

CURRENT TOPIC

Systematic review of prophylactic *vs* rescue surfactant

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Surfactant treatment has been shown by careful randomised trials to reduce the mortality and morbidity of very premature babies.¹ However, whether surfactant should be given as soon as the baby is born or withheld until the baby has respiratory distress syndrome (RDS) is controversial.

The objective of this review is to set out the reasons for and against giving surfactant at birth, present the clinical trial data available to date with a systematic review of those trials, and the conclusions that can be drawn from them.

“Prophylactic treatment” is defined as surfactant given down an endotracheal tube at initial resuscitation. “Rescue treatment” is when the surfactant given to an intubated baby several hours after birth when RDS has been diagnosed.

Reasons for prophylactic surfactant treatment

The lung epithelium of very premature babies is damaged within minutes of ventilation.² This causes protein to leak on to the surface and interferes with surfactant function.³⁻⁴ Animal studies have shown that surfactant treatment, given as soon as possible after birth, reduces the severity of RDS and airway damage,⁵ and improves blood gases, lung function, and survival.⁶⁻⁷ Clinical trials have shown that surfactant treatment for very premature babies is very beneficial and remarkably safe.¹ For example, the Ten Centre Trial of ALEC⁸ used prophylactically showed a 30% reduction in the incidence of RDS compared with control babies and a 48% reduction in neonatal mortality with no side effects.

It is impossible to know which baby will develop RDS and who, therefore, might benefit from surfactant treatment. The shorter the gestation the more likely the baby is to develop RDS, but older babies who are compromised in some way are also at risk of RDS and its complications. Normal neonatal practice is to anticipate and try to prevent problems. To wait until a baby requires ventilation and a high level of inspired oxygen⁹ before giving a treatment which has now been shown to reduce the severity of RDS and save lives is counterintuitive.

Reasons for not giving surfactant at birth

If surfactant is given at birth some babies will be given surfactant unnecessarily.¹⁰ It is expensive and should be used only when the babies need it. In the early days of surfactant treatment there was concern that surfactant might be harmful and it was decided, for some clinical trials, that it should be given only to babies who had severe RDS. There were also concerns that surfactant treatment at birth would interfere with resuscitation and destabilise the baby, and that if surfactant is administered without knowing the position of the endotracheal tube, it may be delivered into one area of the lung.¹¹ If surfactant treatment is equally effective when given a few hours after birth, the problems associated with early administration become irrelevant.

Selection of studies and criteria for analysis

A searched was made for all clinical randomised trials that compared surfactant treatment given at birth with that used to treat established RDS. They were obtained from a personal knowledge of published findings, a Medline search, information from research workers in this field and from the National Perinatal Epidemiology Unit. Ten appropriate published randomised clinical trials were found.¹⁰⁻¹⁹

The criteria for inclusion of trials in the analysis were: trials should have been appropriately randomised; the prophylactic surfactant had to have been given at initial resuscitation and certainly within minutes of birth; rescue surfactant should only have been given to infants ventilated for RDS.

Four trials were excluded from the analysis. They were:

The OSIRIS trial¹⁶ because the early or prophylactic treatment was not given at birth. The median time for the first dose was 118 minutes. Merritt *et al*¹⁷ because rescue treated babies were excluded if the tracheal aspirate had an L:S lecithin: sphingomyelin ratio of 2.0 or more with phosphatidyl glycerol present, even though they were ventilated in at least 50% oxygen. This did not happen to the prophylactically treated babies. Only babies with RDS were included in the final analysis.

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Table 1 Summary of data from randomised controlled trials

