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Respiratory Syncytial Virus (RSV) Update

By Leonard R. Krilov, MD

Introduction

Respiratory Syncytial Virus (RSV) is the leading cause of Lower Respiratory Tract Infection (LRTI) in infants and young children, accounting for >100,000 hospitalizations/year in the United States. This translates to 0.5%-3% of all newborns every year. Additionally, up to 800,000 infants or 20% of the birth cohort per year require medical attention due to RSV infection. On a worldwide basis, RSV infections account for up to 200,000 deaths annually for children < 5 years of age.

The virus is ubiquitous, with virtually all children infected at least once by their third birthday. Immune responses to RSV are incomplete in that reinfection occurs throughout life with subsequent infections typically less severe and limited to the upper respiratory tract. These recurrent infections are often the source of the virus in vulnerable infants.

Recent studies have also recognized severe RSV infection in adults >65 years of age, and in those with Chronic Obstructive Pulmonary Disease; significant mortality has been documented in these groups with >14,000 deaths/yr reported.

Transmission

As a respiratory infection, RSV can be acquired through contact with respiratory droplets or secretions (e.g. coughing in close proximity) or secretions on one's hands (hand-to-hand transmission). Furthermore, RSV can survive on environmental surfaces (e.g. countertops, toys, stethoscopes) for up to 24 hours.

Environmental features that contribute to increased risk for acquiring RSV infection include: multiple pre-school and school-aged siblings, child care center attendance, and crowded living conditions.

Exposure to cigarette smoke or a wood burning stove in the household are risk factors for more severe RSV infection as well.

Virology

RSV is a member of the paravyxovirus family, which also includes the respiratory viruses, parafluenze Types 1-4, human metapneumovirus, and the invasive viruses measles and mumps. After RSV infection the normal host develops immunity to the virus including: neutralizing IgG antibodies. It is believed these responses including IgG antibodies help modify, if not prevent, reinfections.

"Respiratory Syncytial Virus (RSV) is the leading cause of Lower Respiratory Tract Infection (LRTI) in infants and young children accounting for >100,000 hospitalizations/year in the United States. This translates to 0.5%-3% of all newborns every year. Additionally, up to 800,000 infants or 20% of the birth cohort per year require medical attention due to RSV infection. On a worldwide basis, RSV infections account for up to 200,000 deaths annually for children < 5 years of age."

High Risk Groups

As noted before, all infants are at risk of severe RSV infection; however, there are groups of infants even more susceptible to this virus. These include: premature infants, infants with Chronic Lung Disease of Infancy (CLDI) or hemodynamically significant Congenital Heart Disease (cyanotic or acyanotic), immunodeficiency disorders, cystic fibrosis, Down Syndrome and neuromuscular disease. Approximately 1 in 10 babies are born prematurely (≤35 weeks gestation), making this the largest group of high-risk infants (up to 400,000 births/year in

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References: 1. Agency for Healthcare Research and Quality. National Guideline Clearinghouse website. http://www.guideline.gov/search/search.aspx?term=hyperoxia. Accessed August 18, 2015. **2.** Kulkarni AC, Kuppusamy P, Parinandi N. Oxygen, the lead actor in the pathophysiologic drama: enactment of the trinity of normoxia, hypoxia, and hyperoxia in disease and therapy. *Antioxid Redox Signal*. 2007;9(10):1717-1730.

the United States). Their risk for more severe RSV infection is due in part to their significantly decreased lung volumes and surface area, making these babies less able to handle a respiratory infection. Additionally, maternal antibody transfer across the placenta occurs during the second half of the third trimester. Thus, premature infants fail to receive this passive transfer of maternal anti-RSV IgG antibodies which, when present, may help modify the course of the infection. Additionally premature infants may have poorer muscle tone and be less able to clear a respiratory infection.

As evidence of this increased risk, Boyce and colleagues documented RSV hospitalizations and visits that were two times higher in premature compared to full-term infants. Furthermore, Horn and colleague documented ICU admission rates and requirement for mechanical ventilation were 2-3x higher in premature compared to full-term infants hospitalized with RSV infection. More recently, a two-year observational multi-center (Sentinel 1) study conducted at 43 sites across the United States, documented the severe morbidity of premature infants hospitalized with RSV infection. (Figures 1, 2) The combination of young chronological age (≤3 months) and extent of prematurity at time of the RSV infection led to ICU admission rates of >60 % and mechanical ventilation rates of >40%, when these babies were hospitalized for this condition. Updated information on hospitalization rates for RSV disease in premature babies in conjunction with these observations are needed to fully appreciate the impact of RSV on these babies.

