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In This Issue

National Perinatal Association 2018 Respiratory Syncytial Virus (RSV) Prevention Clinical Practice Guideline: An Evidence-Based Interdisciplinary Collaboration

PEER REVIEWED

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Background

Respiratory Syncytial Virus (RSV) is a virus that typically causes mild, cold-like symptoms in adults, children and most term infants. In premature and "at-risk" infants, as well as the elderly, RSV can cause severe disease, and is a very serious health concern. RSV is a leading cause of worldwide morbidity, and mortality in children less than five years of age and causes approximately 3.4 million hospitalizations and greater than 66,000 deaths per year in this group.[1] Although 99% of these deaths occur in developing countries, of all infectious diseases affecting children worldwide, only malaria is more deadly.[2]

A number of different strategies have been studied to reduce the risk from RSV. Although efforts to reduce droplet transmission, good handwashing, and avoidance of known infected patients have been found to be effective, palivizumab is currently the only FDA-approved biologic for RSV prophylaxis. There is a high level of evidence that RSV prophylaxis is effective. The best data available at this time supports the practice of continuing to insure access of RSV prophylaxis for neonatal and pediatric patients at greatest risk.[3-6] Over the course of the past several years, the proportion of infants eligible for RSV prophylaxis who have actually received it has decreased, as providers and insurers have increasingly followed guidelines and policies that are not in compliance with Food and Drug Administration (FDA) indication resulting in needless morbidity and increased hospitalization.[7, 8] Most babies at risk for RSV are now deemed ineligible for prophylaxis by such guidelines and polices.[9-11] Parent groups, concerned about this trend, have published recommendations for obtaining FDA-approved coverage for RSV prophylaxis using techniques such as appeals, letter-writing campaigns and political activism. A number of examples are documented on the "preemiebabies101" website http://www.preemiebabies101.com/2014/08/12-tips-getting-synagis-injections-approved/, as well as the "Hand to Hold" website http://handtohold.org/resources/helpful-articles/rsv-101-what-every-nicu-parent-needs-to-know/. The continued need to appeal what should be covered by FDA indication, delays in the appeals process, and complete denials have all contributed to delays in the administration of immunization to babies at risk resulting in irregular, sub-optimal dosing regimens and a reduction of palivizumab levels necessary to prevent illness. This leads to increased hospital admission as well as increased morbidity.[8, 12]

Provider confusion is a serious concern. Although there is no substitute for clinical judgement, recommendations on dosing and

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timing should be issued in a manner consistent with the broadest FDA indication for dosing to accommodate provider discretion.[7] Guidelines do not apply in every condition and for every case. Variation from the guideline is still acceptable practice; however these guidelines should never deny access. A policy that mandates attenuated palivizumab administration is not reasonable when that policy countermands the FDA indication. The indication provides the most clarity in preventing use of a pharmaceutical product outside of its carefully studied parameters. Following FDA indication is important from a medico-legal perspective as insurers should use the FDA indication to guide remuneration without a *proviso* for denials due to consensus guidance that deviates from the FDA indication. Major deviation from the established FDA indication and insurance reimbursement based on policy statements created from consensus guidance contributes to much confusion for providers as well as parents, may also lead to provider disenfranchisement, and lack of universal acceptance of a standard of practice (http://www.infanthealth.org/rsv). This is unfortunate. Despite clear Medicaid regulation, State Medicaid formularies have not met all of the requirements of section 1927(d)(4)(C) of the Social Security Act, since they exclude treatment with an approved therapy despite clear FDA indication. Palivizumab meets all the criteria (significant and clinically meaningful therapeutic advantage, safety profile and effectiveness in clinical outcomes) necessary for coverage by Medicaid programs via the "medically acceptable indication" criteria. The ramifications of a policy for reduced dosing is concerning, as it not only restricts access, but it causes state Medicaid programs to violate their legislative mandate. Under the legal doctrine of "loss of chance," practicioners assume legal liability for not offering and advocating for the use of the only approved pharmaceutical for a specific approved indication.[13]

Of particular public concern has been a de-emphasis on the best available evidence and a focus on adjudicated studies to generate selective expert opinion. Regimens with fewer doses than FDA indication have not been tested in a randomized clinical trial (RCT). Use of an abbreviated dosing schedule for immunoprophylaxis of RSV, in an effort to ration therapy and reduce costs, is contrary to published evidence and the FDA-approved product indication for palivizumab.[14] Not dosing according to indication (under dosing) is considered an "off label" use of a medication.[15] Although cost effectiveness is increasingly important, decisions regarding appropriate RSV prophylaxis must be based on the evidence.[16-19] Denial of full coverage based on gestational age, without consideration of other risk factors, discriminates against certain populations of premature infants and may put certain populations at even greater risk due to health disparities.[20, 21] Making RSV a reportable disease may be important in documenting the actual extent of RSV prevalence and costs.[20] To date, despite widespread efforts to protect infants according to the FDA indications, further restrictions on the use of palivizumab have made prophylaxis potentially unavailable for as many as 75% of the infants in whom it is clearly indicated by FDA guidance.[7, 22]

Even in high-risk infants from 32-35 wGA (weeks' gestational age), RSV can result in serious morbidities. In one study, Ambrose, et al., evaluated 1,642 subjects across a multitude of outpatient clinics in 38 states and the District of Columbia. In two RSV seasons (2009-2011), ED visits, outpatient respiratory infection, and other clinical factors that place babies at-risk for RSV disease were evaluated. Of the preterm infants 32-35 wGA who were <6 months on November 1st, 4.9% were hospitalized with RSV-related illnesses each season. Pre-school aged siblings and daycare attendance increased the risk of RSV disease. Among the subset of 32-34 wGA infants eligible under a risk-related criteria, the RSV-related hospitalization rate was 9.1%.[12, 23] A study by Blanken, et al., supports the original evidence presented in the IMpact RSV trial. Palivizumab decreased RSV-related hospitalization in 33-35 wGA infants by 82%, whereas the original IMpact study described a 78% decrease.[11, 24] A Cochrane review using data from a number of randomized controlled trials found high quality evidence to support the association of palivizumab and reduction in RSV-related hospitalization (RR 0.49, 95% CI 0.37-0.64) as well as high quality evidence to

support an association of palivizumab and reduction in RSV ICU admissions (RR 0.5, 95% CI 0.3-0.81).[1, 25-27]

Confoundation by indication limits the effectiveness of well-designed randomized control studies designed to study the efficacy of palivizumab. Farber et al., described a 38% lower rate of hospitalization for RSV in infants born at 29 to 32 wGA, with ≥1 insurance claim for palivizumab.[28] However, this group received <50% of the indicated doses. Studies that are retrospective, nonrandomized, and with confounding of the indication should not supersede the data from carefully designed randomized trials.[29]

Winterstein, et al., evaluated 247,566 patients in Florida and Texas to determine the age at which at-risk infants born from 32-34 wGA experienced a risk of developing RSV equivalent to that of term babies. At one month of age, these babies had a risk of being hospitalized comparable to that of term babies. The RSV-related hospitalization rate of these preterm infants was 3.1% in Florida and 4.5% in Texas. Incomplete coding and testing for RSV was a consistent issue. Increased prematurity was associated with a higher risk for hospitalization, and the issues pertaining to disparity could not be separately identified in the populations studied.[30] In another at-risk population in Florida, Winterstein, et al., demonstrated that palivizumab prophylaxis was associated with a reduction in severe RSV infection.[31] Analysis of the Kids' Inpatient Database of hospitalizations between 2000-2009 (n=325,494) showed that while, overall, the bronchiolitis-related hospitalizations were decreased by 17% among all children less than two years of age, bronchiolitis hospitalizations actually increased by 29% in the sub-group in which there was an FDA indication for palivizumab prophylaxis.[10, 32]

In a study conducted by Hall, et al., RSV-related hospitalizations among preterm and term infants were evaluated in three United States counties. RSV acute respiratory illnesses were tallied and relative risk was identified by age from birth certificate data. This study has been used as justification for reduced immunoprophylaxis, yet the study included an insufficient number of premature infants to justify generalizing the results to this population. Premature infants represented only 10% of the 2,140 subjects studied. RSV rates in this study were not found to be significantly different between preterm and term infants, an expected result since 70% of the palivizumab- eligible patients in the study populations had received palivizumab (supporting the efficacy of palivizumab in decreasing the rate of RSV infection in preterm infants to be closer to that of term infants). Black infants greater than or equal to 6 months of age were hospitalized more often, documenting ethnic disparities in RSV-related health risks.[21] Previous studies such as that by Boyce, et al., had identified a two-fold higher hospitalization rate for preterm infants.[33] This higher rate of hospitalization might be expected to drop, if adequate compliance to RSV prophylaxis could be assured.[34]

Since 2014, more restrictive control over the prescription of palivizumab has resulted in increased morbidity. Zuccotti, et al, demonatrated worse outcomes in the 29-32 wGA group who did not receive prophylaxis as well as increased costs of hospitalization.(35) In another study, Capizzi, et al., found a high proportion of admission for the <36 wGA infants, the great majority born at 33 to <36 wGA and a chronological age of <6 months. Of those admitted, a high proportion of preterms were treated with high flow nasal cannula ventilation delivering continuous positive airway pressure. These results suggest the need to re-evaluate the role of prophylaxis in infants up to 36 wGA.[36] In a multicenter test case negative control study, palivizumab efficiency for preventing Intensive Care Unit (ICU) admission of infants 29-35 wGA and ≤6 months of chronologic age (without chronic lung disease of prematurity or Congenital Heart Disease) was 74% (95% CI 56%-85%).[37]

SENTINEL1 evaluated 29-35 wGA <12 months old infants hospitalized for confirmed RSV disease who had not received

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Indication

INOMAX is indicated to improve oxygenation and reduce the need for extracorporeal membrane oxygenation in term and near-term (>34 weeks gestation) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension in conjunction with ventilatory support and other appropriate agents.

