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Colfosceril Palmitate

A Pharmacoeconomic Evaluation of a Synthetic Surfactant Preparation (Exosurf® Neonatal™) in Infants with Respiratory Distress Syndrome

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Contents

Summary

Synopsis

Comprehensive clinical data provide strong evidence of the efficacy of the synthetic lung surfactant colfosceril palmitate (Exosurf® Neonatal™) administered as prophylaxis or rescue therapy in infants with respiratory distress syndrome (RDS). The use of rescue therapy with colfosceril palmitate is further supported by cost-effectiveness analyses which report a 9 to 48% reduction in the cost per survivor compared with placebo or historical controls, despite divergent study methodology and location. Importantly, the savings were evident in both larger (≥1250g) and smaller (700 to 1350g) infants. All studies considered costs or charges accrued during initial hospitalisation through to 1 year; measurement of long term resource use data and all resulting costs are required for a more complete pharmacoeconomic evaluation.

The optimal timing of surfactant administration is likely to be an important economic issue given that efficacy data from a large international trial support earlier administration of colfosceril palmitate versus delayed therapy in high risk patients. Further economic benefits may be realised by the sequential use of antenatal corticosteroids and surfactant therapy, although this has yet to be prospectively investigated.

In conclusion, clinical and pharmacoeconomic data strongly support the use of rescue therapy with colfosceril palmitate. Additionally, recent clinical data indicating that even better results may be achieved with earlier administration and/or combined use with antenatal corticosteroids should be assessed from an economic standpoint to determine the optimal prescribing strategy for this agent.

Disease Considerations

Respiratory distress syndrome (RDS) affects 0.3 to 1.3% of the total neonatal population. 50 to 70% of preterm infants (<30 weeks' gestation) develop RDS. Improved maternal and neonatal care, leading to decreased mortality but increased costs, has been documented in this field over the past 2 decades.

Direct costs accrued in neonatal care are determined by the intensity of care delivered. The primary predictors of resource use are assisted ventilation and low birthweight, with RDS, oxygen consumption and duration of stay in intensive care also contributing to direct costs. Lifetime direct, indirect and intangible costs to both patient and family are also likely to be considerable in around 10% of surviving patients with RDS in whom impaired intellectual or neurological function prevents them from leading a productive life.

Therapeutic Efficacy and Tolerability

Colfosceril palmitate, a synthetic lung surfactant consisting of colfosceril palmitate, cetyl alcohol and tyloxapol (marketed as Exosurf® Neonatal™), improves oxygenation and stabilises lung function in infants with RDS. Results from a number of large well-designed trials provide strong evidence for the efficacy of colfosceril palmitate administered either as rescue therapy or prophylaxis in infants with RDS. This is supported by a meta-analysis which showed a significant reduction in mortality with either prophylaxis or rescue therapy with synthetic surfactant. Follow-up data at 1 year suggest that surfactant use is not associated with neurological or developmental impairment, although longer term investigation is required.

While colfosceril palmitate offered clear benefits to infants weighing ≥700g, only early benefits (within 72 hours) were evident in smaller infants and mortality was not reduced. Comparative trials suggest that there is a faster response to bovine lung surfactant (beractant) in the first 72 hours compared with colfosceril

palmitate, although outcome according to the key study end-points (bronchopulmonary dysplasia and/or mortality) did not differ between agents.

The large OSIRIS trial (Open Study of Infants at high risk of or with Respiratory Insufficiency – the role of Surfactant) provides evidence that early (<2 hours of age) selective use of colfosceril palmitate in high risk infants offers advantages over delayed use in the same population.

Pharmacoeconomic Evaluation

Four cost-effectiveness analyses of colfosceril palmitate administered as rescue therapy have been performed. All assessed short term (initial hospitalisation or through to 1 year) direct costs or charges only. According to these studies, colfosceril palmitate rescue therapy was associated with a reduction in cost per survivor of 9 to 48% compared with controls (historical or placebo). Reductions in the cost per survivor were evident in both larger (≥1250g) and smaller (700 to 1350g) infants administered colfosceril palmitate. Subanalyses of cost data for nonsurviving infants showed that while costs were increased in treated nonsurvivors, the costs for all patients (survivors + nonsurvivors) were similar whether or not surfactant was administered.

Results of preliminary pharmacoeconomic analyses concerning colfosceril palmitate administered as a single prophylactic dose described an increased cost per survivor associated with surfactant use. However, this outcome is inconsistent with results obtained from larger studies using other surfactant preparations which demonstrated cost savings.

Other issues concerning colfosceril palmitate that warrant pharmacoeconomic evaluation are: the optimal timing of therapy; the efficacy of colfosceril palmitate versus other surfactant products; the sequential use of antenatal steroids and surfactant therapy; long term follow-up data; and quality-of-life issues.

Colfosceril palmitate (dipalmitoylphosphatidylcholine), the major constituent of endogenous pulmonary surfactant, lowers air-alveolar surface tension, thereby preventing atelectasis during expiration. Respiratory distress syndrome (RDS) in premature infants is a direct result of endogenous surfactant deficiency.[1] Administration of exogenous surfactant, either as treatment or prophylaxis, has been shown unequivocally to provide significant clinical benefit to this patient group.[2]

A number of synthetic surfactants and surfactant preparations derived from natural sources are now available for the treatment or prophylaxis of neonatal RDS. The synthetic product consisting of colfosceril palmitate (85% by weight), cetyl alcohol (9%) and tyloxapol (6%), marketed as Exosurf® Neonatal™, is the focus of this review. Throughout the review, this preparation will be referred to as colfosceril palmitate.

1. Overview of Neonatal Respiratory Distress Syndrome

1.1 Epidemiology

RDS (or hyaline membrane disease) is the most common of the severe respiratory disorders in neonates.[3] Incidence rates range from 0.3 to 1.3% of the neonate population according to the diagnostic criteria applied.[3] The incidence of RDS is greatly increased in preterm infants. It affects 50 to 70% of infants of <30 weeks' gestational age and is almost inevitable in infants of <28 weeks' gestation.[4,5]

Improvements in antenatal and neonatal care have led to a marked decrease in RDS–associated mortality over the past 20 years.[2] Antenatal interventions include the use of tocolytics and maternal use of steroids, while postnatal care includes better observation of neonatal homeostasis and nutrition,

respiratory support, surfactant replacement therapy and management of patent ductus arteriosus.[2]

Infant risk factors for RDS include prematurity, asphyxia at birth, male gender, intact membranes prior to delivery, familial predisposition, hypothermia, and being a second-born twin.[3,5-9] The association between RDS and caesarean section and also the timing of cord clamping are more controversial.[5] Fetal stress (for example that produced by vaginal delivery or premature membrane rupture) may enhance lung maturity.[3,5,10] Maternal risk factors predisposing infants to RDS include poorly controlled diabetes and hypertension,[11,12] while maternal smoking, alcohol (ethanol) ingestion or narcotic addiction appears to reduce the incidence of RDS.[5,13,14]

