



# Neonatal Respiratory Diseases

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## Management of Blood Pressure in Mechanically Ventilated Infants

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**C**ritically ill infants who require intubation and mechanical ventilation and are admitted to newborn intensive care units (NICUs) often receive therapy aimed at cardiovascular support. Clinical trials with NICU infants often focus on blood pressure and

its symptomatic treatment. The focus of research has expanded recently to help clinicians better understand the underlying etiologies of low blood pressure in the ill, ventilated, newborn population, which may allow for directed therapy as opposed to symptomatic therapy.

The goal of maintaining cardiovascular stability in an ill newborn depends on adequate oxygen delivery to organs of the body, which is a function of both oxygen content and blood flow. Recently, bedside functional echocardiographic evaluation has given clinicians keener insight into hemodynamic changes and blood flow occurring in ill and acutely transitioning

newborn infants. However, blood flow measurement is not easily and rapidly attainable at the bedside in most NICUs. Doppler echocardiography remains in the hands of a limited number of specialists, leaving neonatal clinicians to rely on proxy measures, including blood pressure, to determine the treatment of a hemodynamically unstable ill newborn. Although blood pressure is not always proportionate to blood flow, it remains

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### What's Inside

News Briefs .....	10
Self Test.....	11

### UNM Children's Hospital of New Mexico

Affiliated with the University of New Mexico (UNM) Health Sciences Center, the UNM Children's Hospital of New Mexico is located in Albuquerque. The Division of Neonatology, Department of Pediatrics, at UNM encompasses an array of programs, including the Newborn Intensive Care Unit (NICU), two Intermediate Care Nurseries, Neonatal Transport Services, and Developmental Care and Neonatal Outreach Education.

The UNM NICU operates out of the new Bill and Barbara Richardson Pavilion, a 64-bed, state-of-the-art facility that opened in 2007. Caregivers in the NICU are academic neonatologists, neonatology fellows, neonatal nurse practitioners, physician assistants, and residents in pediatrics, as well as house officers in family practice and anesthesia. The NICU services admits more than 800 infants a year, some 20% of whom are transported to the facility from distant community hospitals throughout New Mexico and surrounding states.



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## 2 Neonatal Respiratory Diseases

one of the most commonly used measures to determine hemodynamic support in the ill NICU patient because it is readily available for use, can be fairly accurate, and can be monitored continuously for prolonged periods.

### Blood Pressure Measurement

Because blood pressure remains a standard measurement to determine the need for hemodynamic support, it is important to understand the technique of this measurement and its limitations. Accuracy of blood pressure measurements is important because overestimation of blood pressure may mean the risk of not indentifying poor blood flow to organs, while underestimation of blood pressure would mean introducing unnecessary treatment. In the NICU, blood pressure is measured by noninvasive oscillometry or by invasive intra-arterial catheter recordings.

Blood pressure measurement by oscillometry, first introduced in the mid 1970s, is used extensively in the NICU. The accuracy of oscillometry requires the use of the appropriate cuff size and measuring in the absence of struggling, crying and movement of the newborn.<sup>1</sup> There is no need for special positions, sleep state or a need to repeat and average many measurements.<sup>1</sup> There is no difference between different positions or between arm and calf blood pressures in the first few days of age.<sup>1,2</sup> Not all oscillometric devices are the same, as some measure blood pressure by deflation rates of every 3 mm Hg, others every 6 mm Hg, and these kinds of differences may affect accuracy.<sup>3</sup> When compared to invasive techniques, oscillometric devices may overestimate the mean blood pressure values.<sup>3</sup>

The invention of intra-arterial devices designed for neonates has opened the way for accurate, continuous, and accessible measurements of blood pressure. Both umbilical and peripheral arterial catheters are available to measure pressures in newborns and there is a high correlation of systolic and diastolic pressures.<sup>4</sup> It is important to reduce errors in measurement by recognizing when there are bubbles in the catheter system, kinking of the tubing, incorrect calibration, and incorrect positioning of the catheter. Some of these errors can be recognized by changes in the arterial wave patterns. Systolic and diastolic pressures can be very sensitive

to bubbles in the system and, because of the size of the catheters used in newborns, can create excessive damping and loss of higher frequencies.<sup>5</sup> This is one reason why mean blood pressures are more often relied on rather than diastolic or systolic pressures.

### Definition of Normal Blood Pressure

Once blood pressure measurements are obtained, the next step is to determine whether they are within normal range or in a range where treatment is indicated. Unfortunately, this remains one of the most difficult questions to answer because there is no clear consensus on what constitutes a pathologically low blood pressure in the ill, ventilated newborn infant. As described in a review by Dempsey and Barrington, studies used for normal reference values included populations that varied both between and within studies.<sup>6</sup> Normograms were created from measurements of blood pressure in cohorts of infants who were intubated, in those not intubated, in those on vasopressors, in those off vasopressors, and in infants of varying ages, with varying illnesses, and in those small for gestational age and appropriate for gestational age.<sup>7,8</sup> In addition, these studies describe blood pressure norms based on small numbers of patients, retrospectively collected data, and few data points. For these reasons, it has been difficult to discern normal blood pressure ranges for different populations of infants from existing cohort data. Despite this, surveys of neonatologists suggest that more than 25% rely on blood pressure values alone to determine therapeutic intervention and most use a mean blood pressure of less than gestational age in weeks as the cutoff that determines therapy.<sup>9</sup> Blood pressure alone may be inadequate to direct therapy, and other clinical measures such as metabolic acidosis, tachycardia, and oliguria may provide helpful clues to the adequacy of systemic blood flow.

### Consequences of Low Blood Pressure

A number of studies suggest that cardiovascular instability, particularly hypotension, increases the risk of end organ injury.<sup>10-13</sup> One study of 33 infants found an increase in intraventricular hemorrhage

(IVH) and periventricular leukomalacia in infants with mean blood pressures less than 30 mm Hg.<sup>10</sup> However, no study has confirmed a specific blood pressure threshold value below which there is evidence of worse outcomes. Dempsey and Barrington performed an extensive review of the literature to determine if there is a defined blood pressure threshold in preterm infants that accurately identifies those at risk for poor outcomes and found none.<sup>14</sup> No conclusions could be made from existing studies on the association of hypotension and/or its severity to adverse outcomes because of small numbers, retrospective designs, no corrections for other risk factors, variable low blood pressure definitions, and the inclusion of newborns who were already on inotropes.<sup>14</sup> There may be some population of particularly ill infants with low blood flow whose blood pressure predicts worse outcomes without treatment, but this group has yet to be defined. In addition, by the time inadequate systemic perfusion is reflected as arterial hypotension, damage may have already occurred.

