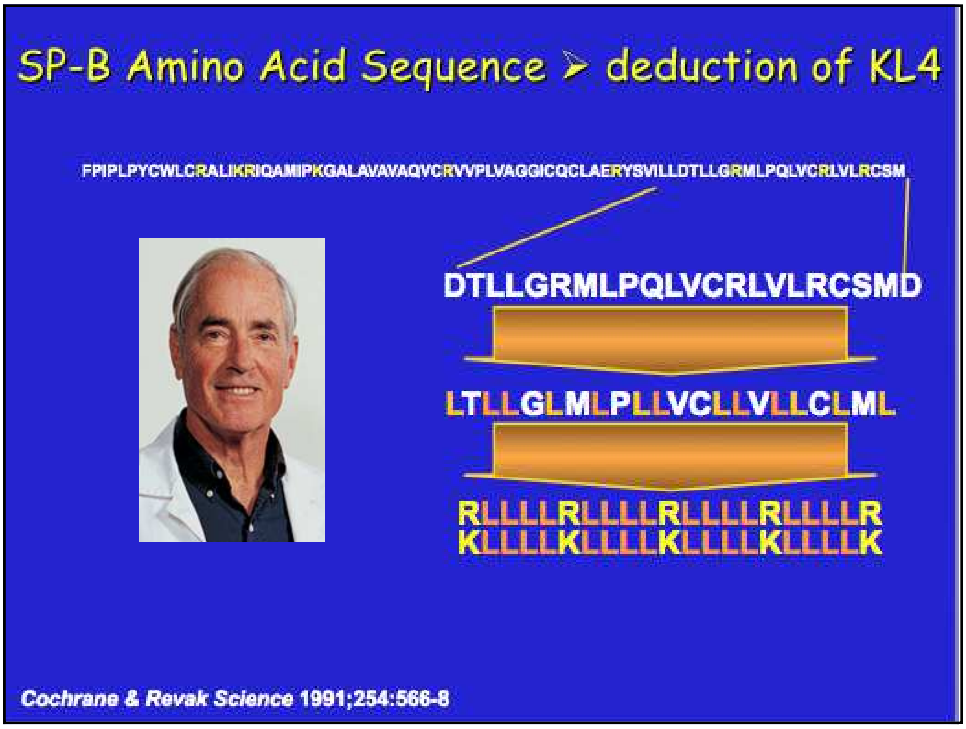
Higher volume administered: better distribution, no atelectasis

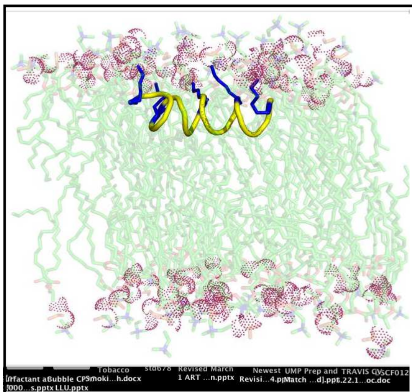
Pulmonary distribution of surfactant given in bolus doses is *better* when given in higher volumes

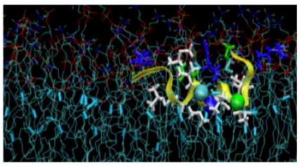
Gilliard N et al. *Am Rev Respir Dis*. 1990;141:743–747.
Van der Bleek J et al. *Pediatr Res.1993*; 34:154–158.

SP-B & SP-C in phospholipids









Philippe Bertani , Verica Vidovic , Tran-chin Yang , Jennifer Rendell , Larry M. Gordon , Alan J. Waring , Burkhar...

Orientation and depth of surfactant protein B C-terminal helix in lung surfactant bilayers

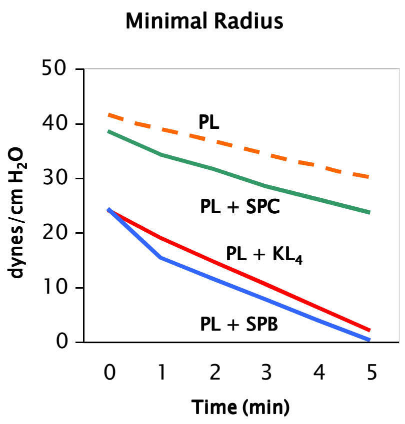
Biochimica et Biophysica Acta (BBA) - Biomembranes, Volume 1818, Issue 5, 2012, 1165 - 1172

http://dx.doi.org/10.1016/j.bbamem.2012.01.001

Structure of KL4 and Phospholipid Membrane Interactions: Mills, F.D. Long, J. et al The Helical Structure of Surfactant Peptide of KL4 When Bound to POPC: POPG Lipid Vesicles, Biochemistry 2008; (47) 8292

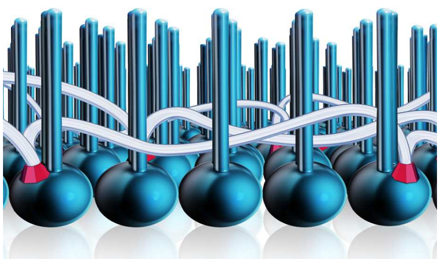
KL_4 Functions Like SP-B

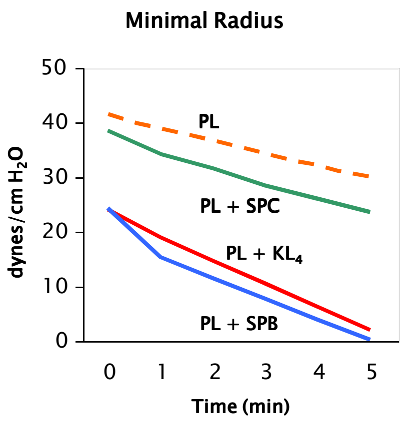
Multiple combinations of peptides RL4, KL4, DL4, added to phospholipids DPPC, DOPG, Palmitic Acid, at various concentrations compared to Phosphlipids alone, and Phospholipids and SP B or SP C. Phospholipids + KL4 minimiked the biophysical properties of SP B + PL.



