YEAR BOOK®

YEAR BOOK OF NEONATAL AND PERINATAL MEDICINE 1991

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The Year Book of NEONATAL AND PERINATAL MEDICINE

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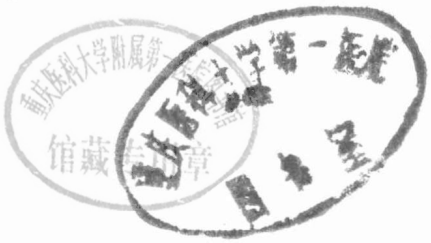

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Journals Represented

Mosby–Year Book subscribes to and surveys nearly 850 U.S. and foreign medical and allied health journals. From these journals, the Editors select the articles to be abstracted. Journals represented in this YEAR BOOK are listed below.

American Heart Journal
American Journal of Cardiology
American Journal of Diseases of Children
American Journal of Epidemiology
American Journal of Human Genetics
American Journal of Obstetrics and Gynecology
American Journal of Perinatology
American Journal of Physiology
American Journal of Public Health
American Journal of Roentgenology
Anesthesiology
Annals of Neurology
Archives of Disease in Childhood
Biology of the Neonate
British Journal of Obstetrics and Gynaecology
British Journal of Plastic Surgery
British Journal of Psychiatry
British Journal of Urology
British Medical Journal
Chest
Child Development
Developmental Medicine and Child Neurology
Diagnostic Microbiology and Infectious Disease
Early Human Development
International Journal of Epidemiology
Israel Journal of Medical Sciences
Journal of Applied Physiology
Journal of Child Neurology
Journal of Clinical Endocrinology and Metabolism
Journal of Clinical Ultrasound
Journal of Developmental and Behavioral Pediatrics
Journal of Family Practice
Journal of Infectious Diseases
Journal of Neurology
Journal of Obstetrics and Gynaecology
Journal of Pediatric Surgery
Journal of Pediatrics
Journal of Perinatology
Journal of Thoracic and Cardiovascular Surgery
Journal of Ultrasound in Medicine
Journal of the American College of Cardiology
Journal of the American Medical Association
Lancet
Laryngoscope
Nature
Neurology
Neuropediatrics
New England Journal of Medicine

Obstetrics and Gynecology
Paediatric and Perinatal Epidemiology
Pain
Pediatric Infectious Disease Journal
Pediatric Research
Pediatrics
Plastic and Reconstructive Surgery
Prenatal Diagnosis
Psychoneuroendocrinology
Radiology
S.A.M.J./S.A.M.T.–South African Medical Journal
Science
Surgical Neurology
Thrombosis and Haemostatis

Standard Abbreviations

The following terms are abbreviated in this edition: acquired immunodeficiency syndrome (AIDS), central nervous system (CNS), cerebrospinal fluid (CSF), computed tomography (CT), electrocardiography (ECG), and human immunodeficiency virus (HIV).

Introduction

Penning this introduction heralds the completion of the fifth edition of the YEARBOOK OF NEONATAL AND PERINATAL MEDICINE. It signifies that the exhaustive review of the perinatal literature has been concluded, the articles selected, and the commentaries written. It remains for you, the reader, to render the verdict on the completed product.

As always the material available for review has been extensive and fascinating. The frontiers of neonatal and perinatal medicine have been expanded and manipulation of the fetus has reached new heights. Major surgical procedures, such as correction of diaphragmatic hernia, have now been successfully undertaken on the fetus and are now under evaluation. Perhaps more fascinating is the concept of reconstituting the bone marrow with stem cells from cord blood and the emerging role of cytokines in the pathogenesis of disease. The ability to control these cytokines will prevent many disorders and even open new avenues for therapy.

Old disorders such as congenital syphilis have reemerged and, together with the cocaine epidemic and HIV infections, tax the public health systems to their limits and even beyond. It was inspiring and at the same time very nostalgic to include the long-term follow-up by Northway of his original cohorts of infants with bronchopulmonary dysplasia (BPD). We are a little wiser concerning this disorder but, despite surfactant, steroids, and all forms of ventilators, BPD is still very prevalent.