1.2 Disease Costs

Both the monetary and social costs of neonatal care in low-birthweight infants are considerable.[15,16] RDS accounts for a large proportion of neonatal care costs,[17] although the precise figures involved have yet to be quantified. Improved healthcare in neonates, which has resulted in a significant reduction in RDS–related mortality, has been accompanied by a marked increase in resource use and costs.[2,18]

Direct costs accrued from neonatal care during hospitalisation are determined by the intensity of care required.[17] Assisted ventilation and low birthweight have been consistently identified as the main predictors of resource use in the neonatal intensive care unit (NICU) in infants with or without RDS. While the presence of RDS increases resource consumption slightly, this is less significant than the 2 major variables.[19-21] Oxygen needs and duration of patient stay also influence final costs.[17]

The daily cost of intensive care for a neonate is 2 to 6 times that of a neonate receiving special/high dependency care,[22-24] which in turn is twice that required for normal babies in neonatal care.[17] Ryan et al.[23] observed that staff salaries were readily the largest component of neonatal care costs (fig. 1). This is consistent with the intensive skilled nursing required by infants on mechanical

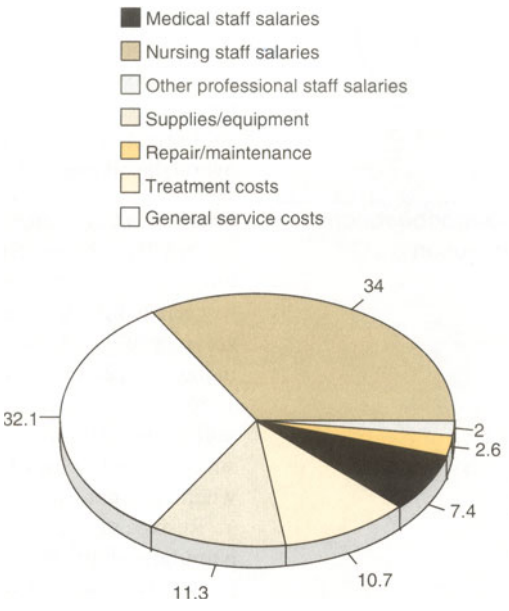

Fig. 1. Proportion (expressed as a percentage) of direct costs attributed to staff salaries, supplies/equipment, repair and maintenance, treatment costs (drugs, laboratory and diagnostic tests, surgery and maternal care) and general service costs (ancillary staff salaries, light, power and heating) over a 6-month period in an English neonatal medical and surgical unit.[23]

ventilation. At 1992 values, Mugford and Howard[17] estimated the daily cost of intensive care for neonates in the UK to be £540 compared with £220 for infants receiving special care and £140 for the lowest level of care.

Low birthweight is also an important predictor of high costs.[16,20] Healthcare costs increase with decreasing bodyweight in neonates weighing less than 2000g; in an analysis of 1185 infants, only 18% weighed 500 to 1500g but these infants accounted for 37% of all costs.[20]

In addition to outcome during the postnatal period, direct and indirect costs that accrue during the life of a patient as a result of RDS should also be quantified. To date, such costs for patients with RDS have not been evaluated. Before the introduction of surfactant therapy, 91% of surviving infants with RDS (birthweight 1400 to 3300g) showed sufficient neurological function and development at 5 years' follow-up (development quotient > 80) that

they could be expected to lead productive lives and contribute to society.[25,26] At 2 years' follow-up, 35% of infants weighing <1001g at birth had developed lower respiratory tract infections and those with bronchopulmonary dysplasia at birth had a higher incidence of respiratory tract infections (86% in the first year). Such infections could result in higher direct costs during childhood.[25]

Direct and indirect costs to other family members should also be considered. One study estimated that parents made a mean of 5 visits per week to infants in intensive care at a total cost of $US250.[27] Immediate and longer term intangible costs (for example, the emotional impact of death or dealing with handicap, protracted concern about the child's vulnerability, outlook for future pregnancies, etc.) are also important in this setting.[16,28]

2. Rationale for the Use of Colfosceril Palmitate

2.1 Therapeutic Efficacy

Surfactant replacement therapy administered as either prophylaxis or rescue therapy (initiated after symptoms of RDS have developed) is effective in infants with RDS.[2] Importantly, recent epidemiological data support the efficacy of surfactant replacement therapy. Within 2 years after the introduction of the first surfactant in the USA (from 1989 to 1990), a 6.2% decline in infant mortality was reported by the National Center for Health Statistics coupled by almost a 30% decrease in the incidence of RDS. It has been suggested that surfactant therapy is the therapeutic advance responsible for much of this decline.[29]

2.1.1 Comparisons with Placebo

Meta-Analysis Results

A meta-analysis performed by Soll and McQueen[2] using data from randomised, double-blind, placebo-controlled trials of synthetic surfactants (predominantly colfosceril palmitate) shows that these agents significantly decrease mortality in infants with RDS when administered either as prophylaxis or rescue therapy (table I). Rescue therapy consistently improved other study end-points on meta-analysis, while the effects with prophylaxis were less consistent. While difficult to quantify, there are large variations in the practice of neonatal medicine which may have implications for the effectiveness of therapy in the general neonatal population. The efficacy of colfosceril palmitate following general use in 471 North American centres (n = 11 455) has been documented in a preliminary report.[30]

Individual Trial Results

Consistent with the results of the meta-analysis described above, colfosceril palmitate, administered as prophylaxis or rescue therapy, was of clear benefit in infants weighing ≥700g (for review, see Dechant & Faulds[31]). However, in infants weighing <700[32] to 750g,[33] colfosceril palmitate offered early clinical benefits (improved gas exchange, oxygen and ventilator requirements), but provided no difference in clinical outcome versus

Table I. Meta-analysis of data from randomised controlled trials with synthetic surfactants used in the prophylaxis or rescue treatment of respiratory distress syndrome (from Soll & McQueen,[2] by permission of Oxford University Press)

Outcome	Prophylaxis			Rescue treatment		
	no. trials analysed[a]	event rate difference (%)	95% confidence intervals	no. trials analysed[a]	event rate difference (%)	95% confidence intervals
Pneumothorax	5 (4)	–2.7	–6.0, 0.6	4 (4)	–10.4	–13.6, –7.2
Patent ductus arteriosus	5 (3)	5.4	0.4, 10.4	3 (3)	–8.0	–12.6, –3.4
Intraventricular haemorrhage	3 (2)	–4.1	–9.6, 1.3	2 (2)	–3.2	–6.9, 0.5
Bronchopulmonary dysplasia	5 (3)	0.5	–4.0, 5.1	3 (2)	–2.8	–4.9, –0.7
Bronchopulmonary dysplasia or death	3 (3)	–5.4	–11.1, 0.1	3 (3)	–6.5	–9.4, –3.6
Death	7 (4)	–6.4	–10.0, –2.7	5 (4)	–4.1	–6.7, –1.6

a Numbers in parentheses indicate the number of trials with colfosceril palmitate.

placebo. The diminished efficacy of surfactant therapy in these extremely low birthweight infants is not unexpected as, in addition to RDS, they have profound multisystem immaturity which also determines their prognosis.[31]