Author	Surfactant	Entry criteria	Exclusions	Primary outcome	Sample size calculation	Number of centres	Control group	Blinded	Technique of randomisation
Dunn ¹⁰	Calf (now called BLES)	< 30 weeks	Malformations, rupture of membranes > 2 weeks and oligohydramnios	Difference in arterial, alveolar oxygen ratio of 0.1 (0.15)	60 per group at 90% power at $\alpha=0.05$	1	Yes	No	Envelopes sequentially numbered. Randomisation not stated. Stratified 24-26 weeks and 27-29 weeks
Kendig ¹¹	Calf (now called Infasurf)	< 30 weeks	Malformations	15% difference in survival	450 total at 80% power and $\alpha=0.05$	3	No	No	Envelopes consecutively numbered for each centre. Randomised blocks of 8
Egberts ¹²	Curosurf	26-30 weeks	Malformations, ROM > 3 weeks	40% increase in transcutaneous oxygen to FiO ₂ ratio, 50% reduction in x ray of RDS	50 per group for 1st outcome and 57 per group for second outcome at 80% power and $\alpha=0.05$	4	No	No	Envelopes in each centre in blocks of 4 or 8
Kattwinkel ¹³	Infasurf	29-32 weeks	Malformations, positive blood culture at birth. Judged too mature, severe perinatal asphyxia	7% difference in moderate RDS (mean airway pressure => 8 cm H ₂ O or FiO ₂ =>0.4)	1320 total at 90% power and $\alpha=0.05$	8	No	No	Envelopes. Randomisation not stated
Walti ¹⁴	Curosurf	25-31 weeks	Malformations, stillborn, ROM > 3 weeks	20% difference in survival without BPD at 28 days	250 total at 90% power and $\alpha=0.05$	12	No	No	Envelopes Randomisation not stated
Bevilacqua ¹⁵	Curosurf	24-30 weeks	Malformations or infection	To reduce by 30% the incidence of grade 3-4 RDS	280 total at 80% power and $\alpha=0.05$	18	No	No	Envelopes stratified for gestation

Some babies, eligible on gestational age criteria, were not enrolled because the amniotic fluid analysis suggested they had mature surfactant. The problem was that not all fetuses were submitted to this analysis. Bevilacqua *et al*¹⁸ was excluded because babies were enrolled in the study after two hours and the first dose was not given before this time. Babies were excluded from the study if their oxygen requirements at enrolment were less than 40% or more than 59%. Therefore, the mildly ill and sickest babies were not enrolled. Konishi *et al*¹⁹ was excluded because gastric aspirate was collected after birth and tested before the decision was made to enrol the baby in the trial. Therefore, this was not prophylactic treatment.

The information about the entry criteria, exclusions, primary outcomes, sample size calculations, number of centres and techniques of

randomisation are shown in tables 1 and 2. The basic demographic data for the enrolled babies are shown in table 3.

Analysis of the trials

The data were analysed using Cochrane Collaboration review manager software, Rev-Man, version 2.1a, 1995. This is designed to facilitate the preparation, production, and analysis of a systematic review and follows previously published techniques.²⁰ The results of the main outcomes are shown in fig 1.

The neonatal mortality was significantly reduced by prophylactic surfactant with an Odds Ratio (OR) and 95% confidence intervals (CI) of 0.55 (0.41 to 0.73) (table 4). This was a 39% reduction in the incidence of neonatal deaths from 139/1251 (11.1%) to 86/1269 (6.8%). The overall mortality by the