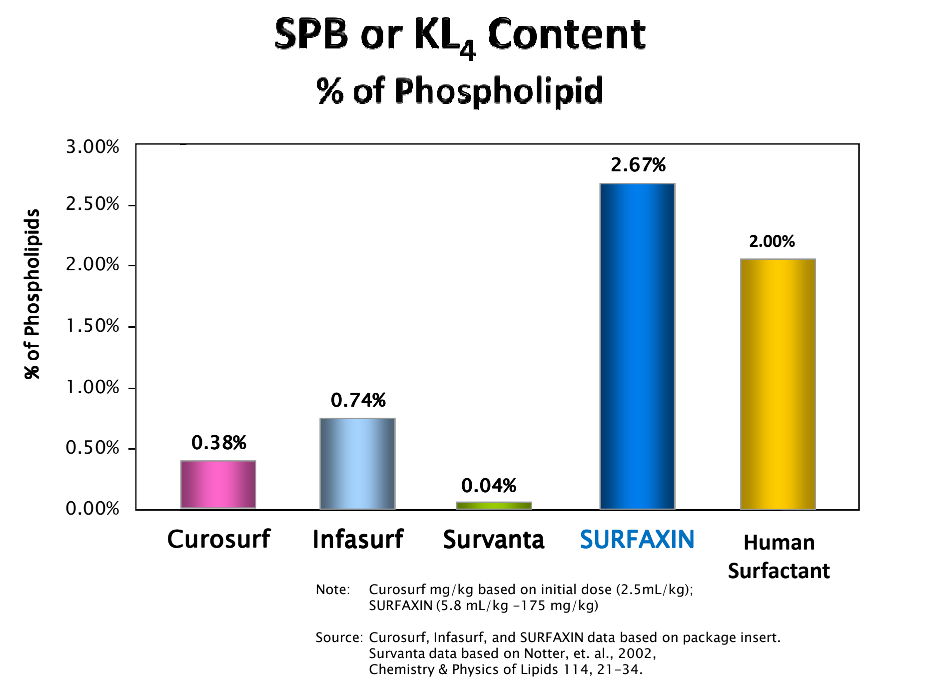
Cochrane CG, Revak SD. *Science*. 1991;254:566-568

KL_4 Functions Like SPB





Cochrane CG, Revak SD. *Science*. 1991;254:566-568



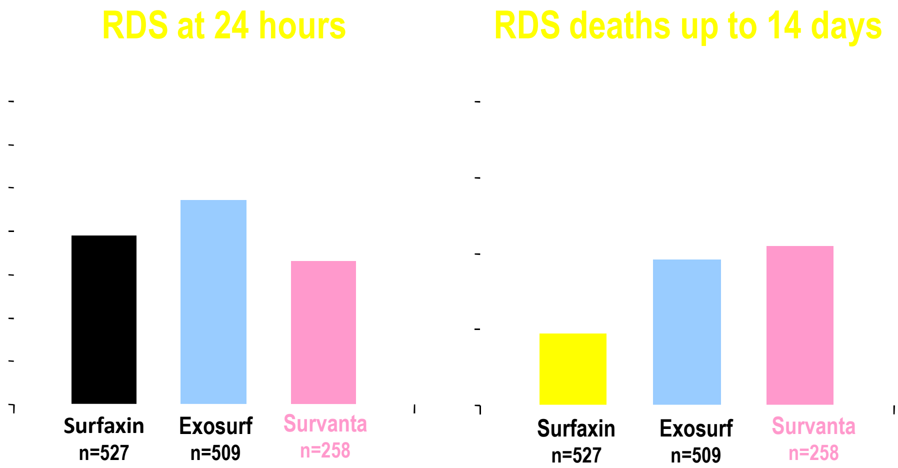
RCT of Lucinactant (Surfaxin) KL4 Surfactant

- SELECT (N=1294)
- Trial Design-Superiority
- Inclusion Criteria-GA 24-32 wks;BW 600-1250g
- Treatment-Surfaxin 175 mg/kg, Exosurf 62.5 mg/kg, Survanta 100 mg/kg
- Primary Outcomes-Incidence of RDS at 24 hr; RDS related deaths to 14 days
- Moya, F et al Pediatrics 2005; 115: 118-129

- STAR (N=252)
- Trial Design-Non-inferiority
- Inclusion Criteria-GA 24-29 wks; 600-1250 g
- Treatment-Surfaxin vs Curosurf (175 mg/kg), & Beractant (100 mg/kg)
- Primary Outcomes-Incidence of being alive without BPD at 28 days
- Sinha, S et al Pediatrics 2005; 115: 130-138

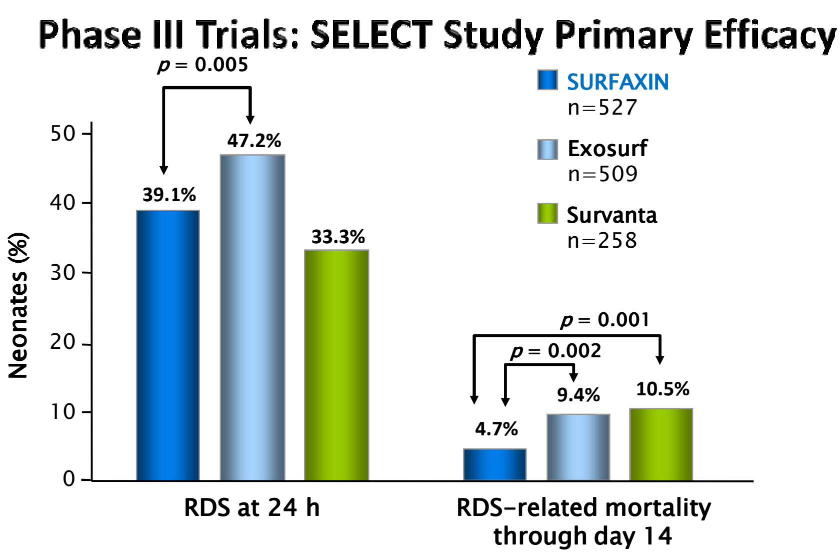
SELECT TRIAL (Europe, Latin America)

