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Neonatology Today (NT) is a monthly newsletter for Neonatologists and Perinatologists that provides timely news and information regarding the care of newborns and the diagnosis and treatment of premature and/or sick infants.

Respiratory Syncytial Virus (RSV) Prevention 2012

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> ***"The National Perinatal Association 2012 guidelines on RSV prevention outline further well-documented evidence supporting the FDA approved use of Palivizumab for RSV prophylaxis."***

Introduction

There has been considerable confusion regarding the appropriate prophylaxis for Respiratory Syncytial Virus (RSV) since the Committee of Infectious Disease (COID) of the American Academy of Pediatrics (AAP) changed its policy statement in August 2009 to "ensure optimal balance of benefit and cost from this expensive intervention." Earlier recommendations were based on strong evidence from more than one well-designed randomized, controlled trial. No peer-reviewed results from randomized clinical trials were presented as a rationale for the 2009 changes. The expert opinions of the COID and their interpretation of the evidence from clinical experience or descriptive studies alone were given as justification. There is no scientific evidence that supports the administration of fewer than five monthly injections of Palivizumab for RSV prophylaxis. The United States Food and Drug Administration (FDA)-approved indication for Palivizumab is clear in this regard. Any recommendation which contrasts with the approved dosing encourages "off label" use of the medication. Denial of full coverage based on FDA indications without consideration of other risk factors may put certain populations at even greater risk due to health disparities. The physician must be given the right to prescribe according to the approved indication. The National Perinatal Association 2012 guidelines on RSV prevention outline further well-documented evidence supporting the FDA approved use of Palivizumab for RSV prophylaxis.

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A Promise for Life

The National Perinatal Association 2012 Guidelines on RSV Prevention

I. Issue: There is a high level of evidence that RSV prophylaxis is effective.The NPA proposes expanding access for certain neonatal and pediatric patients, consistent with the evidence available at this time.[1-3]

II. Background: RSV is the leading cause of hospitalization in all children less than 12 months of age in the United States.[4-6] The majority of these hospitalizations occur in otherwise healthy infants. Sixty percent of the top five hospital discharge diagnoses are attributable to bronchiolitis. Certain groups of infants and children have higher rates of re-hospitalization including children with Chronic Lung Disease (CLD)/Bronchopulmonary Dysplasia (BPD), Congenital Heart Disease (CHD), and premature infants.[7-14] Treatment options for RSV are limited. Supportive care is the only medical therapy available. In addition to strategies to minimize exposure to RSV, prophylaxis with RSV monoclonal antibody is effective at decreasing hospitalization. The best approach to RSV in "at risk" groups is prevention.[9,15-19] In patients with CLD/BPD and premature infants born at less than 36 weeks gestational age, prophylaxis decreased hospitalization by 55%; in the patients born between 32-35 weeks gestation, hospitalization rates decreased by 80%.[15]

III. Respiratory Syncytial Virus Prophylaxis

A. Prophylaxis to prevent RSV is available as intramuscular monoclonal antibody preparation (palivizumab).[20,21]

B. RSV infection is responsible for significant hospitalizations, morbidity, and mortality in infants less than 24 months of age who have CLD/BPD, Congenital Heart Disease, compromised respiratory or immune systems or who have impaired nutritional status and growth.[16,17,22]

