Vol. 26 No. 7
November-December 2013

neonatal INTENSIVE CARE

The Journal of Perinatology-Neonatology

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* Speed, L. & Harding, K. (2012). Tracheostomy teams reduce total tracheostomy time and increase speaking valve use: A systematic review and meta-analysis. Journal of Critical Care, 28(2):216.e1-10.

** HCUP Nationwide Inpatients Sample (NIS), 2011. Agency for Health Care Research & Quality (AHRQ). hcupnet.ahrq.gov

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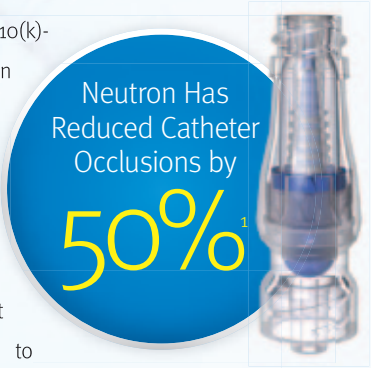

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1. Observational in-vivo evaluation of the Neutron catheter patency device and its effects on catheter occlusions in a home care setting. http://www.icumed.com/media/27672/m1-1315_neutron_homecare_sharp_studysumm_rev.1.pdf
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neonatal
INTENSIVE CARE

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INOMAX® is a vasodilator, which, in conjunction with ventilatory support and other appropriate agents, is indicated for the treatment of term and near-term (>34 weeks) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, where it improves oxygenation and reduces the need for extracorporeal membrane oxygenation.

Utilize additional therapies to maximize oxygen delivery with validated ventilation systems.

Reference: 1. Data on file. Hampton, NJ: Ikaria, Inc; 2013.

www.inomax.com

INOMAX Important Safety Information

- INOMAX is contraindicated in the treatment of neonates known to be dependent on right-to-left shunting of blood
- Abrupt discontinuation of INOMAX may lead to increasing pulmonary artery pressure and worsening oxygenation even in neonates with no apparent response to nitric oxide for inhalation

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INOmax (nitric oxide gas)
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INDICATIONS AND USAGE

Treatment of Hypoxic Respiratory Failure

INOmax® is a vasodilator, which, in conjunction with ventilatory support and other appropriate agents, is indicated for the treatment of term and near-term (>34 weeks) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, where it improves oxygenation and reduces the need for extracorporeal membrane oxygenation.

Utilize additional therapies to maximize oxygen delivery with validated ventilation systems. In patients with collapsed alveoli, additional therapies might include surfactant and high-frequency oscillatory ventilation.

The safety and effectiveness of INOmax have been established in a population receiving other therapies for hypoxic respiratory failure, including vasodilators, intravenous fluids, bicarbonate therapy, and mechanical ventilation. Different dose regimens for nitric oxide were used in the clinical studies.

Monitor for PaO_2, methemoglobin, and inspired NO_2 during INOmax administration.

CONTRAINDICATIONS

INOmax is contraindicated in the treatment of neonates known to be 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 (NO_2) forms in gas mixtures containing NO and O_2. Nitrogen dioxide may cause airway inflammation and damage to lung tissues. If the concentration of NO_2 in the breathing circuit exceeds 0.5 ppm, decrease the dose of INOmax.

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

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.

OVERDOSAGE

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

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

DRUG INTERACTIONS

No formal drug-interaction studies have been performed, and a clinically significant interaction with other medications used in the treatment of hypoxic respiratory failure cannot be excluded based on the available data. INOmax has been administered with dopamine, dobutamine, steroids, surfactant, and high-frequency ventilation. Although there are no study data to evaluate the possibility, nitric oxide donor compounds, including sodium nitroprusside and nitroglycerin, may have an additive effect with INOmax on the risk of developing methemoglobinemia. An association between prilocaine and an increased risk of methemoglobinemia, particularly in infants, has specifically been described in a literature case report. This risk is present whether the drugs are administered as oral, parenteral, or topical formulations.

 IMK111-01540 April 2013

Rookie Doctors: What We Know

Rookie doctors: Who are they? How do they work? and How do they learn with their restricted hours of training?

Muhammad Aslam, MD; Benamanahalli K. Rajegowda, MD

Since the publication of Institute of Medicine (IM) findings in 1999 of patients dying in the hospital mainly from medication errors, rookie doctors were presented to the general public, news media, and health organizations with their role in the above was exaggerated by policy-makers. The issue raised was based on the work of rookie doctors in training who worked very long hours, suffering sleep deprivation, exhaustion, an inability to concentrate and think, with poor supervision by their senior staff members. It was posited that they not only risk their personal and family life, but their long hours can also lead to poor medical outcomes, which cost millions of dollars and raise the risk of legal liability. It is true in every profession that long working hours will cause fatigue. However, rookie doctors do learn from job training, which will help them in the future, provided their work is structured and appropriately supervised.

The typical rookie doctors (interns, residents and even some fellows in training), after receiving a graduate degree, used to work 80 to 120 hours a week and many of us have done this as residents in the 1960s and continued up until the 1990s, at a lower phase. We did not have any studies to connect long hours of work to many safety issues. We were happy, very well-respected by our patients and by our superiors, and we were taken care of very well and treated with respect and dignity. Now medicine has change dramatically, from clinical medicine to controlled medicine to technology. As technology changes, one can assess health services and patient-safety outcomes which are overseen by JACHO. The IM has identified 1 in 3 medication errors and JACHO has identified a 70% failure rate for outcomes due to poor communication.

The Accreditation Council for Graduate Medical Education (ACGME) oversees education in each specialty-mandated curriculum for training under the supervision of experienced board-certified physicians. Since the IM report, in 2003 the ACGME proposed standards for supervision, teamwork, continuity of care, professionalism, and patient safety. It noted that first-year rookie doctors who now work every third night, and their shifts were responsible for more than half of preventable and avoidable errors. In 2010, rookie doctors' work hours were cut to 16 hours, plus an additional 4 hours for sign-out and completion of work without involving direct patient care, whereas a second- and third-year resident should remain on call for 24 hours, with a work week of 80 hours. This went into effect in July 2011. One of the limitations of the 16-hours model is that with time spent signing on and off, there is no continuity of care, persistent communication errors occur, new rookie doctors will have fewer opportunities to learn, which is critical for new doctors in acquiring knowledge and skills particularly in critical care areas.

We are neonatologists and we welcome the ACGME recommendation, as it is good for the rookie doctors and the patients, and we are hoping it will improve the goals of identified issues by IM. The fact remains that it puts a lot of pressure on senior residents in training and senior supervising physicians. These residents will have lost lots of opportunities to learn and many of them will not be able to learn in those limited hours. To avoid all this, their work should have been structured with their supervision more conditionally affected by their seniors and the staff physician. These restrictions and limitations on time spent in critical care areas like the NICU put a lot of the burden on the senior physician, creating a vacuum, and mandating recruitment of physician extenders like NPs, NCs and PAs in all areas where rookie hours of work are reduced. Though this is expensive, it comes with better quality of care and minimal medication errors, in addition to making life easy for senior staff physicians. In this battle, those who are lost are the rookie doctors. Many of them cannot do even minor things like drawing blood, starting an IV, or calculating medications, albeit they are involved with managing complex cases in NICU.

Massachusetts General has a residency program and does not have physician's extenders in the NICU. They depend on residents, who not only learn a lot but are also supervised closely one-on-one by a Senior Board Certified Physician in Neonatology, 24 hours a day, 7 days a week. One can imagine how life will be for a neonatologist who is constantly supervising residents in training and at the same time teaching, acquiring technical skills and solving multiple care issues. By experience, we could have been better off hiring physician extenders since we train them. They are with us all the time and they can provide continuity of care for critical infants with minimum supervision. Despite all this, we have an obligation to train these young doctors to perform their duties to provide care for their patients once they've graduated from training. I [Aslam] believe the way resident training is moving forward, these doctors, when they have a rotation to critical care, will act as observers rather than actual hands-on learners, since they have to compete with the physician extenders. This is good as long as these doctors choose to practice as primary care physicians, but some of them elect to go for specialties that require at least a month or two of extra training to graduate.

Continued on page 16…

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SURVANTA is indicated for prevention and treatment of Respiratory Distress Syndrome (RDS) in premature infants[2]

Trust what time has tested

INDICATION[2]

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

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

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

IMPORTANT SAFETY INFORMATION[2]

Warnings: SURVANTA is intended for intratracheal use only.

SURVANTA can rapidly affect oxygenation and lung compliance. Therefore, its use should be restricted to a highly supervised clinical setting with immediate availability of clinicians experienced with intubation, ventilator management, and general care of premature infants. Infants receiving SURVANTA should be frequently monitored with arterial or transcutaneous measurement of systemic oxygen and carbon dioxide.

Please see Brief Summary of Full Prescribing Information on adjacent page.

References

1. US Food and Drug Administration. Orange book detail record search. Available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=search.drugdetails. Accessed April 12, 2013. **2.** Survanta [package insert].

During the dosing procedure, transient episodes of bradycardia and decreased oxygen saturation have been reported. If these occur, stop the dosing procedure and initiate appropriate measures to alleviate the condition. After stabilization, resume the dosing procedure.

Precautions: Rales and moist breath sounds can occur transiently after administration. Endotracheal suctioning or other remedial action is not necessary unless clear-cut signs of airway obstruction are present. Increased probability of post-treatment nosocomial sepsis in SURVANTA-treated infants was observed in the controlled clinical trials. The increased risk for sepsis among SURVANTA-treated infants was not associated with increased mortality among these infants. The causative organisms were similar in treated and control infants. There was no significant difference between groups in the rate of post-treatment infections other than sepsis.

Use of SURVANTA in infants less than 600 g birth weight or greater than 1750 g birth weight has not been evaluated in controlled trials.

Adverse Reactions: The most commonly reported adverse experiences were transient bradycardia and oxygen desaturation; both were associated with the dosing procedure.

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

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

CONCURRENT EVENT	SURVANTA (%)	CONTROL (%)	*P*-VALUE[a]
Patent ductus arteriosus	46.9	47.1	0.814
Intracranial hemorrhage	48.1	45.2	0.241
Severe intracranial hemorrhage	24.1	23.3	0.693
Pulmonary air leaks	10.9	24.7	<0.001
Pulmonary interstitial emphysema	20.2	38.4	<0.001
Necrotizing enterocolitis	6.1	5.3	0.427
Apnea	65.4	59.6	0.283
Severe apnea	46.1	42.5	0.114
Post-treatment sepsis	20.7	16.1	0.019
Post-treatment infection	10.2	9.1	0.345
Pulmonary hemorrhage	7.2	5.3	0.166

[a] *P*-value comparing groups in controlled studies.

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Intratracheal Suspension
Sterile Suspension
For Intratracheal Administration Only

PROFESSIONAL BRIEF SUMMARY
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INDICATIONS AND USAGE

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

Prevention

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

Rescue

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

CONTRAINDICATIONS

None known.

WARNINGS

SURVANTA is intended for intratracheal use only.

SURVANTA can rapidly affect oxygenation and lung compliance. Therefore, its use should be restricted to a highly supervised clinical setting with immediate availability of clinicians experienced with intubation, ventilator management, and general care of premature infants. Infants receiving SURVANTA should be frequently monitored with arterial or transcutaneous measurement of systemic oxygen and carbon dioxide.

During the dosing procedure, transient episodes of bradycardia and decreased oxygen saturation have been reported. If these occur, stop the dosing procedure and initiate appropriate measures to alleviate the condition. After stabilization, resume the dosing procedure.

PRECAUTIONS

General

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

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

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

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

ADVERSE REACTIONS

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

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

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

Table 3.

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

[a] *P*-value comparing groups in controlled studies

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

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

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

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

Respiratory

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

Cardiovascular

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

Gastrointestinal

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

Renal

renal failure, hematuria.

Hematologic

coagulopathy, thrombocytopenia, disseminated intravascular coagulation.

Central Nervous System

seizures

Endocrine/Metabolic

adrenal hemorrhage, inappropriate ADH secretion, hyperphosphatemia.

Musculoskeletal

inguinal hernia.

Systemic

fever, deterioration.

Follow-Up Evaluations

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

Single-Dose Studies

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

Multiple-Dose Studies

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

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

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

OVERDOSAGE

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

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

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North Chicago, IL, 60064 U.S.A.
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News

☐ November-December 2013

BMC NEW

BioMed Central reports that the AllTrials campaign released a detailed plan on how all clinical trials can be registered and reported, pushing these efforts forward with useful, practical directions. The guidelines released specify actions on behalf of regulators, researchers, funders, and publishers and societies. The campaign suggests journals "commit to making it clear on a trial report if previously undisclosed trials come to light after publication." BMC already does this for its journal Trials and through its Threaded Publications initiative, the aim of which is to clearly connect all published content relating to a trial, including the trial ID, in one secure place… The Academic Senate for the 10 campuses of the University of California passed an open-access policy in late July. Covering more than 8,000 researchers and 40,000 publications a year, the policy requires academics to provide copies of their articles to UC and make them available through Creative Commons licenses. Some controversy ensued however, as faculty can opt out or delay the appearance of an open-access version of their work.