Primary Outcomes

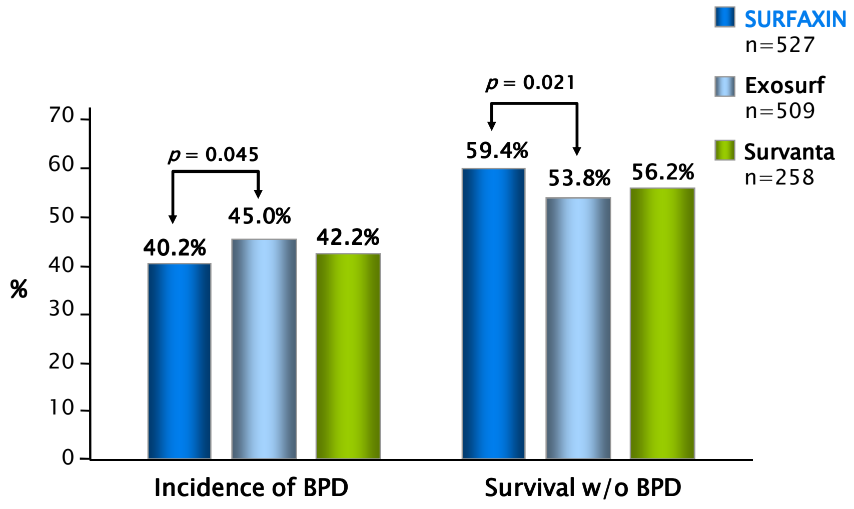


P-values adjusted by BW strata and center using logistic regression

Moya F, et al. *Pediatrics,*2005;115:118-129

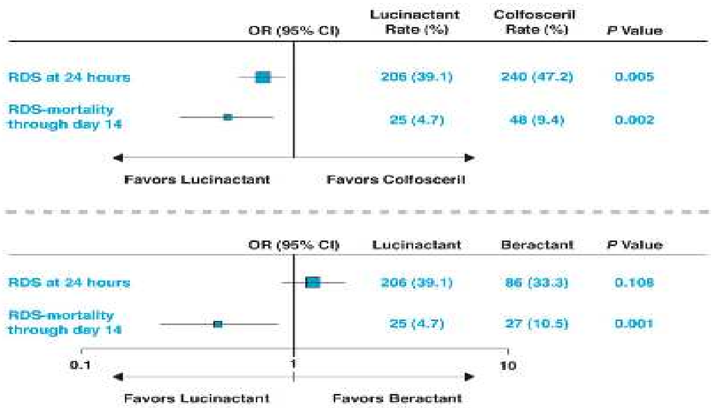


SELECT - BPD at 36 weeks

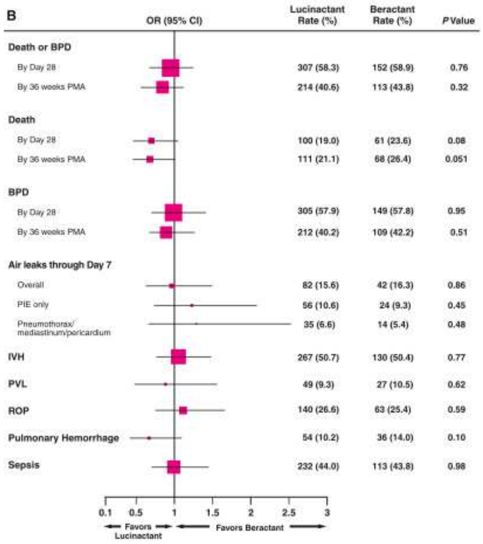


Moya F, et al. *Pediatrics,* 2005;115:118-129

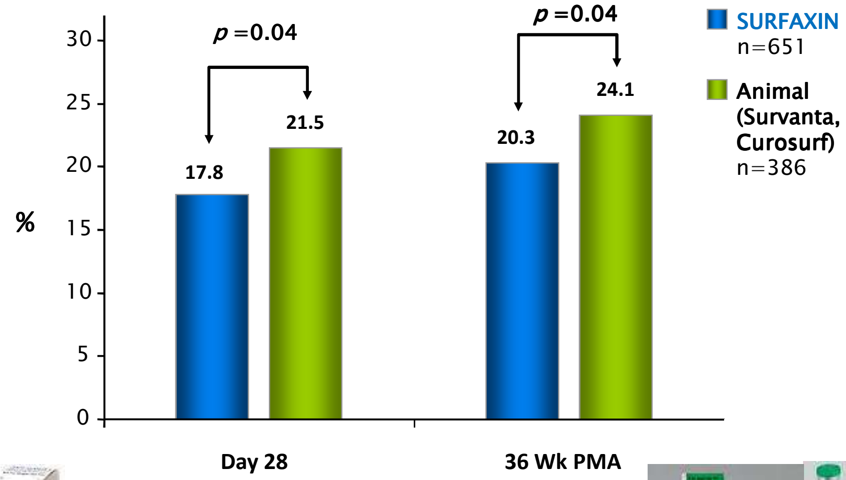
Sinha, S et al Pediatrics, 2005 Star Trial: Comparison of Lucinactant to Exosurf and Beractant (non inferiority trial)