Furthermore, it can be difficult to differentiate whether adverse outcomes result from low blood pressure or from the treatment for it. In one study of ventilated late-preterm newborns, an increased risk of adverse neurological events was found in infants treated with vasopressors (adjusted odds ratio=3.2, confidence interval [CI] 1.8-5.6,  $P<0.001$ ).<sup>15</sup> Another study from the Canadian Neonatal Network found infants who were not hypotensive, as defined by blood pressure below 10th percentile<sup>8</sup> and who received inotropes, were more likely to have a worse outcome of IVH (17.9%) than hypotensive patients who had not received inotropes (5.9%).<sup>6,16</sup> With this lack of information on the relationship of hypotension and its treatments, the clinician should approach hypotension carefully by using all available clinical measures of perfusion and organ blood flow before treating an arbitrary blood pressure.

### Effect of Mechanical Ventilation on Blood Pressure

In adults, ventilator modes and settings have been demonstrated to affect systemic hemodynamics, including ventricular end diastolic volume, left ventricle stroke volume, cardiac index,

**Table 1: Etiology of Hypotension and Shock**

<p><b>Adrenal Insufficiency</b></p> <p><b>Cardiogenic Shock</b></p> <ul style="list-style-type: none"> <li>• Abnormal regulation of peripheral vascular tone</li> <li>• Arrhythmias (tachycardia or bradycardia)</li> <li>• Cardiomyopathies             <ul style="list-style-type: none"> <li>- Myocardial infarction</li> <li>- Dilated cardiomyopathies</li> <li>- Myocarditis</li> <li>- Stunned myocardium after prolonged ischemia (eg, birth asphyxia)</li> <li>- Septic shock</li> </ul> </li> <li>• Mechanical abnormalities             <ul style="list-style-type: none"> <li>- Valvular defects (stenosis or regurgitant)</li> <li>- Aortic stenosis</li> <li>- Atrial myxomas</li> <li>- Ventricular septal defects</li> <li>- Hypoplastic left heart</li> <li>- Hypertrophic obstructive cardiomyopathy (eg, infant of diabetic mother)</li> <li>- Patent ductus arteriosus</li> </ul> </li> <li>• Pulmonary hypertension and resultant decreased left ventricular preload</li> </ul>	<p><b>Extra-cardiac mechanical obstruction</b></p> <ul style="list-style-type: none"> <li>• Mechanical ventilation</li> <li>• Pericardial tamponade</li> <li>• Superior vena cava syndrome</li> <li>• Tension pneumothorax</li> </ul> <p><b>Distributive Shock</b></p> <ul style="list-style-type: none"> <li>• Anaphylaxis</li> <li>• Capillary leak syndrome</li> <li>• Septic (bacterial, fungal, viral)</li> <li>• Thyroid storm</li> </ul> <p><b>Drug Induced</b></p> <ul style="list-style-type: none"> <li>• Barbiturates</li> <li>• Calcium channel blockers, digitalis</li> <li>• Magnesium sulfate</li> <li>• Sedatives</li> </ul> <p><b>Hypovolemic Shock</b></p> <ul style="list-style-type: none"> <li>• External: vomiting, diarrhea, gastric output, polyuria</li> <li>• Insensible losses in extremely preterm newborn</li> <li>• Insensible losses (eg, newborn with gastroschisis)</li> <li>• Hemorrhagic (eg, placental abruption at delivery)</li> </ul> <p><b>Neurogenic Shock</b></p> <ul style="list-style-type: none"> <li>• Acidemia</li> <li>• Central nervous system or spinal cord injury</li> <li>• Hypocalcemia</li> <li>• Maladaptation to transition after birth</li> </ul>
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arterial pressures (by 5 mm Hg) as a result of increased pulmonary vascular resistance and increased ventricular constraint. However, studies in human infants have shown similar mean arterial blood pressures during different modes of ventilation, including assist control (A/C), synchronized intermittent mandatory ventilation (SIMV), and intermittent mandatory ventilation (IMV), although fluctuations in blood pressure were reduced during A/C compared to SIMV, and in SIMV compared to IMV.<sup>21</sup>

Newer modes of ventilation, such as the airway pressure release ventilation mode (APVR), better accommodate the spontaneous breathing efforts of the patient. In a study of adult patients with acute respiratory distress syndrome, APVR improved hemodynamics and organ perfusion, compared to IMV.<sup>17</sup> There are no studies on this mode in newborn infants; however, this study demonstrates the need to continue to evaluate the impact of different ventilator modes and settings on hemodynamic stability in the newborn. When faced with a patient with refractory hypotension and inadequate systemic perfusion, the clinician may consider a brief trial of decreasing the mean airway pressure, monitoring the arterial blood pressure and systemic perfusion in response to this maneuver.

**Etiology and Management of Hypotension**

Before symptomatic therapy for hypotension and associated signs of low systemic flow is instituted, a systematic search for an etiology should be undertaken. In addition to compromise of cardiac output by excessive ventilator pressures, there are many possible reasons for mechanically ventilated newborn infants to be hypotensive (Table 1). Some of these mechanisms clearly lead to specific treatments, such as blood transfusion for hemorrhagic shock or indomethacin for a patent ductus arteriosus. An echocardiogram can be very helpful in evaluating function, filling, shunting, and structure. In time, perhaps hydrocortisone for relative adrenal insufficiency may join this list of specific therapies for known causes (see discussion of glucocorticoids).

Often, however, the clinician finds no obvious or specific cause of low blood pressure and associated signs of

and oxygen delivery.<sup>17,18</sup> In adults, higher positive end-expiratory pressure (PEEP) may optimize lung inflation and improve oxygenation, but it can also decrease cardiac output and possibly impair cerebral blood flow.<sup>18</sup> Much less information is available about the newborn. A recent study of a heterogeneous population of 50 term and preterm newborn infants in the first few hours of age found that a short increase in PEEP reduced right ventricular output but did not change blood pressure or lead to significant changes in systemic blood flow in most

of the infants.<sup>19</sup> To investigate the effect of PEEP on cardiopulmonary hemodynamics, Polglase et al compared measurements from indwelling flow probes with doppler echocardiography in preterm lambs ventilated at varying levels of PEEP.<sup>20</sup> Compared to lower PEEP levels, animals on a PEEP of 10 cm H<sub>2</sub>O had reduced left pulmonary artery flow, increased right-to-left shunting through the patent ductus arteriosus, and a trend towards increased oxygenation. Those ventilated with the higher PEEP also tended to have lower systolic

## 4 Neonatal Respiratory Diseases

inadequate perfusion in the critically ill newborn, and is faced with providing symptomatic treatment. From recent surveys, the stepwise approach most clinicians choose is a volume bolus followed by vasopressors/inotropes, and perhaps followed then by glucocorticoid therapy for hypotension unresponsive to the first two maneuvers.<sup>9</sup>

### Volume

There is evidence that most preterm infants who are hypotensive have normal circulating blood volumes.<sup>22</sup> In support of this, a recent Cochrane meta-analysis by Osborn and Evans found no evidence to support the routine use of early volume expansion in very preterm infants without cardiovascular compromise, and insufficient evidence of benefit for those with cardiovascular compromise.<sup>23</sup> Despite this information, most clinicians faced with uncertainty about blood volume in an ill newborn will give a trial of 10 mL/kg of normal saline and evaluate the clinical response.