STILL DRINKING

Fetal Alcohol Syndrome is still a problem, according to the physicians who first identified it in the 70s. They noted that 1 in 13 women still drink during pregnancy and that the idea that pregnant women can have a few drinks isn't necessarily for all of them. The organization overseeing FAS research is MotherToBaby, which reported that one in 100 babies is affected by prenatal alcohol exposure. It recommends that all moms receive a personalized risk assessment from an expert. For more, contact mothertobaby.org.

REPORT ALL GIFTS

The Wall Street Journal reported that US doctors are bracing for increased public scrutiny of the payments and gifts they receive from pharmaceutical and medical device companies as a result of the new health law, the Sunshine Act. Peter Loftus wrote in WSJ that starting in August, companies had to record and report most transactions with doctors, including gifts of all types from sales reps, and that this info will be posted on a searchable government website starting in the fall of next year. Loftus said doctors are therefore being a lot more selective about meeting with reps and accepting money for speaking fees. The article noted that some companies had already been posting what they pay to doctors. The Centers for Medicare and Medicaid Services advised doctors to keep records of all payments and transfers of value. Also of note: a big exemption to the Sunshine Act is that companies don't have to report compensation to docs who speak at accredited events where they receive CME, as long as the sponsoring company doesn't make the payment directly to the doctor.

CRY CRY CRY

A newborn's cry can offer clues to later developmental and neurological problems and give caregivers a way to assess pain treatment, according to an article by Sumathi Reddi in the Wall Street Journal. He reports that researchers at Brown University and Women & Infants Hospital in Rhode Island devised a computer program to analyze baby cries. The program evaluates 80 parameters, including pitch and volume. It is hoped that eventually the type of cry will be able to link with specific conditions. Studies have already analyzed certain types of cries. For instance, researchers have examined the acoustics of infants at risk for autism and found that these infants had higher-pitched cries with a more variable frequency. It has also been noted that pain cries have a longer pause between the first cry and the next, and the second cry is louder.

BIG GRANT

The House Research Institute (HRI) and Children's Hospital Los Angeles announced final approval of grant funding by the NIH's National Institute on Deafness and Communications Disorders (NIDCD) for a major five-year, FDA-approved clinical trial of the auditory brainstem implant (ABI) in children. The grant provides funding to begin phase one of surgical trials for pediatric ABI in the US. Children considered for the clinical trial must have congenital bilateral deafness resulting from a malformed or nonexistent cochlea or hearing nerve. Such patients cannot receive hearing benefits from a hearing aid or cochlear implant. Children with cochlear implants that have not provided benefit are also suitable candidates for the study. Ten children will have their surgical and audiological care provided by the trial grant. The goal of the study is to establish the safety of both the ABI and the delicate brain surgery procedures required for its successful implantation for American children. To date, children who have been implanted with ABIs outside the US have demonstrated the potential to understand speech, and five US children who were implanted in Europe in recent years receive regular follow-up by the pediatric audiology staff at HRI's CARE (Children's Auditory Research and Evaluation) Center in Los Angeles. Contact houseresearch.org.

DIABETES

University of Maryland School of Medicine researchers have identified a cell-signaling pathway which plays a significant role in causing developmental defects of the fetal spinal cord and brain in babies of women with diabetes. Women with diabetes prior to pregnancy are 3 to 10 times more likely to have a child with NTDs than women without the disease. Folic acid has been shown to prevent NTDs in approximately 70% of pregnancies, but too much folic acid during pregnancy may increase the risk of breast cancer in offspring later in life. Researchers observed that high levels of glucose initiate the apoptotic pathway by activating a protein called apoptosis signal-regulating kinase 1 (ASK1). Once activated, ASK1 turns on a cell-death pathway by activating other pro-cell death proteins. The team found that reducing ASK1 activity, either by deleting the gene or by giving diabetic pregnant mice an ASK1 inhibitor, also reduced the incidence of NTDs. Research on mice suggests that human NTDs might occur using a similar cell-death pathway as in diabetic pregnant animal models. The scientists also said they had promising results in using the human-produced protein

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thioredoxin which is thought to act as an antioxidant and has been used commercially as an anti-aging agent in some cosmetics. As such, they noted that it could be developed into a dietary supplement to be used instead of folic acid.

MONKEY TALK

Human babies' responses to the vocalizations of non-human primates support core cognitive processes, including the formation of object categories. Researchers in Trieste and at Northwestern University found that for 3- and 4-month-old infants, non-human primate vocalizations promoted object categorization, mirroring exactly the effects of human speech, but that by six months, non-human primate vocalizations no longer had this effect; the link to cognition had been tuned specifically to human language. After this, the infant mind identifies which signals are part of its language and begins to systematically link these signals to meaning. Researchers also found that infants' responses to non-human primate vocalizations at three and four months was not just due to the sounds' acoustic complexity, because infants who heard backward human speech segments failed to form object categories at any age. The implication is that the origins of the link between language and categorization cannot be derived from learning alone.

EXPERIMENT

Lauran Neergaard writes in the Huffington Post about how much parents should know when enrolling their babies in clinical trials. She writes about a case in which parents enrolled their preemie in a study of oxygen treatment, "believing she'd get the best possible care," but that the parents "didn't understand it was an experiment to test what dose works best. No one mentioned any risks." Neergaard writes, "Doctors frequently prescribe one treatment over another without any evidence to know which option works best. There's no requirement that they tell their patients when they're essentially making an educated guess, or that they detail the pros and cons of each choice." The baby was involved in the Support study, which took place between 2005 and 2009, and aimed to find out what range of oxygen was best. It involved 1,300 babies at 23 hospitals. More babies who got the lower dose died. According to HuffPost, "The problem: A government watchdog agency last spring ruled that researchers violated federal regulations that required them to spell out the risks of the study for parents. Nowhere in the consent forms that parents had to sign was death mentioned." The NIH offered the counterargument that when the study began, doctors didn't think the lower dose posed a survival risk, and that preemies who weren't in the study who received the oxygen dose deemed appropriate by their doctors turned out to have a higher risk of death, and that the study was originally conducted to find ways of decreasing ROP. But the parents of the baby mentioned above reiterated that all that was neither here nor there and that "they simply didn't understand that they were participating in an experiment."

PAID FOR

Medicaid paid for nearly half of the 3.8 million births in the US in 2010, according to researchers at George Washington University School of Public Health who discovered that in 2010 Medicaid paid for 48% of all births, up from 40% in 2008. This represents a 19% increase in the proportion of all births financed by Medicaid and a 5% increase in the total number of Medicaid-financed births in just two years. The authors found that the number of Medicaid-financed births increased by 90,000 over the course of the study. Other findings: The percentage of births paid for by Medicaid varied among states. For example, just one quarter of births in Hawaii were financed by Medicaid compared to nearly 70% in Louisiana. States in the northeastern and northwestern United States have the lowest proportion of births financed by Medicaid. Southern states have the highest Medicaid coverage.

SMEAR IT ON

The use of topical corticosteroids by pregnant women isn't associated with bad pregnancy outcomes such as orofacial cleft, low birth weight, preterm delivery, fetal death, low Apgar score and mode of delivery, according to a study at Chang Gung University College of Medicine, Taiwan. Researchers enrolled 2,658 pregnant women exposed to topical corticosteroids and 7,246 who weren't exposed. However, there was an increased risk of LBW when more than 300 grams of potent topical corticosteroids were used.

ENZYMES AND AUTISM

The enzyme topoisomerases affects brain development and could lead to autism spectrum disorder, according to researchers at the University of North Carolina School of Medicine. Inhibiting these enzymes has the potential to profoundly affect neurodevelopment, perhaps even more so than having a mutation in any one of the genes that have been linked to autism, according to the researchers. A temporary exposure to a topoisomerase inhibitor in utero has the potential to have a long-lasting impact on the brain by affecting critical periods of brain development. These enzymes untangle tangled DNA. Topoisomerase-inhibiting chemicals are used as chemotherapy drugs. The study's findings could help lead to a unified theory of how autism-linked genes work. About 20% of such genes are connected to synapses and another 20% are related to gene transcription, which translates genetic information into biological functions.

NATURE/NURTURE

Scientists at Cincinnati Children's Hospital Medical Center have found that gene-environment interactions are a major contributor to preterm birth and that using a combinatory treatment strategy can prevent preterm delivery in mice. Scientists tested gene-environment interactions in a robust mouse model of prematurity and identified a similar molecular signature in human tissue samples from women who experienced premature birth. They found that when a genetic predisposition is combined with mild inflammation, the rate of preterm birth is profoundly increased, provoking preterm birth in 100% of females. The results are clinically relevant because aspects of the molecular signatures observed in the mouse studies are consistent with those observed in tissue samples of women who had undergone preterm birth. Progesterone was found to be an effective gene replacement.

EAT, DRINK

Mothers can eat and drink anything they want during labor, and there's no point in restricting foods and fluids, according to researchers at the University of Liverpool. Researchers analyzed studies of 3,130 women who were at low risk for needing general anesthesia. Factors considered were c-section vs vaginal birth and mothers' satisfaction with the birth. The researchers looked at APGAR scores and babies' blood glucose levels. They found no differences in any of the outcomes measured between women who ate and drank during labor and those who didn't. The prohibition of food and drink started in the 40s

when doctors noted that moms under general anesthesia were having the contents of their stomach enter the lungs. However, the researchers pointed out, today's c-section techniques typically use regional anesthesia so this risk has shrunk greatly. Information is from an article by Honor Whiteman in Medical News Today, copyright Medical News Today.

EPILEPSY AND BIRTH DEFECTS

Researchers at The Royal Melbourne Hospital found a link between high doses of valproate and the risk of having a baby with spina bifida or hypospadias. Eighty percent of instances of spina bifida were associated with valproate exposure. However, the researchers found that reducing the dosage during the first trimester greatly reduces this risk — a good thing, because valproate is the only drug that controls epileptic seizures. Unfortunately, cleft palates and heart defects were still found to be common with any dosage of valproate.

BACTERIA AND BABIES

Early-onset neonatal infection is associated with maternal infection and bacterial colonization, according to researchers at Johns Hopkins. Newborns of mothers with laboratory-confirmed infection had an odds ratio of 6.6 for laboratory-confirmed infection compared with newborns of mothers without laboratory-confirmed infection. Newborns of mothers with colonization had an odds ratio of 9.4 of laboratory-confirmed infection compared with newborns of non-colonized mothers. Newborns of mothers with risk factors for infection had an odds ratio of infection of 2.3 compared with newborns of mothers without risk factors. The researchers combed through 448 articles and found 83 relevant studies and 67 which they combined in meta-analyses. They noted that past reviews have evaluated the effect of antibiotics for maternal Group B streptococcal colonization and maternal risk factors of infection in neonatal sepsis, but have not assessed the risks of infection and colonization for other bacterial types.

MOMS AND MIDWIVES

Moms-to-be who have a midwife as the main care provider throughout pregnancy, as opposed to multidisciplinary care, are less likely to have a preterm birth and need fewer obstetric interventions during childbirth, according to a Kings College London study reviewing 13 trials and involving more than 16,000 women. Trials included those where women were at both high and low risk. The Cochrane Library study revealed that moms using midwives were less likely to lose their babies before 24 weeks and less likely to give birth before 37 weeks. They had fewer epidurals, fewer assisted births, and fewer episiotomies. They also reported being happier. Plus, these moms were no more likely to have a c-section birth, though they were in labor 30 minutes longer. Information is from an article by Honor Whiteman in Medical News Today, copyright Medical News Today.

LESS EFFECTIVE

Neonatologists at The Children's Hospital of Philadelphia have found that noninvasive techniques for respiratory support are less effective than widely assumed in reducing the incidence of severe lung injury in very premature infants. The researchers' multinational, randomized trial compared NCPAP and NIPPV for ELBW preemies. Researchers tested the hypothesis that the extra pressure delivered in NIPPV would be more beneficial than CPAP in preventing BPD. The study team randomly assigned 1,009 infants with a birth weight under 1,000 grams (2.2 pounds) and gestational age under 30 weeks to either nasal CPAP or nasal IPPV. The infants were from 34 neonatal intensive care units in 10 countries. The researchers found no significant difference in the primary outcome of either death or survival with BPD at 36 weeks. They also found no significant differences in rates of other neonatal complications between the two treatment groups. The authors said their findings refute the common assumption that noninvasive therapies are reducing severe lung damage in ELBW babies.