STAR: Lucinactant vs Beractant

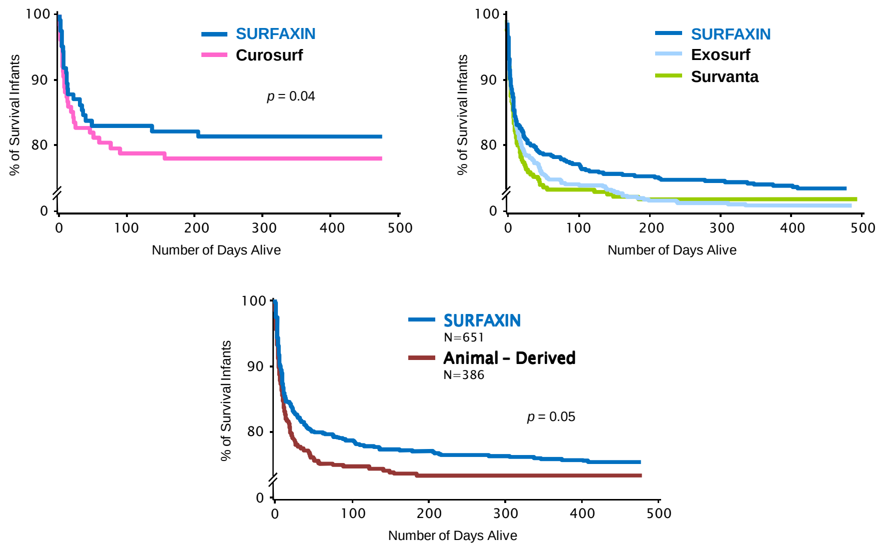


SURFAXIN vs. Animal-Derived Surfactants
Short-Term All-Cause Mortality

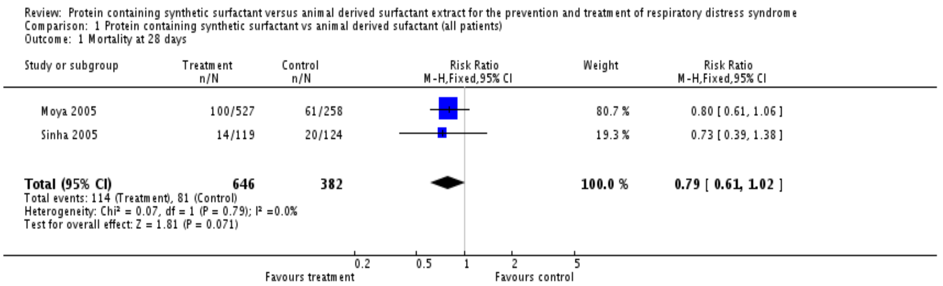


PMA = postmenstrual age
PAS 2005: 57: LB16

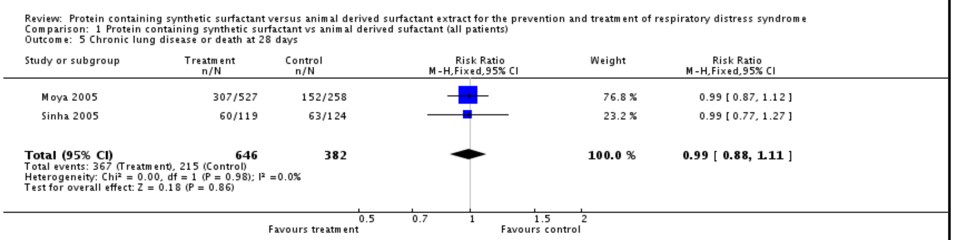
Survival rate through 1 Year of Life



Moya F, et al. *Pediatrics,* 2010;119(6):1361-1370



Analysis 1.1. Comparison 1 Protein containing synthetic surfactant vs animal derived sufactant (all patients), Outcome 1 Mortality at 28 days.



Analysis 1.5. Comparison 1 Protein containing synthetic surfactant vs animal derived sufactant (all patients), Outcome 5 Chronic lung disease or death at 28 days.

Poractant Alfa (Curosurf) Clinica Trials

- ***1988 RCT to placebo***: Improved oxygenation, reduced PIE, Pneumothorax, survival
- ***1992 RCT Multiple v Single dose:***improved oxygenation, reduced airleaks, improved survival
- ***1993 RCT Early v Late:*** improved survival and reduced severe IVH with early treatment
- ***1993 RCT 200 mg v 100 mg*** Improved oxygenation up to 36 hours no other benefits
- ***1997,2002 RCT Prophylaxis v Selective:*** Infants<31 weeks less severe RDS, less CLD, improved survival with prophylaxis
- ***1999 Curosurf & CPAP Combination:*** earlier extubation and may improve survival in infants <30wks
- ***1995-2005 Comparative trials***: Curosurf improved survival over ALEC; More Rapid response than Survanta, and may improve survival

Comparative Trials of Animal Surfactants

- Speer et al 1995 Curosurf v Survanta
- Griese et al 1995 Alveofact v Survanta
- Halahakoon 1999 Curosurf v Survanta
- Van Overmeire et al1999 Alveofact v Survanta
- Baroutis et al 2003 Curosurf v Survanta v Alveofact
- Ramanathan et al 2004 Curosurf v Survanta
- Malloy et al 2005 Curosurf v Survanta
- Bloom et al 2005 Infasurf v Survanta

Major Outcomes differences were that Survival Was Improved with Curosurf (Odds Ratio 1.0 Curosurf vs 1.52 Beractant vs 1.6 InfaSurf)

