

# NEONATOLOGY TODAY

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## Medium-Term Outcomes for Children with Severe Hyperlactatemia After Heart Surgery

By Anthony F. Rossi, MD; Robert L. Hannan, MD; Juan Bolivar, MD; Nancy Dobrolet, MD; Plato Alexander, MD and Redmond P. Burke, MD

### Introduction

Measurement of blood or serum lactate levels in the critically ill is now common place. Serial lactate monitoring has been used as an end point of resuscitation of critically ill patients undergoing goal-directed protocols.<sup>1-3</sup> Lactate monitoring has also been shown to be an excellent prognosticator of hospital mortality in critical illness, including infants and children recovering after congenital heart surgery.<sup>4,8</sup> While it is currently well-accepted that those patients with significant elevation of blood lactate are at high risk of dying in the hospital during their illness, the medium-term impact of such a significant physiologic aberration and its influence on the continued risk of dying after hospital discharge has not been evaluated.

### Methods

The web-based medical records of all patients undergoing congenital heart surgery at Miami Children's Hospital between March 2002 and March 2005 were reviewed. Patients undergoing ligation of a patent ductus arteriosus as the primary procedure were excluded. All patients recovering after congenital heart surgery had serial lactate values measured according to our previously published protocol.<sup>3</sup> Briefly, whole blood lactate was measured with a handheld point-of-care device (i-STAT 1 blood gas analyzer, Abbott PoC, Princeton, NJ) on admission to the cardiac intensive care unit and at predetermined intervals thereafter. An algorithm was developed to direct

physician response to changing lactate levels. Routine measurement of blood lactate was discontinued when the blood lactate level returned to normal (<2.2 mmol/L for the purpose of our study). In neonates, blood lactate was measured hourly for the first 4 to 6 hours after admission to the CICU. If the lactate level was less than 5 mmol/L or if the lactate trend was acceptable (decrease of more than 0.5 mmol/L per hour), lactate was measured every 4 to 6 hours until normal. For all other patients lactate was measured serially every 4-6 hours. Lactate could also be measured at the physician's discretion. Lactate testing was repeated serially until normal or until the lactate trend was consistent with a favorable outcome.<sup>9</sup> For the purpose of this study SL was defined as a measured whole blood lactate level >10 mmol/L.

Patients were divided into three groups:

- Group I: Patients never experiencing postoperative SL,
- Group II: SL resolved within the first 24 hours after admission to the CICU,
- Group III: SL beginning in the first 24 hours after surgery and persisting for greater than 24 hours after admission to the CICU.

Patients who normalized their blood lactate level within 24 hours of surgery, but had a secondary late increase in lactate, and patients who experienced SL for the first time later than 24 hours after admission were included in either Group I or Group II, depending on the highest lactate level they obtained in the first 24 hours after surgery. Mortality was measured at the following time intervals: prior to hospital discharge, one year

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- Neonatal Endocrinology
- Neonatal Nephrology
- Neonatal Infectious Diseases
- Central Nervous System

	Number of Patients	Median Age (range)	Median LOS (range)	% Neonates
<b>Group I</b>	1209	161d* (1d-54.1y)	9d # (1-188d)	26%**
<b>Group II</b>	17	16d (1d-19.8y)	22d (4-108d)	53%
<b>Group III</b>	9	7d (5d-14 y)	51.8d (38-73d)	78%

\* p=0.001 vs. Group II and Group III. # p<0.01 vs. Group II and III. \*\* p<0.01 vs. Group I and Group III.

Diagnosis	Procedure	Age at Surg (days)	POS (days)	Outcome
HLHS	Norwood Stage 1	10	149	HM
HLHS	Norwood Stage 1	16	28	HM
HLHS	Fontan	5485	31	HM
TAPVC mixed	TAPVC repair	1	18	HM
AS/AI	Ross/Konno	4133	19	A
TOF s/p repair	RVOT homograft	5072	31	A
TOF s/p repair	RVOT homograft	5351	11	A
Sinus Valsalva Aneurysm	Repair	7203	8	A
HLHS	Norwood Stage 1	6	20	A
Coarctation	Coarct repair (CPB)	8	11	A
HLHS	Norwood Stage 1	8	16	A
TGA	ASO	11	11	A
TAPVC s/p repair, PVSten	Repair PV stenosis	63	12	A
AS/AI	Ross	3034	12	A
DCRV	Repair	4007	4	A
HLHS	Norwood Stage 1	13	95	A

**Abbreviations:** HLHS: Hypoplastic Left Heart Syndrome; TAPVC mixed: total anomalous pulmonary venous connection, mixed type; AS/AI: aortic stenosis/aortic insufficiency; TOF: Tetralogy of Fallot; Coarctation: coarctation of the aorta; TGA: complete transposition of the great arteries; PV Sten: pulmonary vein stenosis; DCRV: double chambered right ventricle; RVOT: right ventricular outflow tract; ASO: arterial switch operation; HM: hospital mortality; A: currently alive.

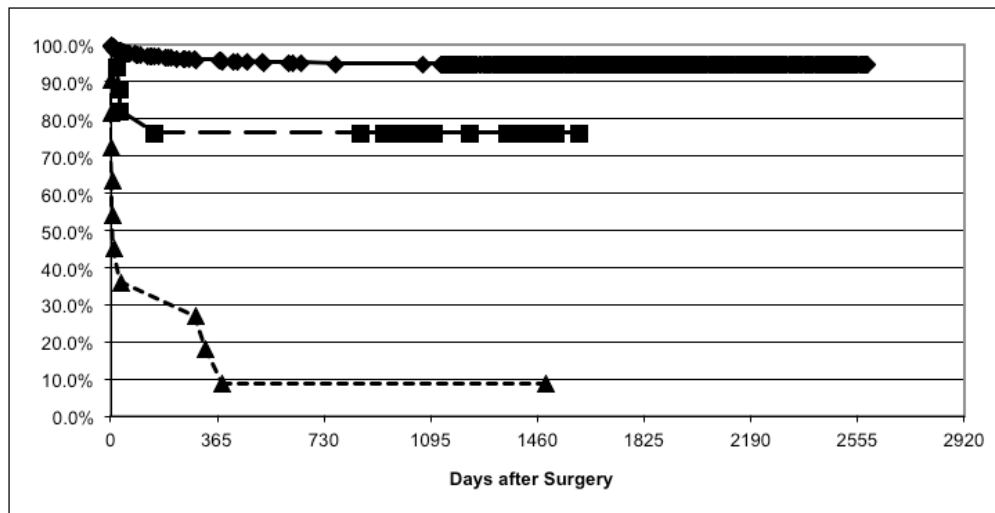


Figure 1. Kaplan-Meier Survival Curve of patients undergoing congenital heart surgery.

after discharge and at a mean follow-up of 5.1 years (+/- 1.1 years).