NANN NEWS

NANN's aggregator news site SmartBrief reports on an NIH program to explore the use of **genomic sequencing** in newborn screening wherein the NIH is awarding four research teams up to $25 million to determine if such sequencing enhances health outcomes [Wall Street Journal]… In healthy term babies, all four schedules for the 13-valent **pneumococcal conjugate vaccine** yielded high immunoglobulin G antibody levels one month after the booster dose. Researchers noted a decline in antibody levels following the initial vaccination series in nearly all the serotypes for all vaccine schedules [InternalMedicineNews.com]… Mothers of preterm infants who participated in a **computer-based education** program had fewer symptoms of trauma and depression compared with their counterparts in a usual care group. More than 90% of mothers completed the intervention, and researchers said that suggested it could be implemented easily in an NICU and would not require specialized staff training [Medscape]… In babies with a family history of **atopy**, exposure to secondhand smoke was linked to a 23% increased length of hospital stay for a lower respiratory tract infection [DoctorsLounge.com/HealthDay News]… Babies who received inhaled racemic **adrenaline** for acute **bronchiolitis** were no less likely to need nasogastric-tube feeding, supplemental oxygen or ventilators than the inhaled saline group. The number of hospital days for them was not significantly different compared with babies receiving saline [Family Practice News]… The Mayo Clinic received federal approval for a stem cell trial that will use babies' own **umbilical cords** to treat heart defects such as hypoplastic left heart syndrome [KTTC-TV, Minneapolis]… St Joseph Medical Center in Tacoma, WA opened a **five-bed NICU**, which officials said will mean fewer transfers of critically ill newborns [The Bellingham Herald]… Doctors at the University of Kansas Medical Center treated an infant's brain aneurysm with **surgical glue** delivered through a micro-catheter. The glue served as an internal cast to seal the blood vessel [The Kansas City Star]… In a study of 254 women suffering from **hyperemesis gravidarum**, adverse pregnancy outcomes including premature births and low birth weight babies were associated with **antihistamine** use, according to a six-year study [Nurse.com]… The use of a **bundled protocol** in mechanically ventilated babies and children may help reduce the incidence of **VAP**. The care bundle includes an elevated bed, age-appropriate oral care, and hand hygiene before and after contact with the patient or the device [BeckersHospitalReview.com]… Premature babies who were placed in a **plastic bag** were 26% less likely to develop hypothermia within an hour after birth than those who got standard thermoregulation, a study from Zambia found [New York Times]… An antimicrobial stewardship program in four NICUs eliminated some, but not all, instances of **antibiotic use** that could be considered inappropriate, according to findings presented at a meeting of the Pediatric Academic Societies [Medscape]… Maintaining a **hand hygiene** compliance rate of more than 80% was linked to a 48% decrease in methicillin-resistant Staphylococcus aureus acquisition in a single-center

neonatal ICU [BeckersHospitalReview.com]… More than two dozen US NICUs now offer **live music therapy** [AP]… **Breast milk** helps fight infections in both babies and their mothers. Researchers found leukocytes increase in breast milk when a mother or baby has an infection, and return to normal ranges once the infection has passed [Perth Now]… The FDA is allowing imports of injection drugs for total parenteral nutrition to ease a **US shortage** [NBC News]… Giving women the **Tdap vaccine** during their second or third trimester of pregnancy could avert about a thousand annual pediatric cases of whooping cough in 1- and 2-month-olds [Daily Rx.com]… The efficacy rate of **acetaminophen** in preventing fever and other adverse reactions following vaccination was approximately 43%, mostly in babies, according to a German study. No difference was seen in fevers among toddlers who received acetaminophen after vaccination compared with those who did not get it [DailyRx.com]… Widespread **drug shortages** are affecting care in the NICU, according to Michigan hospitals. The reasons include a lack of spare capacity for the production of generic drugs, quality issues, and the small number of companies that make the treatments [Michiganradio.org]… **Breast-fed** children were 24% more likely than their formula-fed peers to move up the social hierarchy later in life, according to a UK study, and breastfeeding was associated with increased brain development and lower stress levels [Agence France-Presse]… Data on premature infants born from 2000 to 2009 showed a decline in the use of **invasive medical care**, according to research that included 669 hospitals in North America. Physicians switched to using **surfactant treatment** during deliveries and supported less-invasive neonate respiration strategies [Medscape]… Babies born small for gestational age to mothers with **preeclampsia** were at greater risk of developing **cerebral palsy** whether they were full-term or premature, according to a Norwegian study. Very preterm babies who were not small for their gestational age born to mothers with preeclampsia were less likely to have **cerebral palsy** compared with peers born to women without the complication [MedPage Today]… In a recent study, 47% of 440 babies ages 7 weeks to 12 weeks had positional **plagiocephaly** from lying on their backs [The Huffington Post]… Babies who were **conceived in May** had a 10% higher risk of being born prematurely than those conceived at other times of the year, according to a study in the Proceedings of the National Academy of Sciences. The researchers said the association may be a function of a pregnant woman's increased exposure to the seasonal flu during January and February [HealthDay News]… A German study of 148 babies who had a first-degree relative with **type 1 diabetes** showed that having a respiratory infection during the first six months of life was associated with a more than twofold increased risk of developing islet autoantibodies by age 3. Infections between 6 months and 12 months of age increased the chances of developing the antibodies by 32% [HealthDay News]… Women who took **iron supplements** while pregnant had a 19% lower chance of having low birth weight babies compared with those who did not take them, according to a study in the journal BMJ [DailyRx.com].

PRODUCTS

IT'S A WRAP

Beevers Medical Solutions announced the release of Luma Wrap, a transparent swaddle blanket for babies, specially designed to be phototherapy-compatible. Luma Wrap has been designed in response to customer requests for a see-through swaddle blanket for frantic, panicky, twitchy babies. These behaviors are often associated with, but not exclusive to, babies born with drug addictions. Babies born with drug addictions often exhaust themselves, and their caregivers, while on phototherapy and may benefit from swaddling with the Luma Wrap. The Luma Wrap infant swaddler provides centered and comfortable boundaries that a segment of our baby population needs. Luma Wrap is soft, gentle, easy to use, and disposable. Luma Wrap is highly breathable, made of a non-woven material that is over 90% light-permeable and does not have significant heat build-up. Although Luma Wrap is designed to be phototherapy-compatible, it can also serve as a convenient, disposable swaddle for infants in general. Beevers expects caregivers to find Luma Wrap beneficial for all babies. Luma Wrap can be used on any baby that is hyper-responsive or otherwise responds positively to swaddling. Contact beevers.net/lumawrap.

SCREEN TEST

PerkinElmer announced the first available early onset preeclampsia screening test in the United States. The PreeclampsiaScreen | T1 serum screening test enables physicians to more precisely detect asymptomatic patients in the first trimester of pregnancy who are at high risk for developing the condition, allowing for earlier identification, management and intervention. PreeclampsiaScreen | T1 is administered during the first trimester of pregnancy through a simple blood test to detect three biochemical markers in the mother's blood: PAPP-A (pregnancy-associated plasma protein-A); PlGF (placental growth factor) and AFP (alpha fetoprotein) that, when evaluated collectively with personal demographic data, provide a way to evaluate if there is an individual risk of developing early-onset preeclampsia. Physicians have the option to provide two additional biophysical measurements for their patients, mean arterial pressure (MAP) and uterine artery Doppler pulsatility index (UtAD-PI), each increasing the sensitivity of the screen when included in the testing protocol. Contact perkinelmer.com.

HYPERTENSION

Silvergate Pharmaceuticals Inc announced that the United States Food and Drug Administration (FDA) approved Epaned (enalapril maleate Powder for Oral Solution) to treat hypertension (high blood pressure) in people one month and older. Enalapril is one of the most commonly prescribed medicines in the United States to treat high blood pressure. Epaned enables accurate dosing for children who until now have relied on an adjusted adult dose. Epaned is available through an extensive network of pharmacies and a qualified mail order service. Epaned will be reimbursed by most private insurance plans and state Medicaid programs. Contact (855) 379-0382 or silvergatepharma.com.

PATENTED

PeriGen has received notification from the European Patent Office of their intent to grant a patent for application 07 290 544.1. PeriGen's library has risen to 23 issued patents. This patent covers specialized techniques to display patient data to help obstetrical clinicians more easily recognize important trends and hazardous deviations from normal health conditions. It reduces the problem of information overload which is prevalent in modern electronic medical records. In conjunction with standard fetal heart rate and uterine contraction data, the new displays show multiple time-aligned views of other key data elements such as maternal vital signs, medications administered, or analyses such as heart rate categorization or variability. OB clinicians can choose to display the specific data

elements that are most pertinent to each patient and the mother's unique circumstances, as well as receive alerts when values exceed safety limits. Contact perigen.com.

COMPANY PROFILE

Kubtec

Describe your product and its features.
Kubtec's Digiview 250 flat panel detector, designed for the NICU, offers lowest-dose DR from imaging neonates. A fully portable system with a suite of digital enhancement tools to provide the most detailed examinations, the Digiview 250 operates with any existing x-ray source. Rapid acquisition (750 ms) and low-profile (14" x 11" x .08") package, fitting directly into an isolette, gives the capacity to image fragile patients at the lowest doses without having to transport them.

Discuss the educational services you provide.
Kubtec provides comprehensive product training on the Digiview 250. With Kubtec's training by industry professionals, we offer CEU credit for ASRT members. Post-warranty we offer refresher training and training for new staff.

Tell us about your technical support and services.
The Digiview 250 has a one-year full warranty from effective date, including all parts, software and labor. Our warranty includes guaranteed response time (within 24 hours) for all service and support requests by our factory-trained technicians and on-site repair service, if required. Post-initial-warranty Kubtec offers support options to maintain and upgrade systems.

Discuss the latest neonatal advances germane to your product.
Neonatology teams dealing with the youngest and most fragile patients must be multi-disciplinary. Effective treatments are constantly evolving and often require frequent radiographic monitoring with assured low-dose radiography to reduce cumulative radiation exposure to the most vulnerable patients.

AARC PREVIEW

Hamilton Medical, Inc

Booth 443

What products will you be presenting?
Hamilton Medical, Inc is celebrating 30 years in providing the most advanced ventilator portfolio available. Hamilton Medical Inc has the most current ventilator technology on the market today and we have a ventilator model that meets the requirements of all market segments. Our 30 years in ventilation will be celebrated by featuring our full product line, featuring the HAMILTON G5, HAMILTON C3, HAMILTON C2, HAMILTON C1 and HAMILTON T1, with a brief introduction to the next addition to our product line, the HAMILTON MR1 (pending FDA 510(k)). The Hamilton G5 will be showcased, demonstrating its latest software, designed to provide more functionality in daily use. We will introduce a new model to address the higher standard for neonatal ventilation, additional options in waveforms and loops, and a new transpulmonary waveform to highlight transpulmonary pressure.

Discuss educational/training support materials you'll be featuring.
Hamilton Medical will be focusing on the tools to make ventilation safer and more cost-effective. We will have our licensed clinicians and international product managers in our booth to provide hands-on demonstrations of the G5, as well as all of our unique features, including: • ASV, Adaptive Support Ventilation (closed loop control); • INTELLiCUFF, our automated cuff pressure controller; • PV TOOL Pro, our Protective Ventilation Tool; • INTELLiTRIG, our technology that automatically responds to leaks and adapts sensitivity thresholds in NIV; • INTELLiSYNC, to assist in patient synchrony during spontaneous breaths; and • Dynamic Lung and Wean Window, a true graphical representation of your patient's lung condition. Hamilton Medical will also feature a demonstration of Hamilton Medical College, our on-line e-learning tool, offering courses on mechanical ventilation and the Hamilton Medical ventilators. View how you can train your staff effectively, meet your training requirements and have your staff earn CRCEs without ever leaving the hospital, and all at no charge.

Why should our readers visit your display?
Our 20-x-20 Island booth will house each of our products and product experts, so if you practice adult care, neonatal care, long-term care or are involved in transport care, either on the ground or in the air, Hamilton Medical is available to provide you a solution to address the needs of your daily practice.

