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16 Cove Rd., Ste. 200
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Introducing Allogeneic Human Mesenchymal Stem Cell-based Therapy to Improve Clinical Outcomes in Patients with Hypoplastic Left Heart Syndrome

By Sunjay Kaushal, MD; Helina Mehta, MD; Kristopher Deatrck, MD; Michael Slack, MD; Joshua Hare, MD

Introduction

Hypoplastic Left Heart Syndrome (HLHS) is characterized by significant underdevelopment of the left side of the heart, which is defined by hypoplasia of the left ventricle associated with severe mitral and aortic stenosis or atresia, and hypoplasia of the ascending aorta and aortic arch. Since there is essentially no left ventricle, the right ventricle pumps blood to both pulmonary and systemic circulations. After delivery, survival depends on a Patent Ductus Arteriosus (PDA) and nonrestrictive Atrial Septal Defect (ASD), as well as the absence of aortic restriction (coarctation) of PDA blood flow to the coronary arteries via the ascending aorta.

Until the introduction of the first stage of surgical palliation by William Norwood, MD, in 1981, HLHS was universally fatal within the first weeks of life. Currently, treatment strategies include cardiac transplantation or staged surgical palliation, consisting of a series of operations whereby the right ventricular outflow is reconstructed to provide systemic circulation. The first stage of palliation is now known as the Norwood operation and is performed within the first week of life, with the tripartite goal of providing: unobstructed systemic blood flow, unrestricted mixing of atrial blood, and restrictive pulmonary blood flow. The second stage is broadly termed a superior cavopulmonary anastomosis, and can be constructed as either a "Bidirectional" Glenn, or a Hemi-Fontan between 4 to 6 months of age, with the goal of establishing a direct systemic venous – pulmonary arterial connection, and unloading the volume overload imposed by the systemic-pulmonary arterial connection imposed at the stage 1 operation. The third stage is universally known as the Fontan operation, and creates a total cavopulmonary connection. This operation results in the entirety of the systemic venous blood to be directed to the pulmonary arterial circulation, providing separation of the

systemic arterial and venous circulations, while directing the full systemic venous flow to the pulmonary circulation. This may be performed as early as 18 months, but is more commonly done between 2 and 4 years of age. The overall objective of the Fontan circulation is to rely on the right ventricle to support the systemic circulation and for the systemic venous return to be pulled through the pulmonary circulation in the absence of a ventricular pumping chamber, relying on the vis-a-tergo and negative intrathoracic pressure to facilitate pulmonary circulation.

Approximately 949 infants with HLHS are born in the United States annually, and 318 die during the neonatal period for a neonatal mortality of 33%.¹ In spite of dramatic improvements in pre-, intra- and postoperative care, the mortality rate of these infants is as high as 25% to 35% during the first year of life and the overall 5-year survival rate remains limited with reported survivals over 50%-60%. Even with cardiac transplantation remaining as the only current viable alternative for patients with failing RV function, survival rate continues to remain poor after HLHS surgical staged palliation and transplantation.^{2,3,4} After the Fontan completion operation, the circulatory state is that of chronic systemic venous hypertension. This can lead to multiple clinically difficult and life-limiting complications, including hepatic congestion and cirrhosis, plastic bronchitis, and protein-losing enteropathy. Furthermore, even with optimal care in infancy and childhood, all patients with a Fontan will ultimately experience right heart failure, which may be related to increasing pressure in the pulmonary vascular bed or failure of the systemic right ventricle due to the much higher afterload. Given these surgical limitations, innovative treatment options to regenerate and remodel the RV myocardium to make it more capable of sustaining systemic circulation remain a significant unmet medical need.^{5,6,7}

We are currently one of the first pediatric centers pioneering the clinical application of stem cell therapy for infants with HLHS in a trial entitled "Allogeneic Human Mesenchymal Stem Cell Injection in Patients with Hypoplastic Left Heart Syndrome: An Open Label Pilot



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Study (ELPIS).” In this investigation, we are evaluating the intramyocardial delivery of adjunctive cell-based therapy by directly injecting allogeneic human mesenchymal stem cells (allo-MSCs) during the Stage II operation. To our knowledge, this is the first randomized clinical trial to use allogeneic stem cells in children with HLHS in the world.

Significance of the Study

We aim to overlay a novel cell therapeutic strategy on the staged surgical procedures that HLHS patients typically undergo. During the Stage II superior cavopulmonary operation, allogeneic mesenchymal stem cells will be injected intramyocardially into the right ventricle.

Primary Objective

Evaluate the safety and feasibility of intramyocardial injection of allogeneic mesenchymal cells during the Stage II operation.

Secondary Objective

Observe effects on clinical outcomes including right ventricular myocardial function, severity of tricuspid regurgitation, incidence of serious adverse events, re-hospitalizations, changes in health status, the need for transplantation, or mortality.

Methodology

Study Design and Sample Size

We plan to enroll a total of thirty patients with HLHS in a staged enrollment process. In this open-labeled study, a maximum of 20 patients will eventually receive intramyocardial injection of the allogeneic mesenchymal stem cells and 10 control patients with no cell injection. The enrollment of the patients will occur in two staged groups: Group A and Group B. In Group A, 10 consecutive HLHS patients will be initially enrolled in the allogeneic MSCs treatment arm to determine feasibility and safety. After six months of the last enrolled patient in Group A, all Group A patients will be assessed in order to determine whether the methodology is feasible and safe, including the harvesting, processing, and administering of the allogeneic MSCs. Thereafter, Group B will start enrolling a total of 20 HLHS patients, who will be randomized to the treatment and control arms in a 1:1 ratio, respectively, in order to have 10 allogeneic MSCs treated patients and 10 control patients. At the completion of this Phase I clinical study, the total enrolled cohort will be 20 patients treated with allogeneic MSCs and 10 patients in the control arm.

Study Setting and Period

Recruitment of subjects for the study are ongoing at the University of Maryland Children's Heart Program and Johns Hopkins Hospital. We will be recruiting subjects at additional sites in the near future, including Children's Healthcare of Atlanta.

Inclusion Criteria

In order to participate in this study, a patient must meet all of the inclusion criteria:

1. Subjects with HLHS (all types) requiring Stage II surgery.

Exclusion Criteria

In order to participate in this study, a patient must not:

1. Have HLHS and restrictive or intact atrial septum.
2. Be undergoing the Norwood procedure that does not have HLHS.
3. Have significant coronary artery sinusoids.

4. Require mechanical circulatory support prior to Stage II operation.
5. Have an underlying evidence of arrhythmia requiring anti-arrhythmia therapy.
6. Have a parent or guardian unwilling or unable to comply with necessary follow-up.
7. Be serum-positive for HIV, hepatitis BsAg or viremic hepatitis C.
8. Be unsuitable for inclusion in the study in the opinion of the investigators.
9. Need for concomitant surgery for aortic coarctation or tricuspid valve repair.

Sample Size Considerations

Analyses of bioactivity will be exploratory in nature in order to aid in selection of dosage, endpoints, time points, and sample size determination for subsequent larger trials, but is sufficiently powered to determine safety.

Therapeutic Stem Cell Intervention

During the Stage II operation when the patient is on cardiopulmonary bypass, previously harvested, isolated, and expanded, allogeneic mesenchymal stem cells will be delivered into the right ventricle, directly into the myocardium using a 27-gauge needle syringe. The stem cell transplant occurs after the completion of the repair but before separating from cardiopulmonary bypass. The process and manufacturing of the allogeneic mesenchymal stem cells will be delivered as specified in the POSEIDON-DCM Phase I/II Trial (IND #14419; NCT01392625), led by Dr. Joshua M. Hare (ISCI / University of Miami Miller School of Medicine, FL). The allogeneic hMSC cells will have undergone control testing on the final enriched cell product prior to administration and the cell doses employed will be 2.5×10^5 cells per kg of recipient body weight (5 million / 20kg). The entire dose of the cells, 600 microliters, will be divided and delivered in 6-10 intramyocardial injections. The intramyocardial injection of cells will take approximately 5 to 10 minutes, with a minimal addition to the total bypass time.^{8,9}

Plan for Analysis

All subjects will be cared for according to our standard postoperative protocols. All subjects will receive post-treatment assessments completed at set intervals between two days and 48 weeks after cell injection. Vital signs, complete physical examination, 12 lead electrocardiogram, and complete TTE as well as selected blood work will be included at two days, 24 weeks, and 48 weeks. Also, 24-hour Holter monitor (Month 6 and Month 12), and AE monitoring will be included. The only additional assessment that is not part of the routine standard of care for follow-up after the Stage II or III operated HLHS patients are the following: cardiac MRI scan performed at pre-operation, 24 and 48 weeks post-cell injection; immune monitoring for graft rejection at two days, 24 weeks, and 48 weeks. The following markers will be used for analysis to assess for activated T-cells based upon a CD3+CD25+ or CD3+CD69+ phenotype; biomarkers will be performed at 2 days, 1 week, 4 weeks, 24 weeks, and 48 weeks.

Primary Endpoints

- We will measure safety and feasibility of intramyocardial delivery of allogeneic mesenchymal stem cells in subjects with HLHS after one year of injections. Note: We will monitor major adverse cardiac events including: death, sustained/symptomatic ventricular tachycardia requiring intervention with inotropic support, aggravation of heart failure, new myocardial infarction, unplanned

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Satyan Lakshminrusimha, MD
Chief, Division of Neonatology
Women and Children's
Hospital of Buffalo



Ashley Darcy Mahoney, PhD, NNP-BC
Neonatal Nurse Practitioner,
South Dade Neonatology
Assistant Professor,
Emory University School of Nursing

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 NO₂ 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 PaO₂, inspired NO₂, 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.

Hypoxemia from Methemoglobinemia

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 (NO₂) forms in gas mixtures containing NO and O₂. Nitrogen dioxide may cause airway inflammation and damage to lung tissues.