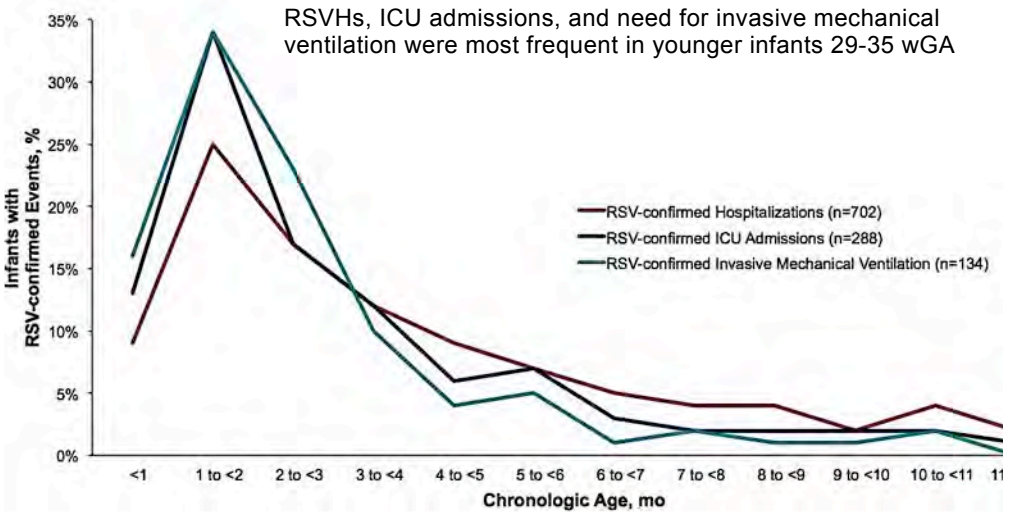

Figure 1. RSV-Confirmed Events by Chronological Age for Infants 29-35 wGA with Community-Acquired RSV

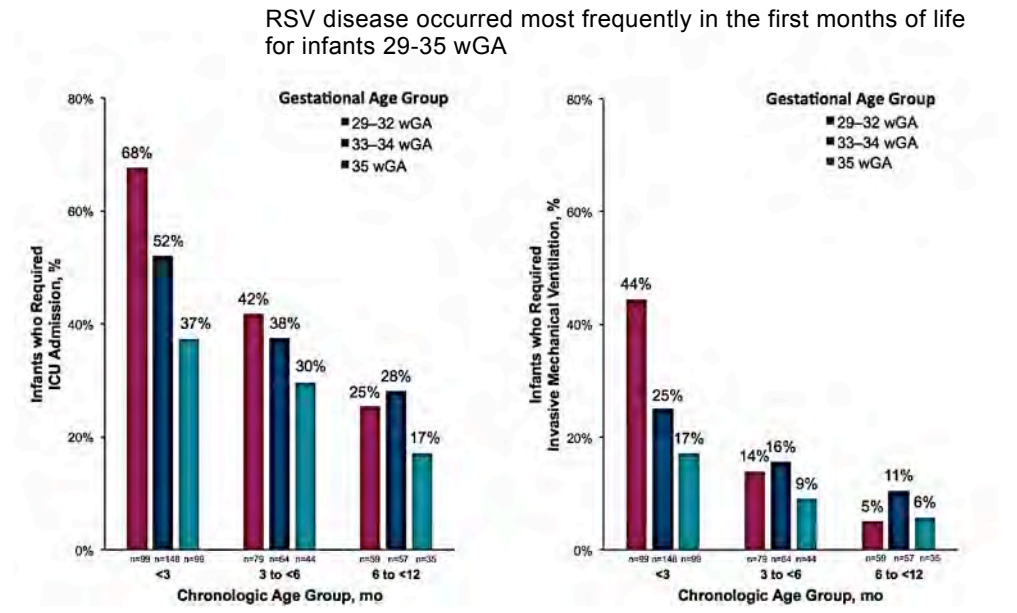

Figure 2. Proportion of Community-Acquired RSV-Confirmed ICU Admissions and Need for IMV Among Infants 29–35 wGA by Gestational and Chronologic Age Groups

Clinical Presentation

Clinically acute RSV infection presents initially as an upper respiratory tract infection with nasal congestion and cough that progresses to bronchiolitis with low grade fever, hypoxemia, tachypnea and diffuse airway inflammation as evidenced by wheezing. In very young infants, apnea may be the presenting manifestation of RSV infection. A number of other respiratory viruses can present with similar findings. However, RSV is the leading cause of bronchiolitis accounting for 80% of cases in typical annual fall-winter epidemics.

For hospitalized children with RSV bronchiolitis, the duration of the admission is typically 2 to 3 days, although it may be several weeks until the infant stops coughing and returns completely to baseline. In premature and other high risk infants, the duration of hospitalization is twice as long on average, and as noted above, the rates of ICU admission and need for mechanical ventilatory support are much higher.

It has long been noted that infants hospitalized with RSV LRTI have higher rates of subsequent wheezing episodes over ensuing years. Whether these subsequent episodes occurring after a severe RSV infection reflect abnormalities of the child's underlying airways that predispose to subsequent reactive airway disease, or whether the RSV infection leads to changes in the airway that contribute to subsequent lung changes that lead to increased wheezing, is not completely understood.

Blanken and colleagues recently observed a 63% decrease in wheezing days over the subsequent one year period in a group of 32 to 35 week gestational aged premature infants receiving palivizumab prophylaxis compared to a matched group not receiving palivizumab. If this observation is confirmed by additional studies, it provides

evidence for a primary role of RSV in the development of subsequent wheezing in at least some children.

Diagnosis

The diagnosis of RSV infection is primarily based on the clinical presentation. Viral testing performed on nasopharyngeal secretions can identify RSV and/or other respiratory viruses. Methods for RSV and other viral detection include antigen detection, viral culture and, most recently, multiplex PCR kits. Routine testing for RSV or other viruses is not routinely indicated per AAP recommendations, but it may be useful in guiding isolation precautions in hospitalized cases, withholding unnecessary antibiotic use, and educating families and health care professionals regarding the illness. Maintenance of hydration with intravenous or oral fluids is the other mainstay of therapy.

