NEONATOLOGY TODAY

News and Information for BC/BE Neonatologists and Perinatologists

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www.Neonate.biz

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NEO: The Conference for Neonatology
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Tracking Nutritional Protein Management in the Preterm Infant Using Vermont Oxford Benchmarks

By Lynn Mayberry, RN; Sue Wolf, RNC-NIC

> ***"Over the past 7 years, we have instituted practices to improve protein intake in our preterm infants and have used the Vermont Oxford Network (VON) data as a benchmark to evaluate our success."***

Background

Extrauterine growth failure occurs in 80% to 100% of Extremely Low Birth Weight (ELBW) infants, and it is recognized that these infants require more protein than has typically been provided to them in the Neonatal Intensive Care Unit (NICU). This is of particular concern as poor NICU growth is associated with poor developmental outcome. However, there is a need to balance providing higher protein intake with the metabolic consequences of doing so. Over the past 7 years, we have instituted practices to improve protein intake in our preterm infants and have used the Vermont Oxford Network (VON) data as a benchmark to evaluate our success. The VON is a voluntary collaboration comprised of over 950 NICUs worldwide dedicated to improving the quality and safety of medical care for babies. The VON maintains a database, including information about the care and outcomes of high-risk newborn infants in NICUs around the world.

Objective

To describe the impact of nutritional strategies to increase protein intake on growth and clinical outcomes in preterm infants.

Methods

Data was collected from NorthShore University HealthSystem (NSUH), a 44 bed, Level 3 NICU in suburban Chicago. Growth outcomes and the incidence of Necrotizing Enterocolitis (NEC) were recorded from 2006-2013 (avg. 586 patients/year) and compared to data from Level 3 NICU's in the VON. Increasing protein intake may result in metabolic intolerance and the incidence of Bicitra treatment was recorded after our implementation of a higher protein acidified liquid human milk fortifier (ALHMF) product in 2011-12.

Results

After the introduction of high protein preterm formulas/fortifier, fewer infants were discharged below the 10th percentile in head circumference on Fenton growth curves, and among these patients, there were lower rates of NEC. We observed a similar pattern for weight at discharge. In the 6 months preceding the ALHMF, 8.9% of infants (weight <2kg) received Bicitra vs. 2.4% in the first 5 months after ALHMF introduction.

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References: 1. Klein CJ. *J Nutr.* 2002;132(6 suppl 1):1395S-1577S. **2.** Agostoni C, Buonocore G, Carnielli VP, et al. ESPGHAN Committee on Nutrition. Enteral nutrient supply for preterm infants: commentary from the European Society of Paediatric Gastroenterology, Hepatology and Nutrition Committee on Nutrition. *J Pediatr Gastroenterol Nutr.* 2010;50:85-91.

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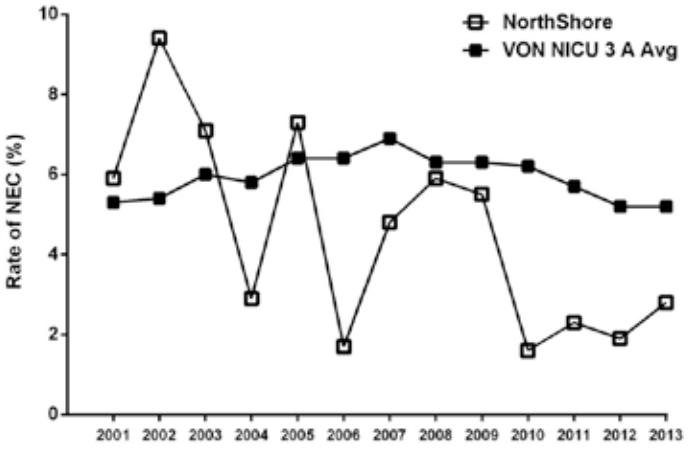
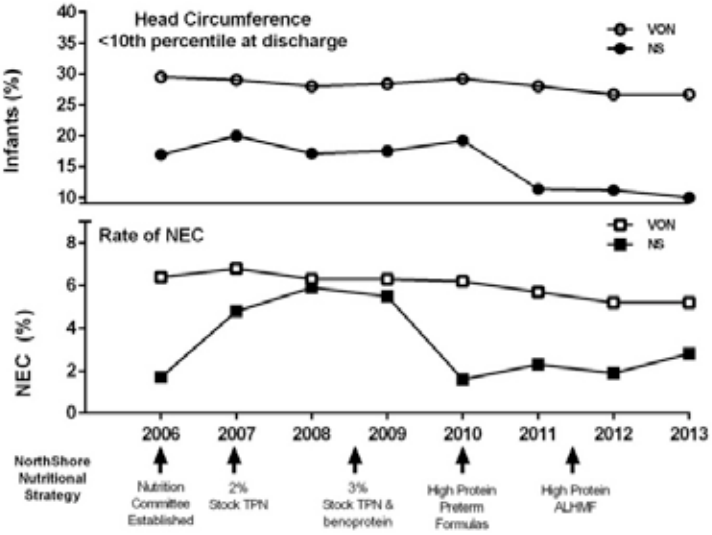


*NEC. *NEC is defined as having one of following clinical signs: bilious gastric aspirates or emesis, abdominal distention, or occult or gross blood in the stool (no fissure); and one of following radiographic findings: pneumatosis intestinalis,hepato-biliary gas, pnemoperitoneum.*

**NorthShore NEC data based on <1500 g population (avg. 130 patients/year).*



Head circumference.