If there is an unexpected change in NO₂ concentration, or if the NO₂ 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 NO₂ analyzer should be recalibrated. The dose of INOmax and/or FiO₂ 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 NO₂. Elevated NO₂ may cause acute lung injury. Elevations in methemoglobin reduce the oxygen delivery capacity of the circulation. In clinical studies, NO₂ 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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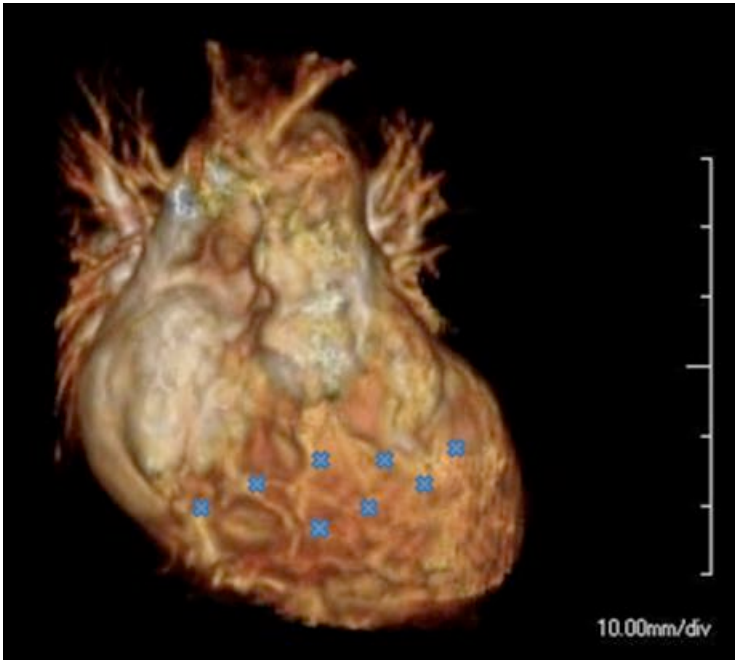


Figure 1. cMRI of an ELPIS patient at baseline. Allogeneic mesenchymal stem cells will be injected to the right ventricle of patients with Hypoplastic Left Heart Syndrome at the time of the bidirectional cavopulmonary connection operation administered intramyocardially at 6-10 injection sites (blue X's = sites of injection).

cardiovascular option for cardiac tamponade and infection in the first month after injection, and serially afterwards.¹⁰

Secondary Endpoints

- To measure improvements of right ventricular function: change from baseline in right ventricular function by measuring right ventricular ejection fraction or fractional area change (RVEF/FAC), right ventricular end-diastolic volume, right ventricular end-systolic volume, right ventricular end-systolic diameter, and tricuspid regurgitation as measured by serial echocardiograms and MRI scans.¹⁰
- To measure incidence of mortality or need for transplantation after the BDCPA operation up to one year follow-up.¹⁰
- To measure changes in somatic growth velocity over time (weight, height, head circumference) from the BDCPA operation out to 12 months post-op.¹⁰
- To measure assessments of co-morbidity: cardiovascular mortality, all-cause mortality, cardiovascular morbidity, re-hospitalizations, and need for heart transplantation.¹⁰

Discussion

The objective of the ELPIS Trial is to advance the clinical application of MSCs in the treatment of HLHS patients and to potentially uncover the mechanism by which MSCs can improve ventricular function in this unique patient subset. In Phase I/II adult clinical trials, we have previously shown the safety and preliminary efficacy of allogeneic MSC treatment in adult ischemic patients by the proposed

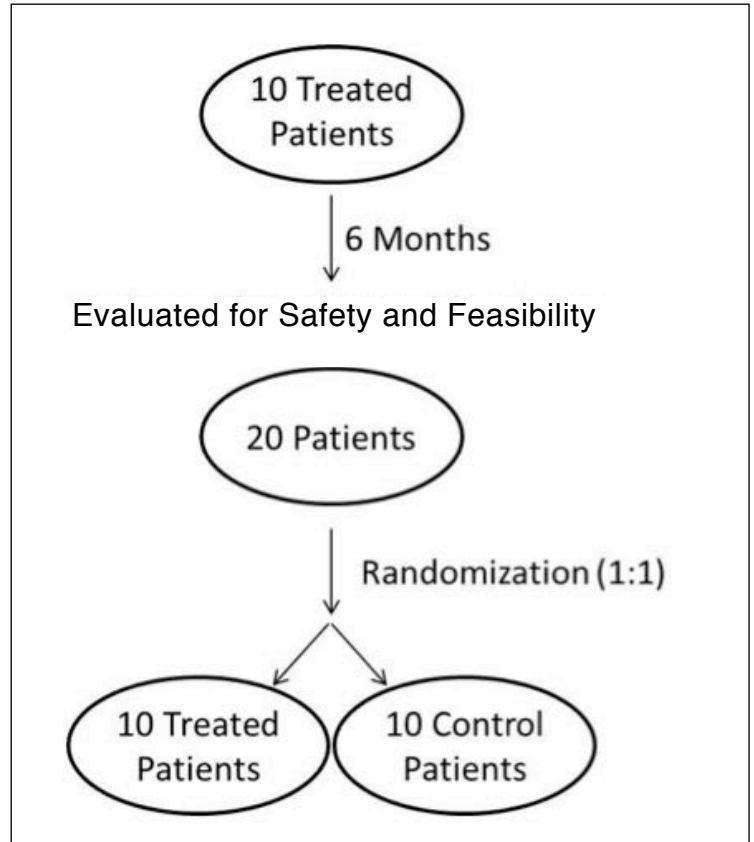


Figure 2. ELPIS Enrollment Plan.

remodeling mechanisms of direct cell-cell interactions with myocardial cells and indirect paracrine effects in order to reduce myocardial fibrosis, stimulate angiogenesis, and stimulate endogenous c-kit+ cardiac progenitor cells (CPCs) in the left ventricle (LV).^{11,12} We have recently shown MSC injections preserve RV ventricular dysfunction by activating endogenous pathways of ventricular remodeling in a swine model of RV pressure overload, replicating features of HLHS.^{13,14} We hypothesize that MSCs will facilitate remodeling of the RV in HLHS patients by both direct and indirect mechanisms and improve ventricular function. We will overlay our novel therapeutic MSC strategy on the stage II bidirectional cavopulmonary anastomosis operation in HLHS patients and rigorously validate potential mechanisms for RV improvement.¹³

MSCs have been thoroughly investigated in animal models, and shown the ability to regenerate the heart directly through formation of new tissue and indirectly through paracrine effects.^{20,21} MSCs are an attractive candidate for stem cell therapy for multiple reasons. First, MSCs have well-defined characteristics due to their ability to differentiate into selected terminally differentiated lineages in vitro and their expression of specific, well-established markers (CD90, CD105, CD73).^{18,19} Second, MSCs are reproducibly isolated from bone marrow and expand robustly in vitro.^{18,19} Third, since MSC engraftment occurs at low rates with <0.1% of injected cells, the current paradigm suggests that MSCs interact with the injured native cells in order to limit tissue destruction or enhance repair by

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a variety of mechanisms. Cross-talk mechanisms, by which MSCs exert effects on various native signaling pathways include:

- a. Secretion of bioactive proteins that act in a paracrine or autocrine fashion;
- b. Upregulation of genes that attenuate destructive inflammation and facilitate repair and;
- c. Secretion of extracellular microvesicles (EVs) that contain proteins and microRNAs.²²

In the injured heart, MSCs remodel the injured or distressed myocardium by modulating endogenous remodeling, attenuating fibrosis, promoting neovessel formation, stimulating cardiomyocyte proliferation, and activating endogenous c-kit+ CPCs.²² Fourth, MSCs have been studied in both cardiac and other conditions with more than 120 clinical trials, listed on clinicaltrials.gov, and have repeatedly been shown to be safe in clinical studies. Finally, MSCs have recently been evaluated in clinical trials in multiple forms of adult cardiac disease, including acute myocardial infarction and chronic heart failure, and treatment has decreased myocardial fibrosis and improved clinical status.^{8,9,11,12}

Allogeneic MSC injections are as effective as autologous MSCs in promoting functional remodeling of the treated ventricle and did not increase immunophenotyping in adult patients with ischemic cardiomyopathy patients.^{11,12} Follow-up on the original POSEIDON trial, (POSEIDON-DCM trial NCT01392625) demonstrated that allogeneic MSC are safe and efficacious. In an early Phase I/IIb study, patients with chronic nonischemic dilated cardiomyopathy (NIDCM) were randomized to receive intramyocardial injections of either autologous or allogeneic MSCs.¹¹ Twelve-month SAE incidence was 28.2% following allogeneic MSC injection versus 63.5% with autologous MSC injection ($p=0.1$). The ejection fraction increased following allogeneic MSC injection by 8.0% ($p=0.004$) and 5.4% with autologous MSC injection ($p=0.116$; allo vs auto $p=0.4887$).¹¹ This improvement in LV function correlated with increased functional capacity as measured by the 6-minute walk test.¹¹ Therefore, allogeneic MSCs are safe and potentially effective in improving left ventricular ejection fraction. Duration of this affect still remains to be determined.

The development of new therapies for right ventricular dysfunction in patients with HLHS remains challenging. The ability to conduct laboratory investigation is limited because no available animal models replicate all of the physiologic derangements present, particularly with respect to a morphologic right ventricle providing the systemic cardiac output. Nevertheless, treatment of other models of ventricular failure with stem cell therapy has been promising, and this promise has been replicated in clinical trials for adult patients.

The hypothesis of our ELPIS Trial protocol is that MSCs transplanted into the myocardium of the right ventricle of patients with HLHS will stimulate favorable remodeling, and thus, improve myocardial function in the long term. We further hypothesize patients treated with MSC injection will have improved long-term survival and functional capacity compared to non-treated control patients, who currently have an average mortality rate of 54% at five years. The existing pre-clinical and clinical data with MSC demonstrates that these cells have a strong regenerative ability. If the anticipated 10% to 15% improvement of right ventricular ejection fraction is seen in these HLHS patients, as was seen in the adult trial and preclinical animal data, we believe that this will lead to significantly improved survival and quality of life. Preserving, but more importantly, improving right ventricular function is critical for long-term survival of the HLHS patient.