Statistical analysis was performed using Sigma Stat for Windows Version 2.03, SPSS Inc. (Chicago, IL). Chi-Square analysis was used to detect differences in mortality between groups. The Fisher exact test was used when appropriate. Mann-Whitney Rank Sum Analysis was used to determine differences in demographic data between groups.

## Results

Demographics for the entire group are displayed in Table 1. Groups II and III are described in Tables 2 and 3. The majority of patients experiencing prolonged SL were neonates. Group I patients were older than either Group II or Group III patients (p=0.001 comparing Group I to both Group II and Group III). Neonates comprised only about a quarter of the patients who were in Group I, but over 50% of Group II and almost 80% of Group III. A statistically higher percentage of patients were neonates when comparing either Group II or Group III with those in Group I (p<0.01 for both). There was no significant difference in the percentage of neonates between Groups II and III. Length of stay was significantly longer for those patients experiencing SL and prolonged SL was associated with the longest postoperative stays.

Patients in Group I had significantly lower mortality at discharge, one year and at medium term follow-up than either Groups II or III (Table 4). Group II patients had statistically lower mortality than Group III patients at one year and at medium-term follow-up, and a lower mortality at hospital discharge that approached significant difference (p=0.06). The Kaplan-Meier Survival Curve for all patients is displayed in Figure 1.

There were three deaths that occurred after discharge, all in Group III patients. The deaths occurred at 229, 288 and 382 days after their initial surgery. The first patient had undergone a Norwood operation for Hypoplastic Left Heart Syndrome and then a bi-directional Glenn shunt. Myocardial pump function was markedly depressed prior to the bi-directional Glenn and did not improve after this volume-unloading operation. The patient was referred to a transplant center and died awaiting transplant. The second death occurred in a former premature infant who underwent repair of Tetralogy of Fallot at 3 months of age and 2.3 kilograms. A sudden, unexpected hypoxic arrest occurred on postoperative Day 2, and the patient suffered a severe hypoxic brain injury. He died unexpectedly at home. The third patient underwent a successful Norwood operation but had a prolonged and complicated postoperative course that included two runs of mechanical circulatory support. An uneventful bi-directional Glenn operation was performed at six months of

Diagnosis	Procedure	Age at Surg (days)	POS (days)	Outcome
HLHS	Norwood Stage 1	6	4	HM
HLHS	Norwood Stage 1	5	3	HM
Tricuspid Atresia	Shunt, MBTS	4	34	HM
TAPVC Single V	TAPVC repair shunt	7	3	HM
Mitral Stenosis	Mitral Valve replacement	5096	10	HM
TOF	TOF repair	94	71	<1 YR
HLHS	Norwood Stage 1	13	40	<1 YR
HLHS	Norwood Stage 1	6	41	>1 YR
HLHS	Norwood Stage 1 (Sano)	5	33	A

**Abbreviations:** HLHS: Hypoplastic Left Heart Syndrome; TAPVC mixed: total anomalous pulmonary venous connection; Single V: single ventricle; TOF: Tetralogy of Fallot; MBTS: modified Blalock-Taussig shunt; HM: hospital mortality; < 1 YR: mortality within 1 year of discharge; >1 YR: mortality occurring greater than 1 year after discharge.

age. This patient collapsed at home and arrived at a local emergency department in extremis and died there.

### Discussion

While mortality for children undergoing congenital heart surgery continues to diminish, it remains substantial for certain high risk patients and procedures.<sup>9,10</sup> Surgical modifications have had significant impact on mortality, but those responsible for caring for this fragile subset of postoperative patients must continue to find ways to improve clinical outcomes.

Measurement of blood lactate is now performed routinely by many clinicians who care for patients recovering after congenital heart surgery.<sup>3,7,11</sup> Lactate is a byproduct of glycolysis. Without oxygen, pyruvate is unable to enter the Krebs Cycle and is transformed into lactate to maintain ATP production. Lactate has repeatedly shown to predict morbidity and mortality in critical illness, including patients undergoing congenital heart surgery.<sup>8,12,13</sup>

Elevated lactate in critical illness is often related to a deficiency in systemic oxygen delivery (such as those patients with cardiogenic or hemorrhagic shock), a derangement of cellular aerobic metabolism (usually seen in patients with septic shock), an increase in oxygen consumption, or a combination of these events. Regardless of the mechanism of diminished availability of oxygen to various tissue beds, hypoxia at the cellular level results in a switch from aerobic to anaerobic metabolism, with a resultant increase in lactate production.