Management

Management of the child with severe RSV infection remains primarily supportive. Clearing nasal secretions with a bulb syringe or suction may provide significant relief. Beyond that, management is based on the assessment of the extent of respiratory distress and hypoxemia with options including: supplemental oxygen, non-invasive and mechanical ventilation.

Pharmacologic agents including: bronchodilators, epinephrine, corticosteroids and hypertonic saline have all been utilized in the management of infants with RSV bronchiolitis, but none have demonstrated definitive benefit, and their use is not routinely recommended for treatment of RSV infected infants.

Ribavirin is a nucleoside analog that was licensed for the treatment of severe RSV infection. The drug is delivered via prolonged aerosolezation. Based on high acquisition cost, concerns for environmental exposure to theoretical teratogenic levels of drug, and uncertainty over clinical benefit, ribavirin is rarely used. In extremely immunosurpressed individuals (e.g. bone marrow transplant recipients where mortality from RSV LRTI is very high), ribavirin may be used, although there are not large trials confirming efficacy in this setting. Newer anti-RSV agents including fusion inhibitors and nucleoside analogues are in development and in the future may offer improved treatment of severe RSV infection.

Given the ubiquity of RSV in the environment, prevention of RSV infections is difficult. Basic hygiene techniques including good and frequent hand washing and environmental cleaning, avoiding crowds, smoke exposure and persons with potential RSV upper respiratory tract infections when feasible may decrease risk of exposure.

For high-risk infants, it has been demonstrated that passive administration of RSV antibodies could provide protection against severe RSV disease. This was initially achieved with the manufacture of high titer RSV immunoglobulin (RSV-IGIV) administered intravenously. Subsequently, development of a humanized monoclonal antibody, palivizumab (Synagis), when given IM monthly through RSV season was demonstrated to significantly decrease RSV hospitalization rates in high-risk infants. Palivizumab was approved by the Food and Drug Administration (FDA) in 1998 for use in high-risk infants <2 years of age. Since then, debate has centered on defining the optimal candidates for palivizumab prophylaxis based on balancing aspects of epidemiological risk of infection, number needed to treat to prevent an RSV hospitalization, and the high cost of prophylaxis. The AAP guidelines in this regard have gotten increasingly restrictive with the 2014 recommendation of the Committee on Infectious Diseases of the American Academy of Pediatrics limiting prophylaxis to premature infants <29 weeks gestational age and <1 year of chronological age at the start of the RSV season, and up to 32 weeks gestational age and one year chronological age in the presence of Chronic Lung Disease or hemodynamically significant Congenital Heart Disease. This approach may maximize the benefits for palivizumab recipients by focusing on the highest-risk infants but, in absence of an exact definition of optimal benefit, it may leave a significant number of

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vulnerable infants at risk. Further determination of the risk criteria for 29-35 week gestational age infants is needed.

Future Directions

Presently, there are new anti-RSV monoclonal antibodies in development that have increased affinity and increased half-lives compared to palivizumab that may improve RSV prophylaxis, and require only 1 or 2 doses per RSV season. Additionally, it is expected that the cost to prophylax an infant with these newer monoclonal antibodies will be significantly less than for palivizumab. This approach, plus the development of safe and effective anti-RSV therapeutic agents, should lead to improvement in the prevention and treatment of RSV disease in the near future.

More importantly, is the progress being made toward development of a safe and effective RSV vaccine. Approaches including: a live attenuated intranasally-administered vaccine, subunit vaccines, and maternal immunization to provide protection to infants, are all being actively pursued. Until these efforts come to fruition RSV infection will continue to be a major burden for infants. Supportive care and approaches to prevention, from hand-washing to palivizumab for select high-risk infants, remain the mainstays of management.

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"More importantly, is the progress being made toward development of a safe and effective RSV vaccine. Approaches including: a live attenuated intranasally-administered vaccine, subunit vaccines, and maternal immunization to provide protection to infants, are all being actively pursued."

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Respiratory Syncytial Virus is a Really Serious Virus for Many At-Risk Babies

Members of the NPA write a regular column in *Neonatology Today*.

By Mitchell R. Goldstein, MD; Vincent C. Smith, MD; Raylene Phillips, MD

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October is Respiratory Syncytial Virus (RSV) Awareness Month, which gives us an opportunity to examine concerns that arise each year during RSV season. RSV infection can be a major health issue for some babies. In term infants, the virus typically causes cold-like symptoms with cough, runny nose, breathing difficulties, and/or fever. The infection is generally self-limited and uncomplicated, but can occur repeatedly during RSV season.

For infants born preterm or with conditions that place them at increased risk, RSV infection is much more significant and in the worse cases, deadly. The IMpact-RSV study in 1998 identified the extent of this risk, and provided the data for the Food and Drug Administration's (FDA) approval for Palivizumab (Synagis®).[1] Palivizumab has been shown to significantly reduce the risk by binding to the F protein of RSV, and thus, reducing RSV's virulence.[2] The recently published Sentinel 1 Trial established the continued risk and presented a concerning perspective on the negative effects of abrogated RSV prophylaxis for vulnerable infants.[3]

Since 2009, the American Academy of Pediatrics (AAP) Committee on Infectious Disease (COID) has altered its AAP RSV prophylaxis guidelines, and in 2014 further distanced their policy from FDA indications to exclude up to 75% of all infants who would have been covered by the FDA RSV prophylaxis indications.[4, 5] Because rates of prematurity and low birth weight are higher among disadvantaged populations, infants from disadvantaged groups make up a disproportionate percentage of the infants who are excluded from coverage.[6]