Although trials of stem cell therapy for adults with cardiac disease have shown great promise, we believe children may be the best responders to stem cell therapy. In the ELPIS trial, we will be testing MSC injection in the right ventricular myocardium of pediatric patients with HLHS. As previous research has shown that neonatal and pediatric cardiomyocytes and cardiac progenitor cells are more responsive to the biological cues directed by transplanted stem cells. We also believe that these patients may be better candidates for functional improvements than adults.¹⁵ While this hypothesis needs further testing with clinical trials, indirect evidence is available from previous human studies examining the growing young human myocardium. Case reports using bone marrow-derived cell preparations and autologous cord blood have shown striking improvements in ventricular function in young HLHS patients. In a recent Japanese Phase I study of CDC therapy for HLHS, the best treatment responders were the smallest,

youngest infants with the lowest ejection fractions.^{16,17} While encouraging, this study was limited by the lack of a proper control group and the heterogeneity of the patients enrolled. These observations are consistent with our data showing 3-fold higher c-kit+ CPC counts in neonates than in infants.¹⁸ Interestingly, levels of c-kit + CPCs in patients with heart failure are similar to those in normal neonatal hearts.²⁰ These findings may have important clinical implications for HLHS patients when the MSCs remodel the RV myocardium by stimulating human c-kit+ CPCs to proliferate and differentiate, as we have shown in swine myocardial infarction model.¹⁹ Although there is no large animal model of HLHS, in a neonatal porcine model of RV failure, we observed that MSC treatment facilitated remodeling of the RV myocardium at a histological and functional levels.¹³ Based on these preliminary insights, the young myocardium may be the best responder to MSC therapies to improve cardiac performance since the developing myocardium is more biologically responsive.

Conclusion

This landmark clinical trial will potentially result in a paradigm shift in HLHS treatment to meet an unmet medical need in this patient population. Our hypothesis that allogeneic MSCs can improve function in the right ventricle by both direct and indirect mechanisms builds on the advances in both surgery and cellular biology over the past thirty years. The ELPIS Trial is intended to address the remaining obstacles by using an allogeneic stem cell-based therapy to improve long-term ventricular function in patients with HLHS. We propose that a cell-based therapy for HLHS patients may prevent RV dysfunction, reducing both mortality and the need for transplantation.

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“This landmark clinical trial will potentially result in a paradigm shift in HLHS treatment to meet an unmet medical need in this patient population. Our hypothesis that allogeneic MSCs can improve function in the right ventricle by both direct and indirect mechanisms builds on the advances in both surgery and cellular biology over the past thirty years.”

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NT

Corresponding Author



Sunjay Kaushal, MD, PhD
 Division of Cardiac Surgery
 University of Maryland Medical Center
 110 S. Paca St., 7th Fl.
 Baltimore MD 21201
 410-328-5842 (O); 410-328-2750 (F)
 skaushal@som.umaryland.edu

Helina Mehta, MD
 Division of Pediatric Cardiology,
 University of Maryland School of Medicine
 110 S. Paca Street, 7th Fl.
 Baltimore, MD USA

Kristopher Deatrck, MD
 Division of Pediatric Cardiology,
 University of Maryland School of Medicine
 110 S. Paca Street, 7th Fl.
 Baltimore, MD USA

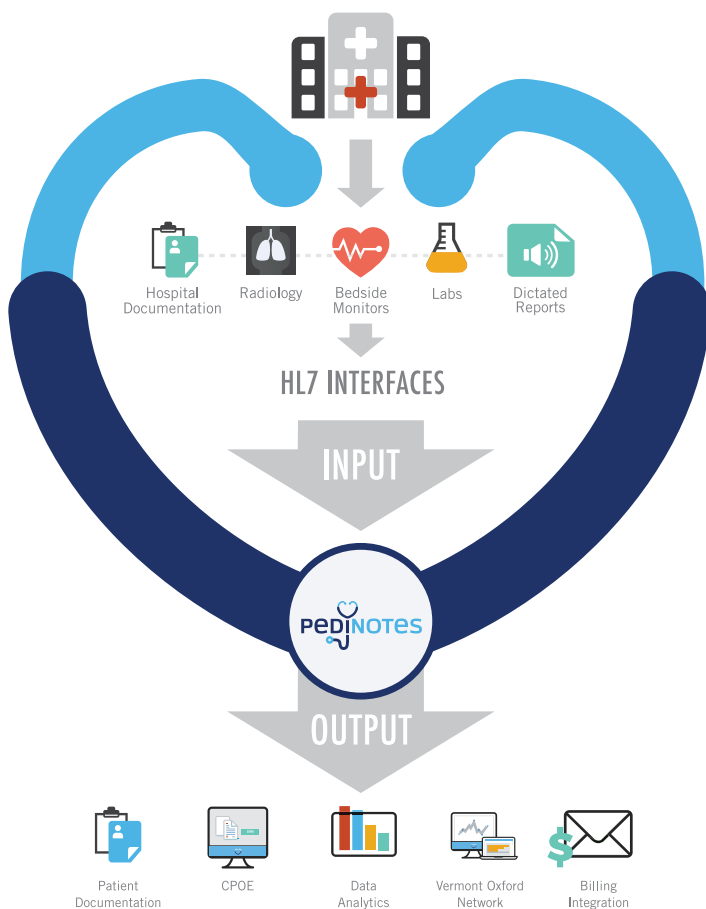
Michael Slack, MD
 Division of Pediatric Cardiology,
 University of Maryland School of Medicine
 110 S. Paca St., 7th Fl.
 Baltimore, MD USA

Joshua Hare, MD
 Interdisciplinary Stem Cell Institute,
 University of Miami Miller School of Medicine
 Miami, FL USA



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Update on Respiratory Syncytial Virus (RSV) Epidemiology and Current Issues in Immunoprophylaxis

By Leonard R. Krilov, MD

Respiratory Syncytial Virus (RSV) Lower Respiratory Tract Infection (LRTI) remains the leading cause of hospitalization in infants and young children with up to 100,000 infants hospitalized and >2 million outpatient visits per year, and 25% to 40% developing LRTI during the first year of life in the United States.^{1,2} Analyses of national databases estimate an annual cost related to RSV infection of >\$50 million.³ On a worldwide basis, RSV infections account for 34 million cases of LRTI and 66,000 to 250,000 deaths per year.⁴

Although all infants are at risk, babies who were born prematurely (with or without Chronic Lung Disease of infancy) and those with hemodynamically significant Congenital Heart Disease (CHD) are at increased risk of severe RSV disease. Other smaller groups of infants, including those with neuromuscular disease, immune deficiency, cystic fibrosis and Down Syndrome, are also susceptible to more severe RSV infection. Other factors associated with RSV LRTI include: crowded living conditions, lower socioeconomic status, having school-aged siblings, multiple births (especially triplets and greater), and passive cigarette smoke exposure.⁵ RSV is also being increasingly recognized as an important pathogen in older adults and adults with Chronic Lung Disease.⁶

Clinically, acute RSV infection in infants begins with coughing, congestion and coryza, which then progresses to involvement of the lower respiratory tract as evidenced by tachypnea and wheezing. This constellation of findings, often in the presence of low grade fever, defines the clinical illness of bronchiolitis. RSV is the leading cause of this illness in infants and young children, although a number of other respiratory viruses have been associated with similar clinical features. Viral pneumonia is also a common component of RSV LRTI with focal consolidation observed in 20% to 25% of cases. Secondary bacterial infection, with the exception of otitis media, is uncommon in RSV infection.⁵

Additionally, children hospitalized with RSV LRTI in infancy have been observed to have an increased incidence of wheezing episodes over subsequent years. Recent data have suggested that prevention of severe RSV infection in infancy with palivizumab is associated with decreased wheezing over subsequent years.^{7,8}

Despite the magnitude and potential severity of RSV infection, no effective anti-viral therapy exists and treatment remains supportive. Supplemental oxygen and mechanical ventilator support may be

needed in more severe cases. Fluid support (intravenous hydration or nasogastric fluid administration) is the other supportive modality that may be beneficial in children hospitalized due to this infection. Despite the diffuse wheezing observed in bronchiolitis, the pathophysiology of RSV-induced wheezing is different from asthma and the bronchodilators and corticosteroids that are the mainstays of treatment of asthma exacerbations have not been demonstrated to be of benefit in RSV bronchiolitis and are not recommended for the routine care of such children.⁹

Ribavirin was approved in the 1980's for the aerosolized treatment of children hospitalized with RSV bronchiolitis. Concerns about the high acquisition cost, escape of the drug into the environment, posing a theoretical teratogenic risk to women of child bearing age, and most importantly, follow-up studies that failed to demonstrate significant clinical benefit have all but eliminated use of the drug for this indication. A number of anti-viral agents active against RSV are currently in development. In addition to assessing efficacy and safety, these agents will also need to look at optimal timing in the course of illness to consider treatment.¹⁰

Much progress has been made toward development of a safe and effective RSV vaccine in recent years. Newer molecular virology studies demonstrating the critical role of the RSV pre-fusion F protein in disease pathogenesis have led to the design of promising vaccine candidates. However, even with these advances, the need for establishing protection at 0 to 3 months of age to achieve maximum benefit against the most severe infections, provides an additional challenge for RSV vaccine development. Clinical trials of F protein and live-attenuated vaccines are underway. Multiple approaches for RSV vaccination are being considered, including maternal immunization to boost immunity in neonates, infant vaccination, and vaccination of older and high-risk adults. A combination of initial passive immunoprophylaxis (see below), along with active immunization may be another strategy to consider.¹¹

There is a long history of effective RSV prevention immunoprophylaxis via administration of a number of immunoglobulin products. High-titer RSV intravenous immunoglobulin (RSV IGIV; RespiGAM) was initially available for RSV prevention in high-risk premature infants. Its use was limited by the need for IV administration over a number of hours and its relatively large fluid volume. This product was subsequently replaced by the development of the humanized anti-F protein monoclonal antibody

palivizumab (Synagis), which was approved by the Food and Drug Administration in 1998 for RSV prevention in high-risk premature infants born at ≤ 35 weeks gestational age and ≤ 6 months of age. After further study, palivizumab received additional approval for prevention of RSV in children <2 years of age with hemodynamically significant CHD.^{12,13}

Subsequent to the approval of palivizumab, the Committee on Infectious Disease (COID) of the American Academy of Pediatrics (AAP) has published guidelines for the use of palivizumab for immunoprophylaxis against severe RSV disease in preterm infants. These recommendations have become increasingly restrictive with the most recent guideline in 2014 advising prophylaxis for premature infants without underlying Heart or Chronic Lung Disease to those <29 weeks gestational age and in the first year of life at the start of RSV season (typically November 1st of each year). In the presence of Chronic Lung Disease, this recommendation increases to 32 weeks gestational age and up to 2 years of age if still requiring medication or oxygen for their lung disease. For those with hemodynamically significant CHD, immunoprophylaxis is recommended for the RSV season during the first year of life. These recommendations were reaffirmed for 2018. In part, these guidelines were justified based on the COID interpretation of the epidemiology of RSV disease, and the high acquisition cost of palivizumab.¹⁴

Other published guidelines have supported broader indications for palivizumab prophylaxis in premature infants. For example, the National Perinatal Association recommends additional consideration of palivizumab immunoprophylaxis for all premature infants <32 weeks gestational age and <6 months chronological age at the start of RSV season. Additionally, premature infants 32 1/7 through 35 6/7 weeks gestational age and with additional risk factors (e.g., child care attendance, school aged siblings, multiple gestation, young chronological age at onset of RSV season, lower socioeconomic status, and parental smoking) may be considered on an individual basis.¹⁵ However, insurers have primarily adapted the COID guidelines in determining a baby's eligibility for reimbursement for palivizumab.