Surfactant Treatment of Meconium Aspiration Syndrome: less pneumothorax, fewer needing ECMO El-Shahed, Dargaville, Ohlsson, Soll Cochane Database 2014

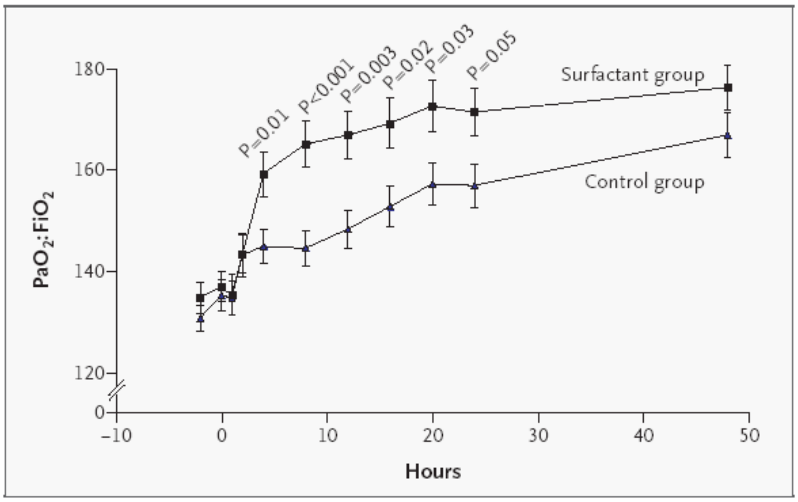
Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 Mortality	4	326	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.41, 2.39]
1.2 Treatment with ECMO	2	208	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.46, 0.91]
1.3 Pneumothorax	3	269	Risk Difference (M-H, Fixed, 95% CI)	-0.02 [-0.08, 0.05]
1.4 Pulmonary interstitial emphysema	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.5 Air leaks (pneumothorax, pneumomediastinum, interstitial emphysema)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.6 Duration of assisted mechanical ventilation (days)	3	158	Mean Difference (IV, Fixed, 95% CI)	0.60 [-0.41, 1.62]
1.7 Duration of supplemental oxygen (days)	2	97	Mean Difference (IV, Fixed, 95% CI)	0.40 [-2.83, 3.64]
1.8 Need for supplemental oxygen at discharge	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.9 Chronic lung disease (age at diagnosis not stated)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.10 Intraventricular haemorrhage (any grade)	2	229	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.31, 1.46]
1.11 Severe intraventricular haemorrhage	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.12 Duration of hospital stay (days)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

Surfactant for treatment of Acute Lung Injury in Children with a limited reduction in ventilator days- Willson et al

Trials of various Surfactants in Adult Respiratory Distress Syndrome

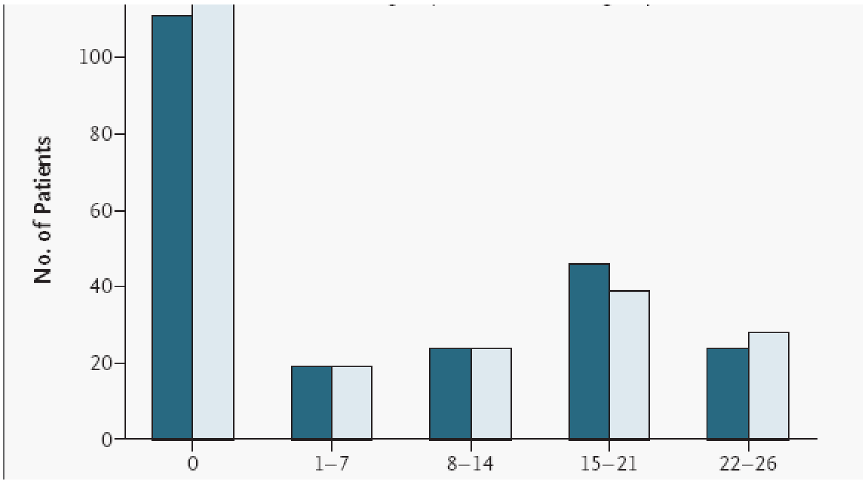
Failure of large multicenter trial of Venticute (rSPC surfactant) to alter outcomes of ARDS or reduce ventilator days- Spragg et al

Mean PaO_2:FiO_2 values
Control group vs. Venticute (rh SP-C) Surfactant In Adult Patients with ARDS



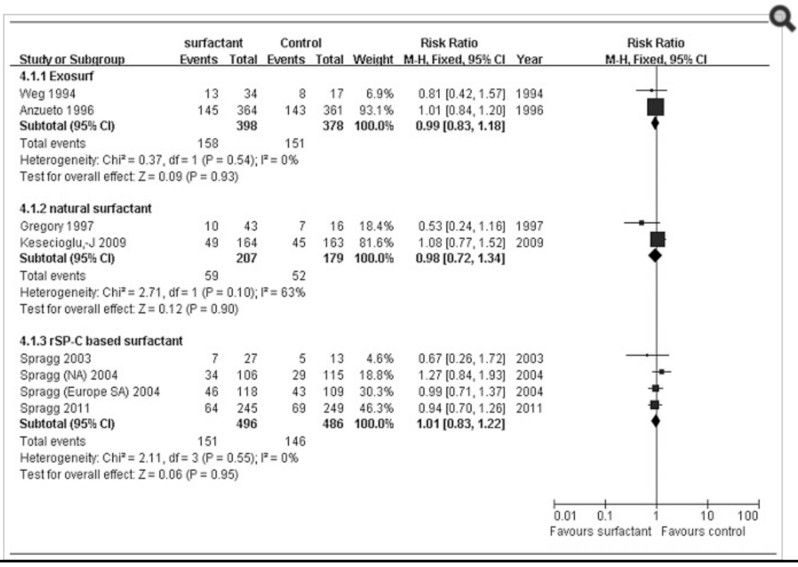
Spragg RG et al. *New Engl J Med.* 2004;351:884-892

Number of ventilator free days in the control group and the surfactant group: A Trial Failure!