Additionally, recent large studies seem to confirm that the recommended regimen of colfosceril palmitate (5 ml/kg administered twice 12 hours apart) is indeed optimal, with no additional benefit obtained with the use of further or higher doses.[34,35]

2.1.2 Comparisons with Other Surfactant Preparations

Results from both pharmacodynamic studies[36,37] and a meta-analysis[2] suggest that the immediate effects of natural surfactants may be more marked than those of synthetic surfactants. This observation appears to be borne out by a number of direct clinical comparisons between colfosceril palmitate and beractant (Survanta® or Infasurf®), modified bovine lung surfactant, in which beractant produced more rapid improvement in oxygenation and lung compliance within the first 72 hours in infants with RDS. However, there were no differences between treatments in the primary end-points of these studies (combined mortality and bronchopulmonary dysplasia or mortality alone).[38-45] A meta-analysis of the data from these trials is currently underway.[46]

Importantly, Solimano et al.[47] recently demonstrated improved respiratory status after use of beractant in infants who had failed initial rescue therapy with colfosceril palmitate; trials which stratify infants according to disease severity are required to confirm this observation.

Given that the various surfactant preparations differ in their composition (notably with respect to surfactant proteins[48] and platelet-activating factor[49]), long term comparative studies of different surfactants will help to determine the relative merits of these preparations.

2.1.3 Timing of Administration

The relative advantages of prophylaxis versus rescue therapy were unclear according to the meta-analysis of Soll and McQueen,[2] although there was a slight trend in favour of prophylaxis. This is supported by the European Exosurf Study Group trial, which demonstrated advantages for prophylaxis compared with selective use of colfosceril palmitate in placebo recipients who developed RDS.[50]

The optimal timing of more selective use of colfosceril palmitate was investigated in the influential OSIRIS trial (Open Study of Infants at high risk of or with Respiratory Insufficiency – the role of Surfactant). This trial provides strong evidence that early intervention in infants deemed to be at high risk of RDS is superior to delayed treatment. Intubated infants <2 hours of age who received early treatment with colfosceril palmitate had a lower risk of oxygen dependence or death compared with those receiving delayed administration (intubated infants >2 hours of age).[34]

2.1.4 Long Term Data

The survival advantage evident with the use of colfosceril palmitate was maintained after 1 year of adjusted age with prophylaxis (neonate birthweight 700 to 1350g),[51,52] and after rescue therapy (neonate birthweight 700 to ≥1250g).[53] Growth and development and the incidence of visual and auditory impairment were equivalent at 1 year of adjusted age in infants treated with colfosceril palmitate or placebo.[54,55] This seems to be consistent with an overview of all long term data, which also suggests no neurological or developmental impairment with the use of surfactant replacement therapy.[2] Data concerning more than 1 year of follow-up are not yet available for colfosceril palmitate.

2.2 Tolerability

Results from the majority of placebo-controlled trials indicate that colfosceril palmitate is associated with an 18 to 35% increase in the incidence of apnoea of prematurity.[31] It has been suggested that since surfactant reduces ventilation requirements and allows early extubation of these infants, they are more likely to manifest this complication.[52] According to an overview of 5 trials (using data from over 2500 infants), pulmonary haemorrhage

occurs in 2% of colfosceril palmitate recipients *vs* 1% of placebo recipients[56] (for an overview of trial data see Rogers[57]). Other short term adverse effects, including blockage of the endotracheal tubes, can occur as a result of introducing surfactant into the trachea.[58]

The incidence of most pulmonary air leak events and patent ductus arteriosus decreases with colfosceril palmitate. This is supported largely by the meta-analysis of Soll and McQueen,[2] although no effect on patent ductus arteriosus was observed with prophylaxis (table I). Overall, pulmonary interstitial emphysema decreases with colfosceril palmitate,[31] although 4 cases of unilateral pulmonary interstitial emphysema in association with colfosceril palmitate, which were possibly attributable to poor distribution of the surfactant, have been reported.[59]

Data from placebo-controlled studies indicate that laboratory abnormalities are not associated with colfosceril palmitate.[60] An important issue which does not appear to have been addressed with colfosceril palmitate is that of possible immunogenicity. While the colfosceril palmitate preparation is free of surfactant proteins, phospholipids are known to be highly immunogenic; thus, the issue of immunogenicity and any possible long term consequences merits investigation.[61]

3. Pharmacoeconomic Analyses

Almost 10 years before the introduction of surfactant therapy, Showstack et al.[18] documented escalating costs associated with the management of infants with RDS. Over the 10-year study period, increased costs were attributed to increased services received by this patient group.[18] The recent introduction of surfactant therapy which is costly (lung surfactant accounted for over 10% of the pharmacy drug budget at 1 institution[62]), has prompted calls for analyses to evaluate the economics of surfactant use. Analyses addressing the pharmacoeconomics of colfosceril palmitate are evaluated in this section and discussed with reference to similar studies performed with other surfactant preparations.

3.1 General Pharmacoeconomic Considerations

The outcomes investigated in a pharmacoeconomic analysis will differ according to the study perspective. While hospital managers will likely be interested in short term costs and healthy survival to discharge, parents and family are more likely to value long term or lifetime costs and outcome.[17] A full economic analysis of surfactant therapy would include both short and long term direct and indirect costs, as well as an estimation of intangible costs. To date, only data up to 1-year's follow-up are available for colfosceril palmitate (section 2.1.4), which restricts the scope of pharmacoeconomic analyses to the short term.

As mentioned in section 1.2, the key determinants of neonatal care costs in the NICU are assisted ventilation, birthweight and, to a lesser degree, oxygen requirements and duration of stay. All of these factors should be monitored in pharmacoeconomic evaluations in order to fully examine the costs of surfactant therapy. However, accurate costing for preterm neonates is difficult because greatly differing levels of care are required during different stages of RDS. As an example, if charges are used, a patient may incur the same charges whether they receive minimal or maximal respiratory support.[63] For this reason, Mugford and Howard[17] suggest that future studies in this field should report either time spent receiving different levels of care or details of continuous variables (for example, time on assisted ventilation) so that economic data can be compiled with more accuracy.

Over and above these variables, the relationship between infant bodyweight and resource use is an important one. It is well established that the cost per survivor increases greatly with decreasing birthweight.[20,64] Indeed, Walker et al.[64] estimated that, before the introduction of surfactant therapy, the costs per survivor for infants weighing <900g exceeded their total predicted lifetime earnings. Increased costs in these very immature infants can be attributed to a more complicated clinical course accompanied by increased resource use.