Two studies published subsequent to the 2014 COID guidelines have demonstrated the ongoing impact of RSV infection in premature infants born at 29 to 35 weeks gestational age. A non-interventional observational study, entitled Sentinel 1, conducted at 43 centers across the United States during the 2014-2015 and 2015-2016 RSV seasons, evaluated the

course of RSV infection in such infants during their first year of life.¹⁶ This study provides updated data confirming the potential severity of RSV infection in 29 to 35 week gestational age infants hospitalized for this condition in the first year of life. Overall, 42% of babies enrolled in this gestational age range that were hospitalized required ICU care and 20% were intubated and placed on mechanical ventilation. The need for ICU admission and mechanical intubation correlated with earlier gestational age and younger chronological age. Of those infants born at 29 to 32 weeks gestational age, who were <3 months chronological age at the time of the RSV hospitalization, 68% were admitted to the ICU and 44% required intubation and mechanical ventilation. Although the Sentinel 1 Study demonstrates the potential severity of RSV infection in these premature infants, it does not provide a denominator to help determine whether RSV hospitalizations are increasing among this group of premature infants subsequent to the 2014 AAP guideline.¹⁴

To investigate the impact of the 2014 AAP guideline on preterm infant hospitalizations related to RSV, Kong and colleagues utilized the Truven Health MarketScan Commercial and Multi-State Medicaid health insurance administrative claim databases to assess changes in utilization of palivizumab immunoprophylaxis and in RSV hospitalizations in infants born at 29 to 34 weeks gestational age. Data for the 2014-2015 RSV season after the publication of the 2014 AAP guideline were compared to the 2010 to 2014 seasons prior to this guideline. Palivizumab usage was assessed from pharmacy or outpatient medical claims for the drug and determinations of RSV hospitalizations were based on inpatient claims with the diagnosis of RSV. Premature infants born at 29 to 34 weeks gestational age and <12 months chronological age represented 2.9 to 3.5% of all births in the two databases. Palivizumab prescriptions decreased 62 to 95% in 2014-2015 compared to the 2013-2014 RSV season. RSV hospitalizations in infants 29 to 34 week gestational age infants and <3 months of age increased 2.7 fold in the commercial database (p=0.02) and 1.4-fold (p=0.03) in the Medicaid set from 2014-2015 compared to 2013-2014. Similar changes were seen comparing RSV hospitalizations for the premature babies in 2014-2015 to the composite of 2010 to 2014 RSV hospitalization rates. In the infants 29 to 34 week's gestational age, RSV hospitalizations were also two to seven times higher than for normal full-term infants. RSV hospitalization rates among full-term infants did not change significantly from 2013-2014 to 2014-2015.¹⁷

In summary, RSV infection remains a major threat for infants and young children and recent studies demonstrate continued increased severity of infection in premature infants up to 35 weeks gestational age during their first RSV season. The future looks promising with new anti-virals, potential RSV vaccines, and

improved monoclonal antibodies for passive protection. At present, however, treatment remains primarily supportive and palivizumab is the only option for immunoprophylaxis against severe disease in high-risk infants. Further evaluations to determine the best indications or palivizumab use are warranted, especially in view of recent data documenting the severity of the disease and increased risk for 29 to 35 week gestational age infants.

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NT

Leonard R. Krilov, MD
Department of Pediatrics
Children's Medical Center at NYU
Winthrop Hospital and SUNY Stony
Brook School of Medicine

Correspondence:

Leonard R. Krilov, MD
Department of Pediatrics
NYU Winthrop Hospital
259 First St.
Mineola, NY 11501 USA
Tel: 516.663.2288; FAX: 516.663.8955
lkirilov@nyuwinthrop.org

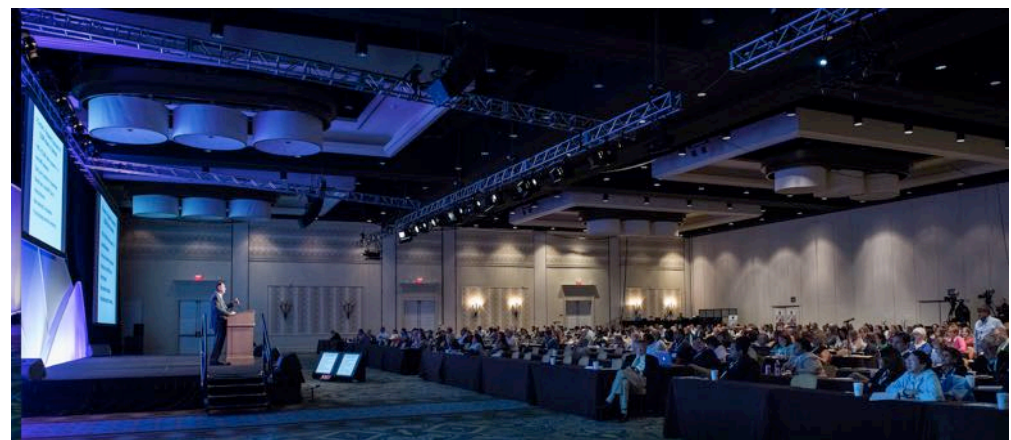
Preview of NEO—The Conference for Neonatology and Specialty Review 2018

By Alan R. Spitzer, MD; Timothy A. Biela, MD

February is just around the corner and that means the *NEO Conference* and *Specialty Review Meetings* will once again take place in beautiful Orlando, Florida! These annual events represent a wonderful opportunity to get out of the cold and snow, while listening to many of the finest speakers in the world discuss the up-to-the minute care of the newborn infant! This year represents the Twelfth Annual *NEO - The Conference for Neonatology*, and we are pleased to describe many of the upcoming sessions of the meeting in this issue of *Neonatology Today*. Once again, it is our desire to also highlight our *Specialty Review Course*, held concurrently with the *NEO Conference*. If you want to hear about the latest and greatest in Neonatal Medicine, then the *NEO Course* is the one to take. If you are preparing for your upcoming Board examination, or simply want a concise, thorough review of the current practice of Neonatology, the *Specialty Review* course cannot be beat. *Specialty Review*, overseen by David Weisoly, DO, and Matt Saxonhouse, MD, is the revised and updated course that was formerly organized and presented in Chicago by Dharmapuri Vidyasagar, MD, one of the “Legends of Neonatology.” In addition, we are proud to have Lucky Jain, MD, Vice Chairman of Pediatrics at Emory University, as our Special Consultant to the course. The educational experience of the course leaders and the outstanding faculty are second to none.

NEO itself began twelve years ago as an extensive redesign of the former *Management of the Tiny Baby Conference*, which ran for 28 years, and was one of the pioneering meetings in Neonatal Medicine. *NEO* now has also become one of the major annual conferences in Neonatal Medicine, highlighted by the unique “Legends of Neonatology,” which honors neonatologists that have dedicated their career to improving the care provided to neonates.

The line-up for this year’s meeting is one of the best that we have attracted to date, with some unique features, and a wide range of topics and world-renowned speakers who will address many of the most critical and controversial issues that influence the clinical practice of Newborn Medicine. It remains the focus of the *NEO* meeting to



provide a wealth of valuable information for our attendees to bring back to their NICUs to improve the care that they provide infants in their units. *NEO* is designed as a very practical meeting that will allow you to better understand and utilize the leading approaches to Neonatal Intensive Care. Last year, the meeting had nearly 150 international attendees, and we look forward to welcoming increasing numbers of our colleagues from around the world for this stellar event.

The main section of the *NEO Conference* starts on Thursday, February 22nd, 2018, and runs through Sunday, February 25th, 2018. The *NEO Conference* is arranged thematically so that we can cover a select series of topics more inclusively and in greater detail. The major themes of this year's meeting include: "Forging New Pathways in Neonatal Nutrition;" "Future of Neonatal Medicine – Where are we Headed?" "Evolving Concepts in Neonatal Respiratory Management;" "Controversies in Cardiology for the Neonatologist;" "Changing Thoughts in Neonatal Sepsis;" and "Pharmacology of Neonatal Neurology – Where Are We Today?" Each of these sessions has many of the foremost experts and best speakers in the country addressing the topics for which they have become noted.

Some of the notable speakers on the morning of Day One include: Camilia Martin, MD, discussing the "Use and Role of SMOFs and Other Enteral Lipids," and Lars Bode, PhD, who will speak about the "Current Thoughts of Oligosaccharides and Their Potential Role in Reducing NEC." Christoph Fusch, MD, will discuss the "Individualization and Targeting of Human Milk Therapy." Lastly, Tarah Colaizy, MD, will speak about "Whether or Not DEBM Is Really the Perfect Food for the VLBW."

The afternoon of the first day features, a special session, "The Future of Neonatal Medicine." Melvin Yoder, MD, will "Identify the Potential Role of Stem Cells for the Fetus and Neonate," and Alan Flake, MD will discuss the "Creation of the Artificial Placenta." The afternoon session will be closed by John Zupancic, MD, whose topic is "Evaluating the Future of Neonatal Medicine in Regards to Outcomes and Reimbursements."