Conclusion

It appears that all the recommended interventions lowered the incidence of extrauterine growth failure, and that higher protein-formula/fortifier, in particular, had the most pronounced effects. Moreover, higher protein was safe and well-tolerated.

Furthermore, it is clear that participation in the VON provides a means to benchmark NICU success. Continuing education about new products and practices that improve long-term outcomes is essential and the VON network supports this effort.

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Using VON as a Quality Improvement Tool to Improve Long-Term Outcomes in Your NICU

- The Vermont Oxford Network (VON) is a voluntary collaboration of health care professionals, dedicated to improving the quality and safety of medical care for babies.
- The Network maintains a database including information about the care and outcomes of high-risk newborn infants in member NICUs around the world.
- The database provides reliable and confidential data to participating units for use in quality management and process improvement within their institutions.
- VON members can be a part of their multidisciplinary improvement teams that work together to identify and implement better practices aimed at achieving measurable improvements in quality and safety.

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A Case Study: Persistent Right Pleural Effusion in a Preterm Infant

Christian Castillo, MD; V. Nanda, MD; A. Rastogi, MD; M. Kamat, MD; M. Akintorin, MD

Abstract

Chylothorax is an abnormal accumulation of lymphatic fluid in the pleural space, and the most common form of pleural effusion encountered in the prenatal and the neonatal period. It can be caused by anatomic malformations of the lymphatic vessels or damage to the thoracic duct. We report a case of a 27 weeks gestational age female infant who developed right-sided pleural effusion possibly after PDA ligation. This is contrary to the left-side pleural effusion that is well-known as a complication of PDA ligation. Management included continuous drainage with a pigtail catheter, intravenous nutrition, MCT-based formula and octreotide. After extensive work up, we were unable to identify an etiology. Regardless of the etiology and the location of chylothorax, conservative management is successful in most cases for resolution of chylothorax and should be initiated as early as possible.

Abbreviations

MCT: Medium Chain Triglycerides; PDA: Patent Ductus Arteriosus; NPO: Nothing by Mouth; TPN: Total Parenteral Nutrition; VSD: Ventricular Septal Defect; DOL: Day of Life; NICU: Neonatal Intensive Care Unit.

Introduction

Chylothorax is an abnormal accumulation of lymphatic fluid in the pleural space, and the most common form of pleural effusion encountered in the prenatal and neonatal period.[1-3] The incidence of congenital chylothorax is reported as 1/1000 - 1/15,000 pregnancies.[4] The chylothorax can be a complication of birth trauma or cardiothoracic surgery causing a tear, laceration or rupture of the thoracic duct.[5]. Other abnormalities that may cause chylothorax include anatomic malformations of the thoracic and pulmonary lymphatic vessel network, pleural or mediastinal malignancies, congenital lymphangiectasia, superior vena caval obstruction, pulmonary sequestration, and dysmorphic syndromes such as Turner Syndrome, Noonan Syndrome and Down Syndrome.[2,3,5,6] Infections such as congenital cytomegalovirus, adenovirus and group B Streptococcus have also been associated with chylothorax.[7] However, in a large number of cases the etiology of the chylothorax remains idiopathic. Although symptoms are variable depending on the location and amount of pleural effusion, most cases show evidence of some degree of respiratory difficulty, often requiring mechanical ventilation. Diagnosis is made by pleural fluid analysis with characteristically high triglycerides, presence of chylomicrons and lymphocyte predominance.[1,6,9,11] There are no current guidelines for optimal treatment, but most authors prefer a trial of conservative management with pleural fluid drainage, dietary modifications such as formula with medium chain triglycerides or total parenteral nutrition, and administration of octreotide.[3,5,6-10] If there is no decrease in the amount of chylothorax, or if a confirmed leak in the thoracic duct is too large to heal spontaneously, surgical intervention may be beneficial earlier in the course.

We conducted a literature review in PubMed of publications dating 1990 to 2013 with keywords “Chylothorax in preterm” and “Chylothorax in neonates”. In order to give a more through understanding of the topic, the search parameters did not have any geographic or institutional limitations. All existing data published to date worldwide was in the form of small case series or reviews based on those case series. Since no randomized controlled trials have been performed, there is insufficient evidence to establish management guidelines. Thus, most of the information regarding the management of the case came from the published case series.

Regardless of etiology, most cases of congenital chylothorax are bilateral, while those after PDA ligation are predominantly left-sided.[2,5,7,12] Our case is unique since the 27 week preterm infant had a persistent right-sided pleural effusion that was first noted after PDA ligation. This case study illustrates how to derive the correct diagnosis, and provides clinicians with management strategies in light of current literature.