C. Candidates for RSV Prophylaxis: Decisions regarding appropriateness of RSV prophylaxis must be individualized.

1. Infants or children with CLD/BPD who are less than 24 months of age at the start of RSV season who have required intervention or maintenance therapy for their CLD/BPD within 6 months of the start of the RSV season will benefit from RSV prophylaxis. Other interventions for CLD/BPD may include use of corticosteroid preparations, methylxanthines, supplemental oxygen, bronchodilators, home apnea monitoring, home pulse oximetry, or diuretics.[12,23,24]
2. Infants born at 32 weeks or less without CLD/BPD will also benefit from prophylaxis:[25]
   a) Infants born at less than 28 0/7 weeks will benefit from prophylaxis if they are less than 12 months of age at the start of the RSV season. Infants born during RSV season who are less than 12 months of age at the start of the subsequent RSV season are still candidates for prophylaxis.
   b) Infants born between 28 0/7 and 32 0/7 weeks of gestation will benefit most from prophylaxis if they are less than 6 months of age at the start of RSV season.
3. Birth at a late preterm gestation may merit special consideration.[26-28] However, prophylaxis for infants born at 32 1/7 to 35 6/7 weeks gestation should be reserved for those infants with additional risk factors that increase risk of RSV exposure or morbidity from RSV disease. An RSV relative risk scale has been proposed and may be useful to the practitioner in identifying "at risk" patients who may benefit from RSV prophylaxis.[29] The cost of prophylaxis should be weighed against the risk of severe RSV disease requiring hospitalization and associated costs to the family, as well as potential for long-term consequences. Direct costs are not the only expenses involved in the long term care of a child who has had RSV. Costs associated with loss of family income with a parent taking time off to care for a child with chronic disability, frequent follow-up appointments, and indirect costs involved developmental disability, as well as loss of academic potential must also be considered.[30-33] A neonatologist, pediatrician, or other primary care provider is often in the best position to assess and interpret relative risk factors. The most consistently identified factors that are associated with increased risk of RSV disease are child care attendance, school-aged siblings, twin or greater multiple gestation, young chronological age at the start of RSV season and maternal smoking; however, exposure to environmental air pollutants, congenital abnormalities of the airways, or severe neuromuscular disease may also justify concern.[23,34-38] Correlations exist between air quality and respiratory function.[37-48] Thus, environmental air quality assessment is important for these patients with special consideration given to unique circumstances of unwarranted air pollution such as residence near a bus station or industrial plant, or use of a wood or coal burning stove as a primary heat source. Efforts to reduce risk by isolation of the "at risk" child, smoking cessation strategies for the parents/caregivers, or relocation to an area with cleaner air may not be practical or workable for the immediate term. Certain risk factors may have greater impact based on the level of exposure (i.e., one school-aged sibling versus three school-aged siblings in three different schools); however, no particular risk factor has been shown to be unique in its predictive value, and frequently many risk factors may exist simultaneously.[14,46] The greater the number of risk factors, the higher the likelihood of RSV hospitalization.[49] A history of maternal smoking during pregnancy may be augmented as a risk factor by a history of breastfeeding for less than 2 months.[41,50-53] These circumstances must be accounted for in the risk assessment. The provider must be aware of risk created by disparity. Minority African-American and Hispanic populations in blighted inner city neighborhoods are at a higher cumulative risk.[54] After assessment of an individual patient, if a provider determines that the patient is at high risk for RSV disease complicated by hospitalization, prophylaxis should be provided.[55] Planning for prophylaxis must begin before the time of discharge if the "at risk" patient has been hospitalized for any of the conditions that have a known association for increased risk. In one study, fewer than 50% of eligible patients received prophylaxis.[56] Lack of parental education, language difficulties, transportation challenges, and issues of potential problems with insurance coverage must be resolved prior to discharge home.[57-59]
4. Palivizumab has been shown to be of benefit to patients with congenital heart disease.[16,60-62] The degree and severity of the heart disease may factor into the decision to provide RSV prophylaxis. In order to exclude an infant from receiving Palivizumab, the infant must have a documented waiver provided by a board certified pediatric cardiologist that their cardiac defect is hemodynamically insignificant and thereby poses no additional risk for RSV. Children who are in need of or status post cardiac transplantation are in a particularly high risk group and should be given RSV prophylaxis.[60,62] During RSV season, children who have received Extracorporeal Membrane Oxygenation (ECMO) management or any other form of cardiac bypass should receive monthly prophylaxis.
5. Infants with severe neuromuscular disease affecting respiratory function may be candidates for palivizumab prophylaxis, including those with neuromuscular maturational disease common in premature infants.[63] CNS injury prior to, during, or after delivery including but not limited to intraventricular hemorrhage (IVH), hypoxic ischemic encephalopathy (HIE),

spinal cord injury, disease of the peripheral nervous system, disease of the neuromuscular junction, and periventricular leukomalacia (PVL) are all considerations for RSV prophylaxis.[22,24,63] IVH, HIE, and PVL may cause cerebral palsy (CP) at a later time. CP alone may be a qualifier for RSV prophylaxis if there is any association with impaired respiratory function.[64,65]