Table II. Summary of controlled studies investigating the cost effectiveness of colfosceril palmitate (CP) administered as rescue treatment (two 5 ml/kg doses administered 12 hours apart) in neonates with respiratory distress syndrome (receiving mechanical ventilation and with an arterial alveolar oxygen ratio of < 0.22) for the initial hospitalisation period or up to 1 year adjusted age

Reference	Country and currency year	Birthweight (g)	Treatment/ control groups	No. of patients	Outcome ($US or $A)[a]		Resource variables evaluated for cost data
					charge or cost/patient[b]	charge or cost/survivor[c]	
North American studies							
Backhouse et al.[66]	USA/Canada (1987-1990)	≥ 1250	CP	216	46 807 (49 799)[d]	53 526[e]	Time on ventilation and O_2, time in NICU, hospital and readmissions to 1 year
			Air	239	59 478 (62 670)[d]	68 868[e]	
Mauskopf et al.[67]	USA	700-1350	CP	113	97 642 (100 732)[d]	119 919[e]	Time on ventilation and O_2, time in NICU, hospital and readmissions to 1 year
			Air	135	97 452 (100 531)[d]	141 593[e]	
Australian studies							
Diwaker et al.[68]	Australia (1990)	730-1905	CP	41	17 986[f]	21 069	Personnel time, equipment and consumable use assessed for 155 procedures required for neonatal care
			Historical	41	35 697[f]	40 655	
Kristensen & Wojnar -Horton[62,69]	Australia (1991)	565-3415	CP	97	33 782	38 552[g]	Time in hospital
			Historical	65	34 163	42 485	

a Conversion factor as of 26 October 1994: $US1.00 = $A1.36.

b Total costs/charges divided by the total number of patients.

c Total costs/charges divided by the number of survivors.

d Charges through to 1 year follow-up.

e Data derived for a hypothetical cohort of 100 infants, using the total charges divided by the expected number of survivors at 1 year.

f Calculated using median total costs/patient.

g Calculated given that an estimated 7 fewer infants survived in the control group.

Abbreviation: NICU = neonatal intensive care unit.

Marginal[1] rather than average costs are likely to be more appropriate for assessing the economic impact of surfactant therapy,[65] although Tubman et al.[24] argue that the difference between marginal and average costs is minimal as staffing constitutes the largest cost in this environment (section 1.2).

3.2 Rescue Therapy

3.2.1 Methodology

To date, 4 studies have been conducted to investigate the cost effectiveness of the standard treatment regimen of colfosceril palmitate (two 5 ml/kg doses administered 12 hours apart) in infants with established RDS. Data from these studies are summarised in table II. In 2 large, well-designed studies, colfosceril palmitate was compared with placebo (air).[66,67] In the remaining studies, unselected[62] or matched[68] historical control groups comprised infants with RDS admitted to the institution before the introduction of surfactant therapy; it was stated in one of these studies that the general management of infants did not alter significantly over the recruitment period.[68]

The degree of precision regarding the estimation of resource utilisation varied in these studies. Two studies assessed time on ventilation and oxygen therapy, length of NICU and hospital stay,[66,67] while Kristensen and Wojnar-Horton[62] assessed length of hospital stay only. Diwaker et al.[68] did

1 Marginal cost is the extra cost of one extra unit of product or service delivered (usually differs from average cost).

the most thorough investigation of resource utilisation, monitoring staff time and equipment required for 155 different procedures associated with neonatal care (ranging from nappy changes to surgical procedures). In converting resource use into monetary values, all studies considered direct inpatient medical costs only, although again the components that were considered differed between studies. One study assumed fixed daily costs based on diagnostic-related group cost data and surfactant cost,[62,69] whereas the most detailed analysis included hotel costs, costs for differing care intensity, fixed costs, administration costs, etc.[68] The 2 North American studies used charges as a proxy for costs. Charges tend to exceed costs, although the precise relationship between the 2 parameters is variable;[70] in their sensitivity analysis, Backhouse et al.[66] converted charges to costs using cost to charge ratios for each study site where available. Since short term direct medical costs or charges, but not indirect or intangible costs, were considered, the perspective of these studies is most likely to be relevant for healthcare providers or third-party payers. Both North American studies discounted benefits (rate 5%) and conducted a sensitivity analysis of their data.[66,67]

3.2.2 Outcome

In all studies, rescue treatment with colfosceril palmitate was associated with a reduction in cost per survivor (ratio of total costs : number of survivors), the primary cost-effectiveness end-point (table II). The percentage decrease in cost per survivor compared with the control group ranged from 9 to 48% over the initial hospitalisation period. The actual dollar values obtained for the cost per survivor varied widely, the North American studies showing greatly inflated figures compared with the Australian studies. This is likely to be attributable to the different healthcare systems and costing methods employed in the 2 countries and the use of charges rather than costs in the North American studies.[17]

North American Studies

The 2 North American studies had different inclusion criteria regarding infant birthweight

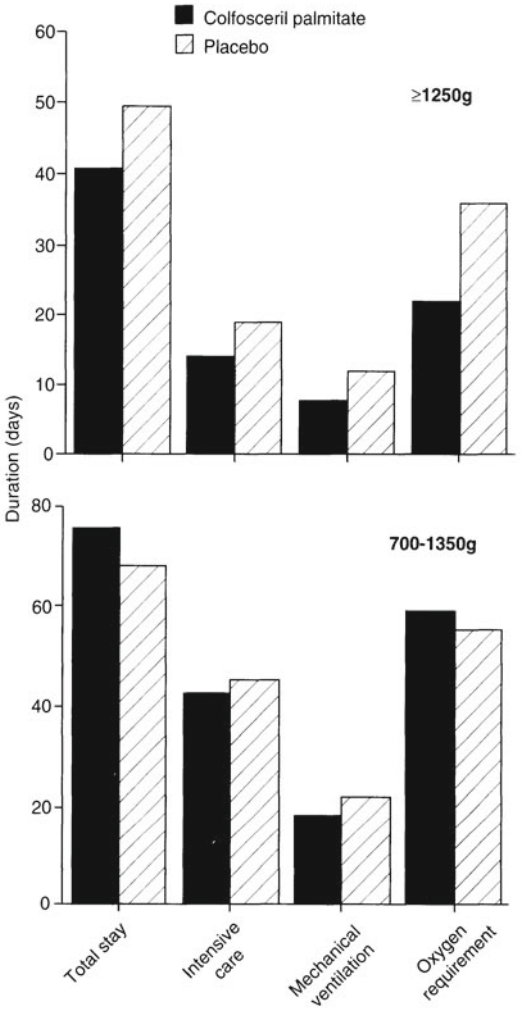

Fig. 2. Hospital resource use over a follow-up period of 1 year (expressed as the mean number of days) in infants weighing (**top**) ≥1250g (n = 1056) and (**bottom**) 700 to 1350g (patient numbers not given) receiving rescue therapy with colfosceril palmitate or placebo (air).[66,67]

(Backhouse et al.[66] included infants weighing ≥ 1250g and Mauskopf et al.[67] included infants with birthweights ranging from 700 to 1350g). Resource use in these studies according to infant birthweight is illustrated in figure 2. Consistent with previously observed trends in neonatal care (section 3.1.1), both costs per patient and per survivor were increased in the smaller versus larger babies (approximately 2-fold in surfactant and

Table III. Percentage change in costs or charges per patient associated with the use of colfosceril palmitate rescue therapy *vs* controls (placebo or historical) in surviving infants according to birthweight. Costs are considered for the initial hospitalisation period only

Birthweight (g)	Change in costs or charges *vs* control (%)	Reference
≤750	−12	62, 69
>750-≤1000	+29	62, 69
700-1350	−16	67
730-1090	−16	68
815-1815	−28	68
>1000-≤1500	−15	62, 69
≥1250	−29	66
970-1905	−31	68
>1500	−21	62, 69

control groups; table III). However, regardless of infant birthweight, there was a 15 to 22% decrease in the cost per survivor associated with surfactant use. In the smaller infants, a reduction in the cost per survivor was evident with colfosceril palmitate despite a longer total stay and greater oxygen requirements compared with placebo (fig. 2).