Lactate monitoring in the critically ill has traditionally fallen into one of two categories: first, as an accurate predictor of clinical outcome; second, as an objective indicator of the effectiveness of resuscitation of the critically ill. Blood lactate levels have previously proven to be an excellent prognosticator for patients recovering after congenital heart surgery.<sup>7,8,11,12,13</sup>

Interestingly, patients experiencing hyperlactatemia in our series did appear to fare much better than those reported from earlier series.<sup>12,13</sup> In the series of patients reported by

Siegel, a blood lactate level of 4.2 mmoles/L had a positive predictive value of postoperative death of 100%. A blood lactate level of less than 10 mmoles/L in our series placed the patient at very low risk for death. It is difficult to speculate why patients being operated on in this era seem to tolerate hyperlactatemia better than in the past. One could hypothesize that the knowledge gained from these earlier studies heightened the clinicians' awareness of the critical importance of hyperlactatemia. This might have led to a heightened sense of urgency to correct aberrancies in the relationship between oxygen delivery and oxygen consumption at the earliest possible time, thus resulting in improved outcomes. There have also been other important clinical advances in the years separating these reports. Advances in drug therapy include the now rather routine use of the inodilator milrinone.<sup>14</sup> Significant progress has also been made in the area of cardiopulmonary support in the perioperative period, which has improved outcomes for all patients undergoing congenital heart surgery.<sup>15, 16</sup> More recently, serial blood lactate monitoring has been proven to be a valuable end-organ of resuscitation for patients undergoing goal-directed therapy in critical disease.<sup>3, 17</sup>

The highest or peak lactate level a patient experiences during a critical illness may not be the best predictor of clinical outcomes. The time it takes to normalize blood or serum lactate (lactime) has shown to be an excellent prognosticator of outcomes in critical illness and may be superior in this respect to peak lactate measurements.<sup>4</sup> Prolonged lactate clearance was proven to be a better predictor of poor outcome than initial or peak lactate in some studies.<sup>4, 8</sup>

Moderate to severe elevation in lactate in patients following congenital heart surgery is most likely related to inadequate tissue oxygen delivery (leading to increased lactate production), and often associated with liver and renal dysfunction (the organs primarily responsible for the metabolism of lactate, leading to de-

	Hospital Mortality			One Year Mortality			Medium Term Mortality					
	% mortality	p value (vs. Group)			% mortality	p value (vs. Group)			% mortality	p value (vs. Group)		
		G I	G II	G III		G I	G II	G III		G I	G II	G III
<b>Group I</b>	1.6	X	<0.001	<0.001	3.3	X	<0.001	<0.001	4	X	<0.001	<0.001
<b>Group II</b>	24		X	=0.06	24		X	<0.01	24		X	<0.01
<b>Group III</b>	64			X	82			X	91			X



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creased metabolism of lactate). The aberration in the relationship between oxygen delivery and oxygen consumption may be the result of diminished oxygen delivery or increased oxygen consumption in the face of a normal, but relatively limited oxygen supply.<sup>18</sup> Improving tissue oxygen delivery or diminishing oxygen consumption in this population may, therefore, diminish the production of lactate and increase the metabolism of lactate (by improving both renal and hepatic function). Patients recovering from congenital heart surgery are noted to have evidence of inadequate oxygen delivery that usually resolves within 24 hours of surgery in survivors.<sup>19,20,21</sup> Estimating the adequacy of oxygen delivery in this patient population remains difficult. Intracardiac shunting and small patient size makes techniques such as mixed venous oxygen saturation monitoring or thermodilution cardiac output monitoring difficult, if not impossible, for many patients. Blood lactate sampling becomes an excellent, noninvasive indicator of adequate tissue oxygen delivery.

Patients in our study who experienced severe hyperlactatemia, even for short periods of time, fared significantly worse than those who did not. With elevations of blood lactate of 10 or greater, survival to discharge became unlikely. When prolonged for greater than 24 hours, patients experiencing SL after heart surgery were noted to have very high hospital mortality, and had a continued risk for mortality following discharge that the other groups did not experience. It is not clear why some patients in our study experienced prolonged SL. Continued diminished systemic oxygen delivery, elevated oxygen consumption, and poor end-organ function with an inability to metabolize or excrete lactate efficiently, or a combination of these phenomena, might be contributing factors. Regardless of the cause of prolonged SL in our patient population, the short- and medium-term outcomes for these patients appears to be very poor.

#### Limitations

Limitations of this study are those implicit in any retrospective review study. Patients in this review were managed at the clinician's discretion with intent to optimize the outcome for the individual patient. This will lead to some significant practice variations between patients. The number of patients with prolonged SL in this study was very small. A larger study might add more insight as to the fate of these markedly distressed patients. Also, the level of hyperlactatemia that we labeled as severe is com-

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***“Efforts made to prevent or limit the degree and duration of hyperlactatemia in the child recovering after congenital heart surgery, in the hopes of improving the relationship between oxygen delivery and oxygen consumption early in the postoperative course, might lead to improved early outcomes.”***

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pletely arbitrary but consistent with early data on lactate and survival as reported by Iberti.<sup>22</sup>

#### Conclusions

Patients experiencing SL have predictably morbid outcomes. Severe elevation in blood lactate after heart surgery in children is associated with a significant risk for hospital mortality. Even short periods of SL are associated with increased risk of death and prolonged hospital stays. The outlook for patients who experience prolonged SL is particularly bleak. The hemodynamic derangements resulting in the development of prolonged SL are associated with long-standing consequences. Even those fortunate enough to survive their hospital stay remain at increased risk of death after discharge.

Efforts made to prevent or limit the degree and duration of hyperlactatemia in the child recovering after congenital heart surgery, in the hopes of improving the relationship between oxygen delivery and oxygen consumption early in the postoperative course, might lead to improved early outcomes.

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# Guest Columnist: Resources for You and for Your Patients' Families

By Deb Discenza

It is a pleasure to be writing for *Neonatology Today*, and to be able to provide you with a regular update on available resources for you and your patients' families. As a long-time advocate, speaker, author and publisher, I am always interested in passing along the "good news" about programs, websites and organizations that can help others.

## Respiratory Syncytial Virus (RSV)

### Parent RSV Education Tool

This straightforward hand-out from the *Alliance for Patient Access* is an easy tool for you to hand out to your families regarding education surrounding RSV. Download it at: <http://bit.ly/RSVLetter>.

### RSV Season Preparation Tool

Parents whose children have been prescribed Synagis®, often get overwhelmed juggling all of their preemies' needs, appointments and prescriptions. This easy sheet can get a spot on the fridge, and be a solid reminder of what needs to be done should their child need to receive Synagis®: <http://bit.ly/RSVSeason>

## Feeding Issues

### Feeding Matters

Parents and professionals alike are often stymied by the consistency of feeding issues surrounding premature infants. Started by a mother of premature triplets (who all had serious feeding issues), *Feeding Matters* has gone on to, not only provide a national awareness surrounding this issue, but also supply resources, events and more for the parent and the professional communities. [www.feedingmatters.org](http://www.feedingmatters.org).