6. Patients with congenital abnormalities of the airways that compromise respiratory function should receive prophylaxis.[8,66-69] This may include persisting wheeze, or disorders of abnormal lung growth. Congenital diaphragmatic hernia is included in this category.
7. Patients with cystic fibrosis and other diseases such as α1-antitrypsin deficiency where there is a genetic basis for changes in the lung milieu may also benefit from prophylaxis.[67,70,71]
8. Immune deficiencies are rare disorders and require collaborative management by pediatricians, infectious disease specialists, and immunologists.[72,73] Although there is no conclusive evidence for a particular disease category, because of the understood high risk of any infectious process, RSV prophylaxis is indicated unless a waiver can be obtained from a board certified pediatric immunologist or infectious disease specialist.
9. Special risk circumstances may occur in homes where another individual is at high risk for RSV infection but who may not be able to receive RSV prophylaxis. Providers should determine if it is reasonable to provide prophylaxis to other members of the household.[74,75]

D. Administration

1. RSV prophylaxis should be initiated prior to the onset of the RSV season and terminated at the end of the RSV season.[3,76,77] Although there are regional variations in the United States, RSV outbreaks begin as early as October and decrease between March and May. Providers should review local historical RSV surveillance data to assist in the decision-making process. Some locales in the Southern United States, Hawaii, and Alaska have high enough incidence of RSV to justify initiation in the late summer months and continuation of monthly prophylaxis into the late spring.[78-82] The burden of severe RSV disease on healthcare resources is greater than other respiratory viruses.[83] Although various cost containment models have been proposed to provide relative risk adjustment based on post conceptual age at a specific month during RSV season, there is risk that adequate levels of Palivizumab will not be achieved or maintained during months when RSV is widespread.[15,77] Use of an abbreviated schedule of RSV prophylaxis (e.g., based on post conceptual age mid season) is contrary to published evidence and Food and Drug Association (FDA) approved product indication for Palivizumab and is strongly discouraged.[84]
2. Non-adherence to FDA approved dosing regimens is considered an off label use of a medication. Off-label use of any medication places the provider at medico-legal risk. The FDA's Center for Drug Evaluation and Research (CDER) has initiated the Bad Ad outreach program with the goal of encouraging health care providers to recognize and report suspected untruthful or misleading drug promotion. Led by the Division of Drug Marketing Advertising and Communications (DDMAC), this effort informs providers about what constitutes misleading promotion and provides a process for reporting suspected violations to FDA. Violators may include state or professional organizations, those who may profit by modifying FDA approved dosing or indications for a medication, or individuals who make unrealistic claims about enhanced action of a medication (e.g., 3 doses are as effective as 5). Reports can be initiated by contacting the United States Food and Drug Administration's Division of Drug Marketing, Advertising, and Communications at 877-RX-DDMAC or (877-793-3622), E-Mail: BadAd@fda.gov, by mail: FDA/CDER/DDMAC, 5901-B Ammendale Rd., Beltsville, MD 20705-1266, or Fax: 301-847-8444.[85] However, in the past, the FDA has not had the resources to act quickly on reports of wayward drug misinformation. The False Claims Act provides another alternative to the Bad Ad outreach program. This fraud-fighting law not only provides substantial rewards for whistleblowers, but it includes an action-enforcing mechanism that statutorily requires the government to investigate allegations of fraud. If providers want to ensure that the government will consider their concerns, they can file a False Claims Act qui tam action.
3. Once a child begins RSV prophylaxis for the RSV season, the child must receive palivizumab monthly through the end of the season.[86]
4. Palivizumab 15 mg/kg IM should be given once a month during the RSV season to increased the likelihood of achiev-