Mercury Medical

Booth 448/450

What neonatal/perinatal products will you be presenting?
The Neo-Tee with in-line adjustable PIP controller. It's the industry's first and ONLY ONE disposable Infant T-Piece Resuscitator with Built-In Pressure Relief and Color-Coded Manometer on the Tee. Mercury is the ONLY ONE company with three types of resuscitation systems: CPR, Hyperinflation and now a T-Piece. Complementing the Neo-Tee will be the new Hyperinflation system, NuFlO2. NuFlO2 has an APL (Adjustable Pressure Limiter) valve and Color-Coded Manometer. The system can be used under MRI procedures as the device is fully MRI conditional. Economical, high-quality disposable CPR bags in a variety of configurations will be exhibited along with the colormetric CO2 line, including Neo- StatCO2<Kg, the ONLY ONE CO2 detector specifically designed for tiny babies with an expanded patient weight range of 0.25kg to 6kgs. The infant air-Q sp (Self-Pressurizing) sizes 1 and 1.5 complements the family of Masked Laryngeal Airways. The air-Q sp design is the ONLY ONE Masked Laryngeal Airway that prevents potential for overinflation. When delivering PPV, the increased airway pressure increases the pressure within the cuff, creating a good seal, (consistently over 20 cm H2O). Increase in cuff seal pressure occurs at the exact time you need it... during the upstroke of ventilation. Key advantages: • Simpler: No Inflation Line or pilot balloon eliminates the extra step of inflation and guesswork of adding air to the mask cuff. • Eliminates mask cuff over inflation. • The removable color-coded connector allows intubation through it using standard ET tubes. Mercury Medical will also be showing the new reusable air-Q sp size 0.5 for use with tiny babies.

Tell us about the R&D efforts you'll be highlighting.
Mercury's new NuFlO2 will be a good representation of one of the many efforts that have been in place.

Discuss educational/training support materials you'll be featuring.
Full product training will be provided at the booth by Mercury Medical Product Specialists. We will provide product information brochures, wall charts/posters with specifications and offer free samples. The samples will be provided by fully trained sales representatives who will provide comprehensive product in-servicing at the attendees' facilities. We will have available a new Neo-Tee in-service training video.

Why should our readers visit your display?
Mercury is a leading manufacturer of neonatal respiratory products and is highlighting several key industry-first disposable products that save money for the hospital and improve patient outcomes at the same time. Mercury is the ONLY ONE company that has introduced the product types mentioned previously: Neo-Tee with in-line controller, Neo-StatCO2<Kg, air-Q sp and NuFlO2. Due to the changing NRP guidelines, it will be important for clinicians like RT directors and NICU nurses to visit our display as they are actively looking for neonatal resuscitation devices that meet these NRP guideline requirements. For instance, the Neo-Tee offers more consistent inspiratory and expiratory pressure than other devices. It is affordable for use at every NICU, L&D and ED bedside. One of the latest requirements is that every NICU stock "size one" laryngeal mask for rescue airways. air-Q is the infant rescue airway solution for meeting this requirement. Furthermore, NRP recommends using a colormetric CO2 on the supraglottic airway connector to ensure proper placement with rapid color change. Mercury provides the ONLY ONE disposable CO2 detector solution for premature infants below 1 kg with the Neo-StatCO2. Clinicians should visit our display to get a first-hand view of our products and advantages.

Passy-Muir Inc

Booth 548

What neonatal/perinatal products will be you be presenting?
In addition to the Passy-Muir Tracheostomy & Ventilator Swallowing and Speaking Valve, our company will highlight the Toby Tracheasaurus Plush Toy, Toby Coloring Book. Toby comes with a pediatric tracheostomy tube and Passy-Muir Valve (for demonstration purposes only). Toby provides therapists with a lighthearted introduction to therapy for use with their tracheostomized patients to facilitate vocalization and enhance therapeutic activities. The Tammy and Toby Tracheasaurus Coloring Book is a pre-surgical or post-surgical teaching aide that offers children a fun, educational way to learn about the tracheotomy procedure and related issues, and to discuss anxieties and concerns the child and family may have. Therapists will find this a delightful tool to introduce patients to tracheostomy placement and for use with those who already have a tracheostomy.

Discuss education/training/support materials you'll be featuring.
At AARC, the Ventilator Instructional Tracheostomy Observation (VITO) mannequin will be featured to demonstrate the ventilator application of the Passy-Muir Valve. This simulated ventilator demonstration will aid clinicians in understanding the important aspects of ventilator application with the neonatal population. Tracheostomy T.O.M. and Pocket T.O.M. are anatomical models for instructors and clinicians and ideal for hands-on demonstration, training of skills necessary for tracheostomy care and discussion of tracheostomy and nasogastric tube-placement issues. Tracheostomy T.O.M is ideal for group and classroom instruction. Pocket T.O.M is a more portable version to take to the bedside for patient and caregiver education. Our newest FREE web-based continuing education opportunities will be featured and new Overcoming Barriers to Speaking Valve Success handouts. These will provide evidence-based information on the keys to successful speaking valve use.

What speakers, clinical papers or promotional items will you be presenting?
Passy-Muir Inc is sponsoring Cory E. Martin, EdS, who will be presenting his poster "Needs Assessment for Tracheostomy Curricular Resources." In his study, respiratory therapy educators were surveyed to gather data on current curricular content regarding tracheostomy-related issues in order to identify potential new curricular resources that could be developed. Information from his poster is valuable to further education related to tracheostomy care, including use of the Passy-Muir Speaking Valve for quality of life.

Why should our readers visit your display?
The Passy-Muir Tracheostomy and Ventilator Swallowing and Speaking Valve is the only closed-position valve that restores more normal physiology, thus offering numerous clinical benefits beyond communication. It has been used on infants as young as a week old! Early rehabilitation with the Passy-Muir Valve can result in a faster weaning process and shorter length of stay. A visit to the Passy-Muir Inc booth will provide the respiratory professional with contemporary evidence-based research and education to improve care and reduce costs associated with tracheostomized and mechanically ventilated patients. Respiratory care professionals are key players in helping to safely and effectively progress these patients to more cost-effective levels of care. Clinicians will learn how early use of the Passy-Muir Valve can accelerate this process, thus reducing costs and improving quality of life. Our expert Clinical Specialists will answer questions and help provide the knowledge needed to advance outcomes of the tracheostomized patient.

Editorial…continued from page 7

I'm an old timer [Rajegowda] and I believe medicine is learned at bedside under the supervision of a senior physician, with proper instruction, supervision of technical procedures and solving critical issues by dealing with challenging clinical cases. Of course reading is essential and teaching maybe helpful in a limited matter, but nothing replaces structured supervised bedside teaching to produce a clinically talented trained physician either in primary care or in a given specialty.

Muhammad Aslam is an Assistant Professor of Pediatrics at Harvard Medical School and Neonatologist and Director of Education at Massachusetts General Hospital. Benamanahalli K. Rajegowda is a Professor of Pediatrics and Chief of Neonatology at Lincoln Medical and Mental Health Center/ Weill Medical College of Cornell University.

Commentary

Lisa Rosenbaum wrote on The New Yorker website about the subject of this month's editorial on rules limiting the number of hours residents can work. She says, "To facilitate the [resultant] marked increase in transfers of care, known as handoffs, trainees now rely on electronic to-do lists describing the necessary tasks for any one patient… But when it comes to preparing young doctors to manage disease, the training environment has been completely transformed.

"For a young doctor, the right course of action isn't always clear. Acquiring the necessary knowledge and experience requires feedback, which strengthens one's ability to anticipate how the many variables and small decisions might affect the patient. What's more, learning how to manage illness demands infinite tweaking; each patient is unique.

"But now, residents spend less time directly caring for patients than they once did, and the feedback inherent in the hours once spent with more seasoned physicians has also diminished. In the earlier years of my training, morning rounds were a sacred time. The whole team would gather to learn about the patients who came in overnight, and discuss patients already in our care. We would hear their stories, examine them, review data, and then, together, make decisions about their care for the day. Now, however, the scheduling is such that overnight residents often have to leave before rounds, and the daily ritual has morphed into a race against the clock. Instead of beginning by asking who the sickest patient is, we now ask which resident needs to leave.

"The stories of our patients, which we used to own, now come in fits and spurts, passed along via an unending game of telephone. 'Anyone know why the heart failure patient's diuretic was held?' the team leader might ask. 'Anyone?' With the resident who made the decision often gone, a mad shuffling of pages invariably ensues, as trainees flip through their lists until someone finds the patient and utters the six saddest words of the shift-limit era: 'I don't know. I'm just covering.'"

Dr Rosenbaum notes that the field of medicine has advanced through measuring, and she quotes the legendary physician Dr Joseph Lieber: "Sometimes the medical field makes the mistake of valuing most what is most easily measured."

She goes on to note, "Our approach to duty-hour limits for residents has been no exception. Everyone knows how it feels to be tired, and there is nothing easier to count than hours worked or slept… [The] conviction that a rested doctor who doesn't know you would be better than a tired doctor who does — fueled the 2003 and 2011 reforms."

A Johns Hopkins study found that a 2011 group of first-year residents slept more, but "they experienced a marked increase in handoffs, and were less satisfied with their education. Equally worrisome, both trainees and nurses perceived a decrease in the quality of care — to such an extent that one of the 2011-compliant schedules was terminated early because of concerns that patient safety was compromised. And another study, comparing first-year residents before and after the 2011 changes, found a statistically significant increase in self-reported medical error.

"While these studies suggest the complex nature of patient safety — that manipulating one variable, like hours worked, inevitably affects another, like the number of handoffs — there is another tradeoff, more philosophical than quantifiable. It has less to do with the variables within the system and how we tinker with them, and more to do with what we overlook as we focus relentlessly on what we can count."

Interview

In this new feature, Neonatal Intensive Care interviews clinicians and healthcare providers about the actual application of specific products and therapies. Our premiere interview is with Andrew Slezak, MEd, RRT-NPS, Neonatal Clinical Education — St Joseph's Women's Hospital, Tampa, FL, discussing his hospital's use of the Neo-Tee by Mercury Medical.

Laszlo Sandor: What areas/departments could the hospital benefit from using the Neo-Tee?
Andrew Slezak: The most value comes from the use of the Neo-Tee in the delivery room. With so much unpredictability in the delivery of a newborn, it is extremely valuable to have a single device that can provide both CPAP for slow transitions and consistent ventilation in emergencies. This is especially true with our premature neonates. Having a Neo-Tee at the bedside for our NICU patients gives us the ability to respond quickly to apneas, bradycardic episodes, and other respiratory emergencies. Using a Neo-Tee allows the therapist to alter the level of support needed quickly while also providing a safer mode of resuscitation for our bedside nurses. A flow-inflating resuscitation bag needs skill and experience to operate safely while the Neo-Tee allows someone with little experience to still give consistent pressures during resuscitation (other than occluding the hole for the respiratory rate and not releasing).

LS: How many L&D and NICU beds does your facility have?
AS: A 64-bed NICU and a 22-bed L&D.

LS: How does the Neo-Tee assist clinicians in providing better patient outcomes?
AS: It reduces the risk of barotrauma during positive pressure delivery by providing consistent pressures during each breath. Due to its simplicity, it allows delivery team members to concentrate on other aspects of resuscitation by taking the guess work out of the breathing equation. With a flow-inflating resuscitation bag, the clinician must concentrate on squeezing the bag appropriately each breath. That's 40-60 breaths a minute!

LS: Do you see a benefit by having a manometer at the patient interface (on the Tee)?
AS: It allows the clinician to check the peak pressure/PEEP while also observing the quality of the seal for the mask and the appearance of the baby. Having a manometer attached to the care center can be distracting and requires the clinician to remove his/her eyes from the baby.

LS: Many clinicians have stated that feeling "lung compliance" with a resuscitation bag is very important. What are your thoughts on this considering that Neo-Tee does not allow for the "feel"?
AS: I do consider this to be a drawback from this device. The Neo-Tee is very mechanical and doesn't allow the clinician to get a feel for what is going on inside the lungs. The flow-inflating resuscitation bag has a distinct advantage in this way, but there are ways to counter this problem. Listening to breath sounds, observing chest rise are still reasonable measures of assessment.

LS: Has the Neo-Tee prevented intubations that may have occurred by the use of other resuscitation devices? If so, how does this help support reducing healthcare costs? (Can an actual dollar savings be applied to your facility?)
AS: The Neo-Tee has helped by way of transporting the baby from the delivery room to the NICU. The Neo-Tee doesn't need to be held on the ETT while squeezing the bag, which can cause the ETT to become dislodged. The Neo-Tee makes it easy to hold the airway in place while also providing consistent breaths during ventilation.

LS: How has Neo-Tee helped your department with respect to infection control?
AS: We've reduced the number of devices required from delivery to bedside emergencies. Having one device that is disposable reduces your chance for infection versus having two or more devices opened and being used.