The Case

A female infant was born at 27 weeks of gestation by emergency cesarean section secondary to placental abruption, oligohydramnios, and fetal distress. The mother was a 36-year-old gravida 4, para 3, who did not receive any prenatal care. She had past medical history of asthma, hypertension, and morbid obesity for which she was prescribed lisinopril and Proventil®. She discontinued lisinopril after the first trimester when she became aware of the pregnancy. Social history was significant for cigarette smoking and alcohol use throughout the pregnancy. Second trimester ultrasound was limited secondary to large pannus and showed breech position, oligohydramnios, and measurements consistent with 26 weeks gestation. The biophysical profile performed at the time was normal. Prenatal labs were significant for positive group B Streptococcus. Membranes ruptured at 26 weeks. The mother received a course of betamethasone prior to delivery. The infant had Apgar scores of 3, 6 and 7 at 1, 5 and 10 minutes respectively. Infant was intubated soon after birth and given a dose of surfactant (Survanta®) soon after birth. Infant was transferred to the NICU and placed on the ventilator. A CBC and a blood culture were taken and infant was started on ampicillin and gentamicin. Initial chest radiograph showed bilateral reticulogranular pattern with decreased lung volume and no effusion. Over the next 48 hours, she received two additional doses of surfactant for severe RDS. A head sonogram was negative for intraventricular hemorrhage. An echocardiogram done on second postnatal day revealed a moderate VSD with left-to-right shunting and no PDA. Due to a deteriorating respiratory status, the baby was switched to a high frequency oscillator ventilator.

Naso-gastric feeds were introduced on the 12th postnatal day. Multiple attempts to wean ventilator support and to advance feeds were unsuccessful. An echocardiogram done on the 14th postnatal day revealed a moderate to large PDA that did not respond to two courses of indomethacin. PDA was ligated surgically at four weeks of age. Nasogastric feeds were resumed after PDA ligation. Right-sided pleural effusion was noted on chest x-ray (Figure 1) approximately five weeks after PDA ligation.

Right-sided pleural effusion was confirmed by an ultrasound of the chest. The infant underwent ultrasound guided needle thoracotomy which drained 18 ml of milky fluid. A pigtail catheter was inserted for continuous drainage (Figure 2). The pleural fluid analysis showed RBC 4850/cu mm, WBC 5650/cu mm (100% lymphocytes), Glucose 124 mg/dl, protein 3 g/dl, LDH 383 IU, triglyceride 363 mg/dl. The pleural fluid analysis was compatible with a diagnosis of chylothorax. Current diagnostic criteria for chylothorax includes triglyceride levels > 110 mg/dL, presence of chylomicrons, cholesterol levels < 200mg/dL, and lymphocytes >70%.[6,10,13]

Based on current management published in literature, we had the option of keeping her NPO with TPN, switching to MCT formula or using octreotide.[10, 12, 14, 15] We initially decided to keep her NPO in view of a large pleural effusion and started her on TPN. Octreotide was administered initially at 60 µg three times daily for a period of two weeks without any improvement followed by continuous infusion at 2µg/kg/h. Five days later: respiratory status stabilized, pigtail had minimal output of 4ml, and bedside sonogram of right chest showed no pleural effusion. Octreotide was discontinued and pigtail was removed four days later. A repeat chest

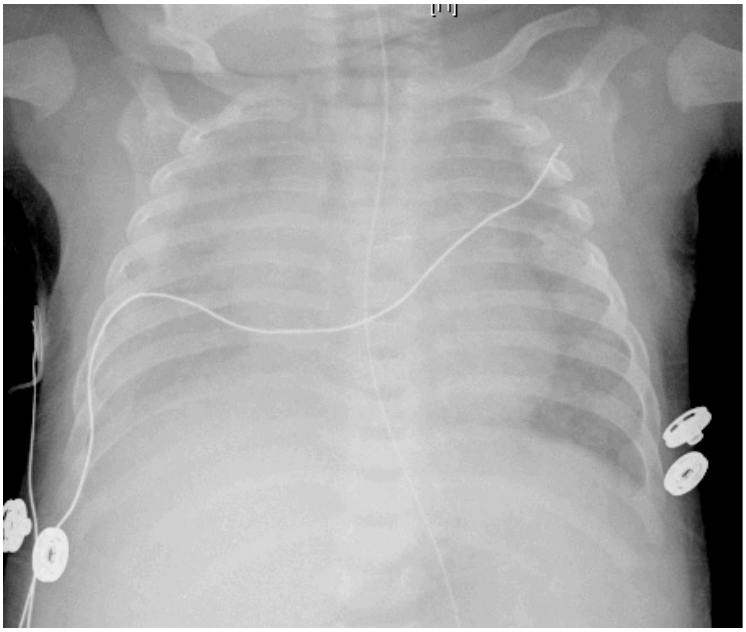

Figure 1. Right-sided pleural effusion seen after PDA ligation surgery.