We are grateful to Dr. Henry Halliday for writing the opening commentary and review on surfactant therapy, still very much a topic of interest in neonatal-perinatal medicine. We have once again called on many of our colleagues and friends to offer their opinions and words of wisdom regarding some of the articles selected. They have graciously given of their time and their thoughtful contributions add considerably to the quality of the book. The staff at Mosby–Year Book has once again provided superb assistance facilitating timely completion of the project. We acknowledge not only Carla White and Nancy Gorham from the Editorial staff also the great folks, literally behind the scenes, who find all the interesting articles from even the most obscure journals. We continue to have fun working on the YEAR BOOK, and hope that the readers will continue to enjoy our efforts.

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Surfacant Replacement

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I take it as a great compliment to be asked to write on this topic, and to follow such a great researcher and clinician as Dr. Don Shapiro who so tragically died on October 15th, 1989.

In 1990 four further randomized controlled trials (RCTs) of surfactant replacement were reported (1–4). There are now at least 32 RCTs that can be used in a meta-analysis to assess the effects of surfactants in prevention and treatment of respiratory distress syndrome (RDS) (5) (Table 1). An odds ratio (OR) of less than 1 suggests that treatment is superior to control and vice versa. If the 95% confidence intervals (CI) are also less than 1 then the difference between treated and control babies is statistically significant.

TABLE 1.—Typical Odds Ratios and 95% Confidence Invervals (CI) for the Effects of Surfactants in Prophylaxis and Treatment Trials

	N	Odds Ratio	95% CI	N	Odds Ratio	95% CI
Prophylaxis		Natural Surfactant			Synthetic Surfactant	
Neonatal death	9	0.55	0.38–0.80	7	0.65	0.50–0.86
PTX	9	0.31	0.22–0.44	3	0.62	0.40–0.96
IVH	7	0.90	0.62–1.30	2	0.87	0.60–1.27
PDA	8	1.17	0.88–1.57	4	1.33	1.01–1.75
BPD	6	0.59	0.40–0.86	6	0.99	0.75–1.31
Death or BPD	6	0.43	0.30–0.63	3	0.84	0.64–1.09
Treatment		Natural Surfactant			Synthetic Surfactant	
Neonatal Death	13	0.60	0.47–0.76	5	0.61	0.46–0.80
PTX	12	0.34	0.26–0.43	4	0.52	0.42–0.65
IVH	9	0.93	0.68–1.27	2	0.83	0.65–1.05
PDA	10	1.14	0.85–1.53	3	0.72	0.60–0.87
BPD	8	0.94	0.64–1.39	4	0.71	0.50–1.00
Death or BPD	9	0.61	0.45–0.84	3	0.56	0.45–0.72

N = number of trials; *PTX* = pneumothorax; IVH = intraventricular hemorrhage; PDA = patent ductus arteriosus; BPD = bronchopulmonary dysplasia.
Data obtained from the Perinatal Clinical Trials Database, Oxford (5).

For neonatal death the ORs for both prophylaxis and treatment with both natural and synthetic surfactants are about 0.60 with 95% CI all less than 1. This means that surfactant replacement reduces the odds of death by about 40%. Similar or greater significant reductions are also found for pneumothorax and other pulmonary air leaks, but for intraventricular hemorrhage and bronchopulmonary dysplasia (BPD), although the ORs are less than 1, the 95% CI generally cross unity, showing that these reductions are not significant. For patent ductus arteriosus (PDA) the ORs are generally greater than 1, suggesting an increase in this complication that is significant for prophylaxis with synthetic surfactants (see Table 1). A number of questions remain to be resolved.

Synthetic or Natural Surfactants?

Although a number of surfactants have now been licensed for use in Japan, the United States, and Europe (Table 2) there have been no comparative trials of synthetic or natural preparations. In April 1991 a multicenter trial comparing Survanta and Exosurf is scheduled to begin in the United States (Lucey JF, personal communication) and other comparative trials are being planned in Europe.