Important Safety Information

- INOMAX is contraindicated in the treatment of neonates dependent on right-to-left shunting of blood.
- Abrupt discontinuation of INOMAX may lead to increasing pulmonary artery pressure and worsening oxygenation.
- Methemoglobinemia and NO_2 levels are dose dependent. Nitric oxide donor compounds may have an additive effect with INOMAX on the risk of developing methemoglobinemia. Nitrogen dioxide may cause airway inflammation and damage to lung tissues.
- In patients with pre-existing left ventricular dysfunction, INOMAX may increase pulmonary capillary wedge pressure leading to pulmonary edema.
- Monitor for PaO_2, inspired NO_2, and methemoglobin during INOMAX administration.
- INOMAX must be administered using a calibrated INOmax DS_{IR}® Nitric Oxide Delivery System operated by trained personnel. Only validated ventilator systems should be used in conjunction with INOMAX.

Please see Brief Summary of Prescribing Information on adjacent page.

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Brief Summary of Prescribing Information

INDICATIONS AND USAGE

Treatment of Hypoxic Respiratory Failure

INOmax® is indicated to improve oxygenation and reduce the need for extracorporeal membrane oxygenation in term and near-term (>34 weeks) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension in conjunction with ventilator support and other appropriate agents.

CONTRAINDICATIONS

INOmax is contraindicated in neonates dependent on right-to-left shunting of blood.

WARNINGS AND PRECAUTIONS

Rebound Pulmonary Hypertension Syndrome following Abrupt Discontinuation

Wean from INOmax. Abrupt discontinuation of INOmax may lead to worsening oxygenation and increasing pulmonary artery pressure, i.e., Rebound Pulmonary Hypertension Syndrome. Signs and symptoms of Rebound Pulmonary Hypertension Syndrome include hypoxemia, systemic hypotension, bradycardia, and decreased cardiac output. If Rebound Pulmonary Hypertension occurs, reinstate INOmax therapy immediately.

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Nitric oxide combines with hemoglobin to form methemoglobin, which does not transport oxygen. Methemoglobin levels increase with the dose of INOmax; it can take 8 hours or more before steady-state methemoglobin levels are attained. Monitor methemoglobin and adjust the dose of INOmax to optimize oxygenation.

If methemoglobin levels do not resolve with decrease in dose or discontinuation of INOmax, additional therapy may be warranted to treat methemoglobinemia.

Airway Injury from Nitrogen Dioxide

Nitrogen dioxide (NO_2) forms in gas mixtures containing NO and O_2. Nitrogen dioxide may cause airway inflammation and damage to lung tissues.

If there is an unexpected change in NO_2 concentration, or if the NO_2 concentration reaches 3 ppm when measured in the breathing circuit, then the delivery system should be assessed in accordance with the Nitric Oxide Delivery System O&M Manual troubleshooting section, and the NO_2 analyzer should be recalibrated. The dose of INOmax and/or FiO_2 should be adjusted as appropriate.

Worsening Heart Failure

Patients with left ventricular dysfunction treated with INOmax may experience pulmonary edema, increased pulmonary capillary wedge pressure, worsening of left ventricular dysfunction, systemic hypotension, bradycardia and cardiac arrest. Discontinue INOmax while providing symptomatic care.

ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from the clinical studies does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Controlled studies have included 325 patients on INOmax doses of 5 to 80 ppm and 251 patients on placebo. Total mortality in the pooled trials was 11% on placebo and 9% on INOmax, a result adequate to exclude INOmax mortality being more than 40% worse than placebo.

In both the NINOS and CINRGI studies, the duration of hospitalization was similar in INOmax and placebo-treated groups.

From all controlled studies, at least 6 months of follow-up is available for 278 patients who received INOmax and 212 patients who received placebo. Among these patients, there was no evidence of an adverse effect of treatment on the need for rehospitalization, special medical services, pulmonary disease, or neurological sequelae.

In the NINOS study, treatment groups were similar with respect to the incidence and severity of intracranial hemorrhage, Grade IV hemorrhage, periventricular leukomalacia, cerebral infarction, seizures requiring anticonvulsant therapy, pulmonary hemorrhage, or gastrointestinal hemorrhage.

In CINRGI, the only adverse reaction (>2% higher incidence on INOmax than on placebo) was hypotension (14% vs. 11%).

Based upon post-marketing experience, accidental exposure to nitric oxide for inhalation in hospital staff has been associated with chest discomfort, dizziness, dry throat, dyspnea, and headache.

DRUG INTERACTIONS

Nitric Oxide Donor Agents

Nitric oxide donor agents such as prilocaine, sodium nitroprusside and nitroglycerine may increase the risk of developing methemoglobinemia.

OVERDOSAGE

Overdosage with INOmax is manifest by elevations in methemoglobin and pulmonary toxicities associated with inspired NO_2. Elevated NO_2 may cause acute lung injury. Elevations in methemoglobin reduce the oxygen delivery capacity of the circulation. In clinical studies, NO_2 levels >3 ppm or methemoglobin levels >7% were treated by reducing the dose of, or discontinuing, INOmax.

Methemoglobinemia that does not resolve after reduction or discontinuation of therapy can be treated with intravenous vitamin C, intravenous methylene blue, or blood transfusion, based upon the clinical situation.

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prophylaxis. Forty-two percent of these were admitted to the ICU, and 20% required intubation and mechanical ventilation. In the younger group, 29-32 wGA and <3 months of age, 68% required ICU admission and 44% required intubation and mechanical ventilation. These results corroborate the original RSV IMpact study, and provide additional information regarding the level of acuity of the hospitalization course.[8]

Following a change in palivizumab dosing patterns for the 2014-2015 season, the TRUVEN database study demonstrated that with a decline in RSV prophylaxis, hospitalization increased among infants born at 29-34 wGA and aged <3 months. Compared with the 2013–2014 season, RSV hospitalization increased by 2.7-fold (p=0.02) in the at-risk group. RSV hospitalizations for infants 29-34 wGA were up to seven times higher than normal term infants.[38]

Increased risk for hospitalization is not the only factor to consider. A number of studies document RSV's association with wheeze and risk of subsequent development of reactive airway disease (39-41). Blanken, et al., demonstrated a significant reduction in wheeze in an at-risk group of infants born at 33-35 wGA that received palivizumab prophylaxis. Recurrent wheeze was 10 percentage points lower in patients treated with palivizumab (11% vs. 21%, p=0.01) (24). Yoshihara, et al., demonstrated reduced wheeze in patients who received palivizumab prophylaxis regardless of whether an at-risk patient was documented to have contracted RSV.[42] Subclinical RSV disease that is not identified in the course of a provider interaction may be clinically significant and result in increased long term morbidity.[17]

In an observational case-control prospective multicenter trial of palivizumab prophylaxis, Mochizuki, et al., was able to establish a two-fold increase in the development of recurrent wheezing (15.3% versus 31.6% in the treated and untreated groups, (p=0.003). Although the study did not show a difference in atopic asthma, the risk for subsequent development of asthma and morbidity associated with recurrent wheese cannot be discounted.[43] Feldman, et al., discussed how RSV infection may not be necessary, but is sufficient to increase likelihood of pediatric asthma. Immune mediation and cytokine production common to both conditions may be set into process if RSV infection occurs at a certain point in time.[44] REGAL (RSV Evidence-a Geographical Archive of the Literature) reviewed 20 years of RSV-related research. Of the 74 prospective, epidemiologic studies qualified by the review, the meta-analysis consistently demonstrated that RSV infection early in life is a significant risk factor for respiratory morbidity characterized by early wheezing and recurrent wheezing as well as asthma within the first decade of life and possibly later.[45] An expert panel sponsored by the Bill and Melinda Gates Foundation (www.gatesfoundation.org) concluded that the association between early onset RSV and subsequent wheeze as well as asthma has been well defined. The effect of prevention of RSV in infancy on reduction of recurrent wheezing and asthma across multiple gestational ages may ultimately demonstrate a causal link.[46]