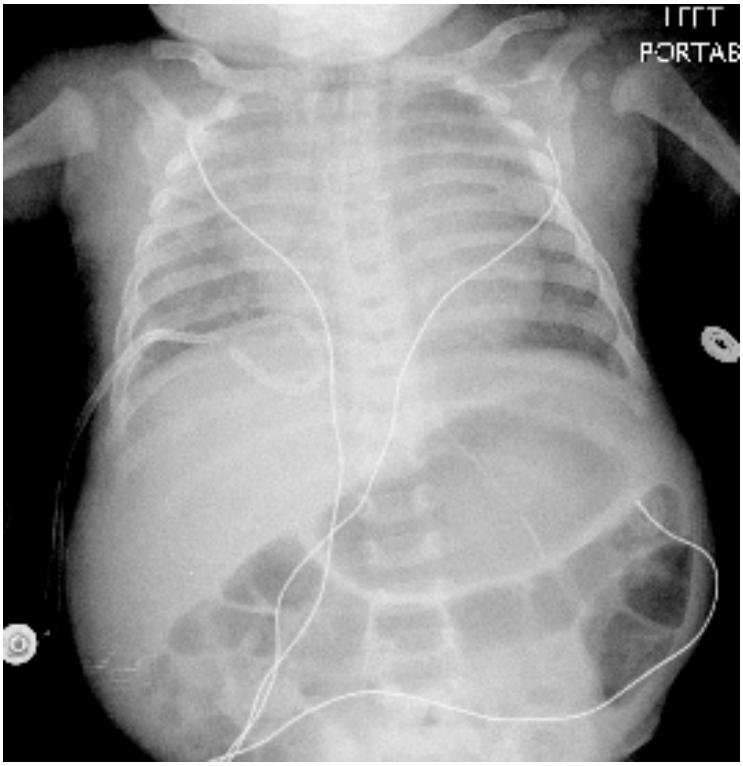

Figure 2. Shows improvement of the chylothorax after pig tail insertion.

X-ray four weeks later again showed right-sided pleural effusion. Octreotide infusion was restarted, and the infant was continued on MCT-based formula (Enfaport). Repeat chest X-ray showed improvement with subsequent resolution as confirmed by sonogram and CT scan of chest. Octreotide was discontinued.

The chylothorax did not recur and the baby was discharged home on Enfaport® formula. The infant was prescibed additional MCT oil at 4 ml three times daily to supplement calorie intake.

After extensive testing during the hospital stay of the patient, we were unable to identify the etiology of the chylothorax. Infant was a product of an atraumatic delivery via cesarean section; she had normal karyotype ruling out some of the most common etiologies of chylothorax. There was no blood group or Rh incompatibility and infant was Coomb's negative.

Discussion

Chylomicrons are complexes comprised of proteins and fats in the form of long chain fatty acids with more than 12 carbons.[6] This gives chyle a characteristic milky, opalescent appearance present in 50% of cases that can become clear or yellow with low fat diet or malnourishment.[12] Dietary fats absorbed by the enterocytes form chylomicrons, which are collected by the lacteals in the intestines and transported through the thoracic duct to enter venous circulation in the region of the left jugular and subclavian veins. The thoracic duct crosses to the left side of the mediastinum at the level of fifth thoracic vertebrae (T5). Any damage to the thoracic duct between the diaphragm and T5 results in a right-sided chylothorax, while damage above T5 results in left sided chylothorax.[6,13] Although our patient had a PDA ligation, she developed right-sided chylothorax, making this case unique.

Once a pleural effusion is identified on a chest X-ray or computed tomography, a needle thoracotomy with drainage of pleural fluid should be the first step, as it is diagnostic and can be therapeutic. Chyle is a sterile, bacteriostatic, alkaline fluid (pH 7.4-7.8) containing cholesterol, fats, electrolytes, proteins, glucose, and lymphocytes. Diagnosis is confirmed when pleural fluid analysis reveals triglyceride levels > 110mg/dL, presence of chylomicrons (confirmed with Sudan III stain), cholesterol levels <200mg/dL, and lymphocytes >70%.[6,10,13] A chest radiograph can also assess the size and location of the effusion. The lateral decubitus radiograph demonstrating free flowing fluid can help differentiate the effusion from empyema. Lymphangiography and lymphoscintigraphy are imaging modalities that can pinpoint the site of leakage or obstruction in the lymphatic vessels. Both require introduction of contrast agent into the lymphatic network while a radiograph or CT delineates the anatomy of the lymph vessel. Lymphangiography is more invasive since it requires cannulating a lymph vessel, a challenging task in an extremely preterm infant. Lymphangiography has low sensitivity in detecting thoracic duct leaks,[6] and can cause complications including infection, respiratory distress and damage to the lymphatics.

Clinical manifestations depend on the size and location of the effusion. A patient may initially be asymptomatic or have gradually worsening symptoms, such as: dyspnea, cough, chest discomfort, hemodynamic instability, and cardiorespiratory difficulties. Our extremely preterm infant had a large effusion that might have been one of the etio-pathogenic factors in causation of bronchopulmonary-dysplasia.