Prophylaxis or Treatment?

At the recent Ross Laboratories Special Conference on "Hot Topics in Neonatology 1990" in Washington four trials comparing very early or prophylactic administration of natural surfactants with late administration (or rescue) were reported (6–9). These trials showed conflicting results that the moderator, Dr. Mary Ellen Avery, scored at 2 for prophylaxis and 2 for treatment. The trials of Konishi et al. (6) and Merritt et al. (7) enrolled only babies with immature lung profiles, the former favoring prophylaxis and the latter treatment. In the larger study there was an increase in moderate or severe developmental delay in the babies treated prophylactically (7). In two trials of calf lung surfactant extract (CLSE), both with considerable numbers of babies, one showed improved survival with prophylaxis (8) and the other showed an increased incidence of BPD and longer hospital stay in the babies treated at birth (9). I think it is fair to say that the jury is still out on this one.

Without lung maturity tests about half of babies less than 31 weeks given surfactant prophylactically will be treated unnecessarily. The United Kingdom trial of Exosurf (OSIRIS) is recruiting 6,000 babies and will compare early and late treatment. We eagerly await the results of this trial, which should be completed by April 1991.

Single or Multiple Doses?

In 1990 two studies of natural surfactants that attempted to answer this question were completed (10, 11). In the study by Dunn et al. (10) using CLSE only relatively mature (30–36 weeks) preterm babies with RDS were enrolled. Improved oxygenation in the babies given multiple doses of surfactant was demonstrated but duration of ventilation was not

TABLE 2.—Surfactant Preparations in Clinical Use

Brand Name (Common Name) Company	Composition	Dose of Phospholipids (mg/kg)	No of Doses	P or T	Approved
Synthetic					
Pumactant (ALEC) Britannica	DPPC: PG 7:3 w/w Phospholipid 50 mg/ml	100	4	P	UK (NPB)
Exosurf (Colfosceril Palmitate Wellcome Foundation	DPPC 13.5 mg/ml Hexadecanol 1.5 mg/ml Tyloxapol 1.0 mg/ml	67.5	2–4	P,T T	USA UK
Natural					
Survanta (Beractant) Abbott	Bovine Mince with Tripalmitin, Palmitic acid	100	3	P,T	USA (TIND) Germany
Surfactant TA	"	100	3	P,T	Japan
Alveofact (SF-RI 1) Boehringer-Thomae	Bovine Lavage Phospholipid 41.7 mg/ml	50	4	T	Germany Holland
Curosurf Chiesi	Porcine Mince Phospholipid 80 mg/ml	200	3	T	Trials
Human Surfactant	Amniotic Fluid 5% protein Phospholipid 20 mg/ml	60	3–4	P,T	Trials
CLSE e.g. Infasurf	Calf lung lavage	100	3	P,T	Trials

P = prophylaxis; T = treatment; CLSE = calf lung surfactant extract; ALEC = artificial lung expanding compound; NPB = named patient basis; TIND = treatment investigational new drug (special FDA protocol); DPPC = dipalmitoylphosphatidylcholine; PG = phosphatidyglycerol.

decreased. Speer et al. (11) studied 357 babies who were both immature (700–2000 g) and had severe RDS (needing at least 60% oxygen) and found that babies given multiple doses of Curosurf had a significantly lower rate of pneumothorax and mortality.

These studies support the recommendations of multiple doses for treatment with human surfactant, Survanta, Exosurf, and ALEC (Pumactant).

What Dose Is Needed?