### Inotropes

Although some groups have reported left ventricular dysfunction in ill, ventilated preterm infants with systemic hypotension,<sup>24</sup> many other studies have not documented this finding. However, in the face of uncertainty and without the immediate availability of echocardiography or doppler blood flow studies, inotropes are generally instituted if an infant does not respond to a volume bolus. Dopamine and dobutamine are the inotropes most commonly administered in the NICU, with epinephrine and vasopressin also used in some circumstances. Dopamine is a precursor to adrenaline and noradrenaline and has dopaminergic as well as both  $\alpha$  and  $\beta$  adrenergic effects, resulting in both peripheral vasoconstriction and positive inotropy. Dobutamine is a synthetic catecholamine with specific  $\beta$ -adrenergic effects, resulting in less vasoconstriction and more specific inotropic effect. Epinephrine, or adrenaline, is a nonselective  $\alpha$  and  $\beta$  adrenergic agonist, and produces significant peripheral vasoconstriction. Vasopressin, an antidiuretic hormone, is occasionally used for vasodilatory shock, again to provide peripheral vasoconstriction. A major concern with all these agents, with the possible exception

**Clinical trials of glucocorticoids for prophylaxis of hypotension in preterm infants have shown improved blood pressure**

of dobutamine, is that they may raise blood pressure but also impair cardiac output by increasing systemic vascular resistance.<sup>25</sup>

A recently published Cochrane review compared the effectiveness of dopamine versus dobutamine in reducing mortality and in improving short-term outcomes in hypotensive preterm infants.<sup>26</sup> Five trials were included and no significant difference was seen between the two inotropes in the incidence of mortality, periventricular leukomalacia, or severe periventricular hemorrhage. One study showed a greater increase in left ventricular output with dobutamine, compared to dopamine, but fewer infants receiving dopamine had treatment failure for hypotension. No long-term neurodevelopment outcome studies have been published to confirm safety or benefit of either inotrope. Epinephrine and vasopressin are used less often, and little information is available on which to base any recommendations.<sup>27</sup> The definition of hypotension varies among studies, leading to variability in the indications for initiation of inotropes. Dosing for dopamine or dobutamine is generally the same; these agents are administered by continuous intravenous infusion, usually initiated at 5  $\mu\text{g}/\text{kg}/\text{min}$ , with a stepwise increase to about 20–30  $\mu\text{g}/\text{kg}/\text{min}$  until hypotension resolves.<sup>9</sup> Epinephrine is generally started at 0.1  $\mu\text{g}/\text{kg}/\text{min}$  with stepwise increase to a maximum dose of about 1  $\mu\text{g}/\text{kg}/\text{min}$ .<sup>9</sup>

### Glucocorticoids

The use of glucocorticoids for treatment of hypotension in the newborn was first described in two abstracts from 1989 and 1991, in which ill preterm newborns presenting with hypotension, oliguria, and hyperkalemia had low cortisol values

and resolved their clinical abnormalities with hydrocortisone treatment.<sup>28,29</sup> Several subsequent studies in preterm infants supported the link between hypotension and low cortisol concentrations,<sup>30–32</sup> which may result from immature levels of enzymes available for cortisol synthesis.<sup>33</sup> Experimental support of relative adrenal insufficiency as a cause of hypotension is provided by well-controlled baboon studies by Yoder et al.<sup>34</sup> Urinary cortisol excretion, a measure of free cortisol, was determined in extremely preterm, intubated, and mechanically ventilated baboons. Baboons with vasopressor-resistant hypotension had significantly lower total cortisol excretion and worse cardiovascular function as measured by echocardiography. Furthermore, these baboons responded to hydrocortisone therapy with significant improvement in blood pressure, left ventricular function, and metabolic acidosis. In human infants, one recent study of 15 preterm and 5 term infants showed that hydrocortisone therapy increased blood pressure, stroke volume, and cardiac output without a change in cerebral or renal blood flow.<sup>25</sup>

Clinical trials of glucocorticoids for prophylaxis of hypotension in preterm infants have shown improved blood pressure and reduced need for vasopressors.<sup>35–38</sup> The few randomized, controlled trials of glucocorticoid therapy to treat hypotension in preterm infants have shown improved blood pressure, decreased administration of vasopressors, decreased days on vasopressors and decreased use of volume compared to placebo.<sup>39,40</sup>

There is much less information available on the incidence and consequences of adrenal insufficiency in term newborn infants. Critically ill term infants may be at a unique risk for adrenal insufficiency compared to pediatric and adult patients because of the transition the hypothalamic-pituitary-adrenal axis has to go through as the corticotrophin-releasing hormone (CRH) produced by the placenta is withdrawn, leaving newborns to produce their own CRH in response to acute stress.<sup>41</sup> Studies in term infants are small and few but have shown a high prevalence of low cortisol values in infants with acute illness and hypotension.<sup>42–45</sup> One recent prospective study found that 26 of 35 (74%) critically ill, intubated infants had cortisol values  $<15 \mu\text{g}/\text{dL}$ , a value that is



An established record of safety and efficacy.



SURVANTA is indicated for prevention and treatment (“rescue”) of Respiratory Distress Syndrome (RDS) (hyaline membrane disease) in premature infants. SURVANTA significantly reduces the incidence of RDS, mortality due to RDS and air leak complications.

- Efficacy for prevention and treatment of RDS in premature infants
- Since being introduced in 1991, over 800,000 infants have been treated with Survanta with over 1 million doses administered.\*



**SURVANTA<sup>®</sup>**  
(beractant) **Rx only**  
intratracheal suspension  
bovine pulmonary surfactant

*Important Safety Information about Survanta<sup>®</sup> (beractant) | SURVANTA is intended for intratracheal use only. See prescribing and safety information on the following page.*

**SURVANTA CAN RAPIDLY AFFECT OXYGENATION AND LUNG COMPLIANCE.** Therefore, its use should be restricted to a highly supervised clinical setting with immediate availability of clinicians experienced with intubation, ventilator management, and general care of premature infants. Infants receiving SURVANTA should be frequently monitored with arterial or transcutaneous measurement of systemic oxygen and carbon dioxide.

**DURING THE DOSING PROCEDURE, TRANSIENT EPISODES OF BRADYCARDIA AND DECREASED OXYGEN SATURATION HAVE BEEN REPORTED.** If these occur, stop the dosing procedure and initiate appropriate measure to alleviate the condition. After stabilization, resume the dosing procedure.

\*IMS DDD Lung Surfactant Market Purchases July 1991 through January 2009.  
On file, Abbott Nutrition Marketing Research.

