



CLINICAL REPORT

Surfactant Replacement Therapy for Preterm and Term Neonates With Respiratory Distress

abstract

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Respiratory failure secondary to surfactant deficiency is a major cause of morbidity and mortality in preterm infants. Surfactant therapy substantially reduces mortality and respiratory morbidity for this population. Secondary surfactant deficiency also contributes to acute respiratory morbidity in late-preterm and term neonates with meconium aspiration syndrome, pneumonia/sepsis, and perhaps pulmonary hemorrhage; surfactant replacement may be beneficial for these infants. This statement summarizes the evidence regarding indications, administration, formulations, and outcomes for surfactant-replacement therapy. The clinical strategy of intubation, surfactant administration, and extubation to continuous positive airway pressure and the effect of continuous positive airway pressure on outcomes and surfactant use in preterm infants are also reviewed. *Pediatrics* 2014;133:156–163

INTRODUCTION

Surfactant replacement was established as an effective and safe therapy for immaturity-related surfactant deficiency by the early 1990s.¹ Systematic reviews of randomized, controlled trials confirmed that surfactant administration in preterm infants with established respiratory distress syndrome (RDS) reduces mortality, decreases the incidence of pulmonary air leak (pneumothoraces and pulmonary interstitial emphysema), and lowers the risk of chronic lung disease or death at 28 days of age (Table 1).^{2–11} Subsequent trials indicated that prophylactic or early administration of surfactant resulted in fewer pneumothoraces, less pulmonary interstitial emphysema, and improved survival without bronchopulmonary dysplasia (BPD). However, recent randomized clinical trials indicate that the benefits of prophylactic surfactant are no longer evident in groups of infants when continuous positive airway pressure (CPAP) is used routinely.⁵

This clinical report updates a 2008 report from the American Academy of Pediatrics.¹ As in the previous report, a number of clinically important topics are reviewed surrounding use of surfactant, including prophylactic versus rescue replacement, preparations and administration techniques, the synergistic effects of surfactant and antenatal steroids, and surfactant therapy for respiratory disorders other than RDS. In addition, the effect of CPAP on RDS and surfactant replacement and the

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KEY WORDS

surfactant, antenatal steroids, respiratory distress syndrome, meconium aspiration syndrome, neonatal pneumonia, neonatal sepsis, congenital diaphragmatic hernia, pulmonary hemorrhage, persistent pulmonary hypertension, preterm, term

ABBREVIATIONS

BPD—bronchopulmonary dysplasia

CI—confidence interval

CPAP—continuous positive airway pressure

ECMO—extracorporeal membrane oxygenation

INSURE—intubation, surfactant administration, and extubation

LOE—level of evidence

NNTB—number needed to benefit

RDS—respiratory distress syndrome

RR—relative risk

SP-B—surfactant protein B

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The guidance in this report does not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

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TABLE 1 Meta-analyses of Surfactant Replacement: Prophylaxis and Rescue Treatment With Animal-Derived and Synthetic Surfactant^{1,2,3,8,11}

Outcome	Prophylactic Surfactant		Rescue Surfactant	
	Animal Derived	Synthetic	Animal Derived	Synthetic
	N RR (95% CI)	N RR (95% CI)	N RR (95% CI)	N RR (95% CI)
Neonatal mortality	8 0.60 (0.47–0.77)	7 0.70 (0.58–0.85)	10 0.68 (0.57–0.82)	6 0.73 (0.61–0.88)
Pneumothorax	9 0.40 (0.29–0.54)	6 0.67 (0.50–0.90)	12 0.42 (0.34–0.52)	5 0.64 (0.55–0.76)
PIE	6 0.46 (0.36–0.59)	2 0.68 (0.50–0.93)	8 0.45 (0.37–0.55)	4 0.62 (0.54–0.71)
BPD ^a	8 0.91 (0.79–1.05)	4 1.06 (0.83–1.36)	12 0.95 (0.84–1.08)	5 0.75 (0.61–0.92)
BPD/death ^a	8 0.80 (0.72–0.88)	4 0.89 (0.77–1.03)	12 0.83 (0.77–0.90)	4 0.73 (0.65–0.83)

N, number; PIE, pulmonary interstitial emphysema.