Table 2 Techniques and criteria for administering surfactant

Author	Dose of surfactant	Technique of giving surfactant	Criteria for intubation prophylactic group	Time of prophylactic dose	Criteria for intubating babies in the rescue group	Criteria for giving surfactant to the rescue group	Criteria for additional doses for both groups
Dunn ¹⁰	25 mg/ml, 24-26 wk - 3 ml, 27-29 wk - 4 ml	Catheter down the endotracheal tube in 3 aliquots. Bag ventilation with each aliquot	Elective at birth	Before the first breath, breathing prevented before surfactant	Apnoea, needing oxygen, has RDS. Unit policy to ventilate all babies <30 weeks	All babies treated no later than 6 hours unless no evidence of RDS	Up to 3 doses in first 5 days, given if FIO ₂ increase by 0.1 over lowest baseline
Kendig ¹¹	90 mg in 3 ml	Catheter down the endotracheal tube in 4 aliquots. Bag ventilation with each aliquot	Elective at birth	Within seconds of intubation	Not stated	If chest x ray shows RDS and FIO ₂ >0.4, mean airway pressure >7.0cm H ₂ O either or both. Hand ventilated before surfactant given	At intervals of 12 to 24 hours if FIO ₂ >0.4, mean airway pressure >7 cm H ₂ O or both
Egberts ¹²	200 mg/kg, 2.5 ml/kg	With a catheter down the endotracheal tube in one bolus	Elective at birth	Within 10 minutes	Intubated at birth	If ventilated and FIO ₂ >0.6 at 6 to 24 hours	Second dose at 6 hours or rescue treatment if FIO ₂ >0.6
Kattwinkel ¹³	4.5 ml per dose, 150 mg per dose	Instilled into the trachea	Elective as soon as practical	By 5 minutes	Chest x ray showed RDS and FIO ₂ ≥ 0.3	Chest x ray shows RDS and FIO ₂ >0.3 and intubated. Given straight after intubation	Repeated if FIO ₂ >0.6 and MAP>10 cm H ₂ O
Walti ¹⁴	100 mg/kg, 1.25 ml/kg	With a catheter down the endotracheal tube in 2 aliquots.	Elective at birth	By 15 minutes	If PaO ₂ less than 6.6 kPa (50 mm Hg) with FIO ₂ ≥ 0.3 and/or PaCO ₂ >7.3 kPa (55 mm Hg)	Chest x ray shows RDS and PaO ₂ /FIO ₂ <150 mm Hg (20 kPa) at mean airway pressure of 8 cm H ₂ O	Up to 3 doses in 48 hours. If PaO ₂ /FIO ₂ <150 mm Hg (20 kPa)
Bevilacqua ¹⁵	200 mg/kg, 2.5 ml/kg	With a catheter down the endotracheal tube as a bolus	At birth on clinical grounds	By 10 minutes	According to the routine of each unit	Chest x ray shows RDS and needing ventilation irrespective of inspired oxygen	Up to 3 doses in 48 hours. If PaO ₂ /FIO ₂ <150 mm Hg (20 kPa)

Table 3 Demographic data for babies enrolled in trial

	Number analysed		Number excluded after enrolment		Gestational age Mean (SD)		Birthweight Mean (SD)		Males		Antenatal steroids		Caesarean section	
	Prophylaxis	Rescue	Prophylaxis	Rescue	Prophylaxis	Rescue	Prophylaxis	Rescue	Prophylaxis	Rescue	Prophylaxis	Rescue	Prophylaxis	Rescue
Dunn ¹⁰	62	60	0	0	26.9 (1.7)	27.2 (1.4)	962 (270)	986 (220)	45%	60%	47%	50%	53%	60%
Kendig ¹¹	235	244	0	0	27.5 (2.1)	27.5 (2.0)	1023 (323)	1040 (295)	55%	56%	28%	34%	60%	64%
Egberts ¹²	75	72	1	1	28.0 (1.2)	27.8 (1.3)	1033 (237)	1126 (295)	55%	56%	25%	32%	60%	46%
Kattwinkel ¹³	627	621	79	71	31.0 (1.3)	30.9 (1.3)	1599 (346)	1608 (350)	53%	54%	NR	NR	48%	49%
Walti ¹⁴	134	122	14	18	28.9 (1.2)	28.3 (1.3)	1211 (289)	1150 (270)	56%	52%	17%	11%	58%	48%
Bevilacqua ¹⁵	136	132	9	9	28.0* (24-30)	28.0* (24-30)	1010 (296)	1002 (310)	52%	47%	28%	28%	64%	66%

* Median and range.

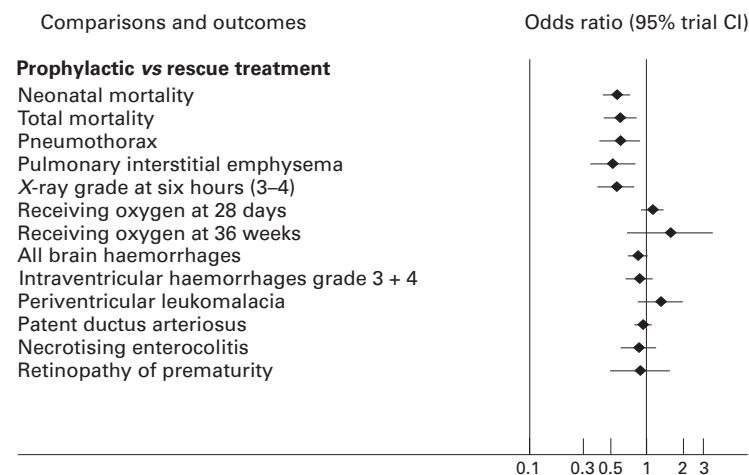


Figure 1 Comparison of outcomes with both types of treatment.