Since there are no randomized controlled trials for treatment of chylothorax, most of our knowledge comes from case series. Conservative management is preferred by most authors and consists of pleural fluid aspiration, administration of octreotide, MCT-based formula or total parenteral nutrition.[10,12,14,15] Pleural fluid drainage can be achieved with multiple thoracocentesis or chest tube insertion. Complications of tube thoracotomy include: increased risk of infection, lymphopenia, hypogammaglobulinemia, hypoproteinemia, and prolonged ventilator use with long-term chest tube insertion.[5,6,10] Monitoring chest tube drainage can help gauge the response to therapy. Dietary modifications with use of MCT-based formula has been shown to decrease production of chyle since medium chain triglycerides are absorbed directly into blood stream via the portal vein bypassing the intestinal lymphatics. No significant difference has been shown in the efficacy of MCT-based formula and TPN for the reduction of chylothorax.[16] Most authors prefer TPN followed by MCT-based formula once there is a reduction in the amount of pleural effusion.[17]

Octreotide is a synthetic analogue of somatostatin, an endogenous hormone with inhibitory effects on the gastrointestinal tract. Octreotide binds to somatostatin receptors to vasoconstrict the splanchnic blood vessels thereby inhibiting gastric, pancreatic and biliary secretions to reduce fat absorption and lymphatic flow through the thoracic duct.[5] Octreotide has a longer half-life than somatostatin and can be administered subcutaneously or as continuous infusion. Several studies have used an initial dose of 0.5 µg/kg/h that can be increased, to 10 µg/kg/h, if there is no reduction in lymphatic flow within 3 to 6 days.[5,6,10,19,20] Octreotide is considered relatively safe. Side effects are rare, and include: hyperglycemia, hypothyroidism, nausea, diarrhea, necrotizing enterocolitis, cramps, renal impairment and liver dysfunction.[5,6]

Most studies suggest a trial of conservative management for 2-3 weeks before proceeding to surgical intervention. If a large leak in the lymphatics is confirmed, then a surgical option could be considered. Surgical options used for management of chylothorax include: pleurodesis, pleuroperitoneal shunts, thoracic duct ligation, pleurectomy, and fluoroscopically-guided percutaneous transabdominal emobolization of thoracic duct with platinum coils.[3, 6, 15, 21]

In conclusion, our preterm patient had persistent right-sided chylothorax of unknown etiology; it was noted four weeks after PDA ligation surgery. Regardless of the etiology, the mainstay of treatment is conservative therapy that includes pleural fluid drainage, octreotide and TPN and/or MCT-based formula. The infant responded to continuous infusion of octreotide, and did not require surgical intervention. Our study is helpful to physicians as they can properly diagnose and initiate treatment early, while searching for an identifiable cause of the chylothorax. Unless the chylothorax is caused by a large anatomic defect, conservative management is successful in a majority of cases. The use of octreotide merits further investigation in a randomized control trial in the preterm population, to determine if there is a relationship between dosing and various etiologies of chylothorax. The mother had hypertension, asthma, and morbid obesity; she used nicotine and alcohol throughout the pregnancy. Could these have been risk factors for the development of a complicated clinical course with persistent pleural effusion? We did not investigate this in our current case study. However, it is a great avenue for future research to discover the causal relationship of such risk factors in the development of chylothorax in both preterm and term neonates.

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INDICATION

SURFAXIN® (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** and see accompanying brief summary on the next page.

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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

Administration of exogenous surfactants, including SURFAXIN, can rapidly affect lung compliance and oxygenation. SURFAXIN should be administered only by clinicians trained and experienced in the resuscitation, intubation, stabilization, and ventilatory management of premature infants in a clinical setting with the capacity to care for critically ill neonates. Infants receiving SURFAXIN should receive frequent clinical assessments so that oxygen and ventilatory support can be modified to respond to changes in respiratory status.

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 $FiO_2 \geq 0.30$) 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[a]

	Study 1[b]			Study 2[c]	
	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
	Total Number of Events (Events per 100 Doses)				
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)

[a] Table includes only infants who received study treatment.
[b] Study 1 doses were administered in 4 aliquots.
[c] 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.

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Medical News, Products & Information

By Tony Carlson, Senior Editor, CCT

Hospitals Not Always Prepared for Full Costs of implementing Electronic Patient Records

Hospitals don't always take into account the full costs of implementing new electronic health record systems and should be better prepared if they are to maximise the benefits, finds research published online in the *Journal of the American Medical Informatics Association* (JAMIA).

Electronic Health Record (EHR) systems can improve the safety, quality, and efficiency of healthcare in hospitals, and their adoption is a priority for the UK and US governments.

But despite their promise and the existence of EHRs in UK primary care for several decades, UK hospitals have been slow to adopt the technology, citing cost as a significant barrier, say the study authors.