^a Defined at 28 d.

efficacy of the INSURE approach (intubation, surfactant administration, and extubation to CPAP) are reviewed.

PRETERM INFANTS AND SURFACTANT EFFECTIVENESS IN CLINICAL TRIALS

Surfactant trials have included infants born between 23 and 34 weeks' gestation and/or with birth weight between 500 and 2000 g.^{1–12} The results of subgroup analyses from such studies indicated that surfactant therapy decreased mortality rates most effectively in infants born at less than 30 weeks' gestation or with birth weight <1250 g.¹² In addition, surfactant replacement reduced the incidence of pneumothorax, pulmonary interstitial emphysema, and the combined outcome of death or BPD, compared with no surfactant replacement¹²; these findings suggest that lung injury is mitigated after surfactant replacement. The incidence of other medical morbidities, such as BPD, intraventricular hemorrhage, necrotizing enterocolitis, health care–associated infections, retinopathy of prematurity, and patent ductus arteriosus, has not changed with surfactant replacement, but this may be attributable, in part, to the large reduction in mortality with surfactant replacement therapy.¹³ The onset of clinical signs of patent ductus arteriosus may occur earlier, and the incidence of pulmonary hemorrhage, especially in infants

born at less than 27 weeks' gestation, may be increased with surfactant therapy. Surfactant replacement is effective for larger and more mature preterm infants with established RDS.

PROPHYLACTIC VERSUS RESCUE SURFACTANT

A prophylactic, or preventive, surfactant strategy is defined as intubation and surfactant administration to infants at high risk of developing RDS for the primary purpose of preventing worsening RDS rather than treatment of established RDS; this has been operationalized in clinical studies as surfactant administration in the delivery room before initial resuscitation efforts or the onset of respiratory distress or, most commonly, after initial resuscitation but within 10 to 30 minutes after birth. This contrasts with a rescue or treatment surfactant strategy, in which surfactant is given only to preterm infants with established RDS. Rescue surfactant is most often administered within the first 12 hours after birth, when specified threshold criteria of severity of RDS are met.

The meta-analysis of studies conducted before routine application of CPAP demonstrated a lower mortality rate (relative risk [RR] 0.69; 95% confidence interval [CI] 0.56–0.85; number needed to benefit [NNTB] 20) and a decrease in the risk of air leak (RR 0.79; 95% CI 0.63–0.98) in preterm infants receiving

prophylactic surfactant versus rescue surfactant.¹⁴ However, when the studies that allowed for routine application of CPAP were included in the meta-analysis (National Institute of Child Health and Human Development SUPPORT Trial and Vermont Oxford Network Delivery Room Management Trial), the benefits of prophylactic surfactant on mortality (RR 0.89; 95% CI 0.76–1.04) and air leak (RR 0.86; 95% CI 0.71–1.04) could no longer be demonstrated.⁵ Furthermore, infants receiving prophylactic surfactant had a higher incidence of BPD or death than did infants stabilized on CPAP (RR 1.12; 95% CI 1.02–1.24). Secondary analyses of studies that did or did not use CPAP to stabilize infants demonstrated a trend to a lower risk of intraventricular hemorrhage (RR 0.91; 95% CI 0.82–1.00) and severe intraventricular hemorrhage (RR 0.87; 95% CI 0.70–1.04) with prophylactic surfactant. That finding cannot be explained; however, there was considerable heterogeneity in the trials included in the meta-analysis. The risks of developing other complications of prematurity, such as retinopathy of prematurity, patent ductus arteriosus, and periventricular leukomalacia, were not significantly different.

When studies investigating infants born at <30 weeks' gestation were analyzed separately,⁵ similar findings were noted. However, there was a trend for an increased risk of chronic lung disease in infants born at <30 weeks' gestation who received prophylactic surfactant (RR 1.13; 95% CI 1.00–1.28) and a significant increase in death or chronic lung disease (RR 1.13; 95% CI 1.02–1.25) with use of prophylactic surfactant.