Indication	Age of Child	Dosing
Chronic Lung Disease Requiring Medical Management	Less than 24 months at start of RSV season	Monthly during RSV season
Born at < 28 0/7 Weeks	Less than 12 months at start of RSV season	Monthly during RSV season
Born at 28 0/7-32 0/7 Weeks	Less than 6 months at start of RSV season	Monthly during RSV season
Born at 32 1/7-35 6/7 Weeks	Less than 6 months at start of RSV season with provider-determined significant risk	Monthly during RSV season
Congenital Heart Disease	Less than 24 months at start of RSV season unless cardiology waiver obtained	Monthly during RSV season
Neuromuscular Disease	Less than 24 months at start of RSV season	Monthly during RSV season
Congenital Abnormalities of the Airways	Less than 24 months at start of RSV season	Monthly during RSV season
Immune Disorders	Less than 24 months at start of RSV season unless infectious disease or immunology waiver obtained	Monthly during RSV season

ing and maintaining appropriate levels for prophylaxis.[20] A dose should be given 24-48 hours prior to discharge from the hospital if the patient meets criteria. The single-dose vial of palivizumab does not contain a preservative. Administration of palivizumab should occur immediately after dose withdrawal from the vial. The vial should not be re-entered.[20]

5. As there is more than one serotype of RSV, RSV disease is not a contraindication to continuing the palivizumab dosing schedule. Infection does not confer lasting immunity. Patients can be re-infected with RSV multiple times during the same RSV season. Thus, monthly dosing should be continued even if the patient is infected with RSV.[20]
6. Fever or other illness including viral syndromes are not contraindications to administration of palivizumab.
7. At present, there are no restrictions on concurrent RSV prophylaxis with any immunization.[87] Immunization with Measles-Mumps-Rubella (MMR) and Varicella vaccines need not be deferred in infants receiving RSV prophylaxis. RSV prophylaxis should not interfere with Hepatitis B vaccine, Diptheria, Tetanus, Pertussis (DTaP) primary immunization schedule, H. Influenza type B (Hib), seasonal influenza vaccination, Pneumococcal Conjugate Vaccine (PCV), or Inactivated Poliovirus Vaccine (IPV).
8. The safety and efficacy of palivizumab have not been demonstrated for treatment of established RSV disease.
9. Contraindications and Adverse Reactions
   a) Palivizumab should not be used in pediatric patients with a history of a severe prior reaction to palivizumab or other components of this product.[20]
   b) Fever, irritability and injection site reaction are the most commonly reported adverse events.[88]

IV. Nosocomial Infection

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

B. The best way to prevent RSV disease is strict adherence to infection control practice, the use of in-hospital screening studies to identify and cohort RSV-infected infants.[4] Proper hand washing is of paramount importance.

C. Cohorting of children with suspected RSV disease is not recommended. Not only are there other viral or bacterial diseases that mimic RSV, but infection with RSV does not preclude co-infection with these viruses or bacteria, or for that matter, another subtype of RSV.[4,89]

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Letters to the Editor

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Results from Study of Mead Johnson's Enfamil® Human Milk Fortifier Acidified Liquid Published in *Pediatrics*

(Business Wire) -- Mead Johnson Nutrition announced in mid-September the results of a new study published in *Pediatrics* that shows Enfamil Human Milk Fortifier Acidified Liquid supports significantly higher growth in premature infants than powdered fortifiers and is well-tolerated. Enfamil Human Milk Fortifier Acidified Liquid is the first and only ultra-concentrated liquid human milk fortifier marketed in the United States that meets safety guidelines from the Academy of Nutrition & Dietetics (AND) and Centers for Disease Control and Prevention (CDC), as well as new preterm nutrition guidelines from the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN).

The study was released online, and appeared in the October print edition of *Pediatrics.* It was also selected for presentation in December 2012 at *Hot Topics*, the nation's premiere neonatal conference, with anticipated attendance of more than 1,000 neonatologists and perinatologists.