Spragg RG et al. *New Engl J Med.* 2004;351:884-892

Meta-Analysis of ARDS Trials treated with Surfactan (Failure of rhSP-C [Venticute], Exosurf, Beractant)



Study or Subgroup	surfactant Events	surfactant Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
4.1.1 Exosurf							
Weg 1994	13	34	8	17	6.9%	0.81 [0.42, 1.57]	1994
Anzueto 1996	145	364	143	361	93.1%	1.01 [0.84, 1.20]	1996
Subtotal (95% CI)		**398**		**378**	**100.0%**	**0.99 [0.83, 1.18]**	
Total events	158		151				
Heterogeneity: Chi² = 0.37, df = 1 (P = 0.54); I² = 0%							
Test for overall effect: Z = 0.09 (P = 0.93)							
4.1.2 natural surfactant							
Gregory 1997	10	43	7	16	18.4%	0.53 [0.24, 1.16]	1997
Kesecioglu,-J 2009	49	164	45	163	81.6%	1.08 [0.77, 1.52]	2009
Subtotal (95% CI)		**207**		**179**	**100.0%**	**0.98 [0.72, 1.34]**	
Total events	59		52				
Heterogeneity: Chi² = 2.71, df = 1 (P = 0.10); I² = 63%							
Test for overall effect: Z = 0.12 (P = 0.90)							
4.1.3 rSP-C based surfactant							
Spragg 2003	7	27	5	13	4.6%	0.67 [0.26, 1.72]	2003
Spragg (NA) 2004	34	106	29	115	18.8%	1.27 [0.84, 1.93]	2004
Spragg (Europe SA) 2004	46	118	43	109	30.3%	0.99 [0.71, 1.37]	2004
Spragg 2011	64	245	69	249	46.3%	0.94 [0.70, 1.26]	2011
Subtotal (95% CI)		**496**		**486**	**100.0%**	**1.01 [0.83, 1.22]**	
Total events	151		146				
Heterogeneity: Chi² = 2.11, df = 3 (P = 0.55); I² = 0%							
Test for overall effect: Z = 0.06 (P = 0.95)							

Surfactant Treatment of Meconium Aspiration Syndrome El-Shahed, Dargaville, Ohlsson, Soll Cochrane Database 2014

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 Mortality	4	326	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.41, 2.39]
1.2 Treatment with ECMO	2	208	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.46, 0.91]
1.3 Pneumothorax	3	269	Risk Difference (M-H, Fixed, 95% CI)	-0.02 [-0.08, 0.05]
1.4 Pulmonary interstitial emphysema	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.5 Air leaks (pneumothorax, pneumomediastinum, interstitial emphysema)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.6 Duration of assisted mechanical ventilation (days)	3	158	Mean Difference (IV, Fixed, 95% CI)	0.60 [-0.41, 1.62]
1.7 Duration of supplemental oxygen (days)	2	97	Mean Difference (IV, Fixed, 95% CI)	0.40 [-2.83, 3.64]
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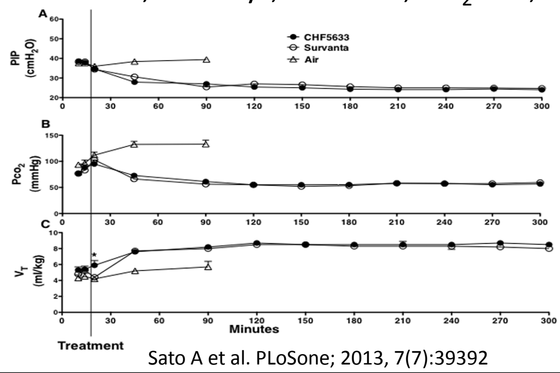
1.9 Chronic lung disease (age at diagnosis not stated)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.10 Intraventricular haemorrhage (any grade)	2	229	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.31, 1.46]
1.11 Severe intraventricular haemorrhage	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.12 Duration of hospital stay (days)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

Synthetic surfactant with SP-C and SP-B analogues

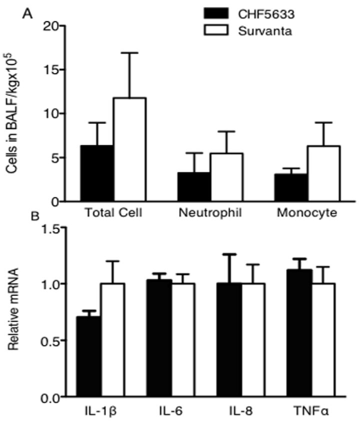
CHF5633 (Chiesi Farmaceutici SpA, Parma, Italy) 200mg/kg
- DPPC:POPG 1:1
- Analogue SP-C (1.5%): 33 aminoacids
- Analogue SP-B (0.2%): 34 aminoacids

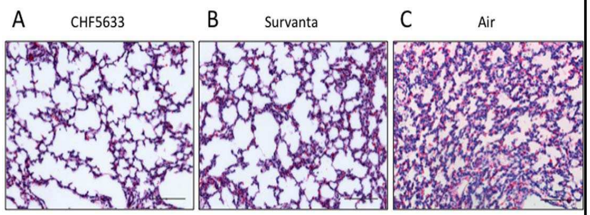
- Survanta (Abbott, Columbus, OH) 100 mg/kg
- Fetal lamb model, 124 days, c-section, FiO_2=1.0, Vt=6mL/kg