EARLY VERSUS DELAYED SELECTIVE SURFACTANT TREATMENT OF RDS

Although there are no statistically significant benefits to prophylactic use of surfactant when compared with

prophylactic CPAP, several studies have investigated whether administration of surfactant early in the course of respiratory insufficiency improves clinical outcomes. Early rescue is defined as surfactant treatment within 1 to 2 hours of birth, and late rescue is defined as surfactant treatment 2 or more hours after birth. A recent meta-analysis of early (within 2 hours) versus delayed surfactant treatment concluded that the risks of mortality (RR 0.84; 95% CI 0.74–0.95), air leak (RR 0.61; 95% CI 0.48–0.78), chronic lung disease (RR 0.69; 95% CI 0.55–0.86), and chronic lung disease or death (RR 0.83; 95% CI 0.75–0.91) were significantly decreased. There were no differences in other complications of prematurity.⁷

EARLY ADMINISTRATION OF SURFACTANT FOLLOWED BY BRIEF VENTILATION AND EXTUBATION TO CPAP (INSURE STRATEGY)

The INSURE strategy is widely used throughout the world. In randomized clinical trials performed before 2008, the INSURE approach, compared with rescue surfactant administration in infants with RDS, was associated with a significantly reduced need for mechanical ventilation (RR 0.67; 95% CI 0.57–0.79) and a reduced need for oxygen at 28 days.⁶ In an analysis stratified by fraction of inspired oxygen requirement at study entry, a significantly higher frequency of patent ductus arteriosus was observed among infants in the rescue surfactant group, who required a fraction of inspired oxygen greater than 0.45 (RR 2.15; 95% CI 1.09–4.23). The Vermont Oxford Network Delivery Room Management Trial ($n = 648$) randomly assigned infants born at 26 to 29 weeks' gestation to 1 of 3 treatment groups: prophylactic surfactant and continued ventilation, prophylactic surfactant and rapid extubation to CPAP (INSURE), or nasal

CPAP without surfactant.¹⁵ When compared with the group of infants receiving prophylactic surfactant and continued ventilation, the RR of death or BPD was 0.78 (95% CI 0.59–1.03) for the INSURE group and 0.83 (95% CI 0.64–1.09) for the CPAP group. However, in the nasal CPAP group, 48% were managed without intubation and 54% without surfactant treatment. A recent meta-analysis demonstrated that prophylactic surfactant (with rapid extubation to CPAP) was associated with a higher risk of death or BPD (RR 1.12; 95% CI 1.02–1.24; number needed to harm of 17) when compared with early stabilization with CPAP and selective surfactant administration.⁵ In infants with birth weight ≥ 1250 g and mild to moderate RDS, elective intubation and administration of surfactant decreased the need for mechanical ventilation but had no effect on the duration of oxygen therapy, ventilator therapy, or hospital stay.¹⁶

ANIMAL-DERIVED VERSUS SYNTHETIC SURFACTANT

A wide variety of animal-derived and synthetic surfactants are available commercially (Table 2); both are beneficial as therapy for RDS in preterm infants. Animal-derived surfactants are modified or purified from bovine or porcine lungs. Treatment with animal-derived surfactants (beractant [Survanta; Abbvie Inc, North Chicago, IL], calfactant [Infasurf; ONY Inc, Amherst, NY], and poractant [Curosurf; Chiesi Farmaceutici, Parma, Italy]) has several advantages over first-generation, protein-free synthetic surfactants (eg, colfosceril palmitate [Exosurf; GlaxoSmithKline, Middlesex, UK]).³ These include lower mortality rates (RR 0.86; 95% CI 0.76–0.98; number needed to harm of 40) and fewer pneumothoraces (RR 0.63; 95% CI 0.53–0.75; NNTB 22).⁴ Animal-derived surfactants contain variable amounts

of surfactant protein B (SP-B). SP-B enhances the rate of adsorption of phospholipids at the air-water interface, is involved in the formation of tubular myelin, and has antiinflammatory properties. However, it is unclear whether significant differences in clinical outcomes exist among the available animal-derived products.

A synthetic surfactant (lucinactant) that contains a 21-amino acid peptide that mimics SP-B activity has recently been approved for the prevention and treatment of RDS in preterm infants.^{18,19} When compared with animal-derived surfactant (beractant or poractant), lucinactant was shown to be equivalent.^{18,19} Neonatal morbidities (intra-ventricular hemorrhage, periventricular leukomalacia, pulmonary hemorrhage, sepsis, patent ductus arteriosus, retinopathy of prematurity, necrotizing enterocolitis, and BPD) were not significantly different between preterm infants treated with animal-derived surfactants and those treated with synthetic surfactants.