LS: What else can you tell us about the Neo-Tee that you hadn't mentioned, but has been beneficial and would be valuable for other clinicians to know?
AS: It helps to have a device that can't be easily manipulated or damaged during a chaotic resuscitation or emergency. PEEP valves and flow restrictors can be moved or changed during hectic procedures. The Neo-Tee is always consistent.

Laszlo Sandor is assistant editor of Respiratory Therapy. Input on questions was provided by Scott Horowitz, Product Manager, Mercury Medical. If you would like to participate in this feature, as a company or healthcare provider, please contact Steve Goldstein at s.gold4@verizon.net.

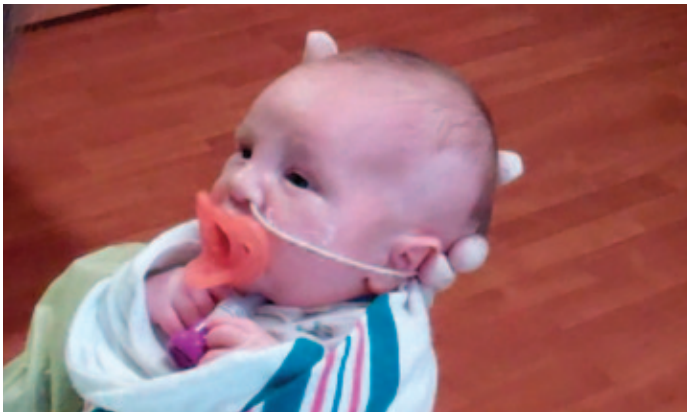
Interview

Neonates with Trachs: Use of the Passy-Muir Valve (PMV) in the NICU

An interview with Catherine S. Shaker, MS/CCC-SLP, BRS-S. She is a Pediatric Speech-Language Pathologist, Board-Recognized Specialist-Swallowing and Swallowing Disorders, Florida Hospital for Children-NICU, Orlando, FL

Les Plesko: I see you are a Pediatric Speech-Language Pathologist in the Neonatal Intensive Care Unit. What is your role with neonates who require tracheostomy?
Catherine S. Shaker: Both short-term and long-term feeding development and communication are adversely affected by the need for a tracheostomy. The NICU Speech-Language Pathologist assesses and provides intervention with neonates to support progression to oral feeding, which is safe and a positive experience for the infant. Swallowing and feeding is a complex task for the neonate with a trach. The presence of the trach alters the infant's swallowing physiology and sensory-motor system. Most importantly there is a need to intervene early to restore airflow through the upper airway for both trached preemies and trached sick newborns that require intensive care. NICU staff awareness of the importance and benefits of early intervention creates a more timely and effective referral process. Depending on the reason for the trach, most trached neonates can benefit from use of a Passy-Muir Valve to support both swallowing, feeding and communication. The respiratory therapist working with the infant is in a unique role to advocate for a consult by the SLP.

LP: I'm intrigued by the use of a PMV in the NICU. Is that fairly common?
CS: An increasing number of facilities are discovering the benefits of the PMV and beginning to use the PMV earlier, while the infant is in the NICU. The biggest roadblock to PMV use in the NICU is lack of information, actually. There is growing understanding of and advocacy for assessing a trached neonate's use of a PMV. While there is emerging data on the positive effects of PMV on the pediatric swallow, there's limited data on the use of the PMV with neonates. Yet, while much of the data regarding neonates is anecdotal, it is compelling. We don't yet have randomized controlled trials, the highest level of evidence-base, to bring to the NICU team. But we do have our clinical wisdom, which is a level of evidence-base, which shows very positive results. The implications of the trach for infant swallowing, feeding and communication are often not well-understood by NICU staff due to lack of information. The SLP, in partnership with the RT, can help to get the word out.



Baby Abel, one month old, with tracheostomy secondary to tracheomalacia, utilizing the PMV 2001 at Florida Hospital for Children.

LP: How do you get the word out?
CS: It starts with bringing information and education to the NICU team. I find a collaborative RT and SLP partnership, from joint education of staff to assessment and use of the PMV, is essential. This can be accomplished through short education sessions, use of videos from www.passy-muir.com, handouts and one-on-one with infants as they move through this team approach. The focus is on, for example, the normal infant swallowing physiology, alterations in anatomy and physiology due to need for a trach, which infants are candidates for use of a PMV, the benefits of the PMV, and how SLP and RT will partner with RN to support each individual neonate.

LP: Tell me more about the impact of trach for neonates. Is it the same as for adults?
CS: There are similarities, but for the infant there are differences too. Early tracheostomy may provide limited-to-no experience with swallowing or feeding. Unlike adults who typically have a "memory" or an experience-base with a normal airway, the infant requiring a trach in the NICU often does not. Because the open trach redirects airflow away from the upper airway, there are many adverse consequences for the developing infant. The infant has reduced laryngeal and pharyngeal sensation, and

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Catherine S. Shaker MS/CCC-SLP, BRS-S, with 35 years of experience in pediatrics, is nationally recognized as an expert in and invited lecturer regarding swallowing/feeding across the continuum of pediatric settings, including neonates, medically fragile infants, and children through school age. An ASHA Board-Recognized Specialist in Swallowing and Swallowing Disorders, she has been an integral part of large Level III Neonatal Intensive Care Units for over 28 years and is known for her work on Cue-Based Feeding Approaches in the NICU. She has published several manuscripts on NICU intervention, and co-authored The Early Feeding Skills Assessment Tool for NICU Infants. Questions for this interview were prepared by the editors in collaboration with Passy-Muir. Les Plesko was editor of Neonatal Intensive Care.

cannot feel or sense secretions. This lack of awareness leads to minimal-to-no drive to clear secretions. The altered cough and reduced or latent airway closure impacts both secretion management and ability to safely feed, when appropriate. The open trach also results in loss of (or inability to experience) the senses of taste and smell; so, feeding with an open trach means the infant does not taste the formula/breastmilk or smell it. This is a significant adverse effect of feeding with an open trach, as sensory information (taste and smell) are critical variables for safe swallowing. The infant swallow is unique in that it requires multiple components of pressure generation to avoid misdirecting fluid toward the airway. The open trach adversely affects oral-pressure generation to propel the bolus, and subglottic pressure generation to effectively close the vocal cords; in addition, there is reduced ability to "sweep" the pharynx after the swallow, so more likelihood for formula/breastmilk to not be fully cleared.

LP: So what does the PMV do? How does it help the infant swallow?
CS: The PMV restores airflow through the upper airway, which restores sensation. So that allows the ability to sense secretions and to then cough. This can be actually frightening at first for the infant who has never "felt" secretions, but it is amazing how quickly many of them adapt to this new sensation. This often leads to less need for suctioning, which is a positive sensory benefit as well. Now the infant can taste while feeding, which increases pleasure and also improves swallowing safety. The PMV normalizes pressure changes within the oral and pharyngeal cavities, so the infant can more effectively close his vocal cords. The infant can also now experience expiratory flow after the swallow, which helps to sweep the pharynx of any formula that may have remained after the swallow. Incidentally, the PMV can be utilized with various levels of respiratory support, including stable levels of mechanical ventilation. Early intervention using the PMV with mechanically ventilated trached neonates has been shown clinically to have benefits as well; these benefits are often not well-understood by NICU staff. Placing the PMV in line with the mechanically ventilated neonate provides the infant with the opportunity to use expiratory muscles while on the vent by breathing past the trach tube, past the infant's own natural anatomy, and out the mouth and nose. This strengthens the respiratory muscles, which can expedite the decannulation and weaning process.

LP: Are there NICU infants who are not typically candidates for using a PMV?
CS: Yes. Medical stability is of course a prerequisite. Some infants may have tighter-fitting trach tubes, reducing the required air leak around the trach tube needed for successful PMV use. If indicated, a change to a smaller diameter tracheostomy tube allows for more airflow around the trach tube and may improve tolerance of the valve. If the infant has a cuffed trach, there must be tolerance for cuff deflation. Inability to sufficiently manage secretions may delay or preclude PMV use. Other contraindications for PMV may include: upper airway obstruction, such as severe tracheal stenosis, or tracheomalacia, which may prevent sufficient exhalation around the trach tube, paralysis of the vocal cords in the adducted position, severe neurological impairment, and respiratory impairment that renders lung elasticity poor and may result in airway trapping. Early discussion by the team of possible PMV use, given the infant's co-morbidities, is optimal.

LP: So how do SLPs and RTs partner in the NICU for use of the PMV?
CS: The partnership between SLPs and RTs involves multiple components. Education of all NICU staff, from neonatologists to Nurse Practitioners, to NICU nurses, as we discussed, is so important. Once an infant is identified as a possible candidate for a PMV, SLPs and RTs collaborate to determine if the PMV will be beneficial for that infant. This includes determining if there is sufficient airleak around the trach, and ability to tolerate cuff deflation, if applicable. The RT typically completes oropharyngeal and tracheal suctioning, deflates the trach tube cuff, if applicable, and modifies ventilator settings (as needed) as per MD order to improve the infant's tolerance of cuff deflation. During initial placement of the PMV, the RT and SLP assess the infant's tolerance from their expert perspectives. The SLP encourages vocalization and distracts the infant, calming the infant if awareness of secretions or unfamiliarity with oral-pharyngeal airflow causes apprehension or distress. Both the RT and SLP monitor vital signs, pulse oximetry, work of breathing, airway patency, and proper positioning. The RT monitors the infant's medical stability and adjusts equipment as needed. When the PMV is used with mechanical ventilation, the ongoing ventilator setting adjustments are made by the RT in consultation with the MD. The infant may require very short, frequent trials on subsequent days to make a gradual transition to brief wearing of the PMV. Coughing is to be expected and desired, as it reflects the infant's beginning awareness of secretions, due to restoration of a closed respiratory system. If the infant exhibits prolonged coughing, the PMV should be removed and airway patency should be re-assessed. Together the RT and SLP, along with the NICU nurse, make a plan for subsequent PMV trials, their length and frequency, which is ordered by the MD. Initially the PMV may be trialed during non-feeding times and then introduction during oral feeding once the infant is tolerating well. The goal is increase valve use during all waking hours as tolerated by the infant. Throughout the process, the RT and SLP work collaboratively. The Passy-Muir website [www.passy-muir.com] has educational videos and webinars to support the interdisciplinary collaboration essential for the NICU infant. "Baby steps" is often the approach, based on the infant's tolerance and the infant's feedback. Each infant's success builds awareness and support from the entire team for the use of the PMV in the NICU. When the neonate wearing the PMV can cry aloud, vocalize and then feed effectively, all members of the NICU team share the rewards!

Care of the Infant with Down Syndrome in the NICU for Post-Discharge Breastfeeding Needs

Carol Chamblin, DNP, APN, RN, IBCLC

Down syndrome is one of the most common genetic syndromes, occurring in one of 800 to 1,000 live births. Infants born with Down syndrome have the presence of extra genetic material from chromosome twenty-one. Among the more common physical findings are hypotonia, small brachycephalic head, epicanthal folds, flat nasal bridge, small mouth, small ears, excessive skin at the nape of the neck, and single transverse palmar crease. There is a significant risk of hearing loss, otitis media, eye disease (i.e. cataracts), congenital heart defects, gastrointestinal atresias, and thyroid disease (Bull, 2011). Congenital heart defects, such as ventricular septal defect (VSD) or atrial septal defect (ASD), and gastrointestinal atresias, such as duodenal atresia may necessitate surgical intervention and extended hospital stay in the NICU.

Vulnerable Infants with Surgical Anomalies

Vulnerable infants with surgical anomalies benefit dramatically from receiving their mothers' breast milk (Edwards & Spatz, 2010). Composition of breast milk has immunological and nutritional factors. These factors offer protection of the gastrointestinal tract from infection, and also improve gastric emptying for the surgically complex infant. Many times these infants cannot accept any nutrition by mouth, termed "nothing by mouth" or "NPO" before and after surgery. It is imperative that these mothers begin to effectively express breast milk as soon as possible after delivery with the use of a hospital-grade double electric breast pump, to be able to initiate and maintain an adequate milk supply.

Feeding issues for infants with Down syndrome may consist of an inability to stay awake during feeding to maintain adequate caloric intake and weight gain. Early supplementation by bottle or tube feeding may be required until the infant no longer exhibits prolonged sleep periods. Infants with marked hypotonia may endure slow feeding sessions with choking or poor oral seal whether on breast or bottle. Lack of weight gain can lead towards a diagnosis of failure to thrive (Bull, 2011). Feeding problems are cited as the main reason for delayed hospital discharge, which can add to the burden of preventable costs for the parents and the health-care system.