Friday's theme of "Evolving Concepts in Neonatal Respiratory Management," starts with a series of presentations by some of the most-recognized leaders in the field: Kristi Watterberg, MD, will discuss "Current Thoughts on the Use of Early Dose Hydrocortisone," and Fernando Moya, MD, will speak on "Whether or Not Surfactant is Necessary in the Modern Era." Lucky Jane, MD will discuss the "Effects of Late Preterm on Respiratory Function," and Hareh Kirpalani, MD, will do a "Critical Review of Non-Invasive Ventilation and When is it Appropriate?"

The "Legends of Neonatology Award Luncheon" will also occur on Friday, making this day extraordinary. Starting in 2007 at the first *NEO Conference*, we have made an effort to acknowledge and show attendees some of the greatest advances in Neonatal Medicine through our "Legends of Neonatology" program. Winners of the Legends Award essentially constitute a 'Hall of Fame' for Newborn Medicine, and prior recipients include: Drs. Mildred Stahlman, Maria Delivoria-Papadopoulou, Mary Ellen Avery, Lu-Ann Papile, Avroy Fanaroff, Marshall Klaus, Jerold Lucey, Robert Bartlett, Stanley Dudrick, George Gregory, John Clements, Forrest Bird, William Norwood, William Oh, Abraham Rudolph, Lilly Dubowitz, M. Jeffrey Maisels, Jen-Tien Wung, Frederick C. Battaglia, Joseph Volpe, Philip Sunshine, Alan Spitzer, John Kattwinkel, Vinod Bhutani, and Dharmapuri Vidyasagar, Alan Jobe, and Richard Polin. All of these honorees have graced us with their presence over the years to accept their awards.

This year's honorees are, once again unique, and are major ongoing contributors to the field of Neonatal Medicine. They are:

Richard Martin, MD, of Case Western Reserve University School of Medicine, one of the long-standing leaders in the specialty of Newborn Medicine, whose work in the field of Developmental Respiratory Neurobiology has been fundamental to the establishment of modern NICU care; and Eduardo Bancalari, MD, from the University of Miami, one of the greatest neonatal researchers of Neonatal Pulmonary Disease and Management. The work of these amazing individuals represents some of the primary reasons why outcomes for critically ill infants have improved so dramatically in the last few decades. At the Legends presentation itself, Dr. Alan Spitzer, Course Director for *NEO*, will review the contributions of these "Legends," and show how their work has become the core upon which much of modern Newborn Medicine is founded. This is always a very special event and a highlight of the meeting that attendees should not miss!



The Friday afternoon's session, after the "Legends Luncheon," should be truly outstanding and very valuable to the clinician with both *Legends* giving presentations. Richard Martin, MD, will discuss the "Causes and Consequences of Hypoxic Episodes in the Neonate," and Eduardo Bancalari, MD will help us "Understand the Management of Closed-Loop Ventilator. Leif Nelin, MD, will close the Friday session with describing the "Unified Approach to the Care of the Chronic BPD Patient."

Saturday's talks start with a special speaker, Alex Kemper, MD, from Duke University, who will discuss "Whether CCHD Screening is Making a Difference, and Is It Cost-Effective?" Dr. Kemper will be followed by Ron Clyman, MD, presenting the "Latest in Our Understanding and Management of the Patent Ductus Arteriosus." The second session on Saturday is "Insights about Neonatal Sepsis." Sagori Mukhopadhyay, MD, will discuss "Sepsis and the Use of the Sepsis Calculation," and lastly, William Benitz, MD, will discuss the "Improved Targeting of Antibiotic Therapy in the Neonate."

Sunday concludes the event with a discussion of one of the most important topics affecting a neonate: "The Pharmacology and Treatment of Neonatal Neurology." Ravi Patel, MD, will outline the rewards and risks of caffeine in a neonate. "The Safety of Neonatal Anesthesia" will be discussed by Saleem Islam, MD. Mohamed El-Dib, MD, will discuss, "Evaluate the Use of Hypothermia for HIE," and, "Are the Outcomes Improving?" The last talk of the conference will be given by Hannah Glass, MD, from the University of California, San Francisco, promises to be stimulating, as she will be discussing, "Neuroprotection Beyond Cooling - Is There a Role for Epogen?"

I think it is very clear that the meeting this year will be a very special one, perhaps the finest that we have ever put together, and we very much hope that you can attend. We are also proud and excited about the annual *Specialty Review in Neonatology* course, which will be held concurrently in Orlando, Florida from February 20th-25th, 2017. The premier board certification review course of its type has been the model for core foundational physiology and problem-based learning since the 1970's, when it was started by Dr. Vidyasagar, who remains an

"This year's honorees [Legends of Neonatology] are, once again unique, and are major ongoing contributors to the field of Neonatal Medicine. They are: Richard Martin, MD, of Case Western Reserve University School of Medicine.... and Eduardo Bancalari, MD, from the University of Miami...."

advisor to the meeting. The newest version of *Specialty Review* is directed by Drs. David Weisoly and Matthew Saxonhouse, as part of the MEDNAX Center for Research, Education, and Quality.

Every year, the *Specialty Review* course grows in content and breadth, with new and innovative offerings to enhance the learning experience of course attendees. The absolute objective of *Specialty Review in Neonatology* is to provide each and every attendee with a clear, focused, and comprehensive educational program to prepare the attendee for the ABP Neonatology Board Certification Exam.

Every lecture and tutorial is provided by master teachers. Some examples include: "Neonatal Pulmonary Physiology" by Dr. Lucky Jain of Emory University School of Medicine, "Neonatal Cardiac Physiology" by Dr. Dara Brodsky, and "Clinical Biostatistics for the Neonatologist" by Dr. John Zupancic of Boston Children's/Harvard University School of Medicine.

The faculty are chosen primarily for their teaching and lecturing skills, and all are committed to providing the absolute best learning experience for the attendees. Faculty also make themselves available for one-on-one instruction after their lectures, and lectures are enhanced by being in the tutorial format, using the Audience Response System (ARS). The full syllabus, with every slide

presented in the course, is available only to course attendees. The MEDNAX Center for Research, Education, and Quality is excited to see you at *Specialty Review in Neonatology 2018*. While the course is geared towards Neonatologists preparing for their ABP Neonatal-Perinatal Certification Examination, it is also a tremendous foundational review in Neonatal-Perinatal Pathophysiology for Advance Practice Nurses, Neonatology Fellows, and Residents-in-Training as well. With 6 days packed full of core fundamental pathophysiology and medical management techniques in an enthusiastic, and entertaining learning environment, we are certain that attendees will agree that *Specialty Review in Neonatology* is the premier review course in the specialty. This year's combined events at the incredible Hyatt Regency Orlando Resort are guaranteed to be the extensive educational program of the year in Neonatal-Perinatal Medicine.

We very much hope that you can join us for one of these meetings and promise you an educational experience (and some very good food—we like to feed our attendees well!) that you will not soon forget. For more information go to: www.neoconference.com and www.specialtyreview.com.

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Corresponding Author

Timothy Biela, MD
2018 Course Co-Director - NEO
Pediatrix Medical Group of Texas -
San Antonio
5430 Fredericksburg Rd., Suite 508
San Antonio, TX 78229 USA
Tel: 210.541.8281

Timothy_Biela@MEDNAX.com



Alan Spitzer, MD
2018 Course Co-Director - NEO
The Mednax Center for Research,
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Hyperammonemia in Neonates: Looking Beyond Sepsis

By Samantha A. Schrier Vergano, MD, FAAP, FACMG; Cynthia Le Mons

Hyperammonemia is a rare, but life-threatening condition in neonates that requires prompt recognition and treatment. The causes of hyperammonemia can be many, including: liver failure, medications, infection, and inborn errors of metabolism (IEM). IEMs occur infrequently, in approximately one in every 35,000 births [Summar et al, 2013]. This prevalence may be underestimated, as many cases go undiagnosed, especially if infants die in the newborn period. Therefore, including an IEM on a differential diagnosis can be difficult, even for experienced physicians.

IEMs can be difficult to recognize, as the symptoms of hyperammonemia often mimic other more common conditions, including sepsis. Due to the rarity of IEMs, hyperammonemia is often not diagnosed until much later in an infant's course, after irreversible brain damage or death has occurred. Msall et al. (1984) demonstrated a decline in IQ with every 24 hours spent in a hyperammonemic coma.

The adage of, "1. Sepsis 2. Sepsis 3. Sepsis" that is taught about differential diagnoses when evaluating a newborn with poor feeding, temperature dysregulation, seizures, or lethargy, unfortunately, leads physicians down a narrow path when treating these infants. Rarer causes of these symptoms, such as IEMs, are often overlooked because of the (not inappropriate) focus on infection as a common diagnosis in this age group.

IEMs that cause hyperammonemia include: urea cycle disorders, organic acidurias, fatty acid oxidation disorders, and others, but the primary detoxification of ammonia in the body occurs in the urea cycle. Protein is broken down into amino acids, with the waste product of nitrogen being ammonia. Ammonia is then converted by the urea cycle to urea, a non-toxic compound, for excretion.

In urea cycle disorders, absence or deficiency of any one of the enzymes in the cycle can result in inadequate conversion of ammonia to urea and accumulation of ammonia in the

bloodstream, leading to neurotoxicity. Symptoms of hyperammonemia reflect this neurotoxicity, and can include lethargy, poikilothermia, difficulty feeding, abnormal respirations, and vomiting; prolonged hyperammonemia leads to encephalopathy, seizures, coma, and death.

Acute treatment of hyperammonemia is severalfold, and consists of infusions of fluids containing high concentrations dextrose and other high-calorie, non-protein sources (such as lipids), nitrogen scavenging agents (oral sodium phenylbutyrate or intravenous sodium phenylacetate/sodium benzoate), and more invasive treatments, such as hemodialysis. A metabolic geneticist should always be consulted when hyperammonemia is suspected or diagnosed in any age group. Long-term treatment to prevent hyperammonemia includes dietary protein restriction and outpatient medications including arginine and nitrogen-scavengers.

Although educating clinicians about the catastrophic consequences of failing to obtain an ammonia level is certainly an important aspect of improving recognition of this condition, the infrequency with which IEMs (and in particular, UCDs) are encountered in the clinical setting makes the swift identification of hyperammonemia challenging.

"IEMs can be difficult to recognize, as the symptoms of hyperammonemia often mimic other more common conditions, including sepsis. Due to the rarity of IEMs, hyperammonemia is often not diagnosed until much later in an infant's course, after irreversible brain damage or death has occurred."