SURFACTANT ADMINISTRATION

Surfactant administration strategies have been based on manufacturer guidelines for individual surfactants.¹ The dose of surfactant, frequency of administration, and treatment procedures have been modeled after research protocols. Furthermore, repeated doses of surfactants given at intervals for predetermined indications have decreased mortality and morbidity compared with placebo or single surfactant doses.¹⁰ However, given the long half-life for surfactant in preterm infants with RDS,²⁰ redosing should not be needed more often than every 12 hours, unless surfactant is being inactivated by an infectious process, meconium, or blood. Dosing intervals shorter than 12 hours recommended by some manufacturers are not based on human pharmacokinetic data.

TABLE 2 Composition and Dosage of Surfactants¹⁷

Surfactant	Main Phospholipids	Proteins	Phospholipid Concentration	Suggested Dose	Phospholipid per Dose
Animal-derived					
Beractant (Survanta ^a) minced bovine lung extract	DPPC and PG	(<0.1%) SP-B and (1%) SP-C	25 mg/mL	4 mL/kg	100 mg/kg
Calfactant (Infasurf ^b) bovine calf lung lavage	DPPC and PG	(0.7%) SP-B and (1%) SP-C	35 mg/mL	3 mL/kg	105 mg/kg
Poractant (Curosurf ^c) minced porcine lung extract	DPPC and PG	(0.6%) SP-B and (1%) SP-C	80 mg/mL	2.5 mL/kg and 1.25 mL/kg	100-200 mg/kg 100 mg/kg
Synthetic					
Colfosceril (Exosurf ^d)	DPPC (100%)	None	13.5 mg/mL	5 mL/kg	67.5 mg/kg
Synthetic, protein analog					
Lucinactant (Surfaxin ^e)	DPPC and POPG	KL4 peptide as SP-B	30 mg/mL	5.8 mL/kg	175 mg/kg

DPPC, dipalmitoyl phosphatidylcholine; PG, phosphatidylglycerol; POPG, palmitoyloleoyl phosphatidylglycerol; SP-C, surfactant protein C.

^a Abbvie Inc, North Chicago, IL.

^b ONY Inc, Amherst, NY.

^c Chiesi Farmaceutici, Parma, Italy.

^d GlaxoSmithKline, Middlesex, UK.

^e Discovery Laboratories, Warrington, PA.

Surfactant administration procedures may be complicated by transient airway obstruction, oxygen desaturation, bradycardia, and alterations in cerebral blood flow and brain electrical activity. The delivery of surfactant can also result in rapid improvement in lung volume, functional residual capacity, and compliance. Thus, expeditious changes in mechanical ventilator settings may be necessary to minimize the risks of lung injury and air leak. Clinicians with expertise in these procedures should be responsible for surfactant administration whenever surfactant is given.

Surfactant has traditionally been administered through an endotracheal tube either as bolus, in smaller aliquots,²¹ or by infusion through an adaptor port on the proximal end of the endotracheal tube.¹⁹ In an animal model, administration of surfactant as an intratracheal bolus while disconnected from the mechanical ventilator resulted in more uniform distribution than an infusion administered over 30 minutes through a side-hole adapter.²² However, a small clinical trial of human preterm infants showed no significant differences in clinical outcomes between methods.²³ During surfactant administration, reflux into the

endotracheal tube occurred more often when the infusion technique was used. Similar clinical outcomes were also found when surfactant was administered as a bolus or as a 1-minute infusion through a side-hole adapter.²⁴ Because data are conflicting and limited, the optimal method of surfactant administration in preterm infants has yet to be clearly proven. Additionally, there is insufficient evidence to recommend the optimal number of fractional doses of surfactant or what body position is best when surfactant is administered.

A number of alternatives to intratracheal administration of surfactant have been evaluated in clinical trials.^{25–32} These include use of aerosolized surfactant preparations, laryngeal mask airway-aided delivery of surfactant, instillation of pharyngeal surfactant, and administration of surfactant using thin intratracheal catheters. Theoretically, each of these methods could allow administration of surfactant without intubation in spontaneously breathing infants. In a recent study, Göpel et al²⁵ randomized 220 preterm infants born at 26 to 28 weeks' gestation to receive either surfactant administered via a thin plastic catheter (using laryngoscopy) or surfactant administered as a rescue therapy.