The large costs associated with the treatment of smaller infants can be attributed to the fact that while surfactant therapy may speed recovery from RDS and reduce mortality, the prematurity of the infant still demands intensive and therefore costly care. In contrast, administration of surfactant can speed recovery from RDS, reduce the need for intensive care and shorten hospital stay in larger infants.

Of interest, recent data concerning resource use collected from 14 US perinatal centres before and after the introduction of surfactant replacement therapy[71] describe a significant ($p < 0.03$) reduction of approximately 10% in adjusted total charges over the study period. The study, which analysed data from 5629 infants (weighing 500 to 1500g), did not identify which patients received surfactant but rather linked the change to the introduction of surfactant as this was identified as the only major modification to neonatal care. This may partially explain the smaller decline in resource use compared with the studies involving colfosceril palmitate (table III), in which all patients in the active treatment arm received surfactant. Ancillary charges (which included pharmacy charges) showed a slight reduction. Extended to a national level, and adjusted for an increase in low birthweight infants and for an increase in infants who survived but would have died without treatment, the total savings for the USA are an estimated US$90 million/year.[71]

For infants who do not survive, concerns have been raised that surfactant therapy may prolong survival and resource use in this patient group. Consistent with this, some studies[66,67,69] described increases in costs or charges incurred by nonsurviving infants receiving colfosceril palmitate compared with control groups, but importantly in all of these studies, no substantive increases in costs or savings were observed when all patients (survivors + nonsurvivors) were considered. Additionally, a decline of 31% in adjusted total charges was observed by Schwartz et al.[71] among decedents after the introduction of surfactant. The large

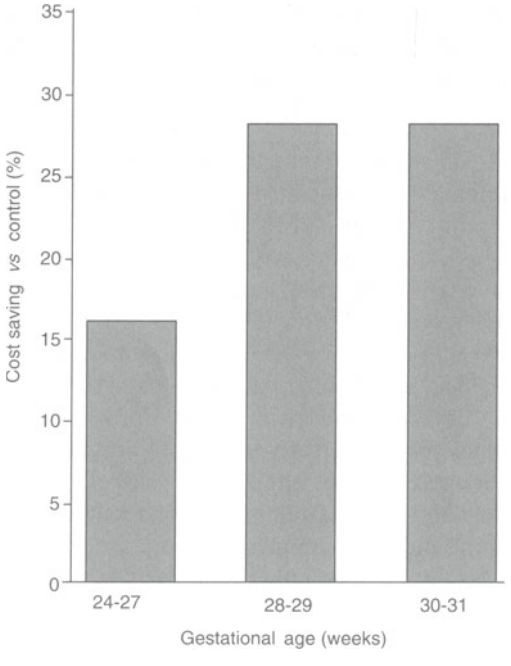

Fig. 3. Percentage decrease in costs associated with rescue therapy with colfosceril palmitate *vs* historical controls in 71 infants according to gestational age.[68]

variability in these results means that definitive conclusions concerning this issue cannot be drawn.

Australian Studies

Both of the Australian studies included infants with a broad range of birthweights. In the study by Diwaker et al.,[68] a 48% decrease in the cost per survivor was observed with colfosceril palmitate treatment. This large decrease may be partly attributable to the careful costing methods employed in this study which allowed an accurate assessment of costs (see section 3.2.1), or possibly because the majority (89%) of infants were ≥28 weeks' gestational age. A subanalysis of the data from this study demonstrated a trend towards greater cost effectiveness in more mature infants consistent with the North American studies; there was a 16, 28 and 31% decrease in costs in infants weighing 730 to 1090g (gestational age 24 to 27 weeks), 815 to 1815g (28 to 29 weeks) and 970 to 1905g (30 to 31 weeks), respectively (personal communication, Dr E. John; fig. 3). A summary of changes in costs associated with colfosceril palmitate compared with controls according to infant bodyweight in all cost-effectiveness studies is provided in table III. Although an increase in costs was evident in infants weighing between >750 and 1000g, cost savings were observed in all other birthweight groups.

Despite the use of simpler costing methods, the costs per survivor documented by Kristensen and Wojnar-Horton[62,69] were of similar value to those observed by Diwaker et al.[68] The cost effectiveness of the surfactant regimen as a percentage of control values was smaller (9%); however, this was possibly a result of the increased costs observed in infants weighing between >750 and 1000g (table III).

3.3 Prophylaxis

To date, only preliminary data concerning the cost effectiveness of colfosceril palmitate administered as single dose prophylaxis are available.

Sell et al.[72] indicated that the cost per extra survivor of single dose prophylaxis with colfosceril palmitate was $US81 487 in infants weighing 700 to 1100g. 17 infants needed to receive prophylaxis in order to produce 1 extra survivor. No methodological details were provided in this study report published as an abstract only.

In a preliminary analysis, Phibbs et al.[73] reported that the costs associated with a single prophylactic dose of colfosceril palmitate were dependent on birthweight. Cost savings during the first year were observed in larger infants compared with controls (no surfactant), with a 'break-even' birthweight of slightly less than 1100g. Overall, colfosceril palmitate increased the cost per survivor by 33%, although it should be noted that the study groups were not matched for birthweight (14 treated *vs* 10 control infants weighed <900g) or congenital infections (5 *vs* 0 infants, respectively). Moreover, this result is inconsistent with larger cost-effectiveness analyses performed using other surfactant preparations.[63,74] In both studies,[63,74] the cost per survivor was reduced by 7 to 22% compared with controls (air or saline placebo). Reductions were evident in infants weighing <1000g in both of these studies. Clearly, further investigation is required to determine the cost effectiveness of colfosceril palmitate when administered as prophylaxis and as the recommended 2-dose regimen.

3.4 Comparisons with Other Surfactants

No formal pharmacoeconomic comparisons of colfosceril palmitate and other surfactants have been conducted. However, the large National Institute of Child Health and Human Development Neonatal Research Network study (n = 617)[40] reported no significant difference in the duration of hospital stay, ventilation or oxygen requirements in survivors or all infants treated with colfosceril palmitate or beractant. In all variables, however, there was a trend in favour of colfosceril palmitate. These results, however, are contradicted by other studies which reported greater requirements for ventilation, oxygen and hospitalisation with colfosceril palmitate than beractant.[75,76] Prospective pharmacoeconomic evaluation is needed to determine the relative benefits of each treatment, and also to clarify whether the early advantages of

beractant therapy (section 2.1.2) yield any economic gain.