The dosage of surfactant used in clinical trials over the past 10 years has varied from 25 to 200 mg of phospholipids per kilogram body weight (5). Two recent trials have compared different doses of surfactant (12, 13). Konishi et al. (12) showed that treatment of established RDS with 120 mg/kg of Surfactant TA improved oxygenation and reduced the incidence of BPD compared to 60 mg/kg. Gortner et al. in an interim analysis (13) of their trial comparing 100 mg/kg and 50 mg/kg of a bovine surfactant (SF-RI 1) showed improved oxygenation with the higher dose. Using Curosurf in a pilot trial of 32 babies we have also found improved oxygenation but no difference in 28-day outcome for babies treated with 200 mg/kg compared to 100 mg/kg (Halliday and Speer, unpublished results). A large European multicenter trial is under way to compare high and low initial doses with repeated doses if needed (Curosurf 4). This trial will recruit 2,000 babies and be completed by the end of 1991.

Larger doses are probably better than smaller ones but how much is optimal? Certainly more than the 5 mg/kg estimated to form the air/liquid interface in the lung and perhaps as much as the 100 to 250 mg/kg estimated to form the total pulmonary surfactant pool (14).

How Should It Be Administered?

All surfactants are administered intratracheally through an endotracheal tube in one or more boluses. With most natural surfactants two bolus doses are used with the infant positioned so that each dependent lung receives surfactant. After instillation the baby is either manually ventilated for a short time or reconnected to the ventilator. A feeding tube is used to deliver the surfactant into the lower trachea. With Exosurf an endotracheal adaptor that has a side port is used. The surfactant is administered slowly so that it does not accumulate in the endotracheal tube, with a minimum recommended time for administration of the full dose of 4 minutes.

In one small study, Curosurf was administered by a slow infusion over 5 to 10 minutes through a fine polyethylene catheter positioned in the lower trachea (Nars and Rudin, unpublished results). The acute improvement in oxygenation was less marked and sustained for only 5 to 6 hours in these 11 babies, compared to those treated by a divided bolus dose.

In a study in Kuwait, in a neonatal unit with no facilities for assisted ventilation, 14 babies weighing more than 1,500 g with severe RDS were intubated only for the administration of the bovine form of Curosurf (15). Twelve babies showed the expected acute responses and 1 of the 2 nonresponding babies was subsequently found to have streptococcal pneumonia. Thirteen babies survived without sequelae.

More studies of methods of adminstration are obviously needed, particularly since acute responses seem to vary with the duration of instillation. Studies comparing the incidence of potentially adverse hemodynamic effects in rapid and slow instillation procedures should be performed.

What About Adverse Effects?

Adverse effects have been reported relatively infrequently. The incidence of PDA is higher with both natural and synthetic surfactants (see Table 1). It has been suggested by Fujiwara (3) that the development of PDA accounts for most relapses after surfactant treatment. The judicious use of Doppler ultrasound and intravenous indomethacin means that in most cases this complication has minimal effects. However, it has been reported that, in babies of less than 27 weeks gestation who develop PDA, pulmonary hemorrhage can occur. This complication has been reported with Exosurf and also with some of the natural surfactants.

Patent ductus arteriosus has also been suggested as a cause of hemodynamic instability, particularly after instillation of natural surfactants in treatment studies. These hemodynamic effects are variable, with some reports suggesting no change in blood pressure and cerebral blood flow velocities (16, 17) and some suggesting reduction of these measurements (18, 19). The babies showing altered cerebral blood flow velocities generally have suffered from severe asphyxia (18) and may not be typical of those usually treated with surfactant. Asphyxia has been shown to lessen the acute response to surfactant (20).

Using near infrared spectroscopy (NIRS) it has been shown that cerebral oxygenation improves after surfactant treatment (19, 21), but this may be associated with transient depression of cerebral electrical activity (19). This also occurs if babies on ventilators are exposed to repeated suctioning or develop a pneumothorax, but there is no evidence that this short suppression of electroencephalogram activity has any adverse effects on the baby (19).

It has been speculated that the rapid improvement of pulmonary mechanics after giving surfactant may in some infants cause overdistension of the lungs with hyperinflation and perhaps hypocarbia (19, 21). It is also possible that circulatory changes with PDA may also have an influence. Further studies of the timing, dose, mode of administration, and ventilator management after surfactant are urgently needed.