All infants were maintained on CPAP. The administration of surfactant through a thin plastic catheter significantly reduced the need for mechanical ventilation and decreased the need for oxygen therapy at 28 days. More data are needed to recommend any of the alternative techniques for surfactant administration.

SURFACTANT REPLACEMENT THERAPY FOR RESPIRATORY DISORDERS OTHER THAN RDS

Surfactant inactivation and secondary dysfunction may occur with conditions such as meconium aspiration syndrome, persistent pulmonary hypertension of the newborn, neonatal pneumonia, and pulmonary hemorrhage.^{33,34} Surfactant administration techniques, surfactant dosage, patient populations, entry criteria, and study outcomes in the small randomized trials and case series of surfactant replacement in neonates with secondary surfactant deficiency vary considerably.^{35–42}

Meconium aspiration syndrome with severe respiratory failure and persistent pulmonary hypertension may be complicated by surfactant inactivation. Surfactant replacement by bolus or slow infusion in infants with severe

meconium aspiration syndrome improved oxygenation and reduced the need for extracorporeal membrane oxygenation (ECMO) (RR 0.64; 95% CI 0.46–0.91; NNTB 6).³⁵ Surfactant did not reduce mortality or decrease the frequency of air leaks (pneumothoraces or pulmonary interstitial emphysema). In a blinded randomized clinical trial of infants receiving ECMO, administration of surfactant shortened the duration of the ECMO. Notably, there were no infants with congenital diaphragmatic hernia in that study.³⁶

Surfactant inactivation may be associated with pneumonia.^{37,38} In a small randomized trial of surfactant rescue therapy, the subgroup of infants with sepsis showed improved oxygenation and a reduced need for ECMO compared with a similar group of control infants.³⁷ Newborn infants with pneumonia or sepsis receiving rescue surfactant also demonstrated improved gas exchange compared with infants without surfactant treatment. The number of neonates who received surfactant for sepsis and pneumonia in these clinical reports is small, and no recommendation can be made.

Surfactant treatment of pulmonary hemorrhage is plausible, because blood inhibits surfactant function. However, only a few retrospective and observational reports have documented the benefits of such therapy, and the magnitude of benefit remains to be established.³⁹

Congenital diaphragmatic hernia may be associated with surfactant insufficiency.⁴⁰ Although measurements of disaturated phosphatidylcholine from lungs of infants with congenital diaphragmatic hernia show synthetic rates similar to those from infants without diaphragmatic hernia, pool sizes and kinetics are altered.⁴⁰ However, surfactant treatment of a large series of infants with congenital diaphragmatic hernia did not improve

outcomes. In fact, the need for ECMO, the incidence of chronic lung disease, and mortality rate were increased with surfactant administration.^{41,42}

ANTENATAL STEROIDS AND SURFACTANT REPLACEMENT

Surfactant trials that proved efficacy were performed at a time when antenatal steroid therapy was given infrequently.⁴³ By the late 1990s, most mothers of preterm infants born at less than 30 weeks' gestation had received antenatal steroids (58% to 92%).^{44–46} Antenatal steroids significantly reduce mortality (RR 0.62; 95% CI 0.51–0.77; NNTB 23), RDS (RR 0.65; 95% CI 0.47–0.75; NNTB 12), and surfactant use in preterm infants (RR 0.45; 95% CI 0.22–0.93; NNTB 9),⁴⁷ most consistently in those born between 28 and 34 weeks' gestation.