Breast milk provides important nutrients and immune factors to help meet the nutritional needs of infants and minimize the risk of illness and other complications. However, breast milk alone may not fully meet the nutritional needs of premature infants.[1] Even currently available powdered human milk fortifiers may not support the increased protein needs of low birth weight infants.[2] The CDC and AND have recommended that for premature or immune-compromised infants, sterile liquid products be used instead of powdered products in the NICU, where nutritionally appropriate.[3] Mead Johnson is the first company to make available an ultra-concentrated liquid fortifier with nearly 20% more protein than current powdered fortifiers when added to breast milk. This ultra-concentrated fortifier minimizes the dilution of breast milk and provides the higher protein levels needed by preterm infants.

"Although liquid fortifiers are already recognized as the new standard of care, this is the first study to demonstrate the nutritional and safety benefits of ultra-concentrated liquid human milk fortifiers over powdered versions," said study co-author Carol Lynn Berseth, MD, director of medical affairs, Mead Johnson Nutrition. "With the development of ultra-concentrated Enfamil Liquid Milk Fortifier, Mead Johnson continues to demonstrate its leadership in pediatric nutrition innovation."

In the third-party blinded, stratified, controlled trial, 146 preterm infants with a gestational age of 23.7 - 30.4 weeks and birth weights between 530 to 1,250 grams received human milk and were randomized to receive Enfamil powder human milk fortifier (control group; 1.1 g protein/4 sachets) or Enfamil Human Milk Fortifier Acidified Liquid (1.8 g protein/4 vials) for 28 days. Weight and length growth were measured on day 28 and metabolic outcomes and other important outcomes--such as necrotizing entercolitis (NEC), a gastrointestinal disease that mostly affects premature infants, and sepsis, a serious infection usually caused by bacteria that make toxins that cause the immune system to attack the body's own organs and tissues - were measured on days 14 and 28.[4] To ensure the highest quality results, Mead Johnson collaborated with a Data Monitoring Board of three industry-leading neonatal academic specialists with expertise in clinical care, neonatal nutrition and statistical design to design and monitor outcomes throughout the study.

Infants who received the Enfamil Human Milk Fortifier Acidified Liquid showed significantly higher linear growth (41.8+/-0.24 vs. 40.0+/-0.23 cm, p=0.010) and weight growth (1770+/-35 vs. 1670+/-33, p=0.038) than the control group. Common markers of protein status, such as prealbumin, albumin and blood urea nitrogen (BUN), were also higher in the liquid human milk fortifier group versus the control group. No infants were treated for acidosis. Further, the study showed no statistically significant difference in the incidence of NEC or sepsis versus the control group. The study demonstrates Enfamil Human Milk Fortifier Acidified Liquid is not only clinically proven to provide better growth than Enfamil powdered fortifier, but is also safe and well-tolerated among preterm infants.[4]

ESPGHAN recommends 3.6 to 4.1 g protein per 100 calories for infants weighing less than 1,000 g.[5] When mixed with breast milk, Enfamil Human Milk Fortifier Acidified Liquid provides 4 g protein per 100 calories, which was shown to promote significantly higher weight, length, head circumference and linear growth than Enfamil powdered fortifier. Linear growth is recommended as a better measure of postnatal growth in premature infants than fat mass deposition.[6] Enfamil Liquid Fortifier also has 24 mg of DHA and 38 mg of ARA per 100 calories when combined with breast milk to help support optimal visual and cognitive development in premature infants.[7] Enfamil Human Milk Fortifier Acidified Liquid is the first and only ultra-concentrated human milk fortifier to have DHA and ARA.

Enfamil Human Milk Fortifier Acidified Liquid is provided in single-dose packaging, commercially sterile and free of microorganisms. The CDC, AND and US FDA have recommended that sterile liquid products be used instead of powdered products for premature or immune-compromised infants. The AND's amended guidelines suggest using ready-to-feed or concentrated formulas rather than powdered formulas in NICUs.[8]

"Mead Johnson designed this ultra-concentrated form of Enfamil Human Milk Fortifier Acidified Liquid to meet the nutritional needs of rapidly growing premature infants, while minimizing the dilution of the mother's breast milk which provides important health benefits," said Dr. Colin Rudolph, VP, global medical affairs and Chief Medical officer, Mead Johnson Nutrition. "From the science of making our product to the support of breastfeeding moms, we are committed to helping give babies the best start in life."