One study has looked specifically for evidence of cerebral ischemia after surfactant administration (22). The authors serially measured creatine kinase isoenzyme (CK-BB) levels and antibodies to brain antigens and performed cerebral ultrasound and could find no evidence of any adverse effect of Curosurf on cerebral function in preterm babies (22). In addition, follow-up studies of babies treated with surfactant are now being reported that give no cause for concern despite increased survival of immature babies (23).

Follow-Up Studies?

There have been ten reported studies of long-term outcome of babies treated with surfactant (23); seven with natural surfactants and three with synthetic surfactants (Table 3). The rates of neurologic handicap are not increased by the use of surfactants despite the increased survival of immature babies. The apparent differences in long-term outcome between natural surfactant treated babies (about 70% normal) and syn-

TABLE 3.—Handicaps and Late Deaths in 10 Follow-Up Studies of Infants Treated With Surfactants

NATURAL SURFACTANTS (N=7)

	Treated (N=156)	Control (N=118)	P Value (Chi square)
Late Deaths	4	4	-
Major Handicap	20 (12.8%)	16 (3.6%)	0.85
Minor Handicap	26 (16.7%)	21 (17.8%)	0.80
Normal Babies	110 (70.5%)	81 (68.6%)	0.75

SYNTHETIC SURFACTANTS (N=3)

	Treated (N=167)	Control (N=171)	P Value (Chi square)
Late Deaths	7	6	-
Major Handicap	14 (8.4%)	9 (5.3%)	0.25
Minor Handicap	11 (6.6%)	7 (4.1%)	0.30
Normal Babies	142 (85.0%)	155 (90.6%)	0.15

thetic surfactant treated babies (about 85% normal) can be accounted for by both the greater gestational age and the prophylaxis design of the latter studies. In prophylaxis trials about half of the babies entered as controls do not develop RDS and would be expected to have an improved outcome.

Costs of Surfactant?

Table 2 lists the surfactants currently being used, some in clinical trials and some available commercially. Exosurf is available in the United States at $450 per vial and in the United Kingdom at £314.29. Up to four doses are needed, so this form of therapy is not cheap. Three studies have looked at costs; Maniscalco et al. (24) showed a savings of $18,500 (U.S. dollars) per surviving baby and Shennan et al. (25) a saving of $10,000 (Canadian dollars) per survivor when CLSE was used prophylactically. In Belfast Tubman et al. (26) showed that the cost per extra survivor was £13,720, which is similar to the costs of caring for any very low birth weight baby. The quality adjusted life year (QALY) was £710, which is much less than that for hemodialysis or coronary artery by-pass surgery (26).

As surfactant replacement improves survival it may lead to increased costs of neonatal health care, but the real bonus is the increased numbers of surviving healthy babies and also decreased costs of producing a healthy baby.

Other Uses of Surfactants

Don Shapiro's group in Rochester has very recently reported acute responses and successful outcome in seven full-term babies with pneumonia and seven with meconium aspiration syndrome after treatment with CLSE (27). Multicenter controlled trials of surfactant for these indications seem warranted.

Secondary surfactant deficiency has also been implicated in adult respiratory distress syndrome (ARDS). Some recent reports suggest that natural surfactant replacement may improve outcome (27, 28). More studies using both synthetic and natural surfactants are needed.

Surfactant deficiency has been found in the lungs of babies dying of sudden infant death syndrome (SIDS) but it is still not clear if lower concentrations of phosphatidylcholine are a primary or secondary phenomenon (30). It is difficult to envisage how replacement therapy could be used to reduce the incidence of SIDS.

The Future?

On the basic science front characterization of the surfactant apoproteins (31) has permitted relationships between structure and function to be further defined (32). Surfactant apoprotein B (SP-B) can now be expressed in *Escherichia coli* (33) so that genetically engineered surfactants will soon be available for clinical trials. These and other developments would surely have been much appreciated by Don Shapiro, and perhaps the greatest tribute that can be paid to him is that his research continues to be published posthumously (27, 34).

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