## Support Groups

### Inspire Premie Support Forum

The largest and most active online support forum for parents of premature infants, this

group boasts over 15,000 members from around the world. Discussion areas include: preemies in the NICU, at home, in school, feeding issues, preemies with CP and preemie angels and more. [www.inspire.com/preemie](http://www.inspire.com/preemie).

### Zoe Rose Memorial Foundation

This organization works to provide emotional support, educational resources, and awareness-focused events for parents of preemies in the NICU, post-discharge and for those who have suffered a pregnancy or infant loss. In collaboration with other organizations, the *Zoe Rose Memorial Foundation* has a lasting impact on preemies in the NICU now and ongoing: [www.zoerose.org](http://www.zoerose.org).

### Papas of Preemies

Started by Joel Brens, a father of a preemie, *Papas of Preemies* is unique organization that, while it supports families as a whole, it also specializes in being there for the fathers. With the research showing that



Ten-year-old Becky Discenza at the beach.

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***“Every NICU professional is interested in neonatal outcomes in order to improve their practice. Numbers are helpful, but so are stories.”***

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fathers of premature infants are struggling with various forms of post-traumatic stress disorder and/or depression due to isolation during the NICU and after the NICU, it is encouraging that fathers now have an outlet. Joel has a regular blog going, and encourages guest bloggings on the site: [www.papasofpreemies.com](http://www.papasofpreemies.com).

## 10 Years After the NICU

Every NICU professional is interested in neonatal outcomes in order to improve their practice. Numbers are helpful, but so are stories. In each edition, I will be giving you an outcome of a baby born prematurely so you can read between the lines and the numbers of reports to see the human side of these babies and these families.

For this issue, I will tell my own story, as I am entering into a milestone that I feel is helpful to all professionals.

I am the mother to Becky, a premature infant born at 30 weeks in 2003, who is now 10 years old. I am extremely grateful to my daughter's team at Inova Children's Hospital in Falls Church, Virginia, for their care of my daughter during her stay there.

### In the NICU

My daughter had various complications in the NICU, and came home on an apnea monitor, oxygen, medications, a team of specialists and more. I will never forget holding my daughter for the first time and wondering, if I would be ever so lucky to bring home this "feather-light" infant in my arms. Needless to say, during each visit in



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the NICU I kept sending my daughter messages of encouragement to grow and “be heavy.” Indeed, after a 38-day stay, she came home, and after a re-admission for feeding and breathing issues, we saw Becky start to really thrive in our care.

#### At Home

Life after the NICU for our family was a series of medical appointments, therapeutic evaluations and therapies, and shedding the equipment. For the longest time I joked that I was my daughter’s personal assistant, because I spent more time scheduling and going to appointments, handling the medical equipment re-orders and data download appointments, filling out paperwork, filling and dosing prescriptions, checking on programs and benefits, than being a regular mom. But I felt lucky to be able to do this because I was one of those parents who got to bring the baby home from the NICU. Becky continued to thrive and every smile and giggle told me that whatever lay ahead of us, we could handle it. Love is a very powerful motivator.

#### Life Gets Easier, Then Harder

The toddler years included Early Intervention therapies to help with catch-up and slowly things improved developmentally bit by bit. By around two years old she was really starting to make progress on that front. Meanwhile Becky maintained the super-selective diet from day one, but we tried our best to just focus on her eating whatever we could get into her and try not to feel judged by family and friends. In their view everything was “okay” now, but I instinctually knew better. Something was just not right.

#### Fast Forward

Becky headed into preschool sans therapy teams, but within 6 months we were suddenly in the ChildFind Preschool program due to regressions in developmental skills. All through this I noted to people around me that I knew something was ahead, but I couldn’t put my finger on it. But all I received in return were a lot of shrugs - more tests, more evaluations, more therapy.

This translated into an IEP meeting in Kindergarten that ended with the school psychologist quizzing me about my daughter

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**“Outcomes and all of their statistical detail are helpful for medical science, but they do not predict the future for every child. There is another side that shows the strength and resilience of the human spirit and the power of love.”**

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possibly having autism. She was diagnosed with Asperger’s later that year, and diagnosed with ADHD in second grade. In third grade a Developmental Pediatrician finally explained why Becky had such a hard time with a lot of coordination issues and motor planning: Developmental Motor Coordination Disorder.

Becky’s feeding issues persist to this day, but she has come a long way over the last few years thanks to a feeding program. On the physical side of things, Becky has asthma that is controlled with medication and is out of school a lot due to her lowered immune system. But is that the end of the story? No.

#### Bragging Rights

Becky may have challenges, but she also has amazing gifts that come along with them. She started reading as a toddler, and has not stopped since. At 10 years old, she voraciously reads adult non-fiction books in the various hard sciences, loves Greek mythology, as well as a good cozy mystery. Her goal is to be an astronaut and to go into space like her hero, Sally Ride. She happily tells the world that she is a “computer geek,” and absorbs technology as easily as she breathes air. As of this writing, Becky heads into fourth grade, and not just in a mainstream class, but a full-time advanced academic program.

But to me, Becky’s greatest gifts are her ability to connect to others, something that has been a life-long work in progress considering her challenges. In her new school environment she has a lot of friends and is

thriving. She is a kind, caring and considerate young lady to adults, especially the elderly. And her love of animals is another trait that shows her gentle spirit.

#### Outcomes

I tell you about my daughter’s story so you can see the other side of the story that ends for you as that baby is discharged from the NICU. Outcomes and all of their statistical detail are helpful for medical science, but they do not predict the future for every child. There is another side that shows the strength and resilience of the human spirit and the power of love.

NT





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Neonatology Today welcomes and encourages Letters to the Editor (LTE). If you have comments or topics you would like to address, please send an email to: [LTE@Neonate.biz](mailto:LTE@Neonate.biz), and let us know if you would like your comment published or not.