The study is sponsored by Mead Johnson Nutrition. Study authors include: Fernando Moya, MD: Coastal Carolina University Neonatology, Wilmington, NC; Paula M. Sisk, PhD: Department of Pediatrics, Wake Forest University School of Medicine, Winston-Salem, NC; Kelly R. Walsh, PhD, RD: Department of Nutrition Science, Research and Development, Mead Johnson Nutrition, Evansville, IN; and Carol Lynn Berseth, MD: Clinical Research, Department of Medical Affairs, Mead Johnson Nutrition, Evansville, IN.

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Documenting Women's Experiences with Chromosome Abnormalities Found in New Prenatal Test

We often hear that "knowledge is power." But, that isn't always the case, especially when the knowledge pertains to the health of an unborn child, with murky implications, at best. A new study, led by researchers from the Perelman School of Medicine at the University of Pennsylvania, begins to document this exception to the general rule.

Barbara Bernhardt, MS, CGC, a genetic counselor at the Hospital of the University of Pennsylvania, and colleagues contacted a small group of women who are participating in a larger Columbia University study investigating the use of a genetic test called a DNA microarray to identify the possibility of prenatal chromosomal abnormalities. Bernhardt is also Co-Director of the Penn Center for the Integration of Genetic Healthcare Technologies.

The study's goal: To document a woman's experience upon learning that her child's genetic material contained chromosomal abnormalities. The women's responses to this type of news were mostly negative, ranging from saying they "needed support" after getting the results to describing the results as "toxic knowledge," that they wish they hadn't received.

DNA microarrays represent a relatively new approach to genetic testing. Classically, chromosomal abnormalities are detected with karyotyping, which uses DNA staining and microscopy to identify such large-scale abnormalities as trisomy 21, associated with Down's syndrome. Yet the technique lacks the resolution to detect smaller – yet still significant -- chromosomal changes.

That's where DNA microarrays come in. Microarrays use an array of DNA "probes" to search for matching bits of DNA from across the genome. In theory, if a piece of DNA is missing or duplicated, that change can be detected on a microarray, even if it is too small to be detected by karyotyping.

DNA microarrays are often used by physicians following birth to identify chromosomal abnormalities in children with unexplained developmental delays or congenital defects. However, the technique is also being applied prenatally. The problem, though, unlike some genetic changes that definitely lead to disease, is that the significance of the changes DNA microarrays identify (called copy-number variants) isn't always clear. Nor is it necessarily obvious what actions parents, doctors, and genetic counselors should take in light of the findings.

Bernhardt set out to document the experiences of women receiving such information. Of the 4,450 women enrolled in the Columbia University trial, Bernhardt and her team selected 54 who had received chromosome microarray results that showed abnormalities in the previous six months. Of those, they interviewed 23 regarding the subjects' recollections of their informed-consent discussions, genetic counseling, test results, and follow-up.

The team identified five "key elements" that describe the women's experiences:

- "An offer too good to pass up." Many of the women accepted the offer for testing because it was offered at no cost and posed no additional risk to them or their unborn child. Yet they did so without necessarily considering the potential significance and ambiguity of the information they could receive.
- "Blindsided by the results." Women reported being caught off-guard by the microarray data, which generally arrived one to two weeks after preliminary (and seemingly normal) karyotype information.
- "Uncertainty and unquantifiable risks." Women had difficulty making sense of the test results, as copy-number variants are often of either uncertain clinical significance, or produce a wide array of possible developmental outcomes. As a result, the women's time-critical and emotionally charged decisions about whether to terminate a pregnancy, for instance, were complicated.
- "Need for support." The women reported needing support from counselors, spouses or partners to digest and consider the information they had received and to make critical decisions regarding their pregnancies.
- "Toxic knowledge." The women noted that in many cases the array results constituted "toxic knowledge" that they, in retrospect, wish they hadn't learned, because it negatively impacted their pregnancy, birth, and postnatal experiences. As Bernhardt describes it, "They watch their babies like hawks, … always waiting for the other shoe to drop."