Children at high risk for RSV include those with other co-morbidities besides prematurity, including chronic lung disease and Congenital Heart Disease (CHD). Using a structured case analysis of the Medline database, Welliver, et al., described a series of patients with severe underlying comorbidities, as well as those with nosocomial RSV who appear to be at increased risk for death after RSV hospitalization.[47] Actual RSV worldwide fatality data may be useful in determining whether including co-morbidities in evaluating acceptable risk is appropriate.[1, 17, 48]

Financial Considerations

Cost stewardship is important. Patients should receive the best possible care at the lowest possible cost.[14] However, any reduction in qualification for RSV prophylaxis must be associated with a model that demonstrates the unequivocal financial benefit without increased attendant morbidity and/or mortality. Further, estimates of cost saving

must incorporate realistic estimates of palivizumab cost, as well as all costs for hospitalization and follow-up care. Included in this consideration must be a risk stratified cost analysis of a patient likely to be hospitalized for RSV-related disease, as well as an estimate of actual prophylaxis cost related to month of birth, extrapolated or actual dosing weight at the time of prophylaxis, and level of discount applied to the list price of palivizumab. An analysis by McLauren, et al., demonstrated modeled costs of 55 to 85% less than list pricing using a blended drug discount of 33% coupled with seasonal and patient weight considerations.[17, 49, 50] For this model, contemporary hospitalization claim data were used to quantify payer-related costs and cost neutrality was demonstrated in patient groups up to 34 wGA.[17, 51] Medicaid-related cost discounts were most significant, and prophylaxis of patients in this cohort produced a cost savings. However, physician fee, follow-up costs, parent time off work, and patient factors including "cost" of discomfort were not considered in either commercial or government insurance programs. Extension of this model to include these considerations and dosing according to the full FDA indication may provide additional cost reduction and further tip the balance towards financial justification for prophylaxis. Long-term epidemiologic data from 16 seasons of national palivizumab prophylaxis in Austria reported by Resch, et al., demonstrated an unequivocal seasonal benefit, as well as long-term societal cost savings.[52]

Introduction

RSV is the leading cause of hospitalization for all children less than 12 months of age in the United States.[33, 53, 54] The majority of these hospitalizations occur in otherwise healthy infants. Sixty percent of the top five hospital discharge diagnoses are attributable to bronchiolitis. Certain groups of infants and children have higher rates of re-hospitalization, including those with Chronic Lung Disease (CLD)/Bronchopulmonary Dysplasia (BPD), Congenital Heart Disease (CHD), and a history of preterm birth.[55-62] Treatment options for RSV are limited. Supportive care is the only medical therapy available. In addition to strategies to minimize exposure to RSV, prophylaxis with RSV monoclonal antibody is effective at decreasing hospitalization. The best approach to RSV in at-risk groups is prevention.[11, 27, 57, 63-65] In patients with CLD/BPD and premature infants born at less than 36 wGA, prophylaxis decreased hospitalization by 55%; in the subgroup of patients born between 32-35 wGA, hospitalization rates decreased by 80%.[11] Although palivizumab may be safe for term infants with no underlying co-morbidities, immunization of otherwise healthy term infants is considered outside of the accepted FDA indication.

Respiratory Syncytial Virus Prophylaxis

A. Prophylaxis to prevent RSV is available as intramuscular monoclonal antibody preparation (palivizumab).[66, 67]
B. RSV infection is responsible for significant hospitalizations, morbidity, and mortality in infants less than 24 months of age who have chronic lung disease, CHD, compromised respiratory or immune systems, or impaired nutritional status and growth.[27, 63, 68]
C. Candidates for RSV Prophylaxis: Areas where strong data exist.
  1. Infants with bronchopulmonary dysplasia (BPD) or chronic lung disease (CLD) will benefit from RSV prophylaxis.
    a. BPD may be defined by oxygen requirement at 36 weeks' corrected gestational age or at 28 days of age regardless of the birth gestational age.
    b. CLD includes these infants and others who have subsequently developed an oxygen requirement or other pulmonary condition requiring treatment or close medical observation.
    c. Infants with CLD/BPD who are less than 24 months of age at the start of RSV season who have required intervention or maintenance therapy for their BPD/CLD within 6

months of the start of the RSV season will benefit from RSV prophylaxis. The administration of palivizumab in a previous month may be sufficient to qualify for administration in a subsequent qualified month.

    d. Other interventions for CLD/BPD may include use of corticosteroid preparations, methylxanthines (e.g., aminophylline or caffeine), supplemental oxygen, bronchodilators, home apnea monitoring, home pulse oximetry, or diuretics.[60, 69, 70]

2. Infants born at 32 wGA or less without CLD/BPD will also benefit from prophylaxis:[71]

    a. Infants born at less than 28 0/7 wGA will benefit from prophylaxis, if they are less than 12 months of age at the start of the RSV season. Infants born during RSV season who are less than 12 months of age at the start of the subsequent RSV season are still candidates for prophylaxis.

    b. Infants born at 28 0/7-32 0/7 wGA will benefit most from prophylaxis, if they are less than 6 months of age at the start of RSV season.

3. Infants born at a late preterm gestation (34 0/7-36 6/7 wGA) may merit special consideration.[72-74] However, prophylaxis for infants born at 32 1/7-35 6/7 wGA should be reserved for those infants with additional risk factors that increase risk of RSV exposure or morbidity from RSV disease.

    a. An RSV relative-risk scale has been proposed and may be useful to the practitioner in identifying at-risk patients who may benefit from RSV prophylaxis.[75] A neonatologist, pediatrician, or other primary care provider is often in the best position to assess and interpret relative risk factors.

    b. The most consistently identified factors that are associated with increased risk of RSV disease are childcare attendance, school-aged siblings, twin or greater multiple gestation, young chronological age at the start of RSV season and parental smoking; however, exposure to environmental air pollutants, congenital abnormalities of the airways, or severe neuromuscular disease may also justify concern.[41, 69, 76-79] Correlations exist between air quality and respiratory function.[40, 78-88] Thus, environmental air quality assessment is important for these patients with special consideration given the unique circumstances of unwarranted air pollution such as residence near a bus station or industrial plant, or use of a wood-burning or coal-burning stove as a primary heat source. Efforts to reduce risk by isolation of the at-risk child, smoking cessation strategies for the parents/caregivers, or relocation to an area with cleaner air may not be practical or workable.

    c. Certain risk factors may have greater impact based on the level of exposure (i.e., one school-aged sibling versus three school-aged siblings in three different schools); however, no identifiable risk factor has been shown to be unique in its predictive value, and frequently many risk factors may exist simultaneously.[40, 62] The greater the number of risk factors, the higher the likelihood of RSV hospitalization.[89] A history of maternal smoking during pregnancy may be ameliorated as a risk factor by a history of breastfeeding for greater than 2 months.[82, 90-93] These circumstances must be accounted for in the risk assessment.

    d. The provider must be aware of the risk created and enhanced by disparity. Minority African American and Hispanic populations in blighted inner city neighborhoods are at a higher cumulative risk.(20)

    e. After assessment of an individual patient, if a provider determines that the patient is at high risk for RSV disease complicated by hospitalization, prophylaxis should be provided.[94] Planning for prophylaxis must begin before the time of discharge if the at-risk patient has been hospitalized for any of the conditions that have a known association for increased risk. In one study, greater than 50% of eligible patients received no prophylaxis, neither prior to nor after discharge.[95] Lack of parental education, language difficulties, transportation challenges, and issues of potential problems with insurance coverage must be resolved prior to the patient's discharge home.[96-98]

    f. Cost of prophylaxis should be weighed against the risk of severe RSV disease requiring hospitalization and associated costs to the family as well as potential for long-term sequelae. Direct costs are not the only expenses involved in the long-term care of a child who has had RSV. Costs associated with loss of family income with a parent taking time off for initial hospitalization and later to care for a child with chronic disability, frequent follow-up appointments, and indirect costs involved in providing support for developmental disability as well as loss of academic potential must also be considered.[99-102]

4. Infants with CHD have been shown to benefit from palivizumab.[27, 103-105] The degree and severity of the heart disease may factor into the decision to provide RSV prophylaxis. Cyanotic Heart Disease places a patient at considerable risk since oxygen delivery is already compromised. Although Acyanotic Heart Disease has been shown to increase the relative risk for RSV-related hospital admission to even higher than that of cyanotic disease, admission rates of palivizumab-immunized infants are similar in both categories.[27] Infants with Complex Congenital Heart Disease (CCHD) are at risk, and should be consider for RSV prophylaxis, including babies with Hypoplastic Left or Right Heart Syndrome, truncus arteriosus, Tetralogy of Fallot, pulmonary atresia, Transposition of the Great Arteries, interrupted aortic arch, Ventricular Septal Ddefect or Patent Ductus Arteriosus with demonstrated heart failure, cardiomyopathies, arrhythmias capable of causing hemodynamic compromise, and infants who are candidates for potential heart transplant. Children who are post cardiac transplantation are in a particularly high-risk group and should be given RSV prophylaxis.[103, 105, 106] In order to exclude an infant from receiving palivizumab, the infant must have a documented waiver provided by a board-certified pediatric cardiologist, which documents that their cardiac defect is hemodynamically insignificant, and thereby, poses no additional risk for RSV. During RSV season, children who have received Extracorporeal Membrane Oxygenation (ECMO) or any other form of cardiac bypass should receive monthly prophylaxis. If the baby is receiving palivizumab during the active RSV season, an extra dose of prophylaxis should be considered as soon as the baby comes off bypass support.[107]

D. Candidates for RSV Prophylaxis: Areas where decisions regarding appropriateness of RSV prophylaxis must be individualized.