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(No. 1040) March, 2009

# SURVANTA®

(beractant)  only  
intratracheal suspension



**SURVANTA®** (No. 1040) March, 2009  
(beractant)  
intratracheal suspension

Sterile Suspension  
For Intratracheal Administration Only

**DESCRIPTION**

SURVANTA® (beractant) Intratracheal Suspension is a sterile, non-pyrogenic pulmonary surfactant intended for intratracheal use only. It is a natural bovine lung extract containing phospholipids, neutral lipids, fatty acids, and surfactant-associated proteins to which colfosceril palmitate (dipalmitoylphosphatidylcholine), palmitic acid, and tripalmitin are added to standardize the composition and to mimic surface-tension lowering properties of natural lung surfactant. The resulting composition provides 25 mg/mL phospholipids (including 11.0-15.5 mg/mL disaturated phosphatidylcholine), 0.5-1.75 mg/mL triglycerides, 1.4-3.5 mg/mL free fatty acids, and less than 1.0 mg/mL protein. It is suspended in 0.9% sodium chloride solution, and heat-sterilized. SURVANTA contains no preservatives. Its protein content consists of two hydrophobic, low molecular weight, surfactant-associated proteins commonly known as SP-B and SP-C. It does not contain the hydrophilic, large molecular weight surfactant-associated protein known as SP-A. Each mL of SURVANTA contains 25 mg of phospholipids. It is an off-white to light brown liquid supplied in single-use glass vials containing 4 mL (100 mg phospholipids) or 8 mL (200 mg phospholipids).

**CLINICAL PHARMACOLOGY**

Endogenous pulmonary surfactant lowers surface tension on alveolar surfaces during respiration and stabilizes the alveoli against collapse at resting transpulmonary pressures. Deficiency of pulmonary surfactant causes Respiratory Distress Syndrome (RDS) in premature infants. SURVANTA replenishes surfactant and restores surface activity to the lungs of these infants.

**Activity**

*In vitro*, SURVANTA reproducibly lowers minimum surface tension to less than 8 dynes/cm as measured by the pulsating bubble surfactometer and Wilhelmy Surface Balance. *In situ*, SURVANTA restores pulmonary compliance to excised rat lungs artificially made surfactant-deficient. *In vivo*, single SURVANTA doses improve lung pressure-volume measurements, lung compliance, and oxygenation in premature rabbits and sheep.

**Animal Metabolism**

SURVANTA is administered directly to the target organ, the lungs, where biophysical effects occur at the alveolar surface. In surfactant-deficient premature rabbits and lambs, alveolar clearance of radio-labelled lipid components of SURVANTA is rapid. Most of the dose becomes lung-associated within hours of administration, and the lipids enter endogenous surfactant pathways of reutilization and recycling. In surfactant-sufficient adult animals, SURVANTA clearance is more rapid than in premature and young animals. There is less reutilization and recycling of surfactant in adult animals.

Limited animal experiments have not found effects of SURVANTA on endogenous surfactant metabolism. Precursor incorporation and subsequent secretion of saturated phosphatidylcholine in premature sheep are not changed by SURVANTA treatments.

No information is available about the metabolic fate of the surfactant-associated proteins in SURVANTA. The metabolic disposition in humans has not been studied.

**CLINICAL STUDIES**

Clinical effects of SURVANTA were demonstrated in six single-dose and four multiple-dose randomized, multi-center, controlled clinical trials involving approximately 1700 infants. Three open trials, including a Treatment IND, involved more than 8500 infants. Each dose of SURVANTA in all studies was 100 mg phospholipids/kg birth weight and was based on published experience with Surfactant TA, a lyophilized powder dosage form of SURVANTA having the same composition.

**Prevention Studies**

Infants of 600-1250 g birth weight and 23 to 29 weeks estimated gestational age were enrolled in two multiple-dose studies. A dose of SURVANTA was given within 15 minutes of birth to prevent the development of RDS. Up to three additional doses in the first 48 hours, as often as every 6 hours, were given if RDS subsequently developed and infants required mechanical ventilation with an  $FI_{O_2} \geq 0.30$ . Results of the studies at 28 days of age are shown in Table 1.

TABLE 1

Study 1	TABLE 1		
	SURVANTA	Control	P-Value
Number infants studied	119	124	
Incidence of RDS (%)	27.6	63.5	<0.001
Death due to RDS (%)	2.5	19.5	<0.001
Death or BPD due to RDS (%)	48.7	52.8	0.536
Death due to any cause (%)	7.6	22.8	0.001
Air Leaks <sup>a</sup> (%)	5.9	21.7	0.001
Pulmonary interstitial emphysema (%)	20.8	40.0	0.001

  

Study 2 <sup>b</sup>	TABLE 1		
	SURVANTA	Control	P-Value
Number infants studied	91	96	
Incidence of RDS (%)	28.6	48.3	0.007
Death due to RDS (%)	1.1	10.5	0.006
Death or BPD due to RDS (%)	27.5	44.2	0.018
Death due to any cause <sup>c</sup> (%)	16.5	13.7	0.633
Air Leaks <sup>a</sup> (%)	14.5	19.6	0.374
Pulmonary interstitial emphysema (%)	26.5	33.2	0.298

<sup>a</sup> Pneumothorax or pneumopericardium

<sup>b</sup> Study discontinued when Treatment IND initiated

<sup>c</sup> No cause of death in the SURVANTA group was significantly increased; the higher number of deaths in this group was due to the sum of all causes.

**Rescue Studies**

Infants of 600-1750 g birth weight with RDS requiring mechanical ventilation and an  $FI_{O_2} \geq 0.40$  were enrolled in two multiple-dose rescue studies. The initial dose of SURVANTA was given after RDS developed and before 6 hours of age. Infants could receive up to three additional doses in the first 48 hours, as often as every 6 hours, if they required mechanical ventilation and an  $FI_{O_2} \geq 0.30$ . Results of the studies at 28 days of age are shown in Table 2.

TABLE 2

Study 3 <sup>a</sup>	TABLE 2		
	SURVANTA	Control	P-Value
Number infants studied	198	193	
Death due to RDS (%)	11.6	18.1	0.071
Death or BPD due to RDS (%)	59.1	66.8	0.102
Death due to any cause (%)	21.7	26.4	0.285
Air Leaks <sup>a</sup> (%)	11.8	29.5	<0.001
Pulmonary interstitial emphysema (%)	16.3	34.0	<0.001

  

Study 4	TABLE 2		
	SURVANTA	Control	P-Value
Number infants studied	204	203	
Death due to RDS (%)	6.4	22.3	<0.001
Death or BPD due to RDS (%)	43.6	63.4	<0.001
Death due to any cause (%)	15.2	28.2	0.001
Air Leaks <sup>a</sup> (%)	11.2	22.2	0.005
Pulmonary interstitial emphysema (%)	20.8	44.4	<0.001

<sup>a</sup> Study discontinued when Treatment IND initiated

<sup>b</sup> Pneumothorax or pneumopericardium

**Acute Clinical Effects**

Marked improvements in oxygenation may occur within minutes of administration of SURVANTA.