Table 4 Neonatal mortality

Trial	Prophylaxis	Rescue	Odds Ratio	95% CI low	95% CI High
Dunn ¹⁰	9/62	8/60	1.82	0.60	5.54
Kendig ¹¹	23/235	40/244	0.56	0.33	0.95
Egberts ¹²	8/75	14/72	0.50	0.20	1.24
Kattwinkel ¹³	3/627	11/621	0.31	0.10	0.89
Walti ¹⁴	15/134	23/122	0.54	0.27	1.08
Bevilacqua ¹⁵	28/136	46/132	0.49	0.28	0.83
Totals	86/1269 (7%)	139/1251 (11%)	0.55	0.41	0.73

Table 5 Total mortality

Trial	Prophylaxis	Rescue	Odds Ratio	95% CI low	95% CI High
Dunn ¹⁰	9/62	8/60	1.10	0.39	3.06
Kendig ¹¹	29/235	49/244	0.56	0.34	0.92
Egberts ¹²	10/75	15/72	0.58	0.25	1.39
Walti ¹⁴	18/134	29/122	0.50	0.26	0.94
Totals	66/506 (13%)	101/498 (20%)	0.59	0.42	0.82

Table 6 Pneumothorax

Trial	Prophylaxis	Rescue	Odds Ratio	95% CI low	95% CI High
Dunn ¹⁰	3/62	5/60	0.56	0.13	2.36
Kendig ¹¹	16/235	29/244	0.55	0.29	1.01
Egberts ¹²	2/75	5/72	0.39	0.08	1.77
Kattwinkel ¹³	8/627	11/621	0.71	0.29	1.77
Walti ¹⁴	3/130	6/121	0.46	0.12	1.75
Bevilacqua ¹⁵	10/136	12/132	0.79	0.33	1.89
Totals	42/1265 (3%)	68/1250 (5%)	0.60	0.40	0.88

Table 7 Pulmonary interstitial emphysema

Trial	Prophylaxis	Rescue	Odds Ratio	95% CI low	95% CI High
Dunn ¹⁰	2/62	5/60	0.39	0.08	1.79
Egberts ¹²	2/75	5/72	0.39	0.08	1.77
Kattwinkel ¹³	3/627	3/621	0.99	0.19	4.92
Walti ¹⁴	16/131	24/121	0.56	0.28	1.11
Bevilacqua ¹⁵	9/136	19/132	0.43	0.19	0.95
Totals	32/1031 (3%)	56/1006 (6%)	0.51	0.32	0.79

time of discharge was also significantly reduced with an OR and 95% CI of 0.59 (0.42 to 0.82) (table 5). However, this was only reported for the four trials with babies less than 32 weeks' gestation.^{10-12 14} There was a 36% reduction in the incidence of total deaths from 101/498 (20.3%) to 66/506 (13.0%). This suggests that prophylactic surfactant would save about seven more lives than rescue treatment for every 100 babies treated.

The incidence of pneumothoraces was significantly reduced with an OR and 95% CI of 0.60 (0.40 to 0.88) (table 6). This is a 39% reduction in the incidence of pneumothoraces from 68/1250 (5.4%) to 42/1265 (3.3%).

The incidence of pulmonary interstitial emphysema was significantly reduced with an OR and 95% CI of 0.51 (0.32 to 0.79) (table 7). This is a 45% reduction in the incidence of pulmonary interstitial emphysema from 56/1006 (5.6%) to 32/1031 (3.1%).

The incidence of severe RDS graded from the chest x ray pictures²¹ was only reported in three trials.^{12 14 15} There was a significant reduction with an OR and 95% CI of 0.54 (0.38 to 0.77) (table 8).

There were no significant differences in the incidence of chronic lung disease, defined by a requirement for oxygen at 28 days of life or 36 weeks' gestation, brain haemorrhages, or periventricular leucomalacia, patent ductus arteriosus, necrotising enterocolitis or retinopathy of prematurity. However, there was a strong trend towards a reduction in brain haemorrhages.