As part of England's £12.7 billion (US$20 billion) National Programme for IT (NPfIT), three EHR systems were procured centrally: iSOFT's Lorenzo Regional Care; Cerner's Millennium; and CSE's RiO. But, their implementation has been fraught with difficulty.

And the English government announced the dismantlement of the programme in September 2011, after a Cabinet Office review concluded it was "not fit to provide the modern IT services that the NHS needs."

The researchers evaluated the implementation of the three systems in 12 diverse healthcare organisations, in three different regions of the country, and at different stages of implementing these systems.

They also carried out 41 semi-structured interviews with 36 hospital staff, members of the local implementation team, and those involved in the implementation at a national level, between February 2009 and January 2011.

They identified four overarching cost categories associated with implementing an EHR system: infrastructure (such as hardware and software); personnel (such as project managers and training teams); estates/facilities (furniture, fittings and space); other (such as training materials).

Many factors affected these costs, with different hospitals choosing varying amounts and types of infrastructure, diverse training approaches for staff, and different software applications.

Some of the hospitals incurred significant costs in testing the software while some spent a lot of money training clinicians and administrative staff to use the new system, using either one-to-one, classroom, or mass training sessions, or different combinations of each.
The decision to backfill staff on the wards varied among hospitals, with one hospital stumping up a one-off cost of £750,000 (over US$1.1 million) to provide cover for clinical staff who were being trained to use EHRs, while another spent no money at all on providing cover.

The analysis showed that, overall, implementation proceeded at a much slower pace than expected, with many challenges along the way.

Out of the four main categories of associated expenditure identified, hospitals were most likely to cut back on training and implementation costs.

Certain factors were systematically underappreciated in project planning, including the need to back fill staff due to lost productivity, and the need to test the system due to inadequate vendor testing.

"With cost considered one of the most significant barriers, it is important for hospitals and governments to be clear from the outset of the major cost categories involved and the factors that may impact on these costs," conclude the authors.

If organisations don't take these factors on board, they risk failure, the authors warn.

"Failure to adequately train staff or to follow key steps in implementation has preceded many of the failures in this domain, which can create new safety hazards," they say.

[A qualitative study identifying the cost categories associated with electronic health record implementation in the *UK Online First* doi:10.1136/amiajnl-2013-002404]

Children's Mercy Physician Leads Effort to Update AAP Policy to Improve Drug Safety and Efficacy in Children

With less than half of medications including specific labeling for children, Kathleen Neville, MD, MS, a physician at Children's Mercy Hospital, recently led an American Academy of Pediatrics (AAP) committee in updating the policy with new recommendations guiding the off-label use of drugs in pediatric patients. The policy statement, "Off-Label Use of Drugs in Children," was published online in the March 2014 issue of *Pediatrics.*

Dr. Neville is Chair of the AAP Committee on Drugs and Director of Experimental Therapeutics in Pediatric Cancer at Children's Mercy. The AAP statement offers guidance to physicians using drugs off-label in the treatment of children, particularly in special populations, including preterm infants and newborns, and those with chronic or rare diseases.

The policy statement updates guidance from nearly a decade ago that resulted in more than 500 labeling changes, including expanded labeling with pediatric information.

"Our goal is to provide children with the best care possible, and scientific evidence remains the best way to make treatment decisions," said Dr. Neville. "There's still much work to be done. Ultimately, all drugs used to treat children should have sufficient age-appropriate evidence to support updated labeling."

Children's Mercy has the largest and most productive pediatric clinical pharmacology program in North America. The program pairs clinicians who identify clinically significant medication-related problems with basic science faculty members who have the expertise necessary to solve them.

Under the direction of Dr. Neville, the Experimental Therapeutics in Pediatric Cancer Program is quickly gaining recognition as a regional referral center, giving children with recurrent or refractory cancer a local option to pursue experimental treatment with early-phase anticancer drugs. Neville has had extensive training in experimental therapeutics for children with cancer, and is leading Phase I research efforts to develop new agents for the treatment of pediatric cancer and supportive care for patients.

In collaboration with the Institute for Advancing Medical Innovation (AMI) and the National Institutes of Health (NIH), the team has begun screening compounds, identifying several that appear promising as potential drug development candidates. The program is currently involved in more than 15 Phase I and Phase II trials.

Study Shows that Premature Infants Benefit from Adult Talk

Research led by a team at Women & Infants Hospital of Rhode Island and The Warren Alpert Medical School of Brown University has been published in the February 10, 2014 online edition of *Pediatrics*, the official journal of the American Academy of Pediatrics. The research indicates that premature babies benefit from being exposed to adult talk as early as possible.

The research, entitled "Adult Talk in the NICU (Neonatal Intensive Care Unit) with Preterm Infants and Developmental Outcomes," was led by Betty Vohr, MD, Director of Women & Infants' Neonatal Follow-Up Program and Professor of Pediatrics, along with her colleagues Melinda Caskey, MD, neonatologist and Assistant Professor of Pediatrics; Bonnie Stephens, MD, neonatologist, developmental and behavioral pediatrician, and Assistant Professor of

Pediatrics; and Richard Tucker, BA, senior research data analyst.