All controlled clinical studies with SURVANTA provided information regarding the acute effects of SURVANTA on the arterial-alveolar oxygen ratio ( $a/APO_2$ ),  $FI_{O_2}$ , and mean airway pressure (MAF) during the first 48 to 72 hours of life. Significant improvements in these variables were sustained for 48-72 hours in SURVANTA-treated infants in four single-dose and two multiple-dose rescue studies and in two multiple-dose prevention studies. In the single-dose prevention studies, the  $FI_{O_2}$  improved significantly.

**INDICATIONS AND USAGE**

SURVANTA is indicated for prevention and treatment ("rescue") of Respiratory Distress Syndrome (RDS) (hyaline membrane disease) in premature infants. SURVANTA significantly reduces the incidence of RDS, mortality due to RDS and air leak complications.

**Prevention**

In premature infants less than 1250 g birth weight or with evidence of surfactant deficiency, give SURVANTA as soon as possible, preferably within 15 minutes of birth.

**Rescue**

To treat infants with RDS confirmed by x-ray and requiring mechanical ventilation, give SURVANTA as soon as possible, preferably by 8 hours of age.

**CONTRAINDICATIONS**

None known.

**WARNINGS**

SURVANTA is intended for intratracheal use only.

SURVANTA CAN RAPIDLY AFFECT OXYGENATION AND LUNG COMPLIANCE. Therefore, its use should be restricted to a highly supervised clinical setting with immediate availability of clinicians experienced with intubation, ventilator management, and general care of premature infants. Infants receiving SURVANTA should be frequently monitored with arterial or transcutaneous measurement of systemic oxygen and carbon dioxide.

DURING THE DOSING PROCEDURE, TRANSIENT EPISODES OF BRADYCARDIA AND DECREASED OXYGEN SATURATION HAVE BEEN REPORTED. If these occur, stop the dosing procedure and initiate appropriate measures to alleviate the condition. After stabilization, resume the dosing procedure.

**PRECAUTIONS****General**

Rales and moist breath sounds can occur transiently after administration. Endotracheal suctioning or other remedial action is not necessary unless clear-cut signs of airway obstruction are present.

Increased probability of post-treatment nosocomial sepsis in SURVANTA-treated infants was observed in the controlled clinical trials (Table 3). The increased risk for sepsis among SURVANTA-treated infants was not associated with increased mortality among these infants. The causative organisms were similar in treated and control infants. There was no significant difference between groups in the rate of post-treatment infections other than sepsis.

Use of SURVANTA in infants less than 600 g birth weight or greater than 1750 g birth weight has not been evaluated in controlled trials. There is no controlled experience with use of SURVANTA in conjunction with experimental therapies for RDS (eg, high-frequency ventilation or extracorporeal membrane oxygenation).

No information is available on the effects of doses other than 100 mg phospholipids/kg, more than four doses, dosing more frequently than every 6 hours, or administration after 48 hours of age.

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

Carcinogenicity studies have not been performed with SURVANTA. SURVANTA was negative when tested in the Ames test for mutagenicity. Using the maximum feasible dose volume, SURVANTA up to 500 mg phospholipids/kg/day (approximately one-third the premature infant dose based on mg/m<sup>2</sup>/day) was administered subcutaneously to newborn rats for 5 days. The rats reproduced normally and there were no observable adverse effects in their offspring.

**ADVERSE REACTIONS**

The most commonly reported adverse experiences were associated with the dosing procedure. In the multiple-dose controlled clinical trials, each dose of SURVANTA was divided into four quarter-doses which were instilled through a catheter inserted into the endotracheal tube by briefly disconnecting the endotracheal tube from the ventilator. Transient bradycardia occurred with 11.9% of doses. Oxygen desaturation occurred with 9.8% of doses.

Other reactions during the dosing procedure occurred with fewer than 1% of doses and included endotracheal tube reflux, pallor, vasoconstriction, hypotension, endotracheal tube blockage, hypertension, hypocarbia, hypercarbia, and apnea. No deaths occurred during the dosing procedure, and all reactions resolved with symptomatic treatment.

The occurrence of concurrent illnesses common in premature infants was evaluated in the controlled trials. The rates in all controlled studies are in Table 3.

TABLE 3

Concurrent Event	All Controlled Studies		
	SURVANTA (%)	Control (%)	P-Value <sup>a</sup>
Patent ductus arteriosus	46.9	47.1	0.814
Intracranial hemorrhage	48.1	45.2	0.241
Severe intracranial hemorrhage	24.1	23.3	0.693
Pulmonary air leaks	10.9	24.7	<0.001
Pulmonary interstitial emphysema	20.2	38.4	<0.001
Necrotizing enterocolitis	6.1	5.3	0.427
Apnea	65.4	59.6	0.283
Severe apnea	46.1	42.5	0.114
Post-treatment sepsis	20.7	16.1	0.019
Post-treatment infection	10.2	9.1	0.345
Pulmonary hemorrhage	7.2	5.3	0.166

<sup>a</sup> P-value comparing groups in controlled studies

When all controlled studies were pooled, there was no difference in intracranial hemorrhage. However, in one of the single-dose rescue studies and one of the multiple-dose prevention studies, the rate of intracranial hemorrhage was significantly higher in SURVANTA patients than control patients (63.3% v 30.8%,  $P = 0.001$ ; and 48.8% v 34.2%,  $P = 0.047$ , respectively). The rate in a Treatment IND involving approximately 8100 infants was lower than in the controlled trials.

In the controlled clinical trials, there was no effect of SURVANTA on results of common laboratory tests: white blood cell count and serum sodium, potassium, bilirubin, creatinine.

More than 4300 pretreatment and post-treatment serum samples from approximately 1500 patients were tested by Western Blot Immunoassay for antibodies to surfactant-associated proteins SP-B and SP-C. No IgG or IgM antibodies were detected.

Several other complications are known to occur in premature infants. The following conditions were reported in the controlled clinical studies. The rates of the complications were not different in treated and control infants, and none of the complications were attributed to SURVANTA.

**Respiratory:** lung consolidation, blood from the endotracheal tube, deterioration after weaning, respiratory decompensation, subglottic stenosis, paralyzed diaphragm, respiratory failure.

**Cardiovascular:** hypotension, hypertension, tachycardia, ventricular tachycardia, aortic thrombosis, cardiac failure, cardio-respiratory arrest, increased apical pulse, persistent fetal circulation, air embolism, total anomalous pulmonary venous return.

**Gastrointestinal:** abdominal distention, hemorrhage, intestinal perforations, volvulus, bowel infarct, feeding intolerance, hepatic failure, stress ulcer.

**Renal:** renal failure, hematuria.

**Hematologic:** coagulopathy, thrombocytopenia, disseminated intravascular coagulation.

**Central Nervous System:** seizures.

**Endocrine/Metabolic:** adrenal hemorrhage, inappropriate ADH secretion, hyperphosphatemia.

**Musculoskeletal:** inguinal hernia.

**Systemic:** fever, deterioration.

### Follow-Up Evaluations

To date, no long-term complications or sequelae of SURVANTA therapy have been found.