Sato A et al. PLoSone; 2013, 7(7):39392

Synthetic surfactant with SP-C and SP-B analogues





- New synthetic surfactant was effective on animal model of RDS

Sato A et al. PLoSone;2013, 7(7):39392

Other Peptide Surfactants in Development or Clinical Trials

- **Chiesi Farmaceutici-SpA**-Peptide Surfactant CHF 5683 containing SP-B (amino and COOH terminus) peptides and SP-C analogues containing KL4-preterm labms studies confirm biologic activity-Seehase, M et al PLOSone 2013
- Walther, FJ et al-lung lavage young rabbits suggest biologic activity-Peer J
- Human Studies are underway (as a liquid)
- **Innovus-So. Africa-**Peptide containing surfactant SP-B/SP-C Animal studies in preterm lambs show similar results to Curosurf Smith 2013, vanZyl et al 2014-adult rabbit lavage-partial restoration of lung function, less lung Inflammation, Human Studies status unknown

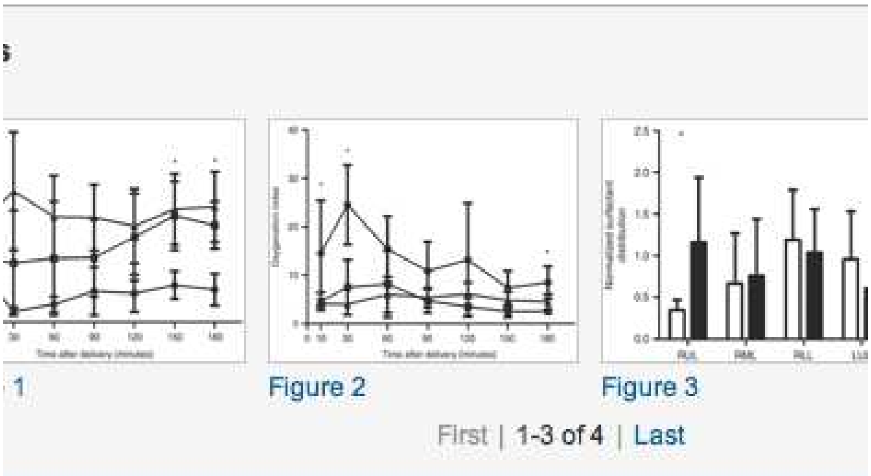
Less Invasive Surfactant Administration (LISA)

Kribs et al in Germany published encouraging results after using a “feeding tube” inserted through the vocal cords and administering surfactant and AMV (avoidance of mechanical ventilation)

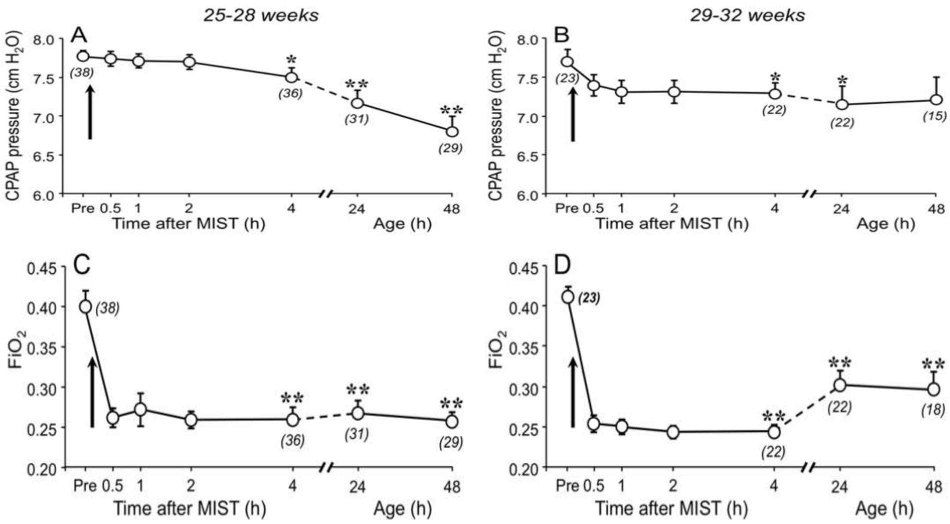
Less Invasive Surfactant Administration (LISA)

- *Kribs et al 2010 LISA vs ETT surfactant among infants < 31 weeks : Less MV in first 72 hr 29% vs 53% p<.001, BPD LISA 11% v 18% p<.004*
- *Göpel et al 2011 LISA vs ET surf/CPAP 26-28 6/7 weeks: Reduced MV on day 2-3 RR .68 (CI 0.42-.0.88) no change in BPD*
- *Lebermass-Schrefhof et al 2013: LISA vs ET surf/CPAP 23-27 weeks: MV LISA 23% vs ET/CPAP 52% p,.001, no change in BPD*
- *Kanmaz et al 2013: LISA vs INSURE infants <32 weeks (<72 hr): MV within 72 h: LISA 30% vs INSURE 45% p<.02, BPD LISA 10% INSURE 20% p= .009*

LISA in SPONTANEOUSLY BREATHING FETAL LAMBS: LESS surfactant in & POORER distribution, but SIMILAR physiologic effects to intubation and NO Mechanial Ventilation (Pediatr Res 2014, KRIBS ET AL)



OptiMIST HOBART METHOD DARGAVILLE ET AL 2013 AND ONGOING INTERNATIONAL TRIAL



Aerosolized surfactants – clinical studies

The only study utilized single naso-pharyngeal (SNP) tube for CPAP and aerosol delivery