Those wishing to have their LTE published will be sent a preproduction draft to review.



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## **INDICATION**

SURFAXIN<sup>®</sup> (lucinactant) Intratracheal Suspension is approved by the FDA for the prevention of respiratory distress syndrome (RDS) in premature infants at high risk for RDS.

## **IMPORTANT SAFETY INFORMATION**

SURFAXIN (lucinactant) Intratracheal Suspension is intended for intratracheal use only. The administration of exogenous surfactants, including SURFAXIN, can rapidly affect oxygenation and lung compliance. SURFAXIN should be administered only by clinicians trained and experienced with intubation, ventilator management, and general care of premature infants in a highly supervised clinical setting. Infants receiving SURFAXIN should receive frequent clinical assessments so that oxygen and ventilatory support can be modified to respond to changes in respiratory status.

Most common adverse reactions associated with the use of SURFAXIN are endotracheal tube reflux, pallor, endotracheal tube obstruction, and need for dose interruption. During SURFAXIN administration, if bradycardia, oxygen desaturation, endotracheal tube reflux, or airway obstruction occurs, administration should be interrupted and the infant's clinical condition assessed and stabilized. Overall the incidence of administration-related adverse events did not appear to be associated with an increased incidence of serious complications or mortality relative to the comparator surfactants.

SURFAXIN is not indicated for use in acute respiratory distress syndrome (ARDS).

For more information about SURFAXIN, please visit [www.SURFAXIN.com](http://www.SURFAXIN.com) and see accompanying brief summary on the next page.

**BRIEF SUMMARY OF PRESCRIBING INFORMATION**

Please see package insert for full prescribing information.

**INDICATIONS AND USAGE**

SURFAXIN® is indicated for the prevention of respiratory distress syndrome (RDS) in premature infants at high risk for RDS.

**CONTRAINDICATIONS**

None.

**WARNINGS AND PRECAUTIONS**

**Acute Changes in Lung Compliance**

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**Administration-Related Adverse Reactions**

Frequently occurring adverse reactions related to the administration of SURFAXIN include bradycardia, oxygen desaturation, reflux of drug into the endotracheal tube (ETT), and airway/ETT obstruction.

**Increased Serious Adverse Reactions in Adults with Acute Respiratory Distress Syndrome (ARDS)**

Adults with ARDS who received lucinactant via segmental bronchoscopic lavage had an increased incidence of death, multi-organ failure, sepsis, anoxic encephalopathy, renal failure, hypoxia, pneumothorax, hypotension, and pulmonary embolism. SURFAXIN is not indicated for use in ARDS.

**Clinical Trials Experience**

The efficacy and safety of SURFAXIN for the prevention of RDS in premature infants was demonstrated in a single randomized, double-blind, multicenter, active-controlled, multi-dose study involving 1294 premature infants (Study 1). Infants weighed between 600 g and 1250 g at birth and were 32 weeks or less in gestational age. Infants were randomized to received 1 of 3 surfactants, SURFAXIN (N = 524), colfosceril palmitate (N = 506), or beractant (N = 258). Co-primary endpoints were the incidence of RDS (defined as having a chest x-ray consistent with RDS and an FiO<sub>2</sub> ≥ 0.30) at 24 hours and RDS-related mortality at 14 days. The primary comparison of interest was between SURFAXIN and colfosceril palmitate with the intent of demonstrating superiority. Beractant served as an additional active comparator. Compared to colfosceril palmitate, SURFAXIN demonstrated a statistically significant improvement in both RDS at 24 hours and RDS-related mortality through Day 14. A second multicenter, double-blind, active-controlled study involving 252 premature infants was also conducted to support the safety of SURFAXIN (Study 2). Infants weighed between 600 g and 1250 g and were less than 29 weeks in gestational age. Infants received 1 of 2 surfactants, SURFAXIN (N = 119) or poractant alfa (N = 124).

The safety data described below reflect exposure to SURFAXIN administered intratracheally to infants at a dose of 5.8 mL per kg (up to 4 doses) in either 4 aliquots (Study 1) or 2 aliquots (Study 2) in 643 premature infants.

Comparator surfactants colfosceril palmitate and beractant were administered at the recommended doses (5.0 and 4.0 mL per kg, respectively) while the first dose of poractant alfa administered (2.2 mL per kg) was less than the recommended dose of 2.5 mL per kg. Any subsequent doses of poractant alfa were at the recommended 1.25 mL per kg dose.

Overall, the incidence of administration-related adverse reactions was higher in infants who received SURFAXIN compared to other surfactants (Table 1) and resulted in a greater proportion of infants treated with SURFAXIN who experienced administration-related oxygen desaturation and bradycardia. For Study 1, oxygen desaturation was reported in 17%, 9%, and 13% and bradycardia for 5%, 2%, and 3% of infants treated with SURFAXIN, colfosceril palmitate, and beractant, respectively. For Study 2, oxygen desaturation was reported in 8% and 2% and bradycardia in 3% and 2% of infants treated with SURFAXIN and poractant alfa, respectively. These adverse reactions did not appear to be associated with an increased incidence of serious complications or mortality relative to the comparator surfactants (Table 2).

**Table 1. Administration-Related Adverse Reactions in SURFAXIN Controlled Clinical Studies<sup>a</sup>**

	Study 1 <sup>b</sup>			Study 2 <sup>c</sup>	
	SURFAXIN (N = 524)	Colfosceril palmitate (N = 506)	Beractant (N = 258)	SURFAXIN (N = 119)	Poractant alfa (N = 124)
Total Doses Administered	994	1038	444	174	160
<b>Total Number of Events (Events per 100 Doses)</b>					
ETT Reflux	183 (18)	161 (16)	67 (15)	47 (27)	31 (19)
Pallor	88 (9)	46 (4)	38 (9)	18 (10)	7 (4)
Dose Interruption	87 (9)	46 (4)	30 (7)	7 (4)	2 (1)
ETT Obstruction	55 (6)	21 (2)	19 (4)	27 (16)	1 (1)

<sup>a</sup> Table includes only infants who received study treatment.