### Single-Dose Studies

Six-month adjusted-age follow-up evaluations of 232 infants (115 treated) demonstrated no clinically important differences between treatment groups in pulmonary and neurologic sequelae, incidence or severity of retinopathy of prematurity, rehospitalizations, growth, or allergic manifestations.

### Multiple-Dose Studies

Six-month adjusted age follow-up evaluations have been completed in 631 (345 treated) of 916 surviving infants. There were significantly less cerebral palsy and need for supplemental oxygen in SURVANTA infants than controls. Wheezing at the time of examination was significantly more frequent among SURVANTA infants, although there was no difference in bronchodilator therapy.

Final twelve-month follow-up data from the multiple-dose studies are available from 521 (272 treated) of 909 surviving infants. There was significantly less wheezing in SURVANTA infants than controls, in contrast to the six-month results. There was no difference in the incidence of cerebral palsy at twelve months.

Twenty-four month adjusted age evaluations were completed in 429 (226 treated) of 906 surviving infants. There were significantly fewer SURVANTA infants with rhonchi, wheezing, and tachypnea at the time of examination. No other differences were found.

### OVERDOSAGE

Overdosage with SURVANTA has not been reported. Based on animal data, overdosage might result in acute airway obstruction. Treatment should be symptomatic and supportive.

Rales and moist breath sounds can transiently occur after SURVANTA is given, and do not indicate overdosage. Endotracheal suctioning or other remedial action is not required unless clear-cut signs of airway obstruction are present.

### DOSSAGE AND ADMINISTRATION

For intratracheal administration only.

SURVANTA should be administered by or under the supervision of clinicians experienced in intubation, ventilator management, and general care of premature infants.

Marked improvements in oxygenation may occur within minutes of administration of SURVANTA. Therefore, frequent and careful clinical observation and monitoring of systemic oxygenation are essential to avoid hyperoxia.

Review of audiovisual instructional materials describing dosage and administration procedures is recommended before using SURVANTA. Materials are available upon request from Abbott Nutrition.

### Dosage

Each dose of SURVANTA is 100 mg of phospholipids/kg birth weight (4 mL/kg). The SURVANTA Dosing Chart shows the total dosage for a range of birth weights.

**SURVANTA DOSING CHART**

WEIGHT (grams)	TOTAL DOSE (mL)	WEIGHT (grams)	TOTAL DOSE (mL)
600-650	2.6	1301-1350	5.4
651-700	2.8	1351-1400	5.6
701-750	3.0	1401-1450	5.8
751-800	3.2	1451-1500	6.0
801-850	3.4	1501-1550	6.2
851-900	3.6	1551-1600	6.4
901-950	3.8	1601-1650	6.6
951-1000	4.0	1651-1700	6.8
1001-1050	4.2	1701-1750	7.0
1051-1100	4.4	1751-1800	7.2
1101-1150	4.6	1801-1850	7.4
1151-1200	4.8	1851-1900	7.6
1201-1250	5.0	1901-1950	7.8
1251-1300	5.2	1951-2000	8.0

Four doses of SURVANTA can be administered in the first 48 hours of life. Doses should be given no more frequently than every 6 hours.

### Directions for Use

SURVANTA should be inspected visually for discoloration prior to administration. The color of SURVANTA is off-white to light brown. If settling occurs during storage, swirl the vial gently (DO NOT SHAKE) to redisperse. Some foaming at the surface may occur during handling and is inherent in the nature of the product.

SURVANTA is stored refrigerated (2-8°C). Date and time need to be recorded in the box on front of the carton or vial, whenever SURVANTA is removed from the refrigerator. Before administration, SURVANTA should be warmed by standing at room temperature for at least 20 minutes or warmed in the hand for at least 8 minutes. ARTIFICIAL WARMING METHODS SHOULD NOT BE USED. If a prevention dose is to be given, preparation of SURVANTA should begin before the infant's birth.

Unopened, unused vials of SURVANTA that have been warmed to room temperature may be returned to the refrigerator within 24 hours of warming, and

stored for future use. SURVANTA SHOULD NOT BE REMOVED FROM THE REFRIGERATOR FOR MORE THAN 24 HOURS. SURVANTA SHOULD NOT BE WARMED AND RETURNED TO THE REFRIGERATOR MORE THAN ONCE. Each single-use vial of SURVANTA should be entered only once. Used vials with residual drug should be discarded.

SURVANTA DOES NOT REQUIRE RECONSTITUTION OR SONICATION BEFORE USE.

### Dosing Procedures

#### General

SURVANTA is administered intratracheally by instillation through a 5 French end-hole catheter. The catheter can be inserted into the infant's endotracheal tube without interrupting ventilation by passing the catheter through a neonatal suction valve attached to the endotracheal tube. Alternatively, SURVANTA can be instilled through the catheter by briefly disconnecting the endotracheal tube from the ventilator.

The neonatal suction valve used for administering SURVANTA should be a type that allows entry of the catheter into the endotracheal tube without interrupting ventilation and also maintains a closed airway circuit system by sealing the valve around the catheter.

If the neonatal suction valve is used, the catheter should be rigid enough to pass easily into the endotracheal tube. A very soft and pliable catheter may twist or curl within the neonatal suction valve. The length of the catheter should be shortened so that the tip of the catheter protrudes just beyond the end of the endotracheal tube above the infant's carina. SURVANTA should not be instilled into a mainstem bronchus.

To ensure homogenous distribution of SURVANTA throughout the lungs, each dose is divided into four quarter-doses.

Each quarter-dose is administered with the infant in a different position. The recommended positions are:

- Head and body inclined 5-10° down, head turned to the right
- Head and body inclined 5-10° down, head turned to the left
- Head and body inclined 5-10° up, head turned to the right
- Head and body inclined 5-10° up, head turned to the left

The dosing procedure is facilitated if one person administers the dose while another person positions and monitors the infant.

#### First Dose

Determine the total dose of SURVANTA from the SURVANTA dosing chart based on the infant's birth weight. Slowly withdraw the entire contents of the vial into a plastic syringe through a large-gauge needle (eg, at least 20 gauge). DO NOT FILTER SURVANTA AND AVOID SHAKING.

Attach the premeasured 5 French end-hole catheter to the syringe. Fill the catheter with SURVANTA. Discard excess SURVANTA through the catheter so that only the total dose to be given remains in the syringe.

BEFORE ADMINISTERING SURVANTA, assure proper placement and patency of the endotracheal tube. At the discretion of the clinician, the endotracheal tube may be suctioned before administering SURVANTA. The infant should be allowed to stabilize before proceeding with dosing.

In the prevention strategy, weigh, intubate and stabilize the infant. Administer the dose as soon as possible after birth, preferably within 15 minutes. Position the infant appropriately and gently inject the first quarter-dose through the catheter over 2-3 seconds.

After administration of the first quarter-dose, remove the catheter from the endotracheal tube. Manually ventilate with a hand-bag with sufficient oxygen to prevent cyanosis, at a rate of 60 breaths/minute, and sufficient positive pressure to provide adequate air exchange and chest wall excursion.