1. Infants with severe neuromusucular disease affecting respiratory function (e.g., myotonic or muscular dystrophy) may be candidates for palivizumab prophylaxis, including those with neuromuscular maturational disease common in premature infants.[108] CNS injury prior to, during, or after delivery including, but not limited to, intraventricular hemorrhage (IVH), hypoxic ischemic encephalopathy (HIE), spinal cord injury, disease of the peripheral nervous system, disease of the neuromuscular junction, and periventricular leukomalacia (PVL) are all possible indications for RSV prophylaxis.[68, 70, 108] IVH, HIE, and PVL may cause cerebral palsy (CP) at a later time. CP alone may qualify an infant for RSV prophylaxis, if there is any association with impaired respiratory function.[109, 110]

2. Patients with congenital abnormalities of the airways that compromise respiratory function should receive prophylaxis.[56, 111-114] Other respiratory viruses may also be

implicated in morbidity, which may include persisting wheeze, symptomatology and/or family history that suggest the possibility of later asthma, or disorders of abnormal lung growth.[42] Congenital diaphragmatic hernia is included in this category. Although large scale randomized control trials have not been performed, patients with surfactant protein deficiencies may also benefit from prophylaxis, as may infants with childhood interstitial lung diseases such as neuroendocrine hyperplasia of infancy (NEHI) or pulmonary interstitial glycogenosis (PIG).

3. Although large-scale randomized control trials in patients with individual at-risk respiratory disorders have not been performed, patients with cystic fibrosis and other diseases such as α1-antitrypsin deficiency where there is a genetic basis for changes in the lung milieu may also benefit from prophylaxis.[115] As respiratory symptomatology is not generally associated with α1-antitrypsin deficiency during infancy; based on the degree of pulmonary involvement, palivizumab may be considered only if there is respiratory compromise associated with another qualifier (e.g., prematurity).[116] Primary Ciliary Dyskinesia may also be an indication for prophylaxis.[117] Identification of cystic fibrosis on a newborn screen may merit special consideration.[112, 115, 118-120] Cystic fibrosis occurring with transient infantile wheezing has been associated with worse lung function in later life, and RSV is the most common cause of transient infantile wheezing.[121] Certainly, infants who would otherwise qualify for palivizumab based on the indication should be screened for cystic fibrosis if the clinical course and history indicate.

4. Immune deficiencies are rare disorders and require collaborative management by pediatricians, infectious disease specialists, and immunologists.[122, 123] HIV, SCID, primary or secondary bone marrow depletion, and any defect of humoral or cellular immunity including that occurring with transplantation places a patient at-risk of severe infection. Palivizumab prophylaxis has been associated with improved survival after bone marrow transplantation.[124] Although there is no conclusive evidence for any particular disease category, because of the understood high risk of any infectious process, RSV prophylaxis is indicated unless a waiver can be obtained from a board certified pediatric immunologist or infectious disease specialist.

5. Certain genetic diseases may place a patient at more cumulative risk for RSV. For the present time, patients should receive prophylaxis to the extent that other qualifiers are met. However, including infants with Downs Syndrome in the recommendations for immunoprophylaxis of RSV disease should be considered.[125]

6. Special risk circumstances may occur in homes where another individual is at high risk for RSV infection (e.g., an elderly immunocompromised relative) who may not be able to receive RSV prophylaxis. Although palivizumab does not prevent RSV infection, decreased cough and aerosolization of RSV may provide some degree of protection. Providers should determine if it is reasonable to provide prophylaxis to other members of the household.[1, 126, 127]

E. Administration
1. The National Perinatal Association Guidelines for RSV Prophylaxis are interdisciplinary peer-reviewed and evidence-based guidelines, but do not represent the sole management criteria for medical care of at-risk infants. Depending on individual case presentations, in selected populations and unique circumstances, these recommendations may not apply. There is no substitute for the clinical judgment of a pediatrician, nurse practitioner, or other licensed provider of pediatric services.

2. RSV prophylaxis should be initiated prior to the onset of the RSV season and terminated at the end of the RSV season.[5, 128, 129] Although there are regional variations in the United States, RSV outbreaks begin as early as October and decrease between March and May. Providers should review local historical RSV surveillance data to assist in the decision-making process. Some locales in the Southern United States (e.g., Florida), Hawaii, and Alaska have high enough incidence of RSV to justify initiation in the late summer months and continuation of monthly prophylaxis into the late spring.[130-134] Transport distance of ill infants and resource allocation as well as socioeconomic factors (e.g., lack of running water) may be considered in the justification of enhanced RSV prophylaxis coverage where the costs to provide hospitalization for patients at great distance greatly exceed that of most urban locales (e.g., Alaska and Canadian Arctic).[135] The burden of severe RSV disease on healthcare resources is greater than other respiratory viruses.[136] Although various cost containment models have been proposed to provide relative risk adjustment based on post-conceptual age at a specific month during RSV season, there is risk that adequate levels of palivizumab will not be achieved or maintained during months when RSV is widespread using this type of model.[11, 12, 129, 137] Use of an abbreviated schedule of RSV prophylaxis (e.g., based on post conceptual age mid-season) is contrary to published evidence and FDA-approved product indication for palivizumab and is strongly discouraged.[138]

3. Once an infant begins RSV prophylaxis for the RSV season, the infant must receive palivizumab monthly through the end of the season.[25]

4. Palivizumab 15 mg/kg IM should be given once a month during the RSV season to increase the likelihood of achieving and maintaining appropriate levels for prophylaxis.[66] A dose should be given 24-48 hours prior to discharge from the hospital if the patient meets criteria. The single-dose vial of palivizumab does not contain a preservative. Administration of palivizumab should occur immediately after dose withdrawal from the vial.[66]

5. Although prophylaxis during active infection will not impact the course of the symptomatology, RSV disease is not a contraindication to continuing palivizumab prophylaxis. Infection does not confer lasting immunity. There is more than one genotype of RSV. Although less common, patients can be re-infected with RSV multiple times during the same RSV season. Thus, monthly dosing should be continued even if the patient has been infected with RSV.[66]

6. Fever or other illness including viral syndromes are not contraindications to administration of palivizumab.

7. There are no restrictions on concurrent RSV prophylaxis with any immunization.[139] Immunization with Measles-Mumps-Rubella (MMR) and Varicella vaccines need not be deferred in infants receiving RSV prophylaxis. RSV prophylaxis does not interfere with Hepatitis B vaccine, Diphtheria, Tetanus, Pertussis (DTaP) primary immunization schedule, H. Influenza type B (Hib), seasonal influenza vaccination, Pneumococcal Conjugate Vaccine (PCV), or Inactivated Poliovirus Vaccine (IPV).

8. The safety and efficacy of palivizumab have not been demonstrated for treatment of established RSV disease. Palivizumab does not alter the disease severity or course of an active RSV infection.

9. Contraindications and Adverse Reactions
   a. Palivizumab should not be used in pediatric patients with a history of a severe prior reaction to palivizumab or other components of this product.[66]
   b. Fever, irritability and injection site reaction are the most commonly reported adverse events.[140]

Indication	Chronological Age	Dosing
Areas Where Strong Data Exist		
Chronic lung disease requiring medical management	Less than 24 months at start of RSV season	Monthly during RSV season
Born at <28 0/7 weeks' gestational age (wGA)	Less than 12 months at start of RSV season	Monthly during RSV season
Born at 28 0/7-32 0/7 wGA	Less than 6 months at start of RSV season	Monthly during RSV season
Born at 32 1/7-35 6/7 wGA	Less than 6 months at start of RSV season with significant provider- identified risk factors.	Monthly during RSV season
Hemodynamically Significant Congenital Heart Disease	Less than 24 months at start of RSV season unless cardiology waiver obtained	Monthly during RSV season
Areas Where Individualized Guidance is Indicated		
Neuromuscular Disease affecting respiratory function	Less than 24 months at start of RSV season	Monthly during RSV season
Congenital abnormalities of the airways (e.g., Congenital Diaphragmatic Hernia)	Less than 24 months at start of RSV season	Monthly during RSV season
Immune Disorders (e.g., HIV, SCID, DiGeorge, IgA deficiency, Hypergammaglobulinemia)	Less than 24 months at start of RSV season unless infectious disease or immunology waiver obtained	Monthly during RSV season
Cystic Fibrosis, Primary Ciliary Dyskinesia, or other rare lung disease resulting in chronic respiratory insufficiency	Less than 24 months at start of RSV season; consultation with pediatric pulmonology suggested	Monthly during RSV season

Nosocomial Infection

A. RSV may be horizontally transmitted in the hospital setting and causes serious disease in high-risk infants and young children.