EFFECT ON THE SEVERITY OF RDS

The trials all recorded different information about the influence of the two surfactant regimens on oxygenation, ventilation, and the severity of RDS. Therefore, it is not possible to compare these in a meta-analysis. However, all the trials showed improvements in gas exchange and the severity of RDS with the use of prophylactic surfactant. Dunn *et al*¹⁰ showed significant improvement in gas exchange in the prophylactic group at 24 and 48 hours compared with the control group. Kendig *et al*¹¹ showed that the babies in the prophylaxis group had consistently lower requirements for supplemental oxygen and ventilatory assistance in the first 72 hours and less severe RDS. Egberts *et al*¹² showed that surfactant treatment at birth was associated with significantly better oxygenation at 6 hours, an improved $\text{tcPO}_2/\text{FIO}_2$ ratio from 39.7 to 28.1 ($P < 0.001$), and a 41% improvement for the early treated group.

Table 8 X-ray grade (3 or 4) at six hours

Trial	Prophylaxis	Rescue	Odds Ratio	95% CI low	95% CI High
Egberts ¹²	14/75	26/72	0.41	0.20	0.86
Walti ¹⁴	18/128	23/119	0.64	0.33	1.26
Bevilacqua ¹⁵	38/136	54/132	0.56	0.34	0.93
Totals	70/339 (21%)	104/323 (32%)	0.54	0.38	0.77

There was a lower incidence of severe RDS, 19% *vs* 36% ($P < 0.05$) and a 36% reduction in the incidence of moderate to severe RDS. The prophylactically treated babies were receiving more than 40% oxygen ($P < 0.01$) for a shorter time.

Kattwinkel *et al*¹³ showed that prophylactic surfactant was associated with a lower incidence of moderate RDS—7% *vs* 12% ($P = 0.004$). This was mainly in the babies of less than 30 weeks' gestation—10% *vs* 23% ($P = 0.021$)—and a lower incidence of ventilation or supplemental oxygen trended over the first few days ($P < 0.02$), lower mean airway pressure over the first 48 hours for ventilated babies ($P < 0.03$) and fewer babies needing supplemental oxygen at 28 days—5% *vs* 7% ($P = 0.071$).

Walti *et al*¹⁴ showed that within 3 to 72 hours of birth the prophylactic group had a higher pH, PaO₂:FIO₂ ratio, and a:A pO₂ ratio and lower FIO₂. They also had a lower respiratory rate, peak inspiratory pressure, and mean airway pressure. Bevilacqua *et al*¹⁵ showed that the maximum FIO₂ during the first 28 days was lower in babies given prophylaxis than in controls.

There was no evidence from any of the trials that prophylactic surfactant had a deleterious effect at the time it was administered or subsequently.

The proportion of babies treated with surfactant in each group and the total number of doses given to each group are shown in tables 9 and 10. The babies treated prophylactically required about 70% more doses of surfactant than the rescue group. However, the babies in the rescue group who were treated with surfactant received an average of 1.5 doses compared with 1.2 in the prophylactic group.

Table 9 Percentage of babies in each group who received surfactant

Trial	Prophylaxis	Rescue
Dunn ¹⁰	100	90
Kendig ¹¹	97	59
Egberts ¹²	100	32
Kattwinkel ¹³	100	43
Walti ¹⁴	98	55
Bevilacqua ¹⁵	100	40
Average % treated	99	48

Table 10 Total number of doses of surfactant given to each group

Trial	Prophylaxis	Rescue
Dunn ¹⁰	112	81
Kendig ¹¹	322	248
Egberts ¹²	83	23
Kattwinkel ¹³	661	321
Walti ¹⁴	234	161
Bevilacqua ¹⁵	142	53
Doses per baby enrolled	1.2	0.7
Doses per baby treated	1.2	1.5

Cost and benefits of prophylactic surfactant

Survival is the most important outcome. The data on overall survival are available from four trials¹⁰⁻¹³ and for babies less than 32 weeks' gestation (table 5). However, these are the group who are most at risk of dying and other serious complications. If 100 babies were treated prophylactically about 148 doses would be used, whereas if they received rescue treatment, about 100 doses would be used. Therefore, prophylactic treatment of 100 babies would require about 48 more doses than rescue treatment.