Results of observational studies and clinical trials have inferred that antenatal steroids may reduce the need for prophylactic and early rescue surfactant replacement in infants born after 27 to 28 weeks' gestation,^{16,48} but no randomized, controlled trials have addressed this issue. In infants born at or earlier than 27 weeks' gestation, the incidence of RDS is not reduced after exposure to antenatal steroids; however, in a recently published study, death or neurodevelopment impairment at 18 to 22 months was significantly lower for infants who had been

exposed to antenatal steroids at 23 to 25 weeks' gestation.⁴⁹ Infants born before 32 weeks' gestation who received both antenatal steroids and postnatal surfactant were found on subgroup analyses to have significant reductions in mortality, severity of respiratory distress, and air leaks when compared with subgroups that received neither steroids nor surfactant, antenatal steroids only, or surfactant only.^{50–52} This finding corroborates evidence from animal models of RDS that the combination of antenatal steroids and postnatal surfactant improves lung function more than either treatment alone.^{53–55}

An important additional benefit of antenatal steroids is a reduction in risk of intraventricular hemorrhage, an advantage not found with surfactant replacement alone.⁵⁶ The effects of antenatal steroids on other neonatal morbidities, such as necrotizing enterocolitis and patent ductus arteriosus, have been inconsistent. However, antenatal steroids have not significantly decreased the incidence of BPD.^{50,51}

CPAP AND SURFACTANT

Randomized clinical trials suggest that nasal CPAP is acceptable as an alternative to surfactant administration in preterm infants with RDS. A clinical report from the American Academy of Pediatrics, "Respiratory Support of the Preterm Infant," is forthcoming.⁵⁷

TABLE 3 Levels of Evidence⁵⁹

Recommendation LOE	LOE	Grade of Recommendation
Preterm infants born at <30 wk of gestation who need mechanical ventilation because of severe RDS should be given surfactant after initial stabilization.	1	Strong Recommendation
Using CPAP immediately after birth with subsequent selective surfactant administration should be considered as an alternative to routine intubation with prophylactic or early surfactant administration in preterm infants.	1	Strong Recommendation
Rescue surfactant may be considered for infants with hypoxic respiratory failure attributable to secondary surfactant deficiency (eg, meconium aspiration syndrome or sepsis/pneumonia).	2	Recommendation

SUMMARY OF SCIENCE

1. Surfactant replacement, given as prophylaxis or rescue treatment, reduces the incidence of RDS, air leaks, and mortality in preterm infants with RDS (level of evidence [LOE] 1).
2. Both animal-derived and newer synthetic surfactants with SP-B–like activity decrease acute respiratory morbidity and mortality in preterm infants with RDS (LOE 1).
3. Early rescue surfactant treatment (<2 hours of age) in infants with RDS decreases the risk of mortality, air leak, and chronic lung disease in preterm infants (LOE 1).
4. Early initiation of CPAP with subsequent selective surfactant administration in extremely preterm infants results in lower rates of BPD/death when compared with treatment with prophylactic surfactant therapy (LOE 1).
5. Surfactant replacement has not been shown to affect the incidence of neurologic, developmental, behavioral, medical, or educational outcomes in preterm infants (LOE 2).
6. Surfactant treatment improves oxygenation and reduces the need for ECMO without an increase in morbidity in neonates with meconium aspiration syndrome (LOE 2).
7. Surfactant treatment of infants with congenital diaphragmatic

hernia does not improve clinical outcomes (LOE 2).

8. Antenatal steroids and postnatal surfactant replacement independently and additively reduce mortality, the severity of RDS, and air leaks in preterm infants (LOE 2).

CLINICAL IMPLICATIONS (TABLE 3)

1. Preterm infants born at <30 weeks' gestation who need mechanical ventilation because of severe RDS should be given surfactant after initial stabilization (Strong Recommendation).
2. Using CPAP immediately after birth with subsequent selective surfactant administration should be considered as an alternative to routine intubation with prophylactic or early surfactant administration in preterm infants (Strong Recommendation).
3. Rescue surfactant may be considered for infants with hypoxic respiratory failure attributable to secondary surfactant deficiency (eg, pulmonary hemorrhage, meconium aspiration syndrome, or sepsis/pneumonia) (Recommendation).
4. Preterm and term neonates who are receiving surfactant should be managed by nursery and transport personnel with the technical and clinical expertise to administer surfactant safely and deal with multisystem illness. Therefore, pediatric providers who are without expertise, or who are inexperienced

or uncomfortable with surfactant administration or managing an infant who has received surfactant should wait for the transport team to arrive.

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DISCLOSURES

Dr Carlo is on the Mednax Board of Directors. Dr Polin is a consultant for Discovery Laboratories.

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