In the rescue strategy, the first dose should be given as soon as possible after the infant is placed on a ventilator for management of RDS. In the clinical trials, immediately before instilling the first quarter-dose, the infant's ventilator settings were changed to rate 60/minute, inspiratory time 0.5 second, and  $FI_{O_2}$  1.0.

Position the infant appropriately and gently inject the first quarter-dose through the catheter over 2-3 seconds. After administration of the first quarter-dose, remove the catheter from the endotracheal tube and continue mechanical ventilation.

In both strategies, ventilate the infant for at least 30 seconds or until stable. Reposition the infant for instillation of the next quarter-dose.

Instill the remaining quarter-doses using the same procedures. After instillation of each quarter-dose, remove the catheter and ventilate for at least 30 seconds or until the infant is stabilized. After instillation of the final quarter-dose, remove the catheter without flushing it. Do not suction the infant for 1 hour after dosing unless signs of significant airway obstruction occur.

AFTER COMPLETION OF THE DOSING PROCEDURE, RESUME USUAL VENTILATOR MANAGEMENT AND CLINICAL CARE.

#### Repeat Doses

The dosage of SURVANTA for repeat doses is also 100 mg phospholipids/kg and is based on the infant's birth weight. The infant should not be reweighed for determination of the SURVANTA dosage. Use the SURVANTA DOSING CHART to determine the total dosage.

The need for additional doses of SURVANTA is determined by evidence of continuing respiratory distress. Using the following criteria for redosing, significant reductions in mortality due to RDS were observed in the multiple-dose clinical trials with SURVANTA.

Dose no sooner than 6 hours after the preceding dose if the infant remains intubated and requires at least 30% inspired oxygen to maintain a  $PaO_2$  less than or equal to 80 torr.

Radiographic confirmation of RDS should be obtained before administering additional doses to those who received a prevention dose.

Prepare SURVANTA and position the infant for administration of each quarter-dose as previously described. After instillation of each quarter-dose, remove the dosing catheter from the endotracheal tube and ventilate the infant for at least 30 seconds or until stable.

In the clinical studies, ventilator settings used to administer repeat doses were different than those used for the first dose. For repeat doses, the  $FI_{O_2}$  was increased by 0.20 or an amount sufficient to prevent cyanosis. The ventilator delivered a rate of 30/minute with an inspiratory time less than 1.0 second. If the infant's pretreatment rate was 30 or greater, it was left unchanged during SURVANTA instillation.

Manual hand-bag ventilation should not be used to administer repeat doses. DURING THE DOSING PROCEDURE, VENTILATOR SETTINGS MAY BE ADJUSTED AT THE DISCRETION OF THE CLINICIAN TO MAINTAIN APPROPRIATE OXYGENATION AND VENTILATION. AFTER COMPLETION OF THE DOSING PROCEDURE, RESUME USUAL VENTILATOR MANAGEMENT AND CLINICAL CARE.

#### Dosing Precautions

If an infant experiences bradycardia or oxygen desaturation during the dosing procedure, stop the dosing procedure and initiate appropriate measures to alleviate the condition. After the infant has stabilized, resume the dosing procedure.

Rales and moist breath sounds can occur transiently after administration of SURVANTA. Endotracheal suctioning or other remedial action is unnecessary unless clear-cut signs of airway obstruction are present.

#### HOW SUPPLIED

SURVANTA (beractant) Intratracheal Suspension is supplied in single-use glass vials containing 4 mL (NDC 0074-1040-04) or 8 mL of SURVANTA (NDC 0074-1040-08). Each milliliter contains 25 mg of phospholipids suspended in 0.9% sodium chloride solution. The color is off-white to light brown.

Store unopened vials at refrigeration temperature (2-8°C). Protect from light. Store vials in carton until ready for use. Vials are for single use only. Upon opening, discard unused drug.

March, 2009

considered to represent relative adrenal insufficiency in other critically ill populations.<sup>46</sup> Additionally, the authors found that 56% of ill newborns with cortisol values <15 µg/dL responded to hydrocortisone with increased blood pressure and decreased receipt of dopamine.<sup>45</sup>

There is insufficient evidence to support the routine use of glucocorticoids for the prophylaxis or treatment of hypotension or low blood flow. Studies are needed to determine indications, populations most likely to benefit, dosing, duration, efficacy, and safety. Because the consistent improvement in blood pressure seen after glucocorticoid therapy may be due to treatment of adrenal insufficiency, the logical therapeutic agent is hydrocortisone, rather than any synthetic glucocorticoid such as dexamethasone.

Based on the limited information available, a practical approach to the use of glucocorticoids in newborn infants with refractory hypotension could include obtaining a blood specimen for cortisol and giving a test dose of 1 mg/kg of hydrocortisone (without waiting for cortisol results).<sup>47</sup> If the blood pressure improves within 2-6 hours, hydrocortisone may be continued at doses that vary with maturity. For example, term infants can be given hydrocortisone at a dose of 0.5 mg/kg every 6-8 hours.<sup>48</sup> In preterm infants, however, the half-life is much longer, so hydrocortisone may be given at the dose, 0.5-1.0 mg/kg, but with a longer dosing interval (q 12 h).<sup>37</sup>

Because of the association of high endogenous cortisol levels and concomitant indomethacin treatment with spontaneous gastrointestinal (GI) perforation in preterm infants, these drugs should not be given at the same time.<sup>38</sup> If the pre-treatment cortisol value is >15-20 µg/dL, the clinician might consider stopping the drug, as this is unlikely to represent adrenal insufficiency. However, hydrocortisone may have direct pharmacologic effects that improve cardiac function.<sup>22,25</sup> If clinical benefit is apparent in the late preterm or term infant who is not at risk of spontaneous GI perforation, the drug may be considered for continuation even in the face of high serum concentration. Because early hypotension in the critically ill newborn generally resolves over the first several days of life, and because the duration of hydrocortisone administration that is safe and effective is unknown, the

clinician should consider stopping the drug after 48-72 hours while monitoring the cardiovascular status closely.

### Conclusion

Although abnormally high or low blood pressure can result in organ dysfunction or damage, it is unclear what consequences there may be from various blood pressures that are not at the extremes. Blood pressure measurements should be used in conjunction with all other available clinical measures of blood flow and organ perfusion. In some infants, an identifiable cause of hypotension will clearly direct therapy; however, in many or most infants the underlying etiology will not be apparent, and the clinician must attempt to balance risks and benefits that are not clear. We trust that new diagnostic tools and ongoing investigations will provide a better understanding of the relationship of ventilator parameters, hemodynamics, and adrenal insufficiency to hypotension and its treatment in the critically ill newborn.