However, prophylactic treatment saves about seven extra lives for every 100 treated. Therefore, prophylactic surfactant would cost about seven more doses of surfactant for every extra life saved. The cost of surfactant for each extra life saved, for the different surfactants marketed in the UK in 1997, would be approximately: ALEC £1050 (£150 per phial), Exosurf and Survanta £2142 (£306 per phial), and Curosurf £2800 (£400 per phial).

There are other unmeasurable costs. The babies in the rescue group have more severe RDS and more pneumothoraces and this increases the cost of their care. As more babies survive in the prophylactically treated group the cost of their ongoing care would be greater.

Conclusions

Theoretical, animal, and clinical data now show that surfactant given at birth to babies of less than 32 weeks gestation improves survival and reduces complications. The data from this systematic review show a 39% reduction in the neonatal mortality if the babies are treated with surfactant at birth compared with a few hours later. The odds ratio of 0.55 in favour of prophylactic surfactant is very significant, and is similar to the effect of antenatal steroids where the odds ratio for neonatal mortality is 0.60. It is also similar to the effect of surfactant treatment, overall, where the reduction in neonatal mortality has an odds ratio of 0.55.²²

The trials in this analysis used calf and porcine surfactant. It is likely, but unproved in randomised trials, that other surfactants would have a similar effect.

Systematic reviews cannot be definitive because they only assess the data available to the authors. In this review the trials are heterogeneous in the type of surfactant used, the dose and dosing regimen, the enrolment criteria and the number of patients. This makes comparison and meta-analysis difficult. However, such heterogeneity lends weight to the significance of the main outcomes—reduction in the severity of RDS and increased survival.

Instilling relatively large amounts of fluid into the lungs of premature babies at birth may be difficult. However, those surfactants which use the lowest volumes will be easier to use and probably should be used in preference, although there are no comparative data. My own experience with the surfactant ALEC, at 1.2 ml per dose, is that administration at birth is easy and does not destabilise the baby.²³

There are no data to suggest that prophylactic surfactant treatment causes any more problems than subsequent treatment. The only negative fact against universal prophylactic surfactant seems to be the cost of the extra surfactant. However, although more expensive, there is the considerable benefit of saving seven more babies for every 100 born at less than 32 weeks of gestation. It can be crudely calculated that for these babies the cost of surfactant for each extra survivor is the cost of seven doses. Compared with many treatments, and the total cost of caring for very premature babies, prophylactic surfactant is a relatively cheap way of improving neonatal survival.

The practical decision for neonatologists is which babies to treat prophylactically. The problem is that it is not possible to know immediately at birth which babies will develop RDS. Obviously, the lower the gestational age the more likely the baby is to develop serious RDS and its complications. However, more mature babies can develop severe RDS if they are compromised. The upper gestational age cutoff for prophylaxis is not easy to define because there are few satisfactory data. The data from these trials suggests that at less than 32 weeks of gestation prophylactic surfactant is beneficial. Pragmatically, my personal practice is to recommend that all babies less than 32 weeks gestation should be treated with surfactant as soon as they are intubated. This means that those who need resuscitation and ventilation from birth will be given surfactant at birth, and those who subsequently require ventilation will receive their surfactant when they are intubated.

The varied and almost arbitrary nature of the criteria in these trials about when to give rescue treatment and re-treat babies means that no guidance can be given about how soon to give rescue treatment and when to re-treat the sickest babies.

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- 1 Soll RF, McQueen MC. Respiratory distress syndrome. In: Sinclair JC, Bracken MB, eds. *Effective Care of the Newborn*. Oxford: Oxford University Press, 1992;325-52.
- 2 Gandy G, Jacobson W, Gairdner D. Hyaline membrane disease I. cellular changes. *Arch Dis Child* 1970;45:289-310.
- 3 Robertson B, Berry D, Curstedt T, Grossmann G, Ikegami M, Jacobs M, et al. Leakage of protein in the immature rabbit lung; effect of surfactant replacement. *Respir Physiol* 1985;61:265-76.