The goal of the study was to test the association of the amount of talking that a baby was exposed to at what would have been 32 and 36 weeks gestation if a baby had been born full term, using the Bayley Scales of Infant and Toddler Development, 3rd Edition (Bayley – III) cognitive and language scores. It was hypothesized that preterm infants exposed to higher word counts would have higher cognitive and language scores at seven and 18 months corrected age.

"Our earlier study identified that extremely premature infants vocalize (make sounds) eight weeks before their mother's due date and vocalize more when their mothers are present in the NICU than when they are cared for by NICU staff," explained Dr. Vohr.

At 32 weeks and 36 weeks, staff recorded the NICU environment for 16 hours with a Language Environment Analysis (LENA) microprocessor. The adult word count, child vocalizations and "conversation turns" (words of mother or vocalizations of infant within five seconds) between mother and infant are recorded and analyzed by computer.

"The follow-up of these infants has revealed that the adult word count to which infants are exposed in the NICU at 32 and 36 weeks predicts their language and cognitive scores at 18 months. Every increase by 100 adult words per hour during the 32 week LENA recording was associated with a two-point increase in the language score at 18 months," said Dr. Vohr.

The results showed the hypothesis to be true. Dr. Vohr concluded, "Our study demonstrates the powerful impact of parents visiting and talking to their infants in the NICU on their developmental outcomes. Historically, very premature infants are at increased risk of language delay. The study now identifies an easy-to-implement and cost effective intervention – come talk and sing to your baby – to improve outcomes."

Prenatal Risk Factors May Put Children at Risk of Developing Kidney Disease

Certain prenatal risk factors are associated with the development of chronic kidney disease in children, according to a study appearing in an issue of the *Journal of the American Society of Nephrology* (JASN). Future studies should investigate whether modifying these factors could help protect children's kidney health.

Risks for certain types of kidney disease may arise before birth, and researchers suspect that the development of chronic kidney disease (CKD) may be programmed prenatally. Christine Hsu, MD (University of Washington) and her colleagues sought to determine the association of childhood CKD with prenatal risk factors, including: birth weight, maternal diabetes, and maternal overweight/obesity.

The researchers studied 1994 patients with childhood CKD and 20,032 controls without the disease, and the team linked maternal and infant characteristics in birth records from 1987 to 2008 to hospital discharge data.

The prevalence of CKD was 126.7 cases per 100,000 births. Infants with Low Birth Weight (LBW) were nearly three times more likely to develop childhood CKD than infants with normal birth weight. Infants were also at increased risk if their mothers developed diabetes during pregnancy or if their mothers were overweight or obese.

"We hope this research leads to further research on ways to reduce kidney disease through either early treatment or prevention that might begin even before birth," said Dr. Hsu. "Previous studies show that strict control of maternal diabetes significantly reduces the risk of congenital malformations in children. We hope our work leads to future studies to investigate whether strict control of maternal diabetes and/or reducing maternal obesity/overweight reduces childhood CKD."

Highlights

LBW and maternal conditions, including diabetes and overweight/obesity, are linked to the development of kidney disease in children.

Additional studies are needed to see if modifying these factors can reduce the incidence of kidney disease.

Study co-authors include: Kalani Yamamoto, MD, Rohan Henry, MD, Anneclaire De Roos, PhD, and Joseph Flynn, MD. The authors reported no financial disclosures.

The article, entitled "Prenatal Risk Factors for Childhood CKD," appeared online at http://jasn.asnjournals.org/ on April 17, 2014.

Study of Gut Microbes, Antibiotics: Clues to Improving Immunity in Premature Infants

CHOP researchers' animal study suggests that improving newborns' bacterial environment could fend off infections.

Mothers give a newborn baby a gift of germs—germs that help to kick-start the infant's immune system. But antibiotics used to fend off infection may paradoxically interrupt a newborn's own immune responses, leaving already vulnerable premature babies more susceptible to dangerous pathogens.

A new animal study by neonatology researchers at The Children's Hospital of Philadelphia (CHOP) sheds light on immunology in newborns by revealing how gut microbes play a crucial role in fostering the rapid production of infection-fighting white blood cells, called granulocytes.

"At birth, newborns move from a largely sterile environment to one full of microorganisms," said CHOP neonatology researcher Hitesh Deshmukh, MD, PhD, first author of the study published online in *Nature Medicine*. "Animals and humans adapt to this new situation by ramping up the production of granulocytes within the first days of life."

The current study, said senior author and CHOP neonatologist G. Scott Worthen, MD, suggests that exposure to the mother's microbes initiates the immunological transition. As in human babies, neonatal mice have a spike in white blood cells, but this response was reduced when their mothers had prenatal and postnatal exposure to antibiotics. This left the neonatal mice much more vulnerable to life-threatening sepsis caused by the bacterium E. coli K1, especially when they were born prematurely.