B. The best way to prevent RSV disease is strict adherence to infection control practices, as well as the use of in-hospital screening studies to identify and isolate RSV-infected infants.[53] Proper hand washing is of paramount importance.

C. Cohorting of children with suspected RSV disease is not recommended. Not only are there other contagious viral and bacterial diseases that mimic RSV, but infection with RSV does not preclude co-infection with bacteria, other viruses, or another subgroup of RSV. For management of suspected nosocomial outbreaks of RSV occurring within a pediatric ward, pediatric critical care unit, or neonatal intensive care unit, the advice of infectious disease and hospital-based infection control experts should be obtained.[53, 141]

Use of Palivizumab Outside of the FDA Indications Constitutes Off-Label Use

A. Off-label use of any medication places the provider at medico-legal risk. The FDA's Center for Drug Evaluation and Research (CDER) has initiated the Bad Ad outreach program with the goal of encouraging health care providers to recognize and report suspected untruthful or misleading drug promotion. "Assuring prescription drug information is truthful, balanced, and accurately communicated" is the intent. Led by the Division of Drug Marketing Advertising and Communications (DDMAC), this effort informs providers about what constitutes misleading promotion and provides a process for reporting suspected violations to the FDA. Violators may include state or professional organizations, those who may profit by modifying FDA-approved dosing or indications for a medication, or individuals who make unrealistic claims about enhanced action of a medication.

B. Reports can be initiated by contacting the United States Food and Drug Administration's Division of Drug Marketing, Advertising, and Communications at 855-RX-BADAD or (855-792-2323), E-Mail: BadAd@fda.gov, by mail: FDA/CDER/DDMAC, 5901-B Ammendale Rd., Beltsville, MD 20705-1266, or Fax: 301-847-8444.[142] In the past, however, the FDA has not had the resources to act quickly on reports of wayward drug misinformation. The False Claims Act provides another alternative to the Bad Ad outreach program. This fraud-fighting law not only provides substantial rewards for whistleblowers, but it includes an action-enforcing mechanism that statutorily requires the government to investigate allegations of fraud. If providers want to ensure that the government will consider their concerns, a False Claims Act qui tam action may be filed.

The MEDLINE database, the Cochrane Library, and the National Perinatal Association's own internal resources and documents were used to conduct a literature search to identify relevant articles published on Respiratory Syncytial Virus (RSV). The search was restricted to articles published in the English language. Priority was given to the outcomes of original research. Review articles and commentaries were also consulted when their inclusion added substantively to the guidance. Abstracts of research presented at scientific conference were eligible for inclusion in this document if the abstract was peer reviewed prior to its publication. Guidelines published by other organizations were evaluated for their merit and included where their inclusion was both elucidative and topical. Further, sources from the bibliographies of these guidelines were evaluated and included where appropriate. Expert opinion, while important for the interpretation of the studies, was not judged to be valid independently without substantiation of high level evidence.

Studies were evaluated for quality using the metric provided by the United States Preventive Services Task Force:[143, 144]

I. Evidence obtained from at least one properly designed randomized controlled trial.
II-1. Evidence obtained from well-designed controlled trials without randomization.
II-2. Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.
II-3. Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.

Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

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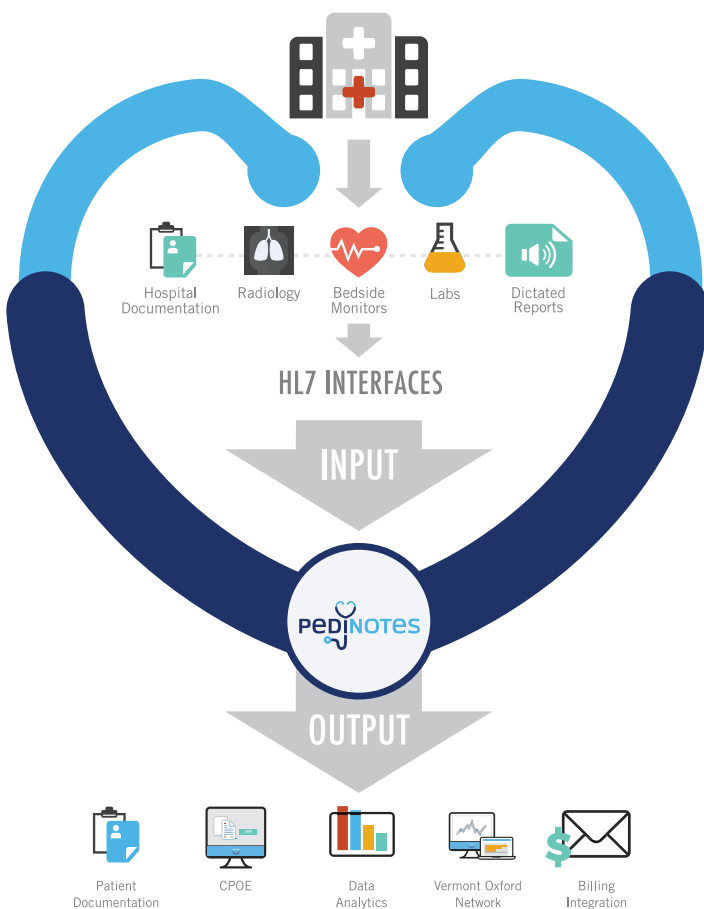
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Based on the highest level of evidence found in the data, recommendations are provided and graded according to the following categories:

Level A – Recommendations based on good and consistent scientific evidence.

Level B – Recommendations based on limited or inconsistent scientific evidence.

Level C – Recommendations based largely on consensus and expert opinion

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To Swim with the Tide: High Tidal Volume, Low Rate Ventilation in a Neonate with Respiratory Failure Due to Severe Broncho-Pulmonary Dysplasia

By Shabih Manzar, MD; Liaqat H. Khan, MD

The infant was the second of the twins, born to a 21-year old gravida 2, para 1. All antenatal labs including HIV, Hepatitis B, and rapid plasma reagin were negative. There was no history of sexually transmitted diseases. Pregnancy was complicated by preterm labor and she delivered twins at 24 weeks of gestation. The mother received two doses of betamethasone prior to delivery. Apgar scores were 4 and 7 at one and five minutes respectively. The infant's birth weight was 543 grams, head circumference 22 centimeters, and length of 32 centimeters.

On admission to the Neonatal Intensive Care Unit (NICU), the physical examination was normal for gestational age. A septic work-up was done including complete blood count and blood culture and the infant was started on antibiotics. Infant was already intubated in the delivery room and was placed on ventilator in NICU. Chest X-ray was compatible with Respiratory Distress Syndrome (RDS). Surfactant was given via endotracheal tube. Blood gas on admission was pH of 7.44 pCO_2 of 34 PO_2 of 61 and HCO_3 of 24 on 60% FiO_2. the Infant

> **"An echocardiogram done at Day of Life 7 showed a small Patent Ductus Arteriosus (PDA), which was managed conservatively per our NICU policy. A follow-up serial echocardiogram performed to screen for pulmonary hypertension, showed trivial tricuspid regurgitation with gradient range 23-33 mm Hg, normal size right atrium, and normal right ventricular function."**

was started on total parental nutrition. Feeds were started on Day of Life (DOL) 2, and gradually advanced to full feeds. By day 24, the infant was on full enteral feeds. The infant had multiple head ultrasounds, all showed no signs of bleed or

Figure 1. Chest X-ray at 120 Days of Life.

Figure 2. Chest X-ray at 1 Week after Intervention.

periventricular leukomalacia. MRI brain did not show any congenital anomalies. An echocardiogram done at Day of Life 7 showed a small Patent Ductus Arteriosus (PDA), which was managed conservatively per our NICU policy. A follow-up serial echocardiogram performed to screen for pulmonary hypertension, showed trivial tricuspid regurgitation with gradient range 23-33 mm Hg, normal size right atrium, and normal right ventricular function.

The infant's respiratory status continued to deteriorate, and he failed several extubation attempts. At 120 DOL, the infant remained on a very high ventilator settings (Oscillator = Fraction Inspired oxygen 100%, Mean Airway Pressure = 24, Amplitude = 60 and Frequency = 5), and was unable to wean. Also, he was noted to have air hunger, and required an increase dose of sedation. The Chest X-ray is shown in Figure 1. Based on the article by Shepherd et al[1], we decided to place the infant on high tidal volume low rate mode of ventilation. The infant tolerated that well, and was able to wean of FiO_2 to 45-50% within 48 hours. The follow-up Chest X-ray showed improvement in the lung fields (see Figure 1). At the time of this report, the infant is tolerating 30 calorie formula via orogastric tube and gaining weight (see Figure 2). The plan is to send him for tracheostomy and gastrostomy to Children's Hospital.