Initiation of Milk Supply

The United States Breastfeeding Committee (2008) defines optimal breastfeeding as initiating breastfeeding immediately after birth. In the event that infants are separated from their mothers by an admission to the NICU, it is imperative that the initiation of effective pumping using a hospital-grade double electric breast pump occurs.

Animal and human studies demonstrate that complex endocrine, anatomic, and biochemical changes occur the first two weeks post-birth that appear to "program" milk production over the course of lactation. The mammary gland is extremely sensitive to the effects of prolactin and its effect on milk-yield programming during this period (Meier et al, 2011). Effective infant sucking and milk removal appear to be major components for later milk yield. When prolactin is secreted, it stimulates the secretory differentiation in the mammary gland. Healthy term newborns are able to effectively suckle immediately after birth.

Often newborns with Down syndrome cannot exhibit suction pressures at the breast to create and maintain nipple shape and transfer milk from the breast. They may compromise adequate intake by readily falling asleep and not being able to remain awake during feedings. These features can interfere with effective milk removal from the breast and consequently impact later milk yield when proper pumping is not initiated soon after birth.

Breast Pump Suction Patterns That Mimic Human Infants

According to Meier et al (2011), mothers dependent on a breast pump for the initiation and maintenance of an adequate milk

Carol's nursing career began in 1982 as a Neonatal Intensive Care Unit (NICU) nurse at Northwestern Memorial Hospital, Chicago, IL. While serving as a NICU nurse, she earned her Bachelors of Science in Nursing at Loyola University, Chicago, IL. In 1987 she graduated with her Masters in Perinatal Nursing from the University of Illinois, Chicago, where she studied with Paula Meier. From there she held various positions for several years as a manager, clinical specialist, and adjunct nursing faculty. Carol became an international Board-Certified Lactation Consultant (IBCLC) in 1995 and worked in a hospital setting for 5 years before opening her private practice in 1999. She expanded her practice to offer IBCLC services within 3 pediatric offices of a major medical group, plus an independent pediatric office. Carol has been advocating for IBCLC services reimbursement and has navigated the insurance reimbursement process. In June, 2012 Carol went back to earn her Doctor of Nursing Practice (DNP) from Rush University, Chicago, IL with Janet Engstrom and Paula Meier as her mentors. Her work focused on offering lactation services by the Advanced Practice Nurse (APN) in pediatric practices. Project data demonstrated higher rates of breastfeeding exclusivity and duration rates than national targets. Carol would like to be able to educate others on evidence-based clinical care for breastfeeding mothers and infants.

supply need to use one that features breast pump suction patterns (BPSPs) as close as possible to an actual infant at breast. Healthy term infants exhibit effective sucking and milk removal to regulate an adequate milk supply. The Medela Symphony® breast pump mimics the BPSPs of a healthy term newborn at breast. Infants with Down syndrome often exhibit weak sucks which delay their ability to feed at breast. Therefore, mothers must effectively pump and feed their expressed breast milk. Both feeding at breast and breast milk feeding provide health benefits for vulnerable infants.

Clinician Support for Use of Breast Pumps

Despite the efforts by the Joint Commission Perinatal Care Core Measure on Exclusive Breast Milk Feeding (2010), and the Baby-Friendly Initiative (2010) in the promotion of breastfeeding, clinicians still struggle with encouraging effective use of hospital-grade double electric breast pumps based on scientific findings. Sometimes clinicians resist discussing the use of breast pumps because they feel it is unethical to be pressuring a mother at this sensitive time in the NICU (Meier et al, 2010). However, evidence-based breast pump use should be offered like any other therapeutic aspects of clinical care.

According to Meier et al (2010), the United States Breastfeeding Committee has competencies that include skills such as "know how and when to use technology and equipment to support breastfeeding" and "the ability to preserve breastfeeding under adverse conditions." One mother that breastfed a former child for two years began expressing her milk for her infant with Down syndrome within one hour of delivery. Her experience with the NICU nurses and neonatologists was not supportive of her choice to breastfeed as a high priority. Discouraging comments, such as that she would not ever be able to express enough milk for her infant's needs, did not support her decision to breastfeed. However, she did continue to pump and was able to express 30-35 ounces in a 24 hour period.

Mothers who are pump-dependent need to express breast milk with the use of a reliable breast pump to be able to continue to breast milk feed or to readily transition to feeding at-breast during and after the NICU stay. These mothers must rely on a breast pump to replace the sucking stimulation and milk removal of an actual healthy newborn (Meier et al, 2010). Factors such as an ineffective pump type which does not completely empty the breast or improperly fitting breast shields can compromise a mother's milk supply. It is felt to be unethical by lactation experts to recommend a specific pump type despite research findings that support the Medela Symphony pump as being the most efficient, effective, and comfortable breast pump.

One mother using a Medela Symphony pump while her infant with Down syndrome spent time in the NICU before and after a surgical procedure had been expressing eight to ten ounces of breast milk per pumping session. Two weeks after delivery a different type of breast pump came from her insurance. She began using the pump but was only able to express one ounce per pumping session. The pump from her insurance did not have the BPSPs of a Symphony. Being educated about the importance of an effective pump type, she was able to protect her milk supply by going back to using the Symphony and not the pump covered by her insurance.

Proper Tongue Movement and Oral Vacuum

As the infant with Down syndrome gains more muscle tone, there will be the ability to optimize the efficiency for complete emptying of the breast by milk removal. According to Geddes et al (2008), vacuum is created by downward motion of the tongue in response to milk flow, and peaks when the tongue is at its lowest position. As the healthy newborn's tongue moves up and down, there is minimal distortion of the nipple. Tongue protrusion as a common feature of the infant with Down syndrome can interfere with normal tongue movement and intraoral vacuum for effective breastfeeding. Reassurance needs to be conveyed to mothers that over time their infant will be able to exert enough vacuum to be able to transfer breast milk directly at-breast. Breastfeeding can become established with participation by speech and physical therapy if necessary. These oral motor skills enhanced by breastfeeding can also have a positive impact on future speech and language skills.

Early Intervention

Early intervention is a program of therapy to address developmental delays that may be experienced by infants with Down syndrome (National Down Syndrome Society; accessed 5/27/13). Early intervention should begin any time shortly after birth, and usually continue until the age of three. Specific milestones occur in four areas of normal childhood development. These areas are gross and fine motor abilities, language skills, social development, and self-help skills. Infants with Down syndrome usually achieve the same milestones as other children, but on their own timetable.

Early intervention for infants includes physical therapy, and speech and language therapy. Physical therapy focuses on motor development for infants such as gaining head control and the ability to pull to a sitting position without head lag, and enough strength in the upper torso to maintain an erect posture. Infants with Down syndrome often have low muscle tone, which interferes with the ability to have head control for usual positioning at breast. Speech and language therapy may work with oral motor skills such as using the tongue or moving the lips as pre-speech and pre-language skills.

Speech therapists may assist with oral-motor feeding problems due to hypotonia and weakness of the muscles of the cheeks, tongue, and lips. Breastfeeding uses the same anatomical structures used for speech. Despite the fact that breastfeeding is encouraged for helping to strengthen jaw and facial muscles for later speech skills, most speech therapists suggest positioning and feeding techniques for bottle feeding rather than for feeding at-breast. Clinicians need to focus on techniques to foster the ability to sustain latch and transfer milk from breast.

Post-Discharge Breastfeeding

One mother committed to breastfeed her infant with Down syndrome was not able to perform at-breast feeds during the NICU stay. She continued to attempt to breastfeed but was not able to successfully transition the infant to breast before being discharged from the NICU. In-home early intervention care was implemented for physical therapy, occupational therapy, and speech therapy modalities to enhance torso strength and oral-motor skills to sufficiently feed primarily from a bottle. The infant was fed exclusive breast milk while achieving adequate weight gain. This mother's commitment to providing breast milk to her infant enabled her to continue pumping effectively to maintain her established milk supply.

Early interventionists were able to effectively improve oral-

motor tone and torso strength to achieve the readiness to feed from a bottle, but not directly at-breast. This mother decided to work with an experienced lactation expert to achieve her goal to breastfeed. This clinician assessed for proper torso strength and appropriate oral-motor skills with the use of a bottle. There appeared to be adequate muscle control around the infant's mouth with little tongue protrusion to achieve good bottle feeding technique.

Usual positions (i.e. cradle, cross-cradle, football, side-lying) for breastfeeding may not be effective for hypotonic infants with Down syndrome. In this particular case the infant was not able to breastfeed in the usual cross-cradle hold. The lactation specialist was able to assist this mom with positioning her infant slightly upright with his legs placed along the outer side of her body. Mother's hand and arm were positioned across his back for support of the infant's weak torso. Teaching her to place a finger on the bone at the tip of the infant's chin offered counter-pressure for a better seal and less spillage created by his tongue protrusion as a feature of Down syndrome. Infant readiness for these interventions often does not happen until after discharge from the NICU. Therefore, more clinicians with these clinical skills need to be encouraged to pursue the necessary continuing education for promoting this aspect of breastfeeding-related care.

Summary

Frequently, mothers of infants with Down syndrome are not encouraged to breastfeed, or taught how to properly use a breast pump in order to initiate and maintain adequate milk supply. Despite hospital policies to promote direct breastfeeding for healthy term newborns, there is a need to provide effective interventions based on scientific findings when unusual circumstances arise. Many times vulnerable infants are not managed according to their unique needs. Instead they are often managed as though they are healthy term newborns. Consequently, infant weight gain and maternal milk supply can be compromised. Furthermore, the participation of insurances to provide mothers with breast pumps has not provided proper pump selection in many cases. One reason for the continuation of using a hospital-grade double electric breast pump after discharge is the vulnerable infant with Down syndrome.

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From the Preemie Parent Trenches: Helping NICU Families Handle RSV Season

Deb Discenza

"Mama Bear" is a term used to denote a mother who is over-protective of her newborn and rightfully so. Yet society as a whole tends to lend a collective eye-roll at any mother who seems to define this type of parenting. Make that newborn an early baby and attach all sorts of equipment, tests, surgery and life-long health and developmental concerns and you have parents in a very different realm. They feel the need to protect that child to the tenth power.

I remember my daughter Becky's neonatologist talking about Respiratory Syncytial Virus (RSV) and how we needed to keep her protected during the season and to make sure she got her regular monthly injection of medication. While I was grateful that the medication would be there to help us, I also knew there were still risks for my daughter getting very sick. I wondered aloud how in the world we were supposed to protect our daughter from something invisible. With each day until discharge I was diligent about scrubbing my hands and putting on a mask and a gown and more. As I was slowly preparing and celebrating the eventual homecoming, I was also getting more and more anxious about how I would protect her from well-meaning family and friends.

Professionals in the NICU often hear about the trials and tribulations of parents after discharge and how the public at large is ignorant about RSV and its ramifications for a premature infant. But how do you go about arming families with the ability to protect their child and hold their ground?

Blame the Professionals

Preemie moms often feel like they have left the NICU with a medical degree but the reality is that they didn't and they have a hard time defending their requests in the face of belittling family and friends. While doctors and nurses cannot go home with the parents, the next best thing is for them to write a short and to-the-point letter to the baby's family and friends stating the need for caution regarding RSV. The parents can make copies or send it out by email or whatever is needed to prepare people ahead of time. This gives parents the ability to "blame" the professionals in order to protect their child and prevent family and friend fights. I assure you, the parents will be silently thanking you for this as they endure the first "curiosity-seekers" after discharge.

Invite the Grandparents to a Beside Chat

As discharge day approaches, suggest that the parents bring a grandparent or an aunt or close friend in to visit and help out with taking some discharge preparation notes. A doctor or nurse taking the time to go over specific instructions regarding RSV season will not only stick in the parents' minds but also educate the other person involved. Having a "witness" to the discussion helps cement the information but also to provide an instant ally for the baby and the family. Hearing it from "the professional's lips" directly can go a long way.

RSV Awareness Documentation

Having an "awareness" brochure or document will also help immensely. Here is one from the Alliance for Patient Access (AfPA) that may be copied for distribution: http://bit.ly/RSVLetter. If your NICU decides to create one on its own, make sure it is short and to the point. No one will read anything that is more than two pages long.

Support the Parents When Others Visit

Suppose the grandparents or the aunts and uncles or a close friend are coming to visit the baby. Make sure to work in a hello to everyone and tell the visitors that you appreciate the family getting such great support. Then remind them that even if the baby is preparing to come home soon, discharge still means being careful about colds, germs, smoking around the baby and strong concerns about RSV season. Assure them that the parents have been fully educated in this manner but should they themselves have any questions, to please feel free to ask you.