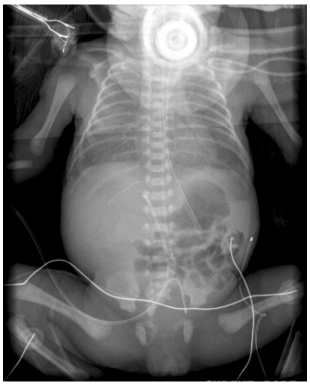
	Surfactant	*Method*	*Population*	*Outcome*
Jorch G	Alveofact®	Jet nebulizer 150 mg x 2 SNP tube CPAP	28-35 wks	A-a O_2 gradient, PCO2 & Silverman score improved
Arroe M	Exosurf®	Side stream nebulizer prongs CPAP	23-36 wks	No significant benefits
Berggren E	Curosurf	Jet nebulizer IF CPAP	27-34 wks	No significant benefits
Finer N	Aerosurf	Aeroneb Pro® prongs CPAP	28-32 wks	Procedure safe

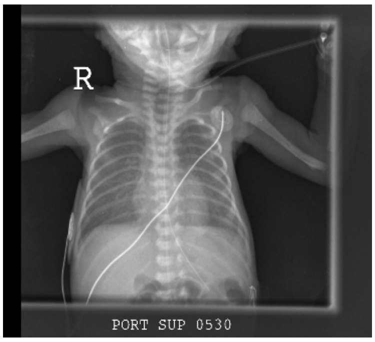
QUESTION: Was the right patient interface used?

Mazela et al, Curr Opin Pediatr 2007; 19: 155

Nebulization of Lucinactant: First study using AeroNeb Pro Vibrating Mesh Nebulizer in USA, 17 infants and all showed improvement: Finer, Merritt, Mazela, Henderson, 2010

Aerosurf Aerosolization + CPAP 5 cm at 0.5-hr start and 3-hr Posttreatment in Infant with RDS





Multicenter pilot study of aerosolized lucinactant delivered via nCPAP (KL4-CPAP-01 Phase 2A)

Clinical Outcomes According to Gestational Age

	28-29 weeks (n=6)		30-32 weeks (n=11)		All Enrolled (N=17)	
	No.	%	No.	%	No.	%
Survival through day 28	6	100	11	100	17	100
Survival without BPD	5	83.3	10	90.1	15	88.2
BPD through day 28	1	16.6	1	9.1	2	11.8
RDS at 24 hours	3	50	1	9.1	4	23.5
Intubation/mechanical ventilation through day 28	3	50	2	18.2	5	29.4
ET surfactant administration	3	50	2	18.2	5	29.4

QUESTION: What is the best nebulizer to be used?

Finer N et al, J Aerosol Med Pulm Drug Del 2010;23:1-7.

AEROSURF™ lucinactant for inhalation

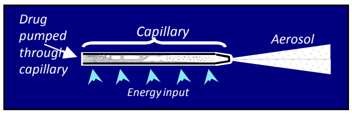
Aerosolized KL4 surfactant with CAG for RDS

- New aerosol generation and delivery system: CAG and AFFECTAIR™ (AARC, November 2011)
- GA Dated Pregnant Ewe
- Cesarean Delivery
- Preterm Lamb (6 vs. 6)
  - 128-134 d gestation
  - term = 147 +/- 3 d
  - ~28-32 wk human equivalent
  - AEROSURF™ Emitted dose 22.4 mg/min TPL (60% of nominal dose) vs CPAP

Wolfson, M., et al., *E-PAS2008:3764.1.*

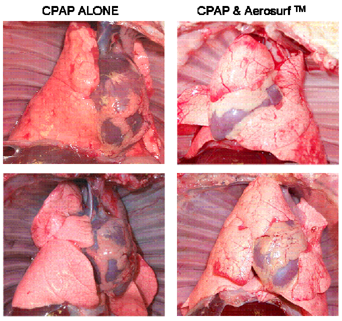
Capilary aerosol generator for surfactant aerosolization

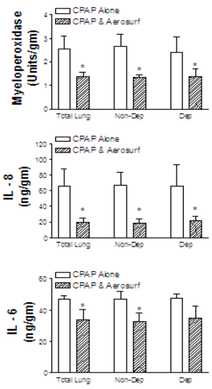
- Lucinactant (Surfaxin®, Discovery Laboratories, Inc.)
- Capillary Aerosol Generator (CAG), ventilator connector (Afectair®)
  - MMAD = 1.9 µm ± 0.6 GSD
  - Time = 90 min
  - Emitted dose = 22.4 mg/minTPL



- 128-134 d preterm lambs, tracheo, CPAP

- Better lung aeration
-Lower levels of:
-MPO,
-IL-6
-IL-8





Wolfson M et al, E-PAS2008:3764.1.

Multicenter Randomized, Open Label, Controlled Trial to Assess the Safety and Toleratility of Aerosurf® for Inhalation in Preterm Neonates—On going study in US & Europe 29-34 wks

Summary – Surfactant Trials

- Meta-analysis of CPAP vs INSURE show no significant differences in mortality but fewer overall airleaks with INSURE
- LISA and MIST treatment with various surfactants are moving ahead
- RCT trials of Aerosolized Aerosurf® versus CPAP are underway
- RCT trials of other peptide surfactants are underway in Europe and possibly So Africa

Summary – Trials of Aerosol Delivery vs InSure or CPAP

- Neonatologists are ready for true non-invasive surfactant therapy
- There is need to utilized specific aerosol generator and delivery system which can be used for surfactants in combination with positive end-expiratory pressure support
- Surfactants will become the “carrier” of other drugs into the airways and alveoli—to make make therapies directed to the lungs more effective

Surfactant Therapy has been a Great Personal Journey permitting me to learn about surfactant, clinical trials, treating babies and making life-long friends in Finland, Poland, United Kingdom, Sweden, and Canada

"I would rather discover a single fact, even a small one, than debate the great issues at length without discovering a thing"—Galileo Galilei

Thank you for your attention.