No one denies the effectiveness of RSV prophylaxis. Part of the rationale for the change in AAP guidelines could be the significant upfront cost associated with the monthly injections or a perception that preterm neonates will have an increased rate of hospitalization, regardless of prophylaxis.[7] However, when other costs associated with RSV disease, such as hospitalization, level of acuity, ongoing medical care, and chronic health issues are taken into account, RSV prophylaxis is actually cost saving.[8]

Changing the guidelines for RSV prophylaxis has left many families who have at-risk infants with limited options for getting the RSV prophylaxis their babies need. Usually, they have only two options:

1. Some private health plans offer an appeal process for infants that are at risk, but excluded by the current RSV prophylaxis guidelines;
2. Families with substantial financial resources can pay for palivizumab (Synagis®) out-of-pocket.

Families who are unable to manage either of these options have few alternatives. Disadvantaged families are disproportionally affected, increasing existing disparities in access to healthcare.[6]

The FDA has a very stringent process for approving any medication and the gestational parameters selected for the original FDA indications were intended to provide optimal coverage for the most vulnerable infants. To deter potential deviation or abbreviation of FDA-approved treatment regimens by manufacturers, medical groups or insurers, the FDA has established a "Bad Ad" program (http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/DrugMarketingAdvertisingandCommunications/ucm209384.htm). As described on the FDA website, the FDA wants to know if a claim outside of FDA indication is made such as, "3 doses are as effective as 5," or other non-indicated use of the product. Yet, for RSV prophylaxis, this mandate is not being followed, even though significant deviations from FDA indications for use of RSV prophylaxis are being recommended.[9] Despite continued evidence of effectiveness in support of the original indications for RSV prophylaxis, there is no effort by insurance companies and most professional organizations to support those providers who would choose to follow the FDA indications in prescribing RSV prophylaxis.

In addition to negative short- and long-term health consequences for infants affected by RSV and increased financial and emotional stress for families, there is another issue. The precedent being set threatens innovation in new drug development and research. If pharmaceutical companies go through the trouble and expense of producing a product with a known and well-established relevant indication only to be denied access to their market by a guideline or policy that succeeds in severely restricting access, why would these companies continue to develop new products for the pediatric population? The answer is obvious. Restrictive under-dosing or under indication sends a clear message to pharmaceutical companies, "development for pediatric patients is not worth the risk." If we are to expect great innovation and research leading to the development of useful biologics, pharmaceuticals, and medical devices for our most fragile patients, we must make every effort to dose appropriately to the FDA indications, and to effectuate a process where restrictive guidance on the use of novel products is not accepted.

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Prolonging Antibiotic Courses in the NICU: The Cost of Fear

By Michael Narvey, MD

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The literature over the last few years has ballooned with reports of adverse outcomes related to antibiotic overuse. The most common adverse outcome noted on the worldwide stage is that of antimicrobial resistance and the so-called "superbugs," but in the Neonatal Intensive Care Unit (NICU) a whole host of other outcomes have been noted. Prolonging antibiotics beyond the first couple days of life has led to changes in the microbiome towards more pathogenic bacteria in the NICU. This shift has been accompanied by a rise in the rate of necrotizing enterocolitis in such units, as well as many outcomes including some which affect us as adults such as asthma, which has been discussed on my Facebook page before.

New Consequences of Prolonging Antibiotics Beyond 48 hours

This month, a colleague with a particular interest in this story, forwarded our team the following paper. "Prolonged Early Antibiotic Use and Bronchopulmonary Dysplasia in Very Low Birth Weight Infants" by Novitsky et al. What this retrospective study demonstrated (comparing 747 infants treated for less than 48 hours to 159 treated beyond), was that the prolongation of antibiotics beyond the first 48 hours was associated with increased propensity to develop Bronchopulmonary Dysplasia (BPD). This finding remained true even when factoring in other risks for such outcomes including: gestational age, maternal antibiotics, inborn status, clinical chorioamnionitis, prolonged rupture of membranes, preeclampsia, cesarean delivery, Apgar at 5 minutes, SNAP score, and mechanical ventilation. Curiously it is not just the initial course that is of concern, but ongoing exposure as well. "After adding total cumulative hospital course antibiotic days, the odds of BPD remained increased with > 48 hours of antibiotic coverage in the 1st week. Furthermore, for every additional day of antibiotic coverage after the 1st week of life, there was an increased odds of developing BPD (OR, 1.16 per antibiotic day, 95% CI, 1.11–1.2). "

Prolonging antibiotics has another downstream consequence of increasing the rates of endotracheal tube colonization with bacteria to the tune of 38% vs. 16%. Additionally, there was a shift in endotracheal tube culture patterns towards the emergence of resistant gram negative organisms (7% vs. 2%), if prolonged treatment up to 7 days was chosen. As has been shown in other studies, rates of NEC were increased as well ,which should be no surprise based on previous similar work.

Wanting To Be Safe And Do The Right Thing

"Once bitten, twice shy" as the saying goes. Any clinician who has missed an episode of sepsis in a newborn after not starting antibiotics is no doubt scarred to some degree. I have no doubt that all of us wish to do the right thing and protect the infants in our care when risk factors for sepsis indicate to us that there is a higher likelihood of sepsis being present. Looking at this study, one can see the following risks were indeed more prevalent in the group treated beyond 48 hours.