Give the Parents Suggestions for Preparing the Home

Parents are scrambling to get a crib ordered and so they need some tips on what to get to prepare to protect the child from RSV. Consider a list of items that could be useful such as bar soap, hand sanitizer, and perhaps hand sanitizer with lotion. Do you have a creative staff member? Perhaps he or she can create a friendly reminder sign that parents can copy and use by the front door, and wherever else needed in the home.

One More Tactic for the Desperate

There will always be a person who becomes some sort of exception to all of the tactics listed above. It is the family member or friend who believes that medical professionals are blowing things out of proportion and that he or she is the important person who absolutely must see the child. For this person provide a mock "invoice" that can be presented showing a sample of what it costs to treat a premature infant with RSV. Listing items like ventilator support, breathing treatments, feeding tubes and other potentially "scary" items and the extreme cost might make that person think twice. Money usually speaks volumes to people who cannot understand medical terminology and medical practices.

Getting a baby through RSV season should not have to have a mother resort to becoming Mama Bear to the tenth power. With a little help from you, preemie parents can come through the season safe, healthy, and a little less stressed.

Deb Discenza is the mother of Becky, a 30-weeker, now 10 years old. Ms Discenza is the co-author of "The Preemie Parent's Survival Guide to the NICU," is a speaker at conferences and events and provides free tools at www.PreemieWorld.com.

Wharton's Jelly Peptides and Skin Aging

B. M. Petrikovsky, MD, PhD

Early Fetal Skin Development

By the end of eight weeks' gestation, the basic components of most organ systems have been laid down. Over the next several weeks, more layers are added to the intermediate zone of the epidermis, such that by 22-24 weeks, the epidermis contains four to five layers in addition to the periderm. After the onset of stratification, the basal layer becomes more cuboidal and begins to synthesize keratin peptides. During early fetal development, the basal cell skin layer also begins to express the hemidesmosomal proteins BPA1 and BPA2, and to secrete collagen types V and VII.

Late Fetal Development

Maturation of the epidermis during late fetal development is characterized by the advent of granular and stratum corneal layers, the formation of a water-impermeable barrier, and the sloughing of the periderm. Keratinization, which is characterized by an increase in cytoplasmic density of keratinocytes, is first initiated between eleven and fifteen weeks. The early granular layer continues to mature with the formation of more granules. More superficial layers undergo terminal differentiation, resulting in the formation of transglutaminase-mediated, cross-linked envelopes. At later stages, the terminal differentiation is complete, resulting in the complete absence of organelles in keratinized cells. During the third trimester, the cornified cell layers increase in number. Although the third-trimester stratum corneum is structurally similar to that of an adult, functional studies indicate that it is much less effective at preventing water loss. All these processes contribute to the perfect appearance of newborn skin — a golden standard for cosmetology. However, the skin appearance of premature and postmature infants does not conform to this golden standard. All skin layers (ie epidermis, dermis, and subcutaneous fat) are thinner in the preterm infant than at term. The stratum corneum begins to form around hair follicles at about 14 weeks' gestational age. During the ensuing weeks, the thickness of the stratum corneum increases to several cell layers. The "excess," outermost layers of the stratum corneum are then shed during the first days of life; this process of physiologic desquamation is accentuated in postmature babies. As pregnancy progresses, the skin becomes less transparent as a result of a thickening stratum corneum. Our original hypothesis was that Wharton's jelly proteins contribute to the youthful appearance of healthy newborn skin by stimulating skin stem cells. The amount and quality of Wharton's jelly content are directly related to skin appearance. The abnormally thin umbilical cords of premature babies and the devitalized and wrinkled cords found in postmature newborns have an effect on skin status. Fetal skin is an invaluable source of stem cells, many of which migrate from the Wharton's jelly.

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One out of every 200,000,000 cord blood cells is a stem cell, while one in every 300 cells in Wharton's jelly is an omnipotent stem cell. The true anti-aging frontier in cosmetic research lies in the exploration and application of a specific peptide from Wharton's jelly to incite the safe and efficient arousal of stem cells in adult skin. Research was conducted on a complex of bioactive substances from embryonic tissue — Wharton's jelly. Wharton's jelly is the least studied part of the umbilical cord. As a result of years of scientific work, it has become possible to isolate such a substance and synthesize it chemically. The preparation was called Wharton's jelly Peptide P199. It was shown that in a cell culture, Peptide P199 causes an increase in the expression of IL-1, IL-3, IL-6, IL-8, keratinocyte growth factor, fibroblast growth factor, epidermal growth factor, and endothelial growth factor. It also causes an increase of cytokines, which is necessary for the activation of stem cell proliferation.

Methods and Materials

The purpose of the present study was to determine the effect of Peptide P199 on the activity and proliferative capacity of stem cells in human skin. The epidermal stem cell content was evaluated based on the expression of the following markers: B1 integrin , cytokeratin 15, and cytokeratin 19. It is known that B1 integrin, cytokeratin 15, and cytokeratin 19 are the markers of epidermal stem cells. The study was performed on skin biopsy samples obtained from 15 patients, aged 35-45.

A cream containing the peptide was used on one side of the face for 28 days. Upon completion of the treatment a second biopsy was taken from both sides of the face. Histological samples were stained with hematoxyline-eosin and analyzed with a fluorescent microscope. The total collagen content was determined through collagen autofluorescense via computer image analysis.

The post-treatment samples demonstrated significant changes in the papillary and reticular dermal layer, with the appearance of new collagen fibers. Thus topical application of Peptide P199 led to improved fibroblast functionality and resulted in the synthesis of new collagen fibers.

Aging starts when cells stop growing. Skin aging types can be divided into three distinct groups. Thus, in Caucasians, the first signs of aging can be seen on the face, then on soft tissue (eg the abdomen, buttocks, and breasts), and then on one's hands and legs.

Types of Skin Aging

1) Gravitational – so-called "tired face"

People with gravitational-type aging retain fluid in the soft tissue below the epidermis; which manifests itself as "bags" under the eyes, dropped corners of the mouth, and hanging cheeks.

Continued on page 29…

Neonatal Extravasation Injury: prevention and management in Australia and New Zealand – a survey of current practice

Matthew Restieaux, Andrew Maw, Roland Broadbent, Pam Jackson, David Barker, Ben Wheeler

Abstract

Background: Extravasation injury remains an important cause of iatrogenic injury in neonatal intensive care. This study aims to describe the current approach to extravasation injury (EI) prevention and management in Neonatal Intensive Care Units (NICUs) in Australia and New Zealand.

Methods: A literature review regarding extravasation injury in the newborn was carried out to inform questionnaire design. An Internet-based survey was then conducted with the clinical directors of the 27 tertiary NICUs in Australia and New Zealand.

Results: The survey received a 96% response rate. Approximately two-thirds of Australian and New Zealand NICUs have written protocols for prevention and management of extravasation injury. Considerable practice variation was seen for both prevention and treatment of EI. Ninety-two percent of units had experienced cases of significant EI.

Conclusions: Australian and New Zealand tertiary neonatal units clearly recognize EI as an important cause of iatrogenic morbidity and mortality. Significant variation still exists among units with regards to guidelines for both prevention and management of EI. We recommend that neonatal staff should remain vigilant, ensuring that guidelines for the prevention and treatment of EI are available, and rigorously followed.

Background

The use of intravenous (IV) access for provision of nutrition and medication is essential in modern neonatal intensive care. Neonatal veins are small and fragile, and intravenous lines are often required for long periods of time. This, in combination with a neonate's inability to communicate clearly, increases their susceptibility to extravasation injury (EI). EI occurs when fluid from an IV line leaks into the surrounding tissues or other extra-vascular space. Tissue damage occurs as a result of differences in physiochemical characteristics, including pH and osmolarity, between the extravasate substance and the host tissue.[1] Depending on IV line location (central or peripheral), the infiltrate can cause damage potentially resulting in: skin loss, tendon and nerve damage, limb amputation,[2] and central injuries (eg hepatic and cardiac). Commonly used neonatal infusions prone to EI include: total parenteral nutrition (TPN), calcium, potassium, bicarbonate, and dextrose in high concentrations. Some particular intravenous medications are also well-known for their potential to cause EI such as: acyclovir, vancomycin, and inotropes eg dopamine.[3]

A number of studies have looked at rates of EI in neonatal intensive care units (NICUs). A 1985[4] study of 100 NICU survivors 16-29 months following discharge identified 61% as having scars consistent with an EI. A grading system ranging from grade 1 (barely perceptible) to grade 4 (functionally significant) was used to indicate the severity of the scarring. While the vast majority of these cases had only minor scarring, four cases had scarring deemed cosmetically or functionally significant. A more recent study[5] from the United Kingdom found that 38/1000 neonates undergoing neonatal intensive care suffered an EI severe enough to result in skin necrosis. The majority of these injuries were at gestations 26 weeks or less (ranging from 23-35 weeks).

Numerous treatment protocols have been published on the management of EI. The only step common to all is that the intravenous infusion should be stopped immediately. Recent protocols appear to favor the use of hyaluronidase injection plus saline flush in the treatment of EI.[2,6-8] However, there are many other treatment regimes described including the use of various creams, ointments, and occlusive dressings. Specific treatments are also available depending on the infusate eg topical nitroglycerin for vasoactive medications.[9]

Despite the growing literature in this area, there appears to be little consensus between units and countries on how EI should be prevented and/or treated with much of the available evidence coming from case reports and clinical reviews. No studies have been done looking specifically at current practice across NICUs. With this in mind, we utilized the Australian and New Zealand Neonatal Network (ANZNN), to conduct an Internet-based survey exploring current practice in tertiary neonatal units concerning EI prevention and management.

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Methods

Twenty-seven NICUs providing tertiary care (defined by the ANZNN as providing regular advanced airway support/intensive care) were identified using the 2012 ANZNN directory. This included 21 units in Australia and six in New Zealand. All units were contacted over a 4 week period during June/July, 2012. In the first instance, the Clinical Director/Head of each unit was contacted by email and invited to participate in the survey. This was to ensure the most consistent and authoritative response to questions regarding unit extravasation treatment practices. Informed consent consisted of an explanation of the survey and its purpose given in an email to all potential participants, with consent done via an email link which connected directly to a Survey Monkey Internet-based questionnaire.

In eight instances, where there was difficulty in contacting the Director, the Deputy Director or a staff neonatologist was contacted to provide this information. All data was confidentially and automatically stored on-line at completion of the survey for later analysis.

Survey content was informed by a literature review. This involved an Ovid MEDLINE search for relevant articles published between 1946 and 2012 using the following words or terms: Neonates, extravasation, peripheral cannulae, neonatal intensive care, scars, dopamine, total parenteral nutrition, infiltration, ischemia, alpha-adrenergic, receptor, complications, therapy, intravenous.

Units were excluded from our survey if they were not classified as providing tertiary level neonatal care within the ANZNN. The two listed neonatal emergency transport services in Australia were also excluded. Ethics approval was provided by the University of Otago ethics committee.

Results

Responses were obtained from 26/27 units, giving a 96% response rate. Table 1 gives a summary of our findings.

Prevention: A written policy for the prevention and recognition of EI was used by 69% (18/26) of units. A further 23% (6/26) had no written policy but utilized a standard practice. 8% (2/26) of units had no written policy or standard practice. Broken down by country, 83% (5/6) of the New Zealand units had a written policy, compared to 65% (13/20) of Australian units.

Of units with a written policy or standard practice, these contained: regular recorded nursing observations of the site in 88% (21/24), keeping the skin over the tip of the IV catheter visible in 75% (18/24), and a saline flush before administration of potentially harmful substances in 58% (14/24).

85% (22/26) of units permit the infusion of TPN via peripheral access. In addition, 58% (15/26) of units have concentrated TPN solutions available for exclusive central use (eg containing 12.5-15% dextrose). However nine of the units that do infuse TPN peripherally qualified their answer with specific comments such as: "used reluctantly when no other options available", "prefer and encourage use of central/long line, but allow peripheral", "only when swift transition to milk anticipated", and "occasionally, for short term use when central IV access not available".

69% (18/26) of the units allow dopamine/inotropes to be infused via a peripheral line. However, ten of these units made additional clarifying comments such as "short term only whilst central access being obtained", and "if we have no other choice". 50% (13/26) of units keep a list of drugs which are particularly likely to cause significant EI.

Treatment: Regarding the treatment of EI, 65% (17/26) of units have a written policy, with another 27% (7/26) having a standard practice. The remaining 8% (2/26) have neither. Comparing the countries, 83% (5/6) of the New Zealand units have a written policy, compared to 60% (12/26) of Australian units.

To assess severity of EI, 58% (14/24) of units with a written policy or standard practice, use a staging system. One unit, without a formal staging system, uses clinical photographs to monitor severity.