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## News Briefs

**Patterns of respiratory disease during the first 2 postnatal weeks in extremely premature infants**

Pulmonary disease among infants of <28 weeks' gestation (extremely low gestational age newborns) often follows this pattern: the infant has little need for supplemental oxygen and ventilatory support in the first postnatal week, but then experiences pulmonary deterioration in the second postnatal week, with an increased need for supplemental oxygen and respiratory support. This study evaluated the antecedents and correlates of patterns of early lung disease, with emphasis on pulmonary deterioration, in a large cohort study, the Extremely Low Gestational Age Newborn (ELGAN) study. The researchers examined data collected prospectively on 1,340 infants born between 2002 and 2004 at 23 to 27 completed weeks of gestation and who survived to 14 days. Pulmonary deterioration was defined as receipt of fraction of inspired oxygen <0.23 on any day between days 3 and 7 and receipt of fraction of inspired oxygen  $\geq$ 0.25 on day 14. The investigators found that 20% of the infants had consistently low fraction of inspired oxygen, approximately two fifths (38%) had pulmonary deterioration, and the remaining approximately two fifths (43%) had consistently high fraction of inspired oxygen (early and persistent lung dysfunction). Compared with infants who had consistently low fraction of inspired oxygen, infants who experienced pulmonary deterioration had lower gestational ages and lower birth weights, had higher scores for neonatal acute physiology, and received more intensive modes of respiratory support. Gender, multifetal pregnancy, cesarean delivery, antenatal steroids, chorioamnionitis, and funisitis were not associated with pulmonary deterioration. The incidence of chronic lung disease, defined as oxygen therapy at 36 weeks' postmenstrual age, was 17% in the consistently low fraction of inspired oxygen group, 51% in the pulmonary deterioration group, and 67% in the early and persistent pulmonary dysfunction

group. The incidence of death in these 3 groups before 36 weeks' postmenstrual age was 1%, 3%, and 5%, respectively. The study concluded that nearly 40% of extremely low gestational age newborns experience pulmonary deterioration in the first 2 postnatal weeks, and half of them develop chronic lung disease. Indicators of developmental immaturity and illness severity were associated with both pulmonary deterioration and chronic lung disease. Studying the antecedents of pulmonary deterioration might provide new insights about chronic lung disease pathogenesis.

Laughon M, Allred EN, Bose C, et al, and the ELGAN Study Investigators: *Pediatrics* 2009;123(4):1124-1131.

**Airway obstruction during mask ventilation of very low birth weight infants during neonatal resuscitation**

The delivery of adequate but not excessive ventilation remains one of the most common problems encountered during neonatal resuscitation, especially in very-low-birth weight infants. The researchers' observations suggest that airway obstruction is a common occurrence after delivery of such infants. Consequently, they used colorimetric carbon dioxide detectors during bag-and-mask resuscitation to assist in determining whether the airway was patent. They then reviewed their experience to determine the frequency of the occurrence of recognizable airway obstruction during resuscitation of very-low-birth weight infants. The previous prospective trial randomly assigned preterm infants <32 weeks' gestation to resuscitation with either room air or 100% oxygen using pulse oximetry. Colorimetric carbon dioxide detectors were used to assist with bag-and-mask ventilation and to confirm intubation. From the video recordings, the number of positive pressure breaths without a color change in the detector until the breaths were associated with an unequivocal color change was counted as obstructed breaths. From the analog tracings, the number of breaths that had a

peak pressure plateau of  $\geq$ 0.2 second and were not associated with a color change was recorded as the number of obstructed breaths. The study found that all of the infants were judged to have an effective circulation during resuscitation. Six of the 24 infants enrolled in the trial received only continuous positive airway pressure. The remaining 18 infants received a median of 14 obstructed breaths (range: 4–37 breaths) delivered over a mean and median interval of 56.7 and 45.0 seconds, respectively (range: 10.0–220.0 seconds). A subgroup of 11 infants was analyzed using airway-pressure data. The target peak inspiratory pressure was 30 cm H<sub>2</sub>O. Ten of these 11 infants had obstructed breaths as defined by no change in the PediCap despite reaching the target pressure for  $\geq$ 0.2 second. The researchers concluded that airway obstruction occurs in most very-low-birth weight infants who receive ventilation with a face mask during resuscitation and that the use of a colorimetric detector can facilitate recognition and management of airway obstruction.

Finer NN, Rich W, Wang C, Leone T: *Pediatrics* 2009;123:865-869.

**Antenatal steroid therapy for fetal lung maturation: is there an association with childhood asthma?**

This study was designed to test the hypothesis that fetal exposure to corticosteroids in the antenatal period is an independent risk factor for the development of asthma in childhood. A population-based cohort study was conducted of all pregnant women who resided in Nova Scotia, Canada, and gave birth to a single fetus between January 1989 and December 1998 and lived to discharge. After exclusions, 79,395 infants were available for analysis. Using linked health-care utilization records, the investigators identified asthma cases in study children between 36 to 72 months of age. Generalized estimating equations were used to estimate the odds ratio of the association between exposure to corticosteroids and asthma, while controlling for confounders. The researchers found that

over the 10 years of the study corticosteroid therapy increased by threefold and that exposure to corticosteroids during pregnancy was associated with a risk of asthma in childhood: adjusted odds ratio of 1.23 (95% confidence interval: 1.06,

1.44). The study investigators suggested that antenatal steroid therapy appears to be an independent risk factor for the development of asthma between 36 and 72 months of age. They further advocate that more research is needed into the

smallest possible steroid dose required to achieve the desired postnatal effect and to reduce the risk of developing childhood asthma.

Pole JD, Mustard CA, To T, et al: *J Asthma* 2009;46(1):47-52.

## Self Test

*This self-assessment quiz is presented as an educational adjunct to the monograph. Completion of this brief quiz will help reinforce the material you have read. Answers are elsewhere on this page.*

1. Which of the following remains a significant risk in critically ill premature infants treated with concomitant hydrocortisone and indomethacin?
  - a. cardiac hypertrophy
  - b. gastrointestinal (GI) perforation
  - c. intracranial hemorrhage
  - d. hypoglycemia
2. Blood pressure measurement using invasive arterial catheters and transducer systems may be inaccurate because of which of the following:
  - a. bubbles in the catheter system
  - b. kinking of the tubing
  - c. incorrect calibration
  - d. incorrect positioning of the catheter
  - e. all of the above
3. All of the following have been found regarding an ill patient's response to hydrocortisone *except*:
  - a. increase in blood pressure
  - b. increase in left ventricular function
  - c. improved metabolic acidosis
  - d. decreased renal blood flow
4. All of the following statements regarding the administration of hydrocortisone are true *except*:
  - a. High endogenous cortisol levels and simultaneous administration of hydrocortisone increases the risk of GI perforation in preterm newborns.
  - b. Indomethacin given simultaneously increases the risk of GI perforation in preterm newborns.
  - c. Term infants are not at the same risk of GI perforation as preterm infants when receiving hydrocortisone.
  - d. There is clear evidence of safety and efficacy for glucocorticoids in the treatment hypotension in newborn infants.
5. Mechanical ventilation pressures have no effect on the hemodynamics in an ill patient.
  - a. true
  - b. false

**Self-Test Answers for This Issue:**

**1. b 2. e 3. d 4. d 5. b**