From the Table, I think we can agree that these infants were smaller and potentially sicker, which likely motivated those clinicians to try and "do the right thing," even if cultures were negative. In this paper, they defined sepsis as a positive culture and the presence of signs suggestive of sepsis, which avoids any confusion, related to such subjective classification as "possible or probable" sepsis where the clinical picture is suggestive, but the culture negative. Despite a perceived increase in risk of sepsis after birth, how accurate were clinicians? Early and Late Onset Sepsis Rates 14% in the < 48 hr and 16% in the > 48 hour group - were not significant at all.

Risk	Antibiotics < 48 hours in 1st week	Antibiotics > 48 hours in 1st week	P value
Birth weight	1053 +/- 296	944 +/- 274	<0.01
SNAP score	13 +/- 9.2	17.8 +/-7.1	<0.01
Clinical Chorio %	5	18	<0.01
Prolonged ROM	14	26	<0.01

The Cost of Fear

What is significant is the consequence of fear that motivates such decisions in the face of negative blood cultures. There is no difference in our ability to predict, yet doing so, increases the risk of recovering bacteria from the endotracheal tube and, more so, resistant ones. The likelihood of obtaining bacterial growth in the endotracheal tube is more than doubled; NEC increased 2.5 times, gram-negative resistance tripled and the odds of developing BPD approximately doubled with an increasing tendency to this outcome simply by prolonging antibiotics. The cost of fear is that we trade our poor ability to truly predict sepsis with significant adverse risk that impacts the infant not only during their stay, but long after they leave the NICU.

It is human nature to wish to "do no harm." In order to truly achieve this, we have to quell our need to "feel good" by knowing we have covered for sepsis and replace this with the fear of causing serious harm from such action. The decision to prolong the antibiotic course is the easy route as we go home comfortable that the baby is "covered" in case we are wrong. It makes us feel better, but at significant cost. Only by changing our perspective of what constitutes harm, will we ever move forward in this fight to change practice. Are you prepared to do it?

NT

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Clinical Trials (from ClinicalTrials.gov)

The Impact of Non-Routine Events on Neonatal Safety
This study is not yet open for participant recruitment
Verified April 2016 by Vanderbilt University

Sponsor: Vanderbilt University

Collaborators: Tennessee Initiative for Perinatal Quality Care
Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)

Purpose: The study objective is to decrease neonatal mortality and morbidity by elucidating the etiology of system failures during perioperative care.

In Aim 1, the investigators will use a novel event discovery method, based on the construct of the Non-Routine Event (NRE), to efficiently capture dysfunctional clinical microsystem attributes and potentially dangerous conditions. A NRE is defined as any event that is perceived by care providers or skilled observers as a deviation from optimal care based on the clinical situation.

In Aim 2, the investigators will perform a comparative analysis of prospectively collected NRE data to the data collected by conventional event reporting methodologies.

In Aim 3, the investigators will collaborate with the Tennessee Initiative for Perinatal Quality Care (TIPQC) to conduct practical pilot testing of tools and measures developed and refined in the first two Aims.
Products from Aims 1 & 2 will include:

- a taxonomy of NREs and outcomes for perioperative neonates;
- neonatal Comprehensive Open-Ended Non-routine Event Survey (NCONES) data collection tool;
- comparisons of 5 established event reporting systems, including their rates, costs and benefits; and
- a guide to prototype neonatal safety surveillance and risk prediction for hospitals and NICUs.

Aim 3 will capitalize on TIPQC's robust network of NICUs, neonatologists, and patient-level outcome data to conduct a pilot implementation evaluation of the methods and tools developed and refined in Aims 1-2.

Study Type: Observational [Patient Registry]

Study Design: Observational Model: Cohort; Time Perspective: Prospective

Primary Outcome & Measures: National Surgical Quality Improvement Pediatric Mortality [Time Frame: 30-day] [Designated as safety issue: No] American College of Surgeons (ACS) NSQIP Pediatric is a nationally validated, risk-adjusted, outcomes-based approach to measure and improve the quality of surgical care for pediatric patients. It employs a prospective, peer-controlled, validated database to quantify 30-day, risk-adjusted surgical outcomes, which provide a valid comparison of outcomes among all hospitals in the program.

Estimated Enrollment: 500

Study Start Date: April 2016

Estimated Study Date Completion: June 2020

Groups/Cohort: Neonates receiving first-time non-cardiac surgery. No intervention will be administered. This is a prospective observational patient safety study focusing on the safety of care delivered to neonates in perioperative care settings. Neonates who receive NICU care both pre- and post-operatively will be eligible for this study.

Eligibility: Chid, adult, seniors; both sexes; no healthy volunteers

Sampling Method: Non-probability sample

Study Population: Neonates undergoing first-time non-cardiac surgeries and who are treated in the neonatal intensive care unit both pre-operatively and post-operatively.

Inclusion Criteria: Surgical neonates; Pre- and post-operative care provided in the NICU

Exclusion Criteria: Neonates having cardiac surgery

Contacts: Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the Contacts provided below.

- Daniel J France, PhD, MPH (Principal Investigator) - Tel: 615-322-1407; dan.france@vanderbilt.edu
- Martin L Blakely, MD- Tel: 615-936-1050; martin.blakely@vanderbilt.edu

Location: Monroe Carell Jr. Children's Hospital at Vanderbilt, Nashville, Tennessee, United States, 37232

ClinicalTrials.gov identifier: NCT02756195

Study First Received: April 21, 2016

Individual participant data will not be shared. Only aggregate de-identified data will be disseminated.