<sup>b</sup> Study 1 doses were administered in 4 aliquots.

<sup>c</sup> Study 2 doses were administered in 2 aliquots.

**Table 2. Common Serious Complications Associated with Prematurity and RDS in SURFAXIN Controlled Clinical Studies Through 36-Weeks Post-Conceptual Age (PCA)**

	Study 1			Study 2	
	SURFAXIN (N = 527) %	Colfosceril palmitate (N = 509) %	Beractant (N = 258) %	SURFAXIN (N = 119) %	Poractant alfa (N = 124) %
Apnea	52	52	46	66	75
Intraventricular hemorrhage, all grades	52	57	54	39	38
-Grade 3/4	19	18	21	13	8
Periventricular leukomalacia	10	10	12	4	9
Acquired sepsis	44	44	44	45	52
Patent ductus arteriosus	37	35	37	43	44
Retinopathy of prematurity, all grades	27	26	25	32	31
-Grade 3/4	6	7	6	5	9
Necrotizing enterocolitis, all grades	17	17	19	13	15
-Grade 2/3	6	8	14	8	8
Pulmonary air leak through Day 7, all types	15	17	14	9	7
-Pulmonary interstitial emphysema	9	10	10	3	5
-Pneumothorax	3	4	2	4	1
Pulmonary hemorrhage	10	12	14	6	9

All-cause mortality through 36-weeks PCA was similar regardless of which exogenous surfactant was administered.

Adverse reactions reported in the controlled clinical studies through 36-weeks PCA occurring in at least 10% of infants were anemia, jaundice, metabolic acidosis, oxygen desaturation, hyperglycemia, pneumonia, hyponatremia, hypotension, respiratory acidosis, and bradycardia. These reactions occurred at rates similar to the comparator surfactants.

No assessments for immunogenicity to SURFAXIN were performed in these clinical studies.

**Follow-up Evaluations**

Twelve-month corrected-age follow-up of 1546 infants enrolled in the 2 controlled clinical studies demonstrated no significant differences in mortality or gross neurologic findings between infants treated with SURFAXIN and those treated with the comparator surfactants (colfosceril palmitate, beractant, or poractant alfa).

**OVERDOSAGE**

There have been no reports of overdose following the administration of SURFAXIN.

**HOW SUPPLIED/STORAGE AND HANDLING**

SURFAXIN (lucinactant) Intratracheal Suspension is supplied sterile in single-use, rubber-stoppered, clear glass vials containing 8.5 mL of white suspension (NDC 68628-500-31). One vial per carton.

Store SURFAXIN in a refrigerator at 2° to 8°C (36° to 46°F) and protect from light until ready for use. Do not freeze. Vials are for single use only. Discard any unused portion of SURFAXIN. Discard warmed vials of SURFAXIN if not used within 2 hours of warming.

To report SUSPECTED ADVERSE REACTIONS, contact Discovery Laboratories, Inc. at 1-877-SURFAXN (877-787-3296) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

# Medical News, Products & Information

## Unpublished Trial Data 'Violates an Ethical Obligation' to Study Participants, Say Researchers

Almost one in three (29%) large clinical trials remain unpublished five years after completion. And of these, 78% have no results publicly available, finds a study published on [bmj.com](http://bmj.com).

This means that an estimated 250,000 people have been exposed to the risks of trial participation without the societal benefits that accompany the dissemination of their results, say the authors.

They argue that this "violates an ethical obligation that investigators have towards study participants" and call for additional safeguards "to ensure timely public dissemination of trial data."

Randomized clinical trials are a critical means of advancing medical knowledge. They depend on the willingness of people to expose themselves to risks, but the ethical justification for these risks is that society will eventually benefit from the knowledge gained from the trial.

But when trial data remain unpublished, the societal benefit that may have motivated someone to enroll in a study remains unrealized.

US law requires that many trials involving human participants be registered - and their results posted - on the largest clinical trial website [ClinicalTrials.gov](http://ClinicalTrials.gov). But evidence suggests that this legislation has been largely ignored.

So a team of US-based researchers set out to estimate the frequency of non-publication of trial results and, among unpublished studies, the frequency with which results are unavailable in the [ClinicalTrials.gov](http://ClinicalTrials.gov) database.

They searched scientific literature databases and identified 585 trials with at least 500 participants that were registered with [ClinicalTrials.gov](http://ClinicalTrials.gov) and completed prior to January 2009. The average time between study completion and the final literature search (November 2012) was 60 months for unpublished trials.

Registry entries for unpublished trials were then reviewed to determine whether results for these studies were available in the [ClinicalTrials.gov](http://ClinicalTrials.gov) results database.

Of 585 registered trials, 171 (29%) remained unpublished. Of these, 133 (78%) had no results available in [ClinicalTrials.gov](http://ClinicalTrials.gov). Non-

publication was more common among trials that received industry funding (32%) than those that did not (18%).

"Our results add to existing work by showing that non-publication is an important problem even among large randomized trials," say the authors. Furthermore, the sponsors and investigators of these unpublished trials infrequently utilize the [ClinicalTrials.gov](http://ClinicalTrials.gov) results database.

The lack of availability of results from these trials "contributes to publication bias and also constitutes a failure to honor the ethical contract that is the basis for exposing study participants to the risks inherent in trial participation," they add. "Additional safeguards are needed to ensure timely public dissemination of trial data," they conclude.

## Study Examines Adverse Neonatal Outcomes Associated With Early-Term Birth

Early-term births (37 to 38 weeks gestation) are associated with higher neonatal morbidity (illness) and with more neonatal intensive care unit (NICU) or neonatology service admissions than term births (39 to 41 weeks gestation), according to a study by Shaon Sengupta, MD, MPH, now of the Children's Hospital of Philadelphia and formerly of the University at Buffalo, NY, and colleagues.

Researchers examined data over a three-year period from medical records of 33,488 live births at major hospitals in Erie County, NY, 29,741 at a gestational age between 37 to 41 weeks.