3.5 Other Pharmacoeconomic Issues

There is strong evidence to suggest that antenatal use of corticosteroids reduces the incidence of RDS.[77,78] By combining cost estimates and efficacy data derived from overviews, Mugford et al.[79] calculated that the use of antenatal corticosteroids would result in a 9 to 14% reduction in the cost per survivor, depending on gestational age (<31 or <35 weeks). The same research group further estimated reductions of 7 to 16% in the cost per survivor if antenatal corticosteroids or surfactant therapy were administered (surfactant use was restricted to those infants whose mothers had not received corticosteroid therapy). Given that a recent retrospective analysis suggested that antenatal steroids and surfactant therapy may have additive benefits,[80] the cost effectiveness of their combined use may have been underestimated by Mugford et al.[79]

The long term effects of surfactant therapy will also be important in defining the cost effectiveness of this intervention. Preterm infants are more likely to be rehospitalised in the first few years of life, and the long term costs of disability should also be considered (section 1.2), together with quality-of-life issues (both for patient and family). Utility measures suitable for use in this patient population have been developed,[16] but are not widely used.

4. Pharmacoeconomic Positioning of Colfosceril Palmitate

4.1 General Considerations

Lung surfactant replacement therapy has become an indispensable component in the management of infants with RDS. Whether administered as rescue therapy or prophylaxis, natural and synthetic surfactants decrease RDS–associated mortality by around 40% compared with placebo.[2,58] Recent epidemiological data appear to support the efficacy of these agents; a 6.2% decline in infant mortality was observed in parallel with the introduction of surfactant therapy in the USA. Rescue treatment also reduces the incidence of pneumothorax, although the effect is less marked with prophylaxis.[2] Surfactant replacement therapy has no clear therapeutic effect on the incidence of intraventricular haemorrhage or bronchopulmonary dysplasia.[2]

Comparative trials with beractant suggest that the 2 agents have similar efficacy with respect to the major study end-points (section 2.1.2); meta-analysis of comparative trial data are awaited with interest. As well as beractant, other surfactants are available (or are being developed) which should be compared with established products.

Colfosceril palmitate is recommended for prophylactic use in infants with a birthweight of <1350g at risk of developing RDS, or in those weighing >1350g with evidence of pulmonary immaturity.[56] Rescue treatment with colfosceril palmitate is recommended in infants who develop RDS.[56] The recommended dosage regimen of colfosceril palmitate is two 5 ml/kg doses administered 12 hours apart; recent trial data do not support the use of further or higher doses (section 2.1.1).[34,35]

4.2 Formulary Considerations

Consistent with comprehensive clinical data, cost-effectiveness analyses strongly support the use of colfosceril palmitate administered as rescue therapy in infants with RDS. Despite differing study methodologies and geographical location, colfosceril palmitate decreased the cost per survivor by 9 to 48% compared with controls. Data were derived from direct costs or charges monitored to 1 year of adjusted age; long term follow-up and consideration of all costs are required for a full economic evaluation.

Importantly, reductions in the cost per survivor were evident in both larger (≥1250g)[66] and smaller (700 to 1350g)[67] infants. However, while savings were realised in smaller infants treated with colfosceril palmitate, overall costs were over 2-fold greater than those of the larger infants. This is consistent with the well established trend that treatment costs increase with decreasing birth-

weight.[20,64] Despite surfactant use, treatment is likely to remain costly for these very premature infants.

From the perspective of hospital administrators and those involved in policy decisions, the use of colfosceril palmitate rescue therapy results in cost savings overall. The cost savings observed in these studies give some indication of the magnitude of the effect of surfactant therapy on reducing disease severity, since interventions which reduce mortality usually increase healthcare requirements and therefore costs.

The optimal timing of colfosceril palmitate administration is likely to be extremely important from a pharmacoeconomic perspective. The recent results of the large international OSIRIS trial, which demonstrated a clear advantage for early administration (<2 hours of age) of colfosceril palmitate over delayed selective administration in high risk infants, support the use of early administration as a management strategy. However, from an economic standpoint, introducing a strategy that requires surfactant use in an extra 25% of infants (or 47 extra doses per 100 infants treated) is more difficult to justify. Economic analysis of the OSIRIS trial results is awaited with interest. Preliminary data indicate that the use of such a regimen may be justified in economic terms.[81]

Clinical trial data also point to a number of other issues that merit pharmacoeconomic evaluation with colfosceril palmitate. The sequential use of antenatal steroids and surfactant therapy, given that the 2 interventions may have additive efficacy,[80] is likely to have important repercussions on the cost effectiveness of surfactant therapy. Infant gestational age may be an important factor in the overall cost effectiveness of such a regimen.[82] Comparative trials addressing the pharmacoeconomics of colfosceril palmitate and other surfactant products may help distinguish between agents.

In conclusion, both comprehensive clinical data and cost-effectiveness analyses strongly support the use of rescue therapy with colfosceril palmitate in infants with RDS. Additional compelling evidence, which suggests that earlier use of colfosceril palmitate or combined use with antenatal steroids may offer advantages over rescue therapy, should be considered from an economic standpoint to determine the optimal prescribing strategy for this agent.

References

1. Avery ME, Mead J. Surface properties in relation to atelectasis and hyaline membrane disease. Am J Dis Child 1959; 97: 517-23
2. Soll RF, McQueen MC. Respiratory distress syndrome. In: Sinclair JC, editor. Effective care in the newborn infant. Oxford: Oxford University Press, 1992: 325-58
3. Hjalmarson. Epidemiology of neonatal disorders of respiration. Int J Technol Assess Health Care 1991; 7 Suppl. 1: 9-15
4. Greenough A, Roberton NRC. Morbidity and survival in neonates ventilated for the respiratory distress syndrome. BMJ 1985; 290: 597-600
5. Greenough A, Morley CJ, Roberton NRC. Acute respiratory disease in the newborn. In: Roberton NRC, editor. Textbook of neonatology. 2nd ed. Edinburgh; New York: Churchill Livingston, 1992
6. Reed DM, Bakketeig LS, Nugent RP. The epidemiology of respiratory distress syndrome in Norway. Am J Epidemiol 1978; 107: 299-310
7. Hjalmarson O. Epidemiology and classification of acute, neonatal respiratory disorders: a prospective study. Acta Paediatr Scand 1981; 70: 773-83
8. Arnold C, McLean FH, Kramer MS, et al. Respiratory distress syndrome in second-born versus first-born twins: a matched case-control analysis. N Engl J Med 1987; 317: 1121-5
9. Di Renzo GC, Anceschi MM, Guidette R, et al. Requirements of perinatal prevention and treatment of respiratory distress syndrome. Eur Respir J 1989; 2 Suppl. 3: 68-72
10. Chiswick ML. Prolonged rupture of membranes, pre-eclamptic toxaemia, and respiratory distress syndrome. Arch Dis Child 1976; 51: 674-9
11. Robert MF, Neff RK, Hubbell JP, et al. Association between maternal diabetes and the respiratory-distress syndrome in the newborn. N Engl J Med 1976; 294: 357-60
12. Tubman TRJ, Rollins MD, Patterson C, et al. Increased incidence of respiratory distress syndrome in babies of hypertensive mothers. Arch Dis Child 1991; 66: 52-4
13. White E, Shy KK, Daling JR, et al. Maternal smoking and infant respiratory distress syndrome. Obstet Gynecol 1986; 67: 365-70
14. Zuckerman B, Maynard EC, Cabral H. A preliminary report of prenatal cocaine exposure and respiratory distress syndrome in premature infants. Am J Dis Child 1991; 145: 696-8
15. Forsyth JS. Dilemmas in the neonatal management of extremely low birth weight babies. Scott Med J 1988; 33: 356-7
16. Boyle MH, Torrance GW, Sinclair JC, et al. Economic evaluation of neonatal intensive care of very-low-birth-weight infants. N Engl J Med 1983; 308: 1330-7
17. Mugford M, Howard S. Cost effectiveness of surfactant replacement in preterm babies. PharmacoEconomics 1993; 3: 362-73
18. Showstack JA, Stone MH, Schroeder SA. The role of changing clinical practices in the rising costs of hospital care. N Engl J Med 1985; 313: 1201-7