In those with a written policy/standard practice, management included: immediate line removal 88% (21/24) (the remaining units remove the line following specific treatments); elevation of the limb 63% (15/24); a saline washout via small incisions/ punctures around the extravasation site 67% (16/24); the use of hyaluronidase 38% (9/24); and a warm or cold compress in 4% (1/24). No units reported current use of a liposuction technique.

If EI occurred with a vasoactive substance (eg dopamine or other inotrope), other than the above techniques, 27% (7/26) of units used a specific antidote eg Phentolamine or nitroglycerine.

Complications: Frequency of referral to plastic surgical services was considered. 38% (10/26) of units referred the majority of

Table 1 Summary of main survey findings

Recognition & prevention of EI:	
Units with written policy/standard practice	24/26 (92%)
Of these, policy includes:	
Regular nursing observations:	21/24 (88%)
Keeping skin over tip of line visible	18/24 (75%)
Line flush before drug administration	14/24 (58%)
Treatment of EI:	
Units with written policy/standard practice	24/26 (92%)
Of these, treatment policy includes:	
Immediate line removal	21/24 (88%)
Limb elevation	15/24 (63%)
Saline washout via small incisions	16/24 (67%)
Hyaluronidase	9/24 (38%)
Warm or cold compress	1/24 (4%)
Complications of EI:	
Number of units reporting significant extravasation complication	24/26 (92%)
Central injuries reported:	
Cardiac Tamponade (with associated deaths in 2 units)	13/26 (50%)
Hepatic injury	10/26 (38%)
Peritoneal	8/26 (31%)
Retroperitoneal	3/26 (12%)
Pleural	7/26 (27%)
Peripheral injuries reported:	
Limb endangering	6/26 (23%)

patients, while 8% (2/26) never requested a plastic surgery referral. Specific comments regarding criteria for review included: "grade 3 or 4 injury"; "early if skin loss looks likely"; and "large area of extravasation, discoloration, and ulceration".

Finally, we explored unit experience with severe and/or life threatening complications of central or peripheral EI. 92% (24/26) had experienced a significant extravasation complication. Central injuries reported included: cardiac (tamponade) in 50% (13/26), with associated deaths in 2 units; hepatic injury in 38% (10/26); peritoneal in 31% (8/26); retroperitoneal in 12% (3/26); and pleural in 27% (7/26). Peripheral injuries reported included: limb endangering in 23% (6/26).

Discussion

Extravasation injury as a complication of neonatal intensive care remains an important cause of iatrogenic morbidity and mortality. 92% of units surveyed reported having experienced a significant extravasation incident. While much of the focus and concern regarding EI centres around peripheral venous access, the occurrence of life-threatening central complications is high, with half the units in this survey reporting experience of cardiac tamponade, with some associated deaths. This highlights the importance of vigilance and monitoring in both central and peripheral IV access.

As the complexity of neonatal care increases, NICUs are increasingly using evidence-based practice protocols. This is particularly important in an environment where monitoring and management is provided by front-line nursing and medical staff at varying levels of training. Our survey reveals that approximately two-thirds of Australian and New Zealand NICUs have protocols for the prevention and management of EI; however, as previously noted in the UK, considerable diversity exists between units regarding practice.

It is clear that a number of techniques are being employed for prevention and monitoring of EI. Regarding peripheral IV lines, more than three-quarters of units surveyed reported a policy of regular nursing observations and ensuring IV site visibility, as originally described by Millan.[10] Over half the units have concentrated TPN preparations for exclusive use in central lines, with 15% disallowing peripheral TPN altogether. Based on many qualifying comments received to this question, it is clear most units take a cautious approach to peripheral TPN. The practice of peripheral dopamine infusion is similar, with the majority allowing this with significant qualifications and caution, and some disallowing it altogether. Education and identification of preparations posing risk is clearly an important preventative strategy. 50% of units currently identify and document preparations posing particular risk. Regarding central lines, it is well-recognized these carry a risk of potentially serious harm.[11] Nevertheless, it is possible to have a low rate of serious and life-threatening complications with strict adherence to safety criteria.[12]

In terms of treatment, while most agree on line removal, subsequent steps vary. Much of this diversity may be explained by the paucity of robust evidence in the literature. 38% currently use hyaluronidase. Hyaluronidase is an enzyme which breaks down constituents of the extracellular matrix, leading to increased diffusion and a subsequent decrease in concentration of the toxic infuscate substance.[13] The benefits of this in EI have been shown in animal studies and in a number of case reports in neonates.[6,7,13-16] However, as hyaluronidase is generally used in conjunction with the multiple puncture and saline wash-out technique, it is unclear whether it adds anything over saline alone.[17]

Table 2 Staging of extravasation injuries [17] as adapted from Millan [10]

Stage	Characteristics
I	Painful intravenous site, no erythema, no swelling
II	Painful intravenous site, slight swelling, no blanching, good pulse below intravenous site, brisk capillary refill below intravenous site
III	Painful intravenous site, marked swelling, blanching, skin cool to touch, good pulse below intravenous site, brisk capillary refill below intravenous site
IV	Painful intravenous site, very marked swelling, blanching, skin cool to touch, decreased or absent pulse, capillary refill over 4 s, skin breakdown or necrosis.

Techniques such as multiple skin puncture and saline flush with or without hyaluronidase are invasive, and carry some morbidity. Accurate case selection is vital. A staging system (Table 1) is used by over half of the units in this survey, and the practice is referenced in numerous previous papers.[1,17,18] This allows protocols to be devised which guide treatment based on injury severity. For example, stage I and II injuries often do not require treatment, while stage III and IV are likely to require intervention.[1,17] Another strategy is greater involvement of plastic surgical services in decision making around EI. This is now used by over a third of units, for the majority of their EIs. Whatever the method used, with increasing data on the benefits of these or similar treatment techniques, accurate and prompt assessment and treatment is essential (Table 2).

While TPN would be the most implicated agent in EI, dopamine and other catecholamines, widely used as a treatment to support the maintenance of cardiac output and BP, are notorious for causing EI due to their vasoactive properties.[3] The extravasation of dopamine leads to the activation of alpha-adrenoreceptors in the peripheral vasculature,[19] resulting in vasoconstriction and subsequent tissue hypoxia.[20] Various treatment regimes aim to prevent/interrupt this cascade, eg phentolamine[9] and nitroglycerin ointment.[21,22] Phentolamine antagonizes alpha-adrenergic receptors, preventing vasoconstriction and subsequent tissue necrosis,[19] while nitroglycerin acts on vascular smooth muscle in arteries and veins, leading to vasodilation and increased perfusion of tissues.[21] Despite 69% of the units administering vasoactive substances (eg dopamine) by peripheral venous access, only 25% use a specific antidote, such as phentolamine or nitroglycerin ointment, in the treatment of catecholamine-induced EI.

This is the first survey investigating prevention and management of extravasation injury in Australian and New Zealand neonatal intensive care units. Responses were obtained from senior clinicians with close to a 100% response rate, ensuring that this survey provides an accurate and reliable picture of the current practice.

Conclusions

Australian and New Zealand tertiary neonatal units clearly recognize EI as an important cause of iatrogenic morbidity and mortality. Significant variation still exists among units with regards to guidelines for both prevention and management of

EI. Pending further research to inform best practice in this area, neonatal staff should remain vigilant, ensuring that guidelines for the prevention and treatment of EI are available, and conscientiously followed.

Author details

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Wharton's Jelly…continued from page 25

2) "Baby face" aging

So-called "Baby face" aging occurs when people contain large amounts of subcutaneous fat, which with time become too heavy for its collagen carcass. Fat globules start to prolapse, hence the hanging upper lids and cheeks.

3) "Muscular" type of skin aging

People with well-developed facial and mimic muscles age in a different fashion. Facial muscles, when in use, cause collagen disruption of the overlying skin, resulting in the formation of multiple wrinkles, mostly on the forehead, and around the eyes and mouth along the muscle layers.

The Wharton's jelly peptide appears to be effective in diminishing all types of skin aging. The Wharton's jelly peptide rejuvenates skin through an entirely new approach: restoring skin by replenishing natural resources from within instead of covering up the defects. Thus, Wharton's jelly peptides are becoming a valuable new addition to the line of skin regeneration products.

The Prevalence and Risk Factors of Allergic and Respiratory Symptoms in a Regional Cohort of Extremely Low Birth Weight Children (<1000 g)

Przemko Kwinta, Grzegorz Lis, Malgorzata Klimek, Andrzej Grudzien, Tomasz Tomasik, Karolina Poplawska, Jacek Jozef Pietrzyk

Abstract

Background: Children who were <1000 g (ELBW extremely low birth weight) at birth more frequently present with wheezing, which is the most common reason that pediatric consultation is sought. Therefore asthma is diagnosed very often. However, is the asthma that is diagnosed in ELBW subjects atopic in origin, or is there a different etiology?

Aim: To determine if ELBW infants are at higher risk for the development of allergic and respiratory symptoms and to establish if there were any specific risk factors for these symptoms.

Methods: 81 children born with a mean birthweight of 845 g (91% of available cohort) were evaluated at the mean age 6.7 years. The control group included 40 full-term children. The children were examined for clinical signs of allergy, and were subjected to the following tests: serum total IgE, skin prick tests (SPT), exhaled nitric oxide measurement (FeNO) and spirometry.

Results: ELBW children had wheezing episodes more often (64% vs 25%; OR (odds ratio): 5.38; 95% CI (confidence interval): 2.14-13.8) and were diagnosed more frequently with asthma (32% vs. 7.5%; OR: 5.83, 95% CI: 1.52-26) than their term born peers. The most important risk factors for wheezing persistence were hospitalization and wheezing episodes in first 24 months of life. Mean serum tIgE level (geometric mean: 32+/−4 vs 56+/−4 kU/L; p=0.002) was higher and the number of children with positive results of tIgE level (12% vs 32%; p=0.02) were more frequent in the control group. Children from the control group also more frequently had SPT, however this data was not statistically significant (11% vs 24%; p=0.09). All of the ELBW had normal FeNO level (<=20 ppb), but 5 children from the control group had abnormal results (p=0.02). There was no difference between the groups in the occurrence of allergic symptoms.

Conclusion: ELBW children have more frequent respiratory, but not allergic problems at the age of 6-7 years compared to children born at term. The need for re-hospitalization in the first 2 years of life was a more important risk factor of future respiratory problems at the age of 7 than perinatal factors, the diagnosis of bronchopulmonary dysplasia or allergy.

Introduction

Despite improvements in perinatal care, the incidence of late complications of prematurity is not decreasing. On the other hand, what is increasing is the survival of ELBW infants[1] which due to innovations in neonatology/perinatology in the past years such as less invasive treatment strategies aimed at the restriction of excessive oxygen and ventilation, a decrease in postnatal infections and the improvement of nutrition[2] are a completely different population from the ELBW infants of 30 years ago and in consequence require ongoing follow-up and analysis. ELBW infants are also a very distinct population that usually have the most severe complications of prematurity (such as respiratory distress syndrome, patent ductus arteriosus, intraventricular hemorrhage, sepsis and necrotizing enterocolitis), which unfortunately continue to cause health problems later in life. The morbidity and mortality of these complications is highest in infants born at the threshold of viability.[3] In this study we decided to focus on respiratory problems because they contribute significantly to the morbidity of prematurely born children and usually persist at least until school age. Furthermore, it is very likely that some patients who go on to have respiratory diseases in adulthood have a history of premature birth.[4,5] Children who were <1501 g at birth also more frequently present with wheezing[6] which has been shown to be the most common reason that parents seek pediatric consultation. Therefore asthma is diagnosed very often, particularly in children born prematurely and in consequence they are often treated with anti-allergic and anti-asthmatic medications (inhaled or nasal steroids, antihistamines, leukotriene antagonists).

However is the asthma that is diagnosed in ELBW subjects atopic in origin, or does it have a different etiology altogether? Baraldi and colleagues[7] recently showed that nitric oxide fraction in exhaled air (FeNO) values which are an indirect marker of eosinophilic airway inflammation were lower in preterm children than in those with asthma and even as much as four times lower in children with BPD. There are also investigations proving that prematurity reduces the long-term risk of atopy,[8-10] and the occurrence of diseases such as allergic rhinitis, eczema

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and atopic asthma. We will try to cover these and many other issues in this study which deals with the respiratory and allergic outcomes of babies born with a gestational age <30 weeks and birth weight <1000 g (ELBW) compared to term-born children at the age of 6-7 years. Most studies related to this subject up to date have included VLBW subjects, so this study is a rare opportunity to see how these problems evolve in the population of ELBW children.

Material and methods

A cross-sectional observational study was conducted in the Follow-up Pediatric Department of the Polish-American Children's Hospital between August 1, 2009 and October 31, 2010