Heath Authority: US Federal Government; US Institutional Review Board' US Data ad Safety Monitoring Board

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An Optical Neuro-Monitor of Cerebral Oxygen Metabolism and Blood Flow for Neonatology (BabyLux)
This study is not yet open for participant recruitment
Verified June 2016 by Rigshospitalet, Denmark

Sponsor: Gorm Greisen, Rigshospitalet, Denmark

Purpose: Feasibility trial on the use of a hybrid optical device integrating time-resolved near-infrared spectroscopy (TRS) and diffuse correlation spectroscopy (DCS) for measurement of cerebral oxygen metabolism and blood flow in neonates.
The device will be tested in four settings measuring:

- Changes in cerebral oxygenation and haemodynamics after birth;
- Precision and repeatability;
- The cerebral vaso-reactivity to arterial carbon dioxide; and
- Assessment of the user-friendliness and loss of signal in routine care.

Study Type: Observational

Study Design: Observational Model: Case-Only; Time Perspective: Prospective

Primary Outcome & Measures: Cerebral tissue oxygen saturation (StO2) after birth. [Time Frame: 10 min immediately after umbilical cord clamping.] [Designated as safety issue: Yes] Measurement of cerebral haemodynamics immediately after birth.

Precision and repeatability [Time Frame: During second day of life.] [Designated as safety issue: Yes] Test-retest variability estimated by within-subject standard deviation in one-way ANOVA with subject as factor.

Cerebral vaso-reactivity to arterial carbon dioxide [Time Frame: 1 hour after change in ventilator settings.] [Designated as safety issue: Yes] Mean CBFi and tcpCO2 one minute before the change and 15 min after will be used to analyse CBFi-tcpCO2 reactivity.

Assessment of user-friendliness and loss of signal in routine care [Time Frame: 24 hours of continuous measurements.] [Designated as safety issue: Yes] Assessed by Likert-scale questionnaire completed by clinical staff.

Estimated Enrollment: 60

Study Start Date: June 2016

Estimated Study Date Completion: February 2017

Groups/Cohort: Infants delivered by elective caesarean. Infants to be measured immediately after birth and on their second day of life.

Assigned Interventions: Device: BabyLux Neuro-monitor. Measurement of cerebral blood flow index (CBFi) and tissue oxygen saturation (StO2).

Groups/Cohort: Infants on mechanical ventilation. Infants to be measured while changing ventilator settings to normalize arterial pCO2.

Assigned Interventions: Device: BabyLux Neuro-monitor. Measurement of cerebral blood flow index (CBFi) and tissue oxygen saturation (StO2).

Groups/Cohort: Infants on ventilatory support Infants to be measured for 24 hours continuously to assess user-friendliness and loss of signal. **Assigned Interventions: Device:** BabyLux Neuro-monitor. Measurement of cerebral blood flow index (CBFi) and tissue oxygen saturation (StO2).

Eligibility: Child to 4 weeks; both genders; does not accept healthy volunteers

Sampling Method: Non-probability sample

Study Population

Setting 1 and 2: Newborn infants immediately after delivery by elective caesarean and on their second day of life.
Setting 3: Premature infants on mechanical ventilation.
Setting 4: Neonate infants on ventilatory support

Criteria

Setting 1 and 2:

Inclusion Criteria: GA >37 weeks; planned to be delivered by an uncomplicated elective caesarean section

Exclusion Criteria: Need for resuscitation or supplementary oxygen during the first 10 minutes following umbilical cord clamping, congenital malformations

Setting 3:

Inclusion Criteria:
- GA < 37 weeks
- Postnatal age more > 24 hours
- Mechanically ventilated
- Clinically stable
- Normal brain ultrasound
- Transcutaneous pCO2 monitoring (tcpCO2)

Exclusion Criteria: Congenital malformations

Setting 4:

Inclusion Criteria: Postnatal age < 28 days; ventilatory support by mechanical ventilation or nasal CPAP

Exclusion Criteria: Congenital malformations

Contacts and Location: Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the contacts provided below.
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- IRCCS Ca'Granda Ospedale Maggiore Policlinico, Italy: Monica Fumagalli, MD; monica.fumagalli@unimi.it

ClinicalTrials.gov identifier: NCT02815618

Study First Received: June 23, 2016

The sharing of Individual participant data (IPD) has not yet been decided.

Heath Authority: Denmark Danish Medicines Agency; Denmark Danish Dataprotection Agency; Denmark Ethics Committee

Medical News, Products & Information

Compiled and Reviewed by Tony Carlson, Senior Editor

Acute Kidney Injury Identifiable in Preterm Infants

Early diagnosis of acute kidney injury in preterm infants is possible through urinary protein markers. CREDIT: UAB News

UAB News - Researchers at the University of Alabama at Birmingham (UAB) have found that the amount of proteins excreted in the urine of preterm infants with acute kidney injury, or AKI, is different from that excreted by infants with healthy kidneys.

The study, led by principal investigator David Askenazi, MD, was published in the *Clinical Journal of the American Society of Nephrology.*

"The findings in this study could help physicians better diagnose kidney health in newborns," said Askenazi, Associate Professor in the UAB Department of Pediatrics and Director of UAB's Pediatric and Infant Center for Acute Nephrology. "Having better diagnostic tests to diagnose kidney injury will have an important impact on how we care for infants and how we prognosticate outcomes, and will enable us to design studies to prevent and/or mitigate kidney damage in these very vulnerable babies."