According to study results, 27% of all live births were early-term (birth at 37 to 38 weeks). In comparison with term newborns (birth at 39 to 41 weeks), early-term newborns had higher risks for birth complications, including: hypoglycemia (low blood sugar, 4.9% vs. 2.5%), NICU or neonatology service admission (8.8% vs. 5.3%), need for respiratory support (2.0% vs. 1.1%), and requirement for intravenous fluids (7.5% vs. 4.4%). Cesarean deliveries, common among early-term births (38.4%), posed a higher risk for NICU or neonatology admissions and morbidity compared with term births; NICU or neonatology admission was also more common in vaginal early-term births compared with term newborns.

"We conclude that early-term delivery is associated with greater morbidity and with increased admission to the NICU or neonatology service in a geographic area-based setting. This increased risk is more profound

with cesarean section deliveries but exists for vaginal deliveries as well," the study concludes.

*JAMA Pediatr.* Published online September 30, 2013. doi:10.1001/jamapediatrics.2013.2581.

This study was supported by intramural funds from the Division of Neonatology, University at Buffalo, and by an American Academy of Pediatrics Resident Research Grant and the Thomas F. Frawley, MD, Residency Research Fellowship Fund, at the University at Buffalo. Please see the article for additional information, including other authors, author contributions and affiliations, financial disclosures and support, etc.

## Human Error Most Common Cause of Birth Asphyxia

Findings from a 15-year study published in *Acta Obstetrica et Gynecologica Scandinavica*, a journal of the Nordic Federation of Societies of Obstetrics and Gynecology, indicates that human error is the most common cause of infant asphyxiation at birth. Inadequate fetal monitoring, lack of clinical skills, and failure to obtain senior medical staff assistance are most often cited in Norwegian compensation claims following birth asphyxia.

In Norway there are roughly 60,000 births each year, with The Norwegian System of Compensation to Patients (NPE) receiving 65 claims for obstetric injury to the child. A previous study by the current research team found that asphyxia was the most common cause for compensation—between 20 and 25 cases annually. Prior research estimate that lifelong compensation for injury caused by birth asphyxia averages about €430,000 (\$574,000) in Norway, with costs more than 10 times higher in the U.S.

"While fetal brain injury or death is uncommon during childbirth, when it occurs the effects are devastating," explains Dr. Stine Andreassen with the Department of Obstetrics and Gynecology at Nordlandssykehuset (Nordland Hospital) in Bodø, Norway. "Our study investigates claims made to the NPE for neurological injury or death following birth asphyxia."

For the present study, researchers examined 315 claims made to the NPE between 1994 and 2008 that were associated with alleged birth asphyxia. The team looked at hospital records, assessments by experts, along with NPE and courts of law decisions. Of the

claims made, there were 161 cases that were awarded compensation.

Results show that in the compensated cases there were 107 infants who survived, with 96 having neurological injury, and 54 children who died. Human error was the most common cause of birth asphyxia with 50% attributed to inadequate fetal monitoring, 14% lack of clinical knowledge, 11% non-compliance to clinical guidelines, 10% failure to ask for senior medical assistance, and 4% were errors in drug administration. In cases of substandard care, the obstetrician and midwife were documented as the responsible staff at 49% and 46%, respectively.

"In most compensated cases, poor fetal monitoring led to an inadequate supply of oxygen to the infant," concludes Dr. Andreasen. "Training for midwives and obstetricians, along with high-quality audits, could help to reduce claims for compensation after birth asphyxia."

Full citation: "Claims for Compensation After Alleged Birth Asphyxia: A Nationwide Study Covering 15 Years." Stine Andreasen, Bjørn Backe and Pål Øian. *Acta Obstetrica et Gynecologica Scandinavica*; Published online: November 18, 2013 (DOI: 10.1111/aogs.12276).

## Newborn Babies Have Built-in Body Awareness Ability

The ability to differentiate your own body from others is a fundamental skill, critical for humans' ability to interact with their environments and the people in them. Now, researchers reporting in *Current Biology*, a Cell Press publication, on November 21<sup>st</sup> provided some of the first evidence that newborn babies enter the world with the essential mechanisms for this kind of body awareness already in place.

In addition to this insight into normal human development, the researchers stress the importance of the new findings for understanding atypical development, too.

"The identification of these mechanisms at birth in the current study sheds light on the typical trajectory of body awareness across development," says Maria Laura Filippetti of Birkbeck College, University of London. "Our findings may also be relevant to the investigation of early predictors of developmental disorders in infants, such as autism, where an impairment in the discrimination of self/other is believed to be present."

Earlier studies in adults showed that the integration of information from different senses is key to body awareness. If an individual watches another person's face being touched as his or her own face is touched in the same way, the perception of self actually shifts to partially incorporate that other face. In the new study, Filippetti and colleagues wanted to go

back to the very beginning in investigating that phenomenon by studying newborn babies.

Just as in those earlier adult studies, the researchers presented 20 healthy newborns with a video of another baby's face being touched on the cheek with a soft paintbrush while the newborns' corresponding cheeks were stroked either simultaneously or with a time delay. Of course, the babies couldn't explain what they experienced, but they did show greater interest in looking at the other baby's face when it was stroked synchronously with their own. The babies were less interested when the face was presented to them upside down, making it less relatable to themselves.

The researchers interpret their observations as evidence that babies have the essential ingredients for body perception. When what babies see in relation to their own bodies matches what they feel, they notice just as we adults do. In other words, Filippetti says, newborns are "competent creatures," capable of differentiating themselves from others and of forming a coherent perception of their own bodies.

The findings may help in understanding disorders characterized by a lack of self-awareness, and the researchers call for additional research, particularly in the context of autism.

"For years, research on autism has focused on the impairment in social interactions," Filippetti says. "We believe it will be important for further studies to specifically investigate the perception of the self in this population, as well as the relationship of self to other."

## Women & Infants Earns \$3 Million Grant from the National Institute of Health

Advances in technology and medical care have dramatically improved survival for infants born prior to 30 weeks gestation and weighing less than three pounds. However, up to 50% of these infants may develop physical, cognitive, language and/or behavioral impairments that require extensive health care, educational and psychosocial community resources through adulthood. At this time, there is no reliable method to identify those infants who will go on to develop impairments and those who will not.