19. Resnick MB, Ariet M, Carter RL, et al. Prospective pricing system for tertiary neonatal intensive care. Pediatrics 1986; 78: 820-8
20. Phibbs CS, Williams RL, Phibbs RH. Newborn risk factors and costs of neonatal intensive care. Pediatrics 1981; 68: 313-21
21. Phibbs CS, Phibbs RH, Pomerance JJ, et al. Alternative to diagnosis-related groups for newborn intensive care. Pediatrics 1986; 78: 829-36
22. Fordham R, Field DJ, Hodges S, et al. Cost of neonatal care across a regional health authority. J Pub Health Med 1992; 14: 127-30
23. Ryan S, Sics A, Congdon P. Cost of neonatal care. Arch Dis Child 1988; 63: 303-6
24. Tubman TRJ, Halliday HL, Normand C. Cost of surfactant replacement treatment for severe neonatal respiratory distress syndrome: a randomised controlled trial. BMJ 1990; 301: 842-5
25. Pape KE, Buncic RJ, Ashby S, et al. The status at two years of low-birth-weight infants born in 1974 with birth weights of less that 1,001 gm. J Pediatr 1978; 92: 253-60
26. Shannon DC, Crone RK, Todres ID, et al. Survival, cost of hospitalization, and prognosis in infants critically ill with respiratory distress syndrome requiring mechanical ventilation. Crit Care Med 1981; 9: 94-7
27. Giacoia GO, Rutledge D, West K. Factor affecting visitation of sick newborns. Clin Pediatr 1985; 24: 259-62
28. Perrin EC, West PD, Culley BS. Is my child normal yet? Correlates of vulnerability. Pediatrics 1989; 83: 355-63
29. Wegman ME. Annual summary of vital statistics – 1990. Pediatrics 1991; 88: 1081-92
30. Russell L, White A, Andrews E, et al. Observational study of synthetic surfactant in 11,455 infants [abstract no. 586]. Pediatr Res 1992; 31: 100A
31. Dechant KL, Faulds D. Colfosceril palmitate: a review of the therapeutic efficacy and clinical tolerability of a synthetic surfactant preparation (Exosurf® Neonatal™) in neonatal respiratory distress syndrome. Drugs 1991 Nov; 42: 877-94
32. Stevenson D, Walther F, Long W, et al. Controlled trial of a single dose of synthetic surfactant at birth in premature infants weighing 500 to 699 grams. J Pediatr 1992 Feb; 120 (Part 2): 3-12
33. Smyth J, Allen A, Sankaran K, et al. Effects of two rescue doses of Exosurf® Neonatal in 221 500-749 gram infants [abstract no. 1964]. Pediatr Res 1991; 29: 330A
34. OSIRIS Collaborative Group. Early versus delayed neonatal administration of a synthetic surfactant – the judgement of OSIRIS. Lancet 1992; 340: 1363-9
35. Berry DD, Pramanik AK, Philips III JB, et al. Comparison of the effect of three doses of a synthetic surfactant on the alveolar-arterial oxygen gradient in infants weighing ≥1250 grams or more with respiratory distress syndrome. J Pediatr 1994 Feb; 124: 294-301
36. Cotton RB, Olsson T, Law AB, et al. The physiologic effects of surfactant treatment in gas exchange in newborn premature infants with hyaline membrane disease. Pediatr Res 1993 Oct; 34: 495-501
37. Cummings JJ, Holm BA, Hudak ML, et al. A controlled clinical comparison of four different surfactant preparations in surfactant-deficient preterm lambs. Am Rev Respir Dis 1992 May; 145: 999-1004
38. Hudak ML, Matteson EJ, Baus JA, et al. Infasurf v. Exosurf for the treatment of RDS: a 21 center randomized double-masked comparison trial [abstract no. 1370]. Pediatr Res 1994; 35: 231A
39. Hudak ML, Matteson EJ, Baus JA, et al. Infasurf v. Exosurf for the prophylaxis of RDS: a ten center randomized double-masked comparison trial [abstract no. 1369]. Pediatr Res 1994; 35: 231A
40. Horbar JD, Wright LL, Soll RF, et al. A multicenter randomized trial comparing two surfactants for the treatment of neonatal respiratory distress syndrome. J Pediatr 1993 Nov; 123: 757-66
41. Modanlou HD, Beharry K, Norris K, et al. Comparative efficacy of Survanta (SURV) and Exosurf (EXO) on early clinical course of respiratory distress syndrome (RDS) [abstract]. Clin Res 1994 Feb; 42: 110A
42. Sehgal SS, Ewing CK, Richards T, et al. Modified bovine surfactant (Survanta) versus a protein-free surfactant (Exosurf) in the treatment of respiratory distress syndrome in preterm infants: a pilot study. J Natl Med Assoc 1994 Jan; 86: 46-52
43. Stancombe BB, Walsh WF, Bridges WS, et al. Surfactant rescue for respiratory distress syndrome [abstract]. Clin Res 1991 Dec; 39: 865A
44. Modanlou H, Beharry K, Norris K, et al. Comparative effects of Survanta (SURV) and Exosurf (EXO) on the outcome of respiratory distress syndrome (RDS) [abstract no. 1436]. Pediatr Res 1994; 35: 242A
45. Vermont Oxford Trials Network. A multicenter randomized trial comparing synthetic surfactant to modified bovine surfactant in the treatment of neonatal respiratory distress syndrome. Annual Meeting of the American Pediatric Society (APS), the Society for Pediatric Research (SPR) and the Ambulatory Pediatric Association (APA): 1994 May 2-5: Seattle, USA.
46. Halliday HL. Controversies: synthetic or natural surfactant the case for natural surfactant [abstract no. 245]. 14th European Congress of Perinatal Medicine 1994
47. Solimano A, Smyth JA, Fitzgerald C, et al. Bovine surfactant therapy following failure of synthetic surfactant in RDS [abstract no. 1522]. Pediatr Res 1994; 35: 256A
48. Hall SB, Venkitaraman AR, Whitsett JA, et al. Importance of hydrophobic apoproteins as constituents of clinical exogenous surfactants. Am Rev Respir Dis 1992 Jan; 145: 24-30
49. Moya FR, Hoffman DR, Zhao B, et al. Platelet-activating factor in surfactant preparations. Lancet 1993 Apr 3; 341: 858-60
50. European Exosurf Study Group. Early or selective surfactant (colfosceril palmitate, Exosurf®) for intubated babies at 26 to 29 weeks gestation: a European double-blind trial with sequential analysis [doc no. 28]. Online J Curr Clin Trials 1992; 1992
51. Bose C, Corbet A, Bose G, et al. Improved outcome at 28 days of age for very low birth weight infants treated with a single dose of a synthetic surfactant. J Pediatr 1990 Dec; 117: 947-53
52. Corbet A, Bucciarelli R, Goldman S, et al. Decreased mortality rate among small premature infants treated at birth with a single dose of synthetic surfactant: a multicenter controlled trial. J Pediatr 1991 Feb; 118: 277-84
53. Long W, Corbet A, Cotton R, et al. A controlled trial of synthetic surfactant in infants weighing 1250 g or more with respiratory distress syndrome. N Engl J Med 1991 Dec 12; 325: 1696-703
54. Rickert CP, Walter D, Rickert VI, et al. Follow-up at twelve months of preterm infants receiving Exosurf neonatal [abstract]. Clin Res 1993 Dec; 41: 734A
55. Walter D, McGuinness G, Bose C, et al. Double blind one year follow up in 1450 infants randomized to Exosurf® Neonatal or air [abstract no. 1605]. Pediatr Res 1991; 29: 290A
56. Burroughs Wellcome Co. EXOSURF® Neonatal™ prescribing information. Research Triangle Park, North Carolina, USA, 1991
57. Rogers D. Pulmonary haemorrhage, surfactant, and low-birth-weight babies [letter]. Lancet 1993 Mar 13; 341: 698