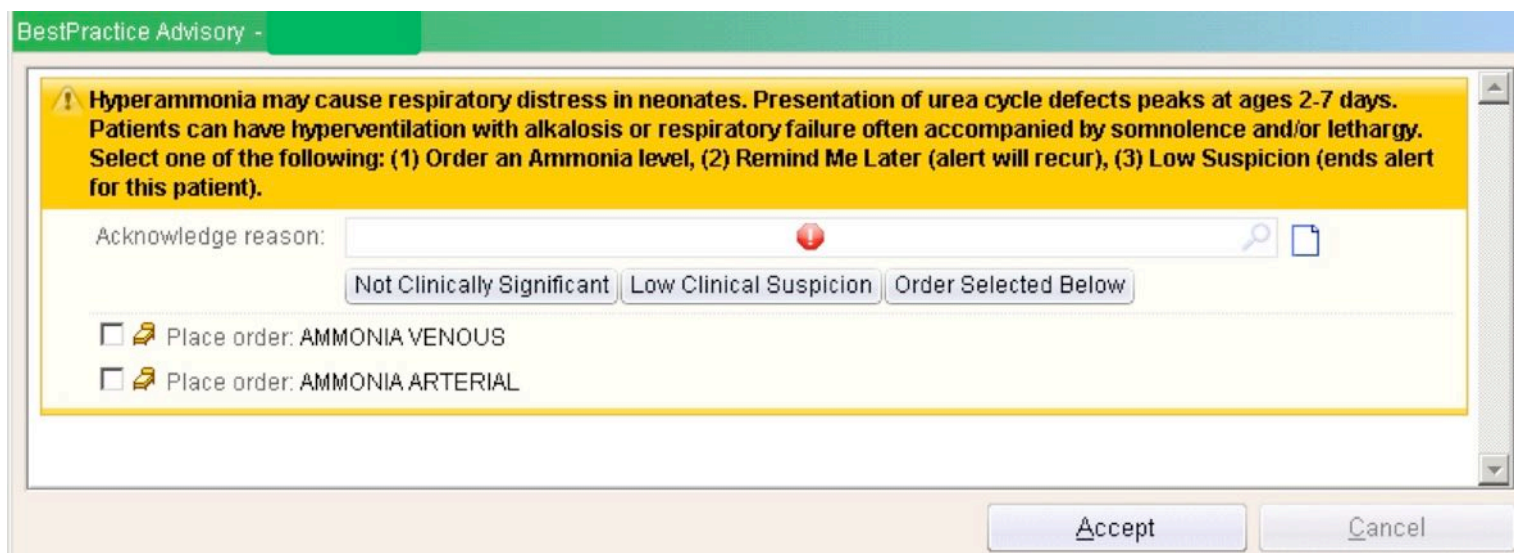


Figure 1. Screenshot of the EMR alert.

Unfortunately, missing the diagnosis, therefore reducing the treatment window, results in significant morbidity and mortality. In an attempt to improve detection rates of hyperammonemia in neonates, a Best Practice Alert (BPA) was created at The Children's Hospital of Philadelphia (CHOP) through the EPIC® electronic medical record (EMR) system in 2012. After examining ten years of medical records from patients presenting with hyperammonemia and the labs ordered at the time of admission, the alert was created to fire on infants 2-7 days of age on whom a first-time blood gas was obtained. The details and methods of the creation of the BPA were subsequently published in *Molecular Genetics and Metabolism* (Vergano et al, 2013).

If an infant meets the inclusion criteria for the alert to fire, the clinicians are given the option to:

- complete the order for an ammonia level,
- decline and dismiss the order due to low clinical suspicion, or
- request a "remind me later" to trigger the alert to recur at a later time (Figure 1).

The alert does not reappear if the 'low clinical suspicion' option is selected.

The BPA is now a software package owned by EPIC® (www.epic.com), which can be purchased by other hospitals wishing to utilize the alert. In April of 2014, it was installed within the Sentara Health System in Eastern Virginia. We have hence undertaken a review of the data generated from the BPA since its implementation in both institutions to determine the effectiveness of the tool in identifying infants with hyperammonemia secondary to IEMs.

At CHOP, the alert has fired almost 1,000 times, resulting in approximately 160 orders of ammonia levels, and identifying one infant with hyperammonemia, who was found to have methylmalonic aciduria. This is consistent with the low positive-predictive value anticipated with this tool (<1%), as well as the overall prevalence of IEMs, estimated at about 10-15 in every 100,000 births. Since its inception with Sentara, the alert has fired 286 times, and has correctly identified one hyperammonemic infant who was found to be a compound carrier for two different fatty acid oxidation disorders. Although the number of alerts and ammonia orders

greatly exceeds the number of infants detected, the benefits are significant when considering the low cost of obtaining an ammonia level and the relative unobtrusiveness of the alert.

However, there still appear to be challenges. In the case of one infant who was evaluated at an institution in Virginia that utilized the alert and who met criteria, the alert fired, but the clinician declined the opportunity to obtain an ammonia level. Only after the infant was transferred to the adjacent children's hospital (which did not utilize EPIC), was it suggested that an ammonia level be obtained. The result was >1000 mmol/L and the infant was ultimately found to have argininosuccinic aciduria, a urea cycle disorder. Fortunately, with intervention, his ammonia levels dropped within 24 hours, and he is now 11 months old, having recently received an orthotopic liver transplant. While the alert itself is helpful in reminding ordering providers about the utility of obtaining an ammonia level, it still relies on clinicians' judgment at the time, which can result in an IEM being overlooked.

We recommend that even if hospitals do not utilize the EPIC EMR, they should consider including an ammonia level as part of their sepsis order set, since infection appears to be the most common diagnosis for which hyperammonemia is mistaken in neonates.

We report here the available statistics from this BPA in two institutions to continually evaluate both the utility and effectiveness of the tool. Thus far, it has identified those

"We recommend that even if hospitals do not utilize the EPIC EMR, they should consider including an ammonia level as part of their sepsis order set, since infection appears to be the most common diagnosis for which hyperammonemia is mistaken in neonates."

infants for whom it was targeted, with no apparent false negative results. We hope this potentially life-saving electronic alert will continue to be implemented in other hospitals across the country, enabling faster recognition of hyperammonemia and ultimately improving the outcomes of children with these conditions.

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Corresponding Author



Samantha A. Schrier Vergano, MD,
FAAP, FACMG
Division of Medical Genetics & Metabolism
Children's Hospital of The King's Daughters
601 Children's Lane
Norfolk, VA 23507 USA

Department of Pediatrics
Eastern Virginia Medical School
Norfolk, VA USA

Samantha.Vergano@CHKD.ORG

Cynthia Le Mons, Executive Director
National Urea Cycle Disorders
Foundation
75 South Grand Ave.
Pasadena, CA 91105 USA
Tel: 626.578.0833
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Artefacts During Amplitude-Integrated EEG (aEEG) Recording

By Karl F. Schettler, MD, MHBA

aEEG is becoming more and more commonly used in Neonatal Intensive Care Units (NICUs). While being a huge step forward in continuous neuromonitoring of our patients, there are also some pitfalls, especially by artefacts. This article is set to give you a first impression and show you some of the most common artefacts you will encounter with using aEEG.

Shift/Drift of Baseline

Permanent artefacts in the raw EEG often lead to what is termed a shift or drift of the baseline. The steadily-repeating artefact amplitudes in the raw EEG mean that, for example, in the burst suppression pattern, there are no longer any suppression phases without an amplitude, because during the suppression phase the artifact amplitude is still recorded. As a consequence, the lower margin of the aEEG increases and the actual baseline of 0 μ V now lies e.g. at 3 μ V, since the artefact constantly interferes with an amplitude of 3 μ V (Figure 1).

Movement Artefact

Artefacts due to movement generally produce a sudden shift in the aEEG and can be misinterpreted as seizures if the raw EEG is not reviewed. Often they look like large-amplitude waves in the raw EEG, but they can also appear with a low-amplitude (Figure 2). Good documentation of the child's rounds, and

“aEEG is becoming more and more commonly used in Neonatal Intensive Care Units (NICUs). While being a huge step forward in continuous neuromonitoring of our patients, there are also some pitfalls, especially by artefacts.”

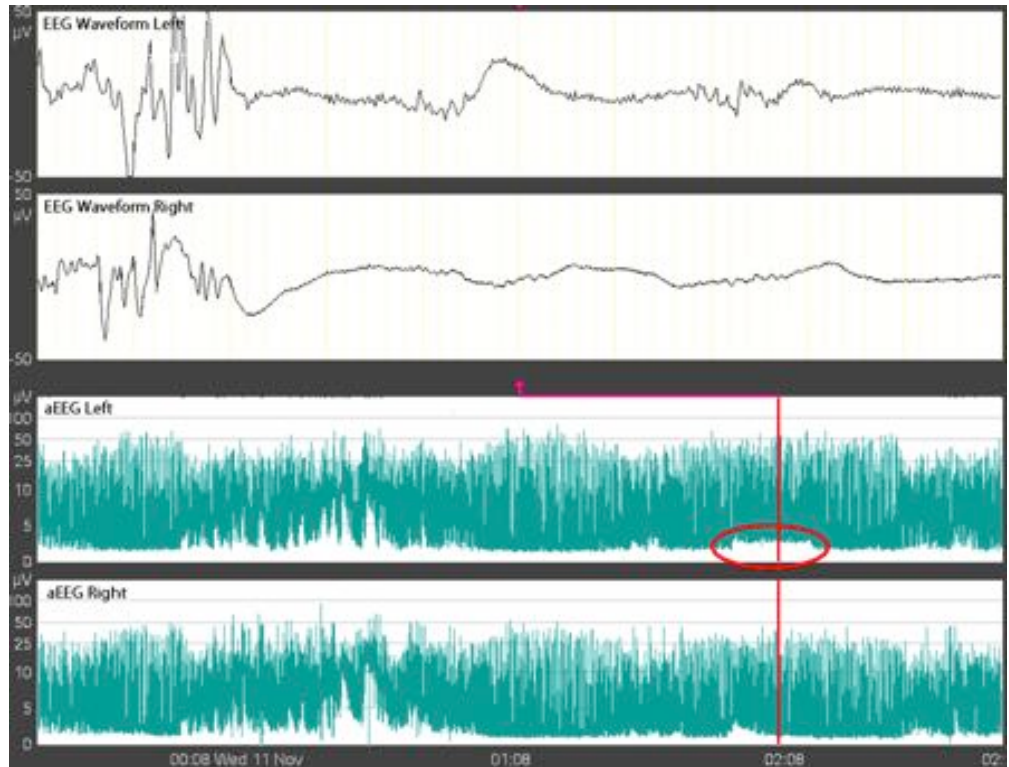


Figure 1. Small shift of baseline of 1-2 μ V in the marked area on the left side in a burst suppression pattern.