Women & Infants Hospital has earned a five-year, \$3 million grant from the National Institute of Health's National Institute of Child Health and Human Development to determine the efficacy of a neurobehavioral exam that may help to identify which infants are at greatest risk for developmental impairment. Barry M. Lester, PhD, Director of the Brown Center of the Study of Children at Risk at Women & Infants Hospital of Rhode Island and The Warren Alpert Medical School of

Brown University, is the principal investigator. Co-principal investigator is T. Michael O'Shea, MD, of Wake Forest University.

Dr. Lester and Edward Tronick, PhD, of the University of Massachusetts, Boston, have developed a neurobehavioral exam called the NNNS, or the NICU (neonatal intensive care unit) Network Neurobehavioral Scale. This exam provides a comprehensive assessment that profiles infant neurobehavior along dimensions that researchers believe will enable them to help identify which infants are at greatest risk for developmental impairment.

"The ability to identify which infants will or will not be developmentally impaired is the 'holy grail' that would usher in a new era of preventive intervention and improve the long-term outcome of these fragile babies," said Dr. Lester.

When infants are discharged from the NICU, many who have medical problems become developmentally impaired, while others do not. Likewise, some infants without medical problems become developmentally impaired, while others do not.

"The impairments that are suffered by these children are costly in many ways," explained Dr. Lester. "There is significant emotional cost to the children themselves, their parents and families, including coping with continuous fear and the possibility of crises associated with the infant's unpredictable medical course, extended hospitalizations, and uncertain neurodevelopmental and quality of life outcomes. In addition, time lost from work and other family activities combine to create an enormous burden on the family, their community, support networks, and society in general."

Over a five year period, Dr. Lester and his team will study approximately 1,000 babies born less than 30 weeks gestation at six sites across the country, including at Women & Infants Hospital. These babies will be tested with the NNNS just before discharge from the NICU and then given a series of developmental tests when they are approximately two and one-half years old.

Dr. Lester said, "We will use information about the infants' medical problems and profiles on the NNNS to predict which infants will be developmentally impaired at two and one-half years. If our predictions are accurate, we will be able to use our findings to help early intervention and follow-up programs in their care plans for the baby and to help counseling parents when the baby is discharged from the NICU. Parenting is a key factor in helping babies recover, so parenting will be a critical part of the intervention."

"The long-term goal here is prevention," Dr. Lester continued. "If we can identify infants at greatest risk, then we can target interventions

# NEONATOLOGY TODAY

News and Information for BC/BE Neonatologists and Perinatologists

## About Neonatology Today

Neonatology Today (NT) is the leading monthly publication that is available free to qualified Board Certified (BC) neonatologists and perinatologists. Neonatology Today provides timely news and information to BC neonatologists and perinatologists regarding the care of newborns, and the diagnosis and treatment of premature and/or sick infants. In addition, NT publishes special issues, directories, meeting agendas and meeting dailies around key meetings.

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to reduce or eliminate later deficits, reduce the pool of infants who need services to only those at greatest risk, and effectively allocate limited resources.”

For more information visit:  
[www.womenandinfants.org](http://www.womenandinfants.org).

### Electronic Health Records Can Measure Patient-Centered Care

Although Electronic Health Records (EHR) are primarily used to store patient clinical data, the non-clinical data they collect may be used to measure patient-centeredness of primary care practices, finds a new study in *Health Services Research*. In addition, two of the process of care measures collected via EHRs, volume of between clinician e-messages and frequency of in-person patient visits, were associated with better patient health outcomes.

“We were looking for ways to leverage the amount of operational information in a practice's EHR and find measurements of the process of care,” said Ming Tai-Seale, PhD, MPH, a senior staff scientist at the Palo Alto Medical Foundation Research Institute in Palo Alto, CA, and lead author on the study. “We were pleasantly surprised to see we could do that,” she said.

The study collected data on more than 15,000 people with diabetes and more than 49,500 patients with high blood pressure who were patients at a large group practice in Northern California during 2010. The clinical data collected included blood glucose and blood lipid levels and blood pressure readings. Then they examined the relationship between that clinical information and various nonclinical types of EHR information, including the volume of secure electronic communication (e-messages) between physicians and patients, e-messages about patients within the practice, and the time to the third-next-available appointment, a measure of how easy it is to schedule non-urgent visits.

The volume of e-messages, the number of days to the third-next-available appointment, and the volume of internal communications were found to be reliable measures of the processes of care within a patient-centered practice. In addition, better blood lipid management and blood pressure control was associated with frequent e-messaging between doctors and patients with diabetes. Practices with more in-person visits had better blood pressure control in patients with high blood pressure.

Key Points:

- Electronic health records collect non-clinical information that can be used to

measure a medical practice's patient-centeredness.

- Primary-care practices with more frequent electronic messaging between clinicians had better blood lipid control in patients with diabetes.

These non-clinical data are the type often evaluated by those looking at how well a large practice operates, but had not necessarily been linked to a clinical outcome, Tai-Seale noted. “The reason we also looked at process-of-care measures—emailing, e-messages with staff, and continuity of care—is because these have not been used to study their linkages with patient health outcomes before,” she said.

“It seems they are trying to solve a problem kind of backwards,” said Jason Mitchell, MD, Director of the American Academy of Family Physicians Center for Health IT in Leawood, KS. The researchers are looking at operational activities and trying to correlate them with clinical outcomes, he commented. “Yes, there is an association, but there isn't any evidence of a cause and effect.” There may be other variables that can change this association, he explained.

Many health policy organizations are trying to measure the value of health care—and not just the cost; but, not every area of medicine has clinical outcomes as clear cut as blood glucose and blood pressure levels, commented Mitchell. Most organizations are frustrated that they are not able to get such direct information and are seeking proxies they can measure. “We really need to be looking at those outcomes and use EHRs to get that directly instead of [using] proxies,” he noted.

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