Improving the ability to diagnose AKI, a sudden decline in kidney function, is critical, as approximately 25% of preterm infants develop AKI. Compared to those without AKI, preterm infants with this common problem have a lower chance for survival, increased hospital stays and increased hospital expenditures.

Importantly, premature infants are at high risk for Chronic Kidney Disease, and AKI may be an important cause for this.

Investigators took a single drop of urine from 113 preterm infants and measured 14 urine proteins. The concentrations of many of these proteins, including cystatin c, neutrophil gelatinase-associated lipocalin, osteopontin, clusterin and alpha glutathione S-transferase, were higher in preterm infants who later showed abnormal kidney function, compared to their counterparts with normal function.

"Additional studies to determine how AKI contributes to chronic kidney disease in these newborns are underway," Askenazi said. "Improving our ability to diagnose AKI accurately is critical to improving our understanding of the natural course of disease and developing strategies to improve outcomes."

Study co-authors include: Rajesh Koralkar, MPH, Neha Patil, MD, Brian Halloran, MS, Namasivayam Ambalavanan, MD, and Russell Griffin, PhD.

Find more information and http://www.uabmedicine.org.

VIDEO: http://www.youtube.com/uabnews
TEXT: http://www.uab.edu/news
TWEETS: http://www.twitter.com/uabnews

Discovery of Infants' Airway Microbiomes May Help Predict Lung Disease

Newswise — In contrast to the general belief that the airways of an infant are sterile until after birth, University of Allabama at Birmingham researchers and colleagues have found that the infant airway is already colonized with bacteria or bacterial DNA when a baby is born — and this is true for infants born as early as 24 weeks gestation.

How microbes get into the airways and the purpose of this pre-birth colonization are still unclear, but the pattern of colonization appears to have an important link to later severe neonatal lung disease.

An early microbial imbalance, or dysbiosis, is predictive for the development of Bronchopulmonary Dysplasia, or BPD, a chronic lung disease of prematurity. The extremely low birth-weight, or ELBW, infants in this study had an average birth weight of 1 pound, 8 ounces. Researchers found that the ELBW infants who went on to develop life-threatening BPD showed abnormal microbial colonization patterns at birth, as compared to pre-term infants who did not get BPD.

“Right at birth, your respiratory microbiome can possibly predict your risk for BPD,” said Charitharth Vivek Lal, MD, Assistant Professor in the UAB Pediatrics Division of Neonatology and the lead investigator of this study.

The study also suggests that the ‘healthy’ pattern of colonization seen in the BPD-resistant ELBW infants — with increased abundance of Lactobacillus — is protective.

"We speculate that the early airway microbiome may prime the developing pulmonary immune system, and dysbiosis in its development may set the stage for subsequent lung disease," the researchers say in their paper in *Scientific Reports*, one of the Nature Publishing Group journals. "Should a disordered airway microbiome prove to be involved in the pathogenesis of disease, it will be of immediate interest to attempt to develop novel therapeutic interventions."

Charitharth Vivek Lal, MD. CREDIT: UAB News

Lal says this is the first unbiased airway microbiome analysis to be done immediately at birth — all the early saline aspirates from the tracheas of the newborns were collected at or within six hours of delivery.

It is also the only infant airway microbiome analysis to be validated at a second medical center. After the first group of 23 ELBW infants and 10 full-term infants were studied at the Regional Neonatal Intensive Care Unit, UAB Women & Infants Center, samples from a second group of 14 ELBW infants were studied in collaboration with Vineet Bhandari, MD, at Drexel University College of Medicine, Philadelphia.

About half of the ELBW infants at both sites, all of them extremely pre-term, later developed BPD. The differences in the microbiomes between infants who were BPD-resistant and BPD-predisposed were similar for infants in both Birmingham and Philadelphia.

Extremely premature infants are at risk for BPD, which is the most common lung pathology of these tiny infants and a significant cause of morbidity, mortality and health care expenditures. Adults and children who had BPD as infants have lungs that failed to develop properly and are more prone to worse lung function, asthma, lung infections and pulmonary hypertension.

The researchers also looked at the airway microbiomes of 18 ELBW infants with established BPD and found that their microbiomes had a decreased diversity of types of microbes, and the pattern was very different from those of ELBW infants shortly after birth or full-term infants at birth.

As to specific groups of microbes, the phylum Proteobacteria, which includes bacteria like E. coli, appeared to be involved in BPD pathology, and the genus Lactobaccillus, part of the phylum Firmicutes, appeared to be involved in disease protection.

Lal and colleagues found decreased Lactobacillus abundance in the airway microbiomes of 10 infants born to mothers who had chorioamnionitis — an infection of the membranes of the placenta and an independent risk factor for BPD, as well as decreased Lactobacillus abundance at birth in the airways of the BPD-predisposed, ELBW infants, as compared to BPD-resistant infants. Research elsewhere has suggested a beneficial role for Lactobacillus against airway diseases and for lung development.

"I predict that researchers will study the use of respiratory probiotics, and the role of the gut-lung microbiome axis in the future," Lal said.

For five ELBW infants who later developed BPD, the researchers collected periodic airway microbiome samples from birth through 9 weeks, and saw extremely similar patterns of change in the microbiomes over time.

As for the source of the microbes, Lal and colleagues wrote, "As it is commonly believed that colonization of neonates originates in the birth canal, we were surprised to find that the airway microbiome of vaginally-delivered and caesarean section-delivered neonates were similar, which suggests that the microbial DNA in the airways is probably transplacentally derived, consistent with reports that the placenta has a rich microbiome."