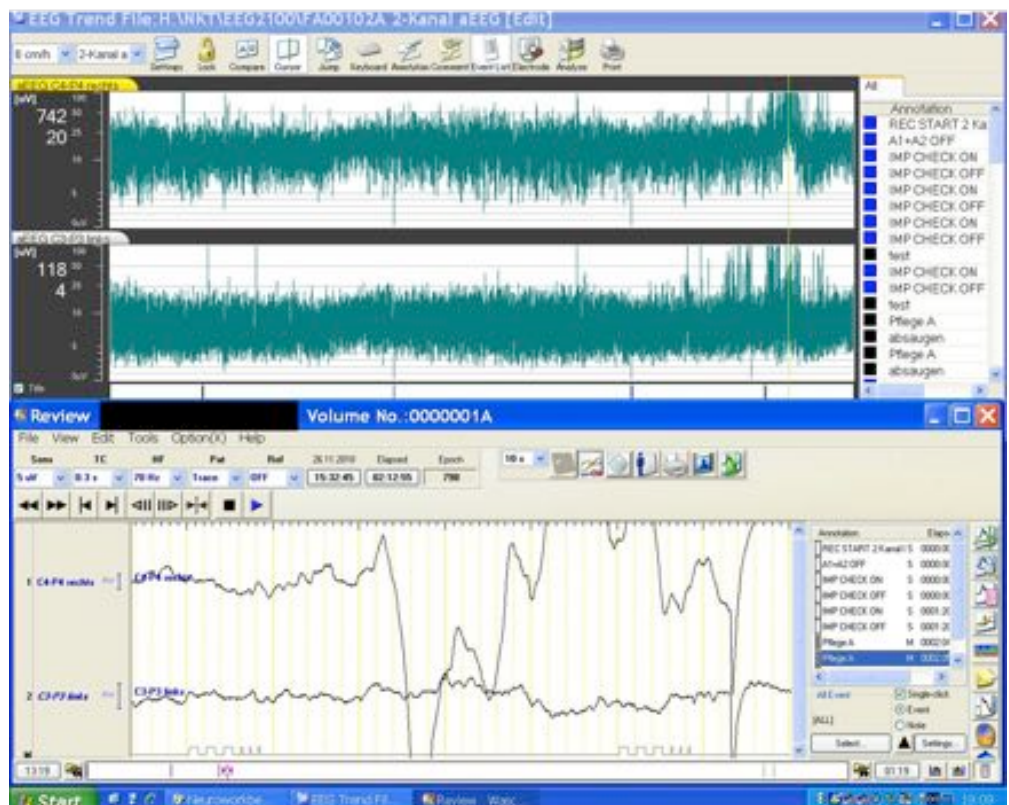


Figure 2. Unilateral movement artefact, visible on the large-amplitude waves in the raw EEG.

if possible, a camera recording, assist in identifying these artefacts more reliably. The regular patting of a baby during feeding can trigger a distinctive movement artefact, known as the patting artefact. Due to the often very regular displacements in amplitude and the frequency, here it is sometimes even more difficult to differentiate from seizures.

Respiratory Artefacts

Respiration can similarly be a process which creates a lot of movement. In the raw EEG, this generates a constant interference signal (Figure 3), which not only lifts the lower margin of the raw EEG, but can also make the entire recording useless. Here it is helpful to determine the frequency of the artefact with precision and to compare it with the respiratory parameters. The amplitude height can be very variable and is, for example, often low during high-frequency respiration.

Muscle Artefact

In proximity to the usual electrode positions of the aEEG, there are many strong muscles, notably the *Musculus temporalis*. In particular, needles placed directly into the muscle result in recording an electromyogram rather than the intended aEEG. Muscle artefacts are characterized by the very high frequency, and are therefore, generally easy to identify (Figure 4). One could practically say the raw EEG looks like "muscle tremor".

ECG Artefact

Occasionally, the aEEG derives heart activity and thus an ECG. Depending on the strength of the interference signal, the resulting artefact has different-height amplitudes. Classically, this similarly results in baseline drift (Figure 5). With a very powerful artefact signal, it is even possible to identify elements such as the P and T wave, and the QRS complex. Here, again, help can be found by determining the frequency of the artefact, and comparing it with the patient's heart rate, in order to identify it reliably as ECG.

Sensor Contact or "Short Circuit" Artefact

If the lead electrodes come into direct contact or some kind of direct electrical contact, one obtains what is practically a flat trace, which can occasionally also have the appearance of a burst suppression pattern in the aEEG thanks to other artefacts. The confusing aspect in this is that according to the rule a very

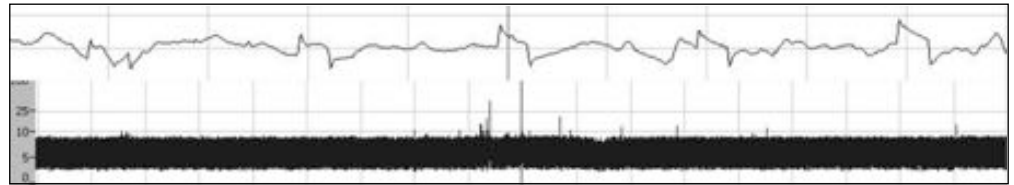


Figure 3. Respiration artefact, the aEEG shows only the breathing amplitudes and the patient's background activity can no longer be assessed.

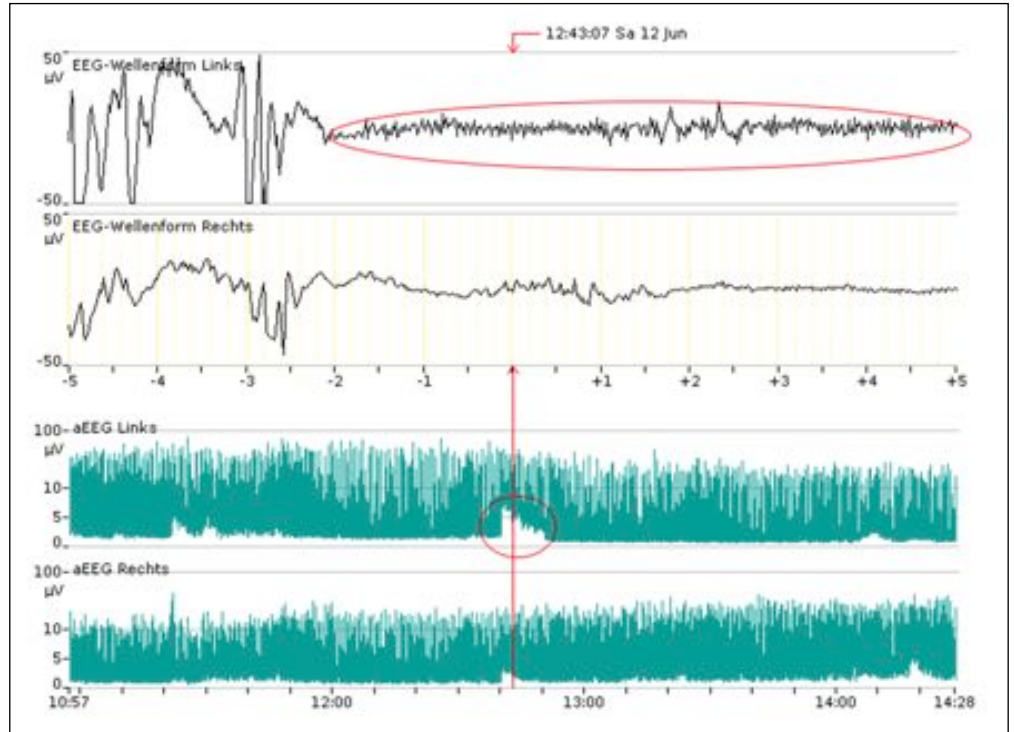


Figure 4. Muscle artefact in a burst suppression pattern in the upper raw EEG, with associated increase in the lower margin of the aEEG.

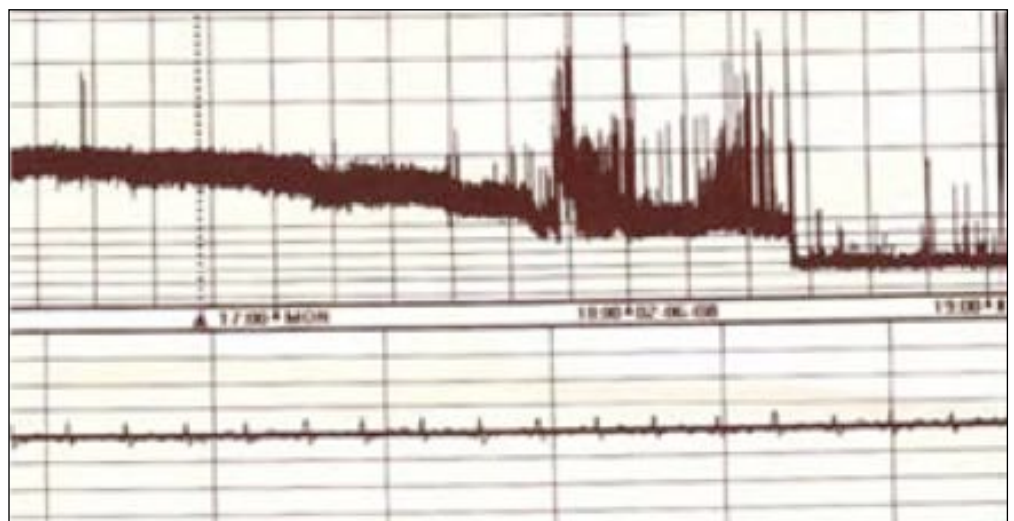


Figure 5. Example of an ECG artefact, where the frequency of the low amplitudes in the raw EEG corresponds precisely to the patient's heart rate, with this causing a shift of the baseline in the aEEG.