- 4 Seeger W, Stohr G, Wolf HRD, Heuhoef H. Alteration of surfactant function due to protein leakage: special interaction with fibrin monomer. *J Appl Physiol* 1985;58:326-38.
- 5 Nilsson R, Grossmann G, Robertson B. Bronchiolar epithelial lesions induced in the premature neonate by short periods of artificial ventilation. *Acta Pathol Microbiol Scand* 1980;88:359-67.
- 6 Lachmann B, Grossmann G, Nilsson R, Robertson B. Effect of supplementary surfactant on the in vivo lung mechanics in the premature rabbit neonate. *Eur J Pediatr* 1981;136:173-9.
- 7 Enhorning G, Hill D, Sherwood G, Cutz E, Robertson B, Bryan C. Improved ventilation of prematurely-delivered primates following tracheal deposition of surfactant. *Am J Obstet Gynecol* 1978;132:529-36.
- 8 Ten Centre Study Group. Ten centre trial of artificial surfactant (artificial lung expanding compound) in very premature babies. *BMJ* 1987;294:991-6.
- 9 Collaborative European Multicenter Study Group. Surfactant replacement therapy for severe neonatal respiratory distress syndrome: An international randomized clinical trial. *Pediatrics* 1988;82:683-91.
- 10 Dunn MS, Shennan AT, Zayack D, Possmeyer F. Bovine surfactant replacement therapy in neonates of less than 30 weeks' gestation - a randomised controlled trial of prophylaxis versus treatment. *Pediatrics* 1991;87:377-86.
- 11 Kendig JW, Notter RH, Cox C, Reubens LJ, Davis JM, Maniscalco WM, et al. A comparison of surfactant as immediate prophylaxis and as rescue therapy in newborns of less than 30 weeks' gestation. *N Engl J Med* 1991;324:865-71.
- 12 Egberts JE, de Winter P, Sedin G, de Kleine MJK, Broberger U, van Bel F, et al. Comparison of prophylaxis and rescue treatment with Curosurf in neonates less than 30 weeks' gestation: a randomised trial. *Pediatrics* 1993;92:768-74.
- 13 Kattwinkel J, Bloom BT, Delmore P, Davis CL, Farrell E, Friss H, et al. Prophylactic administration of calf lung surfactant extract is more effective than early treatment of respiratory distress syndrome in neonates of 29 through 32 weeks' gestation. *Pediatrics* 1993;92:90-8.
- 14 Walti H, Paris-Llado J, Breart G, Couchard M, French Collaborative Multicentre Study Group. Porcine surfactant replacement therapy in newborns of 25-31 weeks' gestation: a randomised, multicentre trial of prophylaxis versus rescue with multiple low doses. *Acta Paediatr* 1995;84:913-21.
- 15 Bevilacqua G, Parmigiani S, Robertson B, On behalf of the trial participants. Prophylaxis of respiratory distress syndrome by treatment with modified porcine surfactant at birth: a multicentre prospective randomised trial. *J Perinat Med* 1996;24:1-12.
- 16 The OSIRIS collaborative group. Early versus delayed administration of a synthetic surfactant - the judgement of OSIRIS. *Lancet* 1992;340:1363-9.
- 17 Merritt TA, Hallman M, Berry C, Pohjavuori M, Edwards DK, Jaaskelainen J, et al. Randomized, placebo-controlled trial of human surfactant given at birth versus rescue administration in very low birth weight infants with lung immaturity. *J Pediatr* 1991;118:581-94.
- 18 Bevilacqua G, Halliday H, Parmigiani S, Robertson B. Randomized multicentre trial of treatment with porcine natural surfactant for moderately severe neonatal respiratory distress syndrome. *J Perinat Med* 1993;21:329-40.
- 19 Konishi M, Fujiwara T, Chida S, Maeta H, Shimada S, Kasai T, et al. A prospective randomised controlled trial of early versus late administration of a single dose of surfactant-TA. *Early Hum Devel* 1992;29:275-82.
- 20 Chalmers I, Altman D, eds. *Systematic reviews*. London: BMJ Publishing Group, 1995.
- 21 Bomsel F. Contribution à l'étude radiologique de la maladie des membranes hyalines: à propos de 110 cas. *J Radiol Electrol* 1970;51:259-68.
- 22 Ahluwalia JS, Morley CJ. Changes in oxygenation and heart rate after administration of artificial surfactant (ALEC) to preterm infants. *Arch Dis Child* 1995;72:F121-F2.



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