The researchers speculate that this transmission of bacteria or bacterial DNA to the in-utero infant could be via blood or amniotic fluid.

Besides Lal, co-authors of the paper, "The Airway Microbiome at Birth," are Colm Travers, Tamas Jilling, Brian Halloran, Waldemar A. Carlo, Jordan Keeley, Gabriel Rezonzew and Namasivayam Ambalavanan, all of the UAB Department of Pediatrics Division of Neonatology; Zubair H. Aghai, Department of Pediatrics, Thomas Jefferson University, Philadelphia; Peter Eipers and Casey Morrow, UAB Department of Cell, Developmental and Integrative Biology; Ranjit Kumar, UAB Center for Clinical and Translational Sciences; and Vineet Bhandari, Department of Pediatrics, Drexel University College of Medicine.

The Regional Neonatal Intensive Care Unit at the UAB Women & Infants Center offers the only Level IV NICU in Alabama and is a part of one of the largest neonatal services in the nation.

Maternal Gastric Bypass May Be Associated with Low Birth Weight Babies

Women who undergo gastric bypass surgery for weight loss risk giving birth to babies that are small or have lower average birth weights. The work was presented in September 2016 at the *55th Annual European Society for Paediatric Endocrinology Meeting*. The findings could lead to different advice and clinical care for pregnant women who have undergone gastric bypass surgery.

Gastric bypass surgery is used to treat people who are severely obese (a body mass index greater than 40kg/m2); food is re-routed past most of the stomach, meaning less is digested. The procedure can lead to up to 70% loss of excess body weight within two years, but is associated with an increased vulnerability to vitamin and mineral deficiencies, as it reduces the body's ability to absorb micronutrients.

Women treated with gastric bypass surgery are advised to wait 18 months after the procedure before trying to become pregnant

in order to establish a stable, healthy weight. They must also follow a daily multivitamin supplementation regime and receive regular clinical follow-up before, during and after the pregnancy.

Despite these precautions, a team of clinical researchers at the Department of Paediatrics, University Hospital, Angers, France found that the birth-weight of babies born to gastric bypass mothers was on average 0.34 kg lower than average, and that 23% of neonates were small for their gestational age. The team studied 56 newborns born to gastric bypass mothers who had waited an average of 32 months between surgery and pregnancy, and compared results to 56 controls.

"Maternal obesity can lead to health conditions for the newborn, such as high birth weight and low blood sugar. It can also cause birthing complications, and gastric bypass can prevent these," says Maxime Gerard, lead researcher of the study. "But our study showed that gastric bypass could have other effects on newborns."

The team saw that, despite supplementation, a proportion of gastric bypass mothers were deficient in key nutrients during pregnancy, such as calcium and zinc. Analysis of the newborns showed that they also suffered lower than average levels of the same nutrients.

"These maternal nutrient deficiencies may be the reason for the same deficiencies and low birth weights seen in the newborns," continues Gerard. "One of our next steps will be to confirm this and determine its impact."

The team also analysed newborn birth weight in relation to the mothers' weight, and determined that birth weight was related to the variation in the mother's weight between the surgery and pregnancy, rather than her weight during pregnancy.

Only preliminary findings were presented, and as the study continues, the team's next key step is to determine if low birth weights have long term consequences for the children in the study. They would also like to establish optimal nutritional supplementation for mothers who have undergone gastric bypass surgery, to ensure they do not suffer from nutritional deficiencies during pregnancy.

Preterm Birth Leads to Smaller Kidneys, Higher Blood Pressure in Adulthood

American Heart Association Meeting Report Abstract 134

Premature birth cuts short kidney development, resulting in smaller kidney size and higher blood pressure in adulthood, according to a study presented at the American Heart Association's Council on *Hypertension 2016 Scientific Sessions* on September 2016.

"Adults born preterm may not present with the 'classical' risk factors for Heart Disease, but they are at increased risk of hypertension and insulin resistance and certainly require regular medical follow-up," said Anne Monique Nuyt, MD, senior author of the study and Head of the Division of Neonatology at the Sainte-Justine University Hospital and Research Center of the University of Montreal, Canada.

Researchers compared kidney size, function, and blood pressure in 40 adults (average age 23.6) born at 29 weeks of gestation or earlier with 40 adults (average age 23.3) born at full term. They found that young adults born preterm had:

- Significantly smaller kidneys relative to their body size;
- Significantly higher systolic (higher number) and diastolic (lower number) blood pressure, both on waking and averaged over 24 hours.

While the differences in blood pressure were not large - for example, the average daily systolic blood pressure was 5 points higher in the adults born preterm (120 mmHg) than those born full term (115 mmHg), the findings raise concerns about high blood pressure and heart disease risk as adults born preterm enter middle-age.

"It is well-known that blood pressure will increase more markedly with aging in people who have higher blood pressures in their young adult lives, than those who had lower values. We do not know for certain whether this will be the case for individuals born preterm because the first survivors of extreme prematurity are only entering their thirties and forties," Nuyt said.

Co-authors are Katryn Paquette, MD; Thuy Mai Luu, MD, MSc; Anik Cloutier, MSc; Marie-Amélie Lukaszewski, PhD; Mariane Bertagnolli, PhD; Ramy El-Jalbout, MD and Anne-Laure Lapeyraque, MD, MSc. Author disclosures are on the abstract.

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