58. Hope P. Exogenous surfactants. They work and are expensive. BMJ 1991 Oct 5; 303: 799-800
59. Abrahamson EL. Unilateral pulmonary interstitial emphysema and treatment with colfosceril palmitate. Lancet 1993 Jun 19; 341: 1603
60. Bose C, Corbet A, Bose G, et al. Results of laboratory surveillance of very low birth weight infants treated with a synthetic surfactant. J Pediatr 1992 Feb; 120 (Part 2): 13-7
61. Strayer DS. Immunogenicity of pulmonary surfactant preparations: implications for therapy of respiratory distress syndrome. Clin Immunother 1994; 1: 441-8
62. Kristensen J, Wojnar-Horton R. Pulmonary surfactant therapy: costs versus benefits [abstract no. 67]. Aust J Hosp Pharm 1994; 24: 114
63. Soll RF, Jacobs J, Pashko S, et al. Cost effectiveness of Beractant in the prevention of respiratory distress syndrome. PharmacoEconomics 1993; 4: 278-86
64. Walker DJB, Feldman A, Vohr BR, et al. Cost-benefit analysis of neonatal intensive care for infants weighing less than 1,000 grams at birth. Pediatrics 1984; 74: 20-5
65. Robinson R. Costs and cost-minimisation analysis. BMJ 1993; 307: 726-8
66. Backhouse ME, Mauskopf JA, Jones D, et al. Economic outcomes of synthetic surfactant rescue therapy in infants weighing 1250g or more with respiratory distress syndrome: results from a randomised trial. PharmacoEconomics 1994; 6: 358-69
67. Mauskopf JA, Backhouse ME, Jones D, et al. Synthetic surfactant for rescue treatment of respiratory distress syndrome in premature infants weighing from 700 to 1350 grams: impact on hospital resource use and charges. J Pediatr. in press
68. Diwaker K, Roberts S, John E. Surfactant replacement therapy in neonates less than 32 weeks gestation: effect on neonatal intensive care resource utilization. J Paediatr Child Health 1993 Dec; 29: 434-7
69. Kristensen JH, Wojnar-Horton RE. Pulmonary surfactant therapy: costs and benefits. 21st Federal Conference of the Society of Hospital Pharmacists of Australia: 1993 Nov 19-22; Sydney, Australia
70. Finkler SA. The distinction between costs and charges. Ann Intern Med 1982; 96: 102-9
71. Schwartz RM, Luby AM, Scanlon JW, et al. Effect of surfactant on morbidity, mortality, and resource use in newborn infants weighing 500 to 1500g. N Engl J Med 1994; 330: 1476-80
72. Sell M, Corbet A, Gong A, et al. Economic impact of a single prophylactic dose of Exosurf Neonatal in 700-1100 gram infants [abstract no. 1576]. Pediatr Res 1991; 29: 265A
73. Phibbs CS, Phibbs RH, Wakeley A, et al. Cost effects of surfactant therapy for neonatal respiratory distress syndrome. J Pediatr 1993 Dec; 123: 953-62
74. Maniscalco WM, Kendig JW, Shapiro DL. Surfactant replacement therapy: impact on hospital charges for premature infants with respiratory distress syndrome. Pediatrics 1989; 83: 1-6
75. Grauaug A, Kohan R, Kristensen J, et al. Pulmonary surfactant therapy – the KEMH experience [abstract no. A57]. Australian Perinatal Society Conference: 1994 Mar; Sydney, Australia
76. Alvarado M, Hingre R, Hakanson D, et al. Clinical trial of survanta vs exosurf therapy in infants < 1500 G with respiratory distress syndrome (RDS) [abstract]. Pediatr Res 1993 Apr; 33 (Part 2): 314A
77. Crowley P, Chalmers I, Keirse MJNC. The effects of corticosteroid administration before preterm delivery: an overview of the evidence from controlled trials. Br J Obstet Gynaecol 1990; 97: 11-25
78. White AD, Andrews E, Marcucci G, et al. Antenatal corticosteroids and neonatal outcomes in the Exosurf® Neonatal™ clinical trials and the Exosurf Neonatal treatment IND [abstract no. 078]. Pharmacoepidemiol Drug Saf 1994; 3 Suppl. 1: S29
79. Mugford M, Piercy J, Chalmers I. Cost implications of different approaches to the prevention of respiratory distress syndrome. Arch Dis Child 1991; 66: 757-64
80. Jobe AH, Mitchell BR, Gunkel JH. Beneficial effects of the combined use of prenatal corticosteroids and postnatal surfactant on preterm infants. Am J Obstet Gynecol 1993; 168: 508-13
81. Wach R, Darlow B, Bourchier D, et al. Respiratory distress syndrome in New Zealand: evidence from OSIRIS trial of exogenous surfactant (Exosurf). N Z Med J 1994; 107: 234-7
82. Pomerance JJ, Schifrin BS, Meredith JL. Womb rent. Am J Obstet Gynecol 1980; 137: 486-90

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