Discussion

The definition of Bronchopulmonary Dysplasia (BPD) has evolved in recent years. For infants born at less than 32 weeks of gestation, who received supplemental oxygen for more than 28 days, are assessed at 36 weeks post-menstrual age (PMA). If the infant is in room air on 36 weeks PMA, the infant has mild BPD. If he/she is on less than 30% oxygen, he/she has moderate BPD, and if he/she is on greater than 30% O_2 or needing respiratory support, he/she will be classified as severe BPD.[2] The infant presented above fits into the category of severe BPD. The management of BPD is teamwork with multidisciplinary approach.[3]

The management includes: mechanical ventilation, oxygen therapy, diet, medications and neurodevelopmental follow-up.[4] As seen the case above, despite of adequate management, was unable to extubate, and the infant ended up on oscillator.
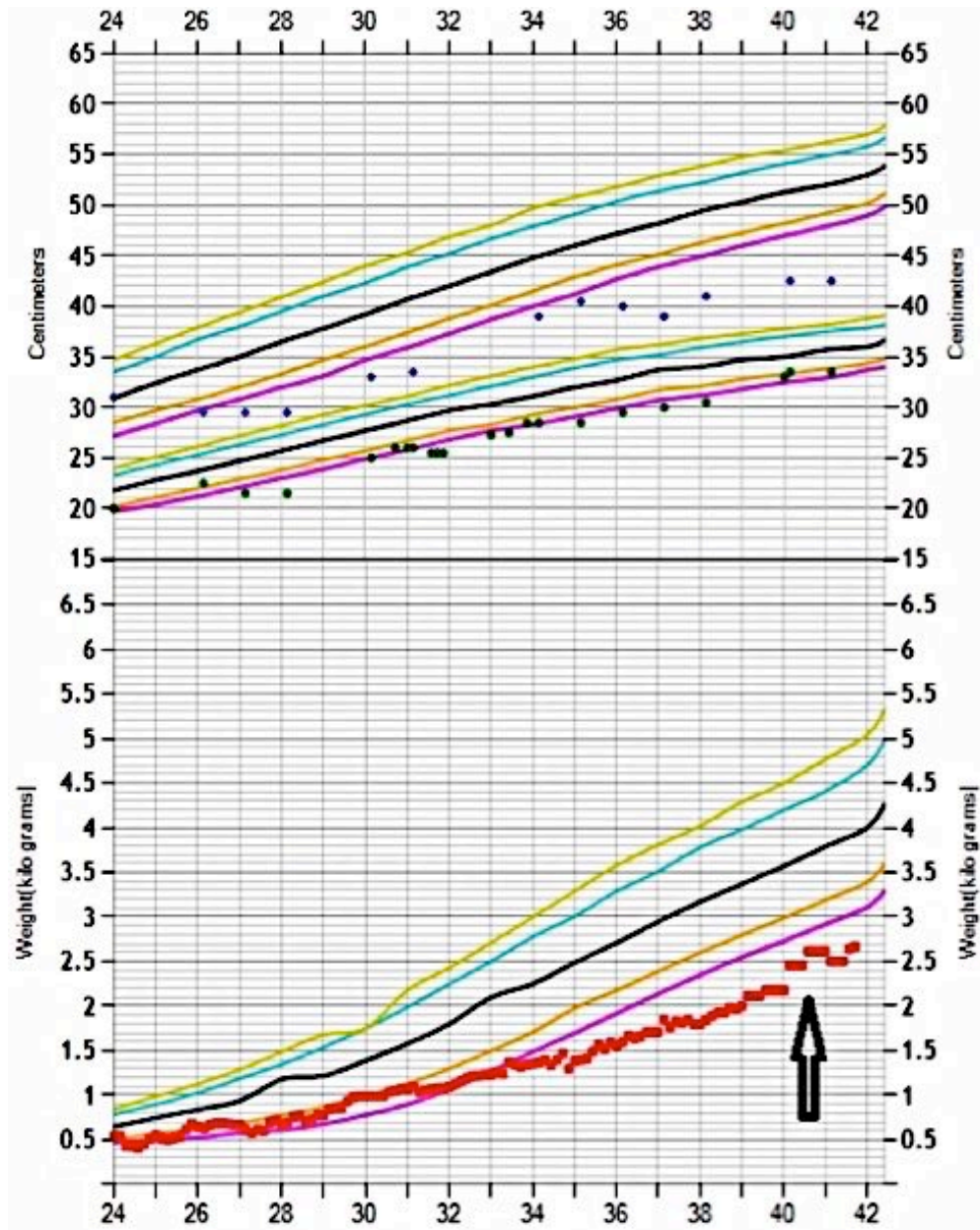
Figure 3. Growth Chart, Black Arrow Depicts the Time f Change in Ventilation.

"The management of BPD is teamwork with multidisciplinary approach.[3]"

Pulmonary function in an infant with severe BPD is dominated by increased resistance making the expiration time constant longer.[5] It means that complete exhalation will require longer time. Shepherd et al[1] suggested that by using a low rate and high tidal volume (Vt), we can achieve a reasonable minute ventilation (MV), as MV is the product of rate and tidal volume (MV = Vt x rate). Further, as carbon dioxide (CO_2) elimination is determined by MV, a change in Vt or rate is reflected as a change in PCO_2 which is a surrogate of adequate ventilation. The infant presented was switched from Oscillator (Fraction Inspired oxygen 100%, Mean Airway Pressure = 24, Amplitude = 60 and Frequency = 5) to Volume-controlled ventilator with the following settings: Fraction Inspired oxygen 100%, Vt of 45 (18 ml/kg), and Rate of 17 per minute. Inspiratory time was set at 0.5 secs, giving an I: E ratio of 1:5, providing long exhalation time for the infant. Within 48 hours of ventilation, the infant was weaned to 55% FiO_2, PCO_2 improved, and the infant required less sedation. The intervention also resulted in weight gain, see Growth Chart, Figure 3.

This case is an anecdotal experience from a single unit showing short-term benefit. A close follow-up is needed to see the long-term effect of such intervention. The main purpose of this report is to make health care providers aware of the successful use of high Vt, low rate ventilator strategy in infant with severe BPD.

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"This case is an anecdotal experience from a single unit showing short-term benefit. A close follow-up is needed to see the long-term effect of such intervention. The main purpose of this report is to make health care providers aware of the successful use of high Vt, low rate ventilator strategy in infant with severe BPD."

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▶ Investigate practical, realistic approaches to partnering with families to create a sense of collaboration and transparency.

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Medical News, Products & Information

Compiled and Reviewed by Tony Carlson, Senior Editor

Mallinckrodt to Acquire InfaCare Pharmaceutical Corporation and Stannsoporfin, Its Proprietary Therapy In Late-Stage Development for Treatment of Newborns At-Risk for Developing Severe Jaundice

- Infantile hyperbilirubinemia (jaundice) affects approximately 750,000 infants born in the U.S. each year; if unresolved with traditional treatment, it can lead to serious medical conditions including permanent neurological injury and death
- If approved, stannsoporfin is expected to become the first and only pharmacologic option - or therapeutic option of any kind - indicated expressly for treatment of neonates at risk for developing severe hyperbilirubinemia, or severe jaundice, in the U.S.; rolling NDA submission underway under FDA's Fast Track status
- Acquisition further expands Mallinckrodt's pediatric offerings; diversifies hospital portfolio pipeline with differentiated, highly durable product --
- Company expects dilution from acquisition to adjusted diluted earnings per share of $0.15 to $0.20 in 2017; dilution modestly higher in 2018 --

Mallinckrodt plc, a leading global specialty pharmaceutical company, and InfaCare Pharmaceutical Corporation today announced in August that they have entered into an agreement under which Mallinckrodt will acquire InfaCare, a privately-held specialty pharmaceutical company focused on development and commercialization of proprietary pharmaceuticals for neonatal and pediatric patient populations. InfaCare's developmental product stannsoporfin, a heme oxygenase inhibitor, is under investigation for its potential to reduce the production of bilirubin, the elevation of which can contribute to serious consequences in infants.

In July 2016, InfaCare and the U.S. Food and Drug Administration (FDA) reached agreement that a New Drug Application (NDA) could be filed for stannsoporfin using the totality of the drug's data package, including: a positive Phase 2(b) trial as its pivotal study, and data from a second positive Phase 2(b) trial, with no additional studies required pre-approval.

This allowance reflects the medical need in infants at risk of developing severe jaundice. There are also challenges in conducting controlled trials in this fragile population.

In December 2016, the FDA also granted stannsoporfin its Fast Track designation, a process designed to facilitate development and expedite the review of drugs to treat serious conditions and fill an unmet medical need[1]. Fast Track status allows for a "rolling" NDA data submission that has recently begun, and approval is anticipated in the first half of 2018. Post-approval commitments required by the FDA would include conducting trials in pre-term infants less than 35 weeks gestational age as part of the pediatric requirements. If approved, the drug will have substantial durability both as a new chemical entity[2] and through its intellectual property which is valid until 2032.