The study team showed that signaling mechanisms within the gut microbiome—the vast colony of microorganisms in the gastrointestinal tract—regulate the production of white blood cells in neonatal mice. Exposing both the mothers and neonatal mice to antibiotics reduced the diversity of gut bacteria, many of which are beneficial, and also impaired resistance to infection in the newborn animals, in comparison to control mice.

The researchers reversed these abnormal effects by taking normal intestinal microbes from mice that were not exposed to antibiotics and transferring them to mice that had received antibiotics. This improved the animals' resistance to E. coli infection.

When a similar procedure is performed in humans, it is called a fecal transplant, and has recently shown success in treating severe bacterial infections in adults. Such transplants have not been performed in human newborns, and the researchers caution that a great deal of work remains before they can determine what implications these animal results may have in guiding human treatment.

Because it is very difficult to determine whether critically ill newborns are infected with bacteria, these babies will continue to be treated with antibiotics, even as clinicians strive to decrease antibiotic use as a long-term goal. However, added Worthen, further investigation may reveal appropriate combinations of microbes that could be used to reconstitute infants' immune systems after they complete a course of antibiotics.

The National Institutes of Health supported this study (including grants HD060556, HL062052, HL079142, AA009803 and HL105834). In addition to his CHOP role, Worthen is on the faculty of the Perelman School of Medicine at the University of Pennsylvania. Another co-author, Jay K. Kolls, MD is from the University of Pittsburgh.

"The microbiota regulates neutrophil homeostasis and host resistance to Escherichia coli K1 sepsis in neonatal mice," *Nature Medicine*, published online April 20, 2014.
http://doi.org/10.1038/nm.3542.

Prenatal Nicotine Exposure May Lead to ADHD in Future Generations

Newswise - Prenatal exposure to nicotine could manifest as Attention Deficit Hyperactivity Disorder (ADHD) in children born a generation later, according to a new study by Florida State University College of Medicine researchers.

Professors Pradeep G. Bhide and Jinmin Zhu have found evidence that ADHD associated with nicotine can be passed across generations. In other words, your child's ADHD might be an environmentally-induced health condition inherited from your grandmother, who may have smoked cigarettes during pregnancy a long time ago. And the fact that you never smoked may be irrelevant for your child's ADHD.

The researchers' findings are published in a recent issue of *The Journal of Neuroscience.*

"What our research and other people's research is showing is that some of the changes in your genome — whether induced by drugs or by experience — may be permanent and you will transmit that to your offspring," said Bhide, Chair of Developmental Neuroscience and Director of the Center for Brain Repair at the College of Medicine.

Bhide and Zhu, Assistant Professor of Biomedical Sciences, used a mouse model to test the hypothesis that hyperactivity induced by prenatal nicotine exposure is transmitted from one generation to the next. Their data demonstrated that there is a transgenerational transmission via the maternal, but not the paternal, line of descent.

"Genes are constantly changing. Some are silenced and others are expressed, and that happens not only by hereditary mechanisms, but because of something in the environment or because of what we eat or what we see or what we hear," Bhide said. "So the genetic information that is transmitted to your offspring is qualitatively different than the information you got from your parents. This is how things change over time in the population."

Building on recent discoveries about how things like stress, fear or hormonal imbalance in one individual can be passed along to the next generation, Bhide and Zhu were curious about a proven link between prenatal nicotine exposure and hyperactivity in mice.

Their work at the Center for Brain Repair has included extensive research around ADHD, a neurobehavioral disorder affecting about 10% of children and 5% of adults in the United States. Researchers have struggled to produce a definitive scientific explanation for a spike in ADHD diagnoses in the last few decades.

"Some reports show up to a 40% increase in cases of ADHD — in one generation, basically," Bhide said. "It cannot be because a mutation occurred; it takes several generations for that to happen."

One possible contributing factor, though unproven, is that the current spike in ADHD cases correlates in some manner to an increase in the number of women who smoked during pregnancy as cigarettes became fashionable in the United States around the time of World War II and in the decades that followed.

"Other research has shown a very high correlation between heavy smoking during pregnancy and the incidence of kids with ADHD," Bhide said.

"What's important about our study is that we are seeing changes occurring in my grandparents' genome because of smoking during pregnancy are being passed to my child. So if my child had ADHD, it might not matter that I did not have a disposition or that I never smoked."

Bhide cautions that the work, though conclusive, is based on a study in mice, which have served as a proxy for human phenotypes.

"It's not that every child born to a mother who smokes has ADHD, and it also isn't true that every person with ADHD will transmit the genetic material responsible," he said.

"But our work has opened up new possibilities. The next question is how does transmission to future generations happen? What is the mechanism? And the second question is, if the individual is treated successfully would that stop the transmission to future generations?"

In addition to Zhu and Bhide, the paper's co-authors are Kevin P. Lee, a research assistant in the FSU College of Medicine, and Thomas J. Spencer and Joseph Biederman, both of the pediatric psychopharmacology unit of Massachusetts General Hospital and Harvard Medical School.

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