According to Bernhardt, chromosomal microarrays pose the same ambiguities after birth as prenatally. The difference is that postnatal testing is done because the child already exhibits an unexplained abnormality, and physicians hope the test can pinpoint its cause. "But when you find [an abnormality] in a fetus it puts the woman and couple into a tailspin because they have no clue what to expect," she says. "And the couple is immediately faced with whether or not to terminate the pregnancy."

The take-home message, Bernhardt says, is that genetic counselors must be prepared to spend more time with parents to help them explore their reasons for wanting microarray testing. Counselors also need to emphasize to parents the potentially ambiguous nature of the microarray results, how to consider potential responses, and how to make the best decisions they can based on both available scientific data and the clients' beliefs.

The study, "Women's experiences receiving abnormal prenatal chromosomal microarray testing results," was published online September 6th in the journal *Genetics in Medicine*. Additional authors include: Penn researcher Danielle Soucier; as well as Karen Hanson, Melissa Savage, and Ronald Wapner from Columbia University College of Physicians and Surgeons; and Laird Jackson, Drexel University College of Medicine.

This work was supported by funding from the National Human Genome Research Institute, National (P50HG004487) and from the National Institute of Child Health and Development (R01HD055651-01 and R01HD055651-03S1).

Use of Fresh Red Blood Cells for Transfusions for Premature Infants Does Not Improve Outcomes

Among premature, very low-birth-weight infants requiring a transfusion, use of fresh red blood cells (RBCs) compared with standard RBC transfusion practice did not improve clinical outcomes that included rates of complications or death, according to a study in the October 10th issue of *JAMA*. The study was published early online to coincide with its presentation at the AABB (formerly the American Association of Blood Banks) Annual Meeting.

"Although RBC transfusions are used routinely in acutely ill patients, including those in neonatal intensive care units, the clinical consequences of the prolonged storage of RBCs have not been firmly established," according to background information in the article. "In recent years, several observational studies conducted primarily in adults have demonstrated that prolonged RBC storage is associated with in-

creased rates of infection, organ failure, death, and increased lengths of stay."

Dean A. Fergusson, MHA, PhD, of the Ottawa Hospital Research Institute, Ottawa, Canada and colleagues conducted a study to evaluate whether RBCs stored for 7 days or less decreased serious neonatal illness and death compared with standard blood bank issue. The randomized controlled trial included 377 premature infants with birth weights less than 2.8 lbs. (1,250 grams) admitted to 6 Canadian neonatal intensive care units between May 2006 and June 2011. Patients were randomly assigned to receive transfusion of RBCs stored 7 days or less (n = 188) vs. standard-issue RBCs in accordance with standard blood bank practice (n = 189). The primary outcome for the study was a composite measure of major neonatal illnesses, as well as death. The primary outcome was measured within the entire period of neonatal intensive care unit stay up to 90 days after randomization. The rate of hospital-acquired (nosocomial) infection was a secondary outcome.

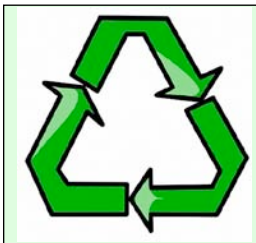
The average age of blood in the fresh RBC group was 5.1 days, compared with 14.6 in the standard RBC group. The average and median (midpoint) volumes transfused were similar in both groups, as were post-randomization co-interventions including modes of ventilation, insertion of lines and catheters, other blood products, and major surgical and diagnostic procedures.

A total of 199 infants (53.0%) experienced the composite primary outcome. The researchers found that among infants in the fresh RBC group, 99 (52.7%) had the primary outcome compared with 100 (52.9%) in the standard RBC group. "The rate of clinically suspected infection in the fresh RBC group was 77.7% (n = 146) vs. 77.2 % (n = 146) in the standard RBC group. Rates of confirmed infections were 67.5% (n = 127) in the fresh RBC group vs. 64.0% (n = 121) in the standard RBC group. Among confirmed cases, rates of bacterial, fungal, and viral infections were similar between the 2 groups. Major sequelae of infections including rates of pneumonia, meningitis and osteomyelitis [inflammation of bone or bone marrow, usually due to infection] were also similar. The median (midpoint) length of neonatal intensive care unit stay was 77 days in the standard RBC group and 84 days in the fresh RBC group."