"Severe hyperbilirubinemia can result in serious complications in infants, including brain damage and, rarely, death," said Steven Romano, MD, Chief Scientific Officer and Executive Vice President of Mallinckrodt. "We look forward to bringing this much-needed treatment option to babies at greatest risk for the consequences of this condition."

"We believe stannsoporfin has the potential to help thousands of infants whose severe jaundice is unresolved by current treatments," said Dan Burns, President and Chief Executive Officer, InfaCare. "We're also excited by the additional development capability and commercial reach that can be gained by becoming part of Mallinckrodt. Together I'm confident we can successfully bring this important treatment to market."

Understanding Severe Jaundice (Severe Hyperbilirubinemia)

Jaundice, or hyperbilirubinemia, is a common clinical condition seen in both term and pre-term newborns. Though lower levels of bilirubin can be benign, some newborns are at greater risk as a result of hemolysis (accelerated breakdown of red blood cells) contributing to the potential of reaching severe bilirubin levels. If a baby develops severe jaundice, there is a risk of bilirubin passing into the brain, a syndrome called Acute Bilirubin Encephalopathy – which can be a serious condition. Prompt treatment may prevent significant lasting damage. But persistent, high levels of bilirubin in the brain can progress to kernicterus, a rare condition associated with severe and permanent brain damage. Symptoms include poor feeding, shrill cry, muscle rigidity, markedly arched back with a backwards hyperextension of the neck, seizures, and stupor or coma. Complications may also include hearing loss and death[4,5]. American Academy of Pediatrics guidelines recommend all newborns be assessed for the risk of hyperbilirubinemia prior to discharge from the hospital.[6]

Stannsoporfin Reduces Potential for Developing Severe Jaundice through Novel Method of Action

Current therapies focus on removing excess bilirubin from the infant's system. Preliminary data from controlled clinical studies show that stannsoporfin's novel method of action demonstrated a robust effect in inhibiting bilirubin production. The drug has also been shown to have a good safety profile when compared to a placebo, and has convenient administration through a single intramuscular injection. If approved, this proprietary therapy is expected to be the first and only pharmacologic treatment indicated for treatment of newborns at risk for developing severe infantile jaundice in the U.S.

"We believe stannsoporfin has the potential to significantly alter the treatment paradigm for infants with this condition which, if unchecked, can have devastating impact to the patient," said Mark Trudeau, Chief Executive Officer and President of Mallinckrodt. "The addition of this highly durable, unique developmental asset to our growing hospital business is an excellent example of Mallinckrodt's investment strategy."

InfaCare's founder and Chairman, Robert Vukovich, added, "A number of years ago we recognized the potential medical importance of stannsoporfin and the role it would play in treating severe neonatal jaundice and the potentially serious neurological consequences of elevated bilirubin levels in newborns. Stannsoporfin is a breakthrough therapy, and I am delighted to see that, with this transaction, the dream we have had to successfully develop this drug is coming to fruition, and we look forward to making it available for clinical use."

<u>Global Severe Jaundice Market and Existing Treatment Paradigm</u>

In the U.S., the total number of term births is estimated at 3.7 million per year[7,8] and, of those, approximately 750,000[9] infants are treated for jaundice. Of those treated, a significant number may be unresponsive to phototherapy – the current standard of care – even with extended and repeated courses of the treatment[10] and face the risk of developing severe jaundice prior to discharge. In severe recurrent or refractory cases, physicians currently must resort to invasive treatment options, most often blood exchange transfusion and, less frequently intravenous immunoglobulin infusions (IVIG), both of which have a more complex and lengthy administration than stannsoporfin's single injection. A small percentage of full-term infants may experience elevated bilirubin levels after discharge and be at risk of severe jaundice[11], requiring hospital readmission. It is anticipated stannsoporfin could reduce the incidence of readmission. The combined potential patient treatments required annually in the U.S. for severe jaundice is approximately 70,000 to 125,000.

Severe jaundice requires extended or recurrent treatment, with current U.S. treatment costs approximately $5,000 per patient[12,13] for infants treated for the condition, which implies an annual cost to the U.S. healthcare system of roughly half a billion dollars.

InfaCare holds worldwide rights to stannsoporfin, and Mallinckrodt estimates the market for severe jaundice patient treatments for term babies in key international countries[14] to be in the range of 150,000 to 275,000 annually. Mallinckrodt will assess regulatory pathways for approvals in markets outside the U.S. post-acquisition.

Stannsoporfin, if approved, is expected to be a highly effective therapy used for near- and full-term infants at risk of developing complications associated with severe jaundice. This new treatment option may reduce the number of newborns advancing to bilirubin levels requiring more intrusive, less specific therapies.

If approved, the drug may also decrease the risks associated with other treatments (e.g., bilirubin rebound) and the risk of prolonged and/or severe bilirubin elevation, which can impact central nervous system development.

1. https://www.fda.gov/forpatients/approvals/fast/ucm405399.htm
2. Adis Insight.
3. U.S. Patent and Trade Office.
4. http://www.mayoclinic.org/diseases-conditions/infant-jaundic e/basics/complications/con-20019637.
5. https://medlineplus.gov/ency/article/007309.htm .
6. http://pediatrics.aappublications.org/content/114/1/297 .
7. https://www.cdc.gov/nchs/data/databriefs/db258.pdf.
8. https://www.cdc.gov/nchs/nvss/births.htm.

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Office: (614) 566-9683 or
email: craig.anderson@centralohionewbornmedicine.com

9. HCUP (Healthcare Cost and Utilization Project) KID Data.
10. Mallinckrodt market research/management projections.
11. http://pediatrics.aappublications.org/content/early/2013/04/03/peds.2012-2634.
12. Mallinckrodt market research/management projections
13. http://pediatrics.aappublications.org/content/early/2013/04/03/peds.2012-2634.

Camera System Brings Families Closer to Babies in the NICU

Parents who have babies in Bronson Children's Hospital's Neonatal Intensive Care Unit (NICU) now can see their little ones even when they can't be at the bedside. A new video camera system allows families to check in on their babies remotely, bringing peace of mind during what can be a challenging time. Bronson is the only children's hospital in southwest Michigan and serves families who come to the hospital from 9 surrounding counties.

"What makes this new camera system even more exceptional for our families, is that this is a gift from our entire community," says Terry Morrow, Vice President of Development and Community Health at Bronson. "The Bronson Health Foundation reached out to individuals, groups and businesses with this idea, and many generous people stepped up to make it a reality." Bronson is proud to be the first hospital in the state to provide NicView cameras for patient families.

Here's how it works: Small video cameras are installed above each of the 45 isolettes in the NICU. They are on most of the day and night. Parents are given a log-in code for the camera in their baby's room. They can share that code with siblings, grandparents and other family or friends. By simply logging on through a cellphone or computer, parents can see a live video feed of their baby's bed.

"Sometimes babies are in the NICU for weeks or months," says Dr. Robin Pierucci, Medical Director of Neonatology at Bronson Children's Hospital. "Families do their best to be at the bedside whenever they can, but it's tough. They can't be here around the clock. The cameras bring such comfort by allowing

Perinatal Substance Use:
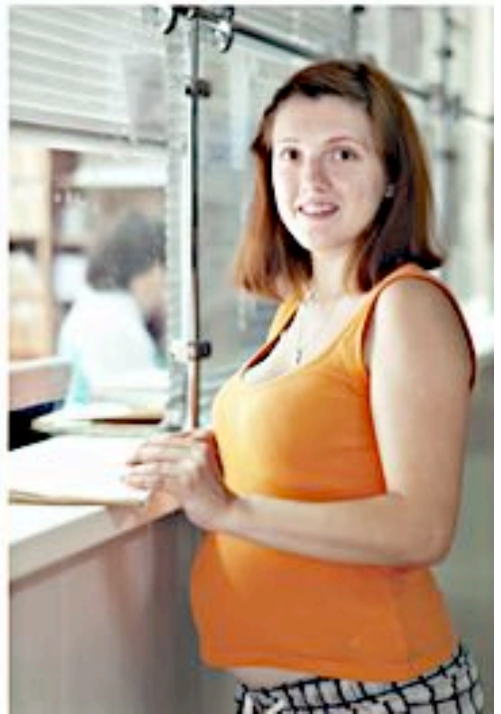Evidence-Based Solutions and Support for the Family

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families to just peak in to get a look at their precious little ones throughout the day or night."

The cameras are also great for siblings to get to know their little brother or sister or for grandparents, aunts and uncles who live out of state or even out of the country who may not get to visit.

Each of the camera units costs about $3,000 to install. Staff members are able to adjust the camera and turn it on or off, while the baby is being tended to or undergoing treatment.

"It is with such gratitude that we say 'thank you' to all of those who saw this as an important gift for families who are in the midst of such a challenging time of having a baby in the hospital. This shows the true giving spirit of our region," says Morrow.