good impedance is measured and therefore, the user does not immediately think that anything is wrong with the electrodes. This artefact tends to occur when using needle electrodes if these are inserted facing towards one another

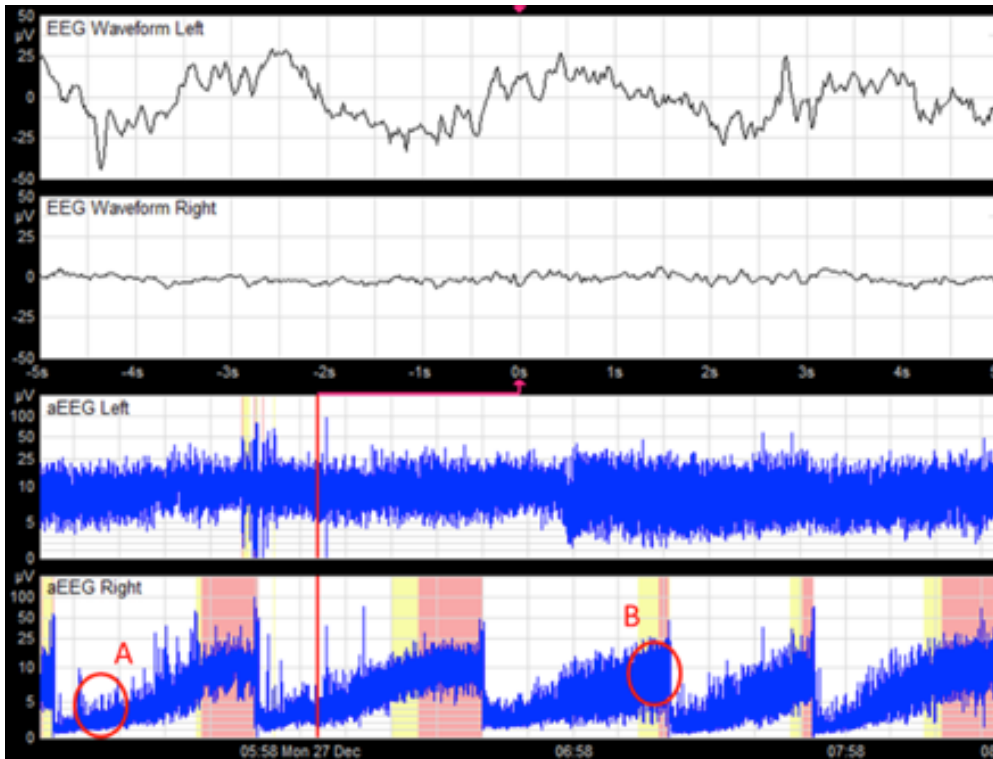


Figure 6. A shows low amplitude after repositioned electrodes, using 5.85% saline solution with good impedance; B shows correct background activity after some time, but at this moment now has a measured worse impedance indicated by the machine as red background. Image used by kind permission of M. Schmid.

or too close to one another. It is also possible for a direct short-circuit contact to be created externally, as in the example given below due to the strong conductivity of a 5.85% saline solution used for contact cleaning (Figure 6).

Edema or Hematoma

Fixing an electrode over a hematoma or larger edema similarly results in an artefact. The EEG signal is weakened and generally produces electrical "shunting," whereby, it is again possible to give the appearance of absent brain activity (similar to Figure 6).

Conclusion

Artefacts are found on average in approx. 12% of the recording period. Of these, around 45% are caused by movement and the remaining 55% by electrical interference (Hagmann CF et al. Artifacts on electroencephalograms may influence the amplitude-integrated EEG classification: a qualitative analysis in neonatal encephalopathy. *Pediatrics* 2006; 118:2552-4). By implementing the raw EEG in the recording, it becomes significantly easier to identify artefacts reliably.

If you are interested in comprehensive training workshops on the use of aEEG and NIRS, then you should attend **NEOCON 2018** in Munich, Germany March 23-25, 2018, <http://www.munich-neocon.com/>.

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Karl F. Schettler, MD, MHBA
Children's Hospital - St. Marien
Grillparzerstr. 9
84036 Landshut, Germany

karl.florian@schettler.com

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Highlights from the 7th Annual Fetal Echocardiography Symposium at UCLA - Los Angeles, California, October 21st, 2017

By Mark S. Sklansky, MD

The 7th Annual Fetal Echocardiography Symposium at UCLA was a tremendous success, continuing UCLA's annual tradition of providing a full day of focused, real-life, clinically-oriented instruction for all clinicians involved with fetal cardiac imaging. State-of-the-art presentations were presented by world-class experts in Obstetric Sonography, Maternal-Fetal Medicine and Pediatric/Fetal Cardiology. As has been the case in previous years, the Seventh Annual symposium sold out, with over 215 registrants (sonographers and physicians—obstetricians, maternal-fetal medicine specialists, and pediatric cardiologists) from across the country. The symposium retained its focus on clinically oriented tips and pearls for both beginning and advanced sonographers and physicians.

In addition, as has become a trademark of this course, the 7th UCLA Fetal Echocardiography Symposium featured special patient testimonials before the lunch break. Actual patients and their families shared their emotional and captivating stories with the registrants, demonstrating first-hand the tremendous impact of prenatal

detection of Congenital Heart Disease (CHD), and the importance of the way a new

diagnosis of CHD is first presented to the patient and her family.



“The 7th Annual Fetal Echocardiography Symposium at UCLA was a tremendous success, continuing UCLA’s annual tradition of providing a full day of focused, real-life, clinically oriented instruction for all clinicians involved with fetal cardiac imaging. State-of-the-art presentations were presented by world-class experts in Obstetric Sonography, Maternal-Fetal Medicine and Pediatric/Fetal Cardiology.”

Top: Dr. Gary Satou; Middle: Dr. Gregory DeVore; Bottom: Dr. Karim Diab



Dr. Alex Soffici and Susan Regenhardt.



all the speakers to offer continuing education and consultation for registrants throughout the year.

The symposium began with Mishella Perez, BS, RDMS, RDCS, delivering an outstanding presentation on “The Sonographer’s Basic Approach to Fetal Cardiac Screening.” Dr. Gregory DeVore then reviewed both “Basic and Advanced Pulsed and Spectral Doppler Techniques.” Dr. Mark Sklansky discussed his thoughts regarding “What Clinicians and Guidelines are Doing Wrong in Terms of Actual Fetal Cardiac Imaging” — offering answers and solutions to why most cases of Congenital Heart Disease continue to be missed prenatally.



Top: Left-to-right: Drs. Sklansky, Satou, Soffici, DeVore, and Robili. Middle: Meeting Exhibit area. Bottom: Dr. Sklansky and patients at the UCLA Mattel Children’s Hospital Toy Drive.

Session Two reviewed traditional and more advanced elements of the three-vessel views, along with traditional and novel (but easy to apply) approaches to the evaluation of fetal arrhythmias. The session ended with Dr. Sklansky demonstrating how to optimize fetal cardiac imaging while performing actual, live scans on multiple models at various gestational ages and with variable fetal positions. *Tricks of the trade* for optimizing image quality and angle of acquisition were demonstrated, and common artifacts were reviewed and minimized.

Before lunch, four young children ages 2-12 years old, and all with various forms of single ventricle, came to the stage along with their parents to give personal testimonials of their own experiences. Many tears were shed throughout the audience, and everyone took home a renewed sense of understanding of both the importance of prenatal detection, and of the very real impact that clinicians have on families for many years following the detection of a heart defect.

Registrants left the meeting with new approaches to the prenatal detection and evaluation of CHD to bring back to their

practices, meaningful insights into the importance of raising the quality of fetal cardiac imaging, and a commitment from

Following lunch, Dr. Karim Diab reviewed Atrial and Ventricular Septal Defects (VSD), including atrioventricular canal. Dr. Gary



Mark S. Sklansky, MD
 Professor & Chief, Pediatric Cardiology
 Co-Director, Pediatric/Congenital Heart Program
 Medical Director, UCLA Children's Heart Center
 Director, UCLA Fetal Cardiology Program
 UCLA Mattel Children's Hospital
 David Geffen School of Medicine at UCLA
 Tel. 310.267.7667
 MSklansky@mednet.ucla.edu



Top: Patient Ambassadors. Bottom: Dr. Sklansky and patient (with her twin sister) at the twins' school's Toy Drive for UCLA Mattel Children's Hospital.

Satou discussed Tricuspid Valve Disease, including: tricuspid regurgitation, tricuspid dysplasia, and Ebstein's Anomaly (EA) of the tricuspid valve. Dr. DeVore then discussed the latest approaches to evaluating cardiac size, shape and function, incorporating state-of-the-art speckle tracking technology.

Session Four focused strictly on outflow tract pathology, including aortic/pulmonary valve stenosis, pulmonary atresia with intact ventricular septum, Tetralogy of Fallot (TOF), Double Outlet Right Ventricle (DORV), Transposition of the Great Arteries (TGA), and Truncus Arteriosus (TA). The special views required for detection of Transposition of the Great Arteries, for example, were reviewed in detail.

The symposium kept registration fees well below the national average through the

generous support of: the Hopeful Hearts Foundation (www.hopeful-hearts.org), GE Healthcare (www.gehealthcare.com), Samsung (www.samsunghealthcare.com), Masimo (www.masimo.com), Natera (www.natera.com), and the Shane McCusker Foundation (www.shanesheart.org).

Reviews of this year's symposium have been glowing. Based on feedback from attendees, plans are already underway for the 8th Annual Fetal Echocardiography Symposium at UCLA next October; exact date and further details to be announced soon.

For more information on the 2018 meeting, please contact Dr. Sklansky at mksklansky@mednet.ucla.edu.

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 11502 Elk Horn Dr., Ste. 201
 Clarksburg, MD 20871 USA
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Editorial offices:
 16 Cove Rd, Ste. 200
 Westerly, RI 02891 USA

Publishing Management:

- Tony Carlson, Founder, President & Senior Editor - TCarlsonmd@gmail.com
- Richard Koulbanis, Group Publisher & Editor-in-Chief - RichardK@Neonate.biz
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