"We did not find any clinically meaningful or statistically significant differences and, therefore, the many laboratory changes that occur with prolonged RBC storage may not be as important as once thought," the authors write.

"In conclusion, the transfusion of fresh RBCs did not improve clinical outcomes in high-risk, premature, very low-birth-weight infants. We thus do not recommend any changes to storage time practices for the provision of RBCs to infants admitted to neonatal intensive care."

Funding for this study was provided by the Canadian Institutes for Health Research. Please see the article for additional information, including other authors, author contributions and affiliations, financial disclosures, etc.



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Global Neonatology Today Monthly Column - World Health Report Card

By Dharmapuri Vidyasagar, MD, FAAP, FCCM

The 2012 report on Millennium Development Goals (MDGs) shows several positive changes. According to UN Secretary General the notable changes are as follows:

1. The number of people living in extreme poverty has fallen in every developing country. In 1990, 47% of the world population lived on less than $1.25 a day. In 2008, it had dropped to 24%. In absolute terms, the reduction was from over 2 billion to less than 1.4 billion. Thus, meeting the first target of MDGs of cutting the extreme poverty rate to half its 1990 level should be achieved well-ahead of 2015!
2. The target for decreasing the proportion of people without sustainable access to safe drinking water was also achieved by 2010. In 1990 only 76% had access to safe water; it increased to 89% in 2010. In absolute terms, between 1990- 2010, over two billion people gained access to improved drinking water sources.
3. According to the report, the living conditions of over 200 million slum dwellers also improved. The number of urban residents living in slums declined from 39% in 2000 to 33% in 2012, thus improving the lives of 100 million slum dwellers around the world. This was also ahead of the 2020 deadline.
4. School children are also enrolling in large numbers around the world. Enrollment of children in schools has increased considerably in primary schools since 2000. It is noted that many countries, even though facing many challenges, have made significant progress towards universal primary education. Enrollment rates of children of primary school age increased markedly in sub-Saharan Africa, from 58% to 76% between 1999 and 2010. Many countries in that region succeeded in reducing their relatively high out-of-school rates even as their primary school age populations were growing. It is good to know that girls have benefited the most. The ratio between the enrollment rate of girls and that of boys grew from 91% in 1999 to 97% in 2010 for all developing regions. This falls within the 3% margin of 100%, the accepted measure for parity.

And in the Field of Health

Progress in child survival is also gaining momentum. The number of annual deaths of children under-five years of age worldwide fell from more than 12.0 million in 1990 to 7.6 million in 2010. The countries in the developing world are progressing well. In Sub-Saharan Africa, where there is the highest level of under-five mortality, progress has been made, but at too slow a pace. The rate of reduction of under-five deaths was 1.2 % a year during the decade of 1990-2000. The rate of reduction during 2000-2010 doubled to 2.4%. However, under-five mortality in Sub-Saharan Africa remains a significant problem

In the area of HIV infection, access to treatment for people living with HIV increased in all regions. At the end of 2010, 6.5 million people were receiving antiretroviral therapy for HIV or AIDS in developing countries. The 2010 target of universal access, however, was not reached.

In tuberculosis, the world is on track to achieve the target of halting and beginning to reverse the spread of tuberculosis. According to the report, global tuberculosis incidence rates have been falling since 2002, and current projections suggest that the 1990 death rate from the disease will be halved by 2015.

The estimated incidence of malaria has decreased globally, by 17% since 2000. Over the same period, malaria-specific mortality rates have decreased by 25%. Reported malaria cases fell by more than 50% between 2000 and 2010 in 43 of the 99 countries with ongoing malaria transmission.

“These results represent a tremendous reduction in human suffering and are a clear validation of the approach embodied in the MDGs. But, they are not a reason to relax,” says Ban K. Moon Secretary General of United Nations.

The Clock is Ticking !!!

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