For more information about the NicView cameras, visit bronsonfoundation.com.

Abbott Initiates Ground-Breaking U.S. Pivotal Study of AMPLATZER Device to Correct Common CHD in Newborns

On August 30th, 2017 – Abbott announced it has initiated a U.S. pivotal clinical study evaluating the safety and effectiveness of a modified version of its AMPLATZER™ device designed to correct a common Congenital Heart Defect (CHD) that occurs in approximately 80,000, pre-term infants in the U.S. each year.

Patent Ductus Arteriosus, or PDA, is a life-threatening vascular pathway, or duct, in the heart that remains open due to failure of the fetal duct to close after birth. The duct, which serves as a bridge between blood vessels, and is located between the main two arteries exiting the heart, is present in normally developing fetuses and typically seals itself after birth. In some cases, primarily in premature babies, the PDA fails to spontaneously close, which can result in serious difficulty breathing and an inability to feed -- two critical tasks for newborn babies.

Abbott is developing the AMPLATZER Duct Occluder II Additional Sizes (ADO II

AS) device, which is already approved for use in Europe, with the goal of providing physicians with a nonsurgical treatment option for closing the PDA defect in newborns and pre-term infants. The wire mesh device is placed non-surgically through a catheter inserted through the leg and guided through vessels to the heart, where it is placed to seal the duct. The new device is similar to the AMPLATZER Duct Occluder II product, available in larger sizes, and it builds upon more than 15 years of clinical success for AMPLATZER Occluder therapies.

"Patent Ductus Arteriosus is one of the most common heart defects, accounting for 5% to 10% of all Congenital Heart Disease," said Evan Zahn, MD, Director of the Guerin Family Congenital Heart Program and Director of the Division of Pediatric Cardiology at the Cedars-Sinai Heart Institute in Los Angeles, and principal investigator for the study. "Surgery has many risks in this delicate population and a minimally-invasive approach is desperately needed."

Pharmaceuticals can sometimes be used to promote closure of the duct, but are less effective in pre-term infants. For pre-term infants not responsive to pharmaceuticals, current treatment options are limited to surgery, which is not always possible, or to leave the duct open, which is not optimal for young infants. When the duct remains open, blood is redirected away from the body to the lungs and heart. Left untreated, the condition can lead to serious complications, including heart and kidney failure, damage to the intestines, bleeding in the brain, altered nutrition and growth, and ultimately, becomes a risk factor for chronic lung disease and death.

The study will enroll approximately 50 patients at up to 10 centers across the United States. The first seven patients were enrolled at Le Bonheur Children's Hospital in Memphis, Tenn., and treated by Shyam Sathanandam, MD, Associate Professor at the University of Tennessee.

If successful, the U.S. trial results will support Abbott's application for U.S. Food and Drug Administration (FDA) approval for pediatric use in the U.S.

"This modified AMPLATZER device has been designed with our youngest and tiniest patients in mind," said Michael Dale, Vice President of Abbott's structural heart business. "These smaller sizes may offer physicians greater flexibility to, hopefully, help these infants live healthy, normal lives."

The ADO II AS trial is a single-arm, prospective, multicenter, non-randomized clinical investigation designed to characterize the safety and effectiveness of the ADO II AS device in patients with a Patent Ductus Arteriosus who are more than three days old. Co-primary endpoints are the rate of major complications through 180 days after an attempted implant, and the rate of effective closure of the ductus arteriosus among patients with a successful implant at six months. The secondary endpoint is the rate of significant obstruction of the pulmonary artery or aorta through six months.

For more information, visit: https://clinicaltrials.gov/ct2/show/NCT030 55858.

For more information on Abbott, go to: www.abbott.com.

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Graham's Foundation provides direct support to parents in the NICU and beyond with the goal of improving outcomes for all preemies. We connect organizations, medical professionals, and brands with thousands of preemie parent voices to impact positive change for preemies and their families. And we represent the needs of preemie parents at conferences around the world attended by neonatologists, neonatal nurses, industry, academics, and other professionals who work closely with preemies and their families.

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Magnetic Acupuncture Coming to a NICU Near You?

Michael Narvey, MD

I would consider myself fairly open-minded when it comes to care in the Neonatology Intensive Care Unit (NICU). I wouldn't call myself a maverick or careless, but I certainly am open to new techniques or technologies that may offer a better level of care for the babies in our unit. When it comes to "non-Western" concepts though, such as therapeutic touch, chiropractic manipulations of infants and acupuncture (needle or otherwise), I have generally been a skeptic. I have written about such topics before with the most popular post being "Laser Acupuncture for Neonatal Abstinence Syndrome." My conclusion there, was that I was not a fan of the strategy, but perhaps I could be more open to non-traditional therapies.

Magnetic Acupuncture

Magnetic Acupuncture would appear to be the newest, and perhaps strangest (to me at least) approach to pain relief that I have seen. I do love name of this study; the MAGNIFIC Trial consisted of a pilot study on the use of auricular Magnetic Acupuncture to alleviate pain in the NICU from heel lances. The study was published in the August 2017 of *Acta Paediatrica*; "Magnetic Non-Invasive Acupuncture for Infant Comfort (MAGNIFIC) – A single-blinded randomized controlled pilot trial." The goal here was to measure

pain scores using the PIPP scoring system for pain in the neonate before, during and after a painful experience (heel lance) in the NICU. Being a pilot study, it was small with only 20 needed per arm based on the power calculation to detect a 20% difference in scores. The intervention used small magnets placed at specific locations on the ear of the infant at least two hours before the heel lance was to occur. Before I get into the results, the authors of the study provide references to explain how the therapy works.

Looking at the references, I have to admit I was not able to obtain complete papers, but the evidence is generally it would appear from adult patients. The explanation has to do with the magnetic field increasing blood flow to the area the magnet is applied to, and in addition, another reference suggests that there are affects the orbitofrontal and limbic regions which then impacts neurohormonal responses as seen in functional MRI. The evidence to support this, I would have thought would be pretty sparse, but I was surprised to find a literature review on the subject that looked at 42 studies on the topic. The finding was that 88% of the studies reported a therapeutic effect. The conclusion, though of the review was that the quality of the included studies was a bit sketchy for the most part; therefore reviewers were not able to find that this should be a recommended therapy.

So What Were the Results?

Despite my clear skepticism what this study did well, was that aside from the magnets, the intervention was the same. Twenty-one babies received the magnetic-treatments vs 19 placebo. There was a difference in the gestational ages of the babies with the magnet-treated infants being about two weeks older (35 vs 33 weeks). What difference that might in and of itself have on the PIPPs scoring I am not sure. The stickers were applied to the ears with and without magnets in a randomized fashion, and the nurses instructed to score them using the PIPP scoring system. Interestingly, as per their unit policy, all babies received sucrose, as well, before the intervention of a heel lance, so I suppose the information gleaned here would be the use of magnets as an adjunctive treatment. No difference was noted in the two groups before and after the heel lance, but during the procedure the magnet-treated infants had a difference in means (SD): 5.9 (3.7) v 8.3 (4.7), p=0.04). No differences were found in secondary measures such as HR or saturation, and no adverse effects were noted. The authors conclusions were that it was feasible and appears safe, and as with most pilot studies, warrants further larger studies to verify the results.

Should We Run Out and Buy It?

One of the issues I have with the study is that in the introduction they mention that this treatment might be useful where Kangaroo Care (KC) is not such, as a critically-ill infant. Having placed infants who are quite sick in KC and watched wonderful stability arise, I am not sure if the unit in question underutilizes this important modality for comfort.

The second and perhaps biggest issue I have here is that, although the primary outcome was reached, it does seem that there was some "fishing" going on here. By that I mean there were three PIPP scores examined (before, during and after), and one barely reached statistical significance. My hunch is that indeed, this was reached by chance, rather than it being a real difference.

The last concern I have is that while the intervention was done in a blinded and randomized fashion, the evidence supporting the use of

"The second and perhaps biggest issue I have here is that, although the primary outcome was reached, it does seem that there was some 'fishing' going on here. By that I mean there were three PIPP scores examined (before, during and after), and one barely reached statistical significance. My hunch is that indeed, this was reached by chance, rather than it being a real difference."

this in the first place is not strong. Taking this into account, and adding the previous concern in as well, I have strong doubts that this is indeed "for real." I doubt this will be the last we will hear about it, and while my skepticism continues, I have to admit if a larger study is produced I would be willing and interested in reading it.

NT

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NEO: The Conference on Neonatology
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www.neoconference.com

Bangkok International Neonatology Symposium
Mar 7-9, 2018; Bangkok, Thailand
www.bkkneonatology.com/regis1.html

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Mar. 14-16, 2018; Loma Linda, CA USA
www.nationalperinatal.org/annualconference2018

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https://shop.aap.org/2018-workshop-on-neonatal-perinatal-practice-strategies/

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www.mcascientificevents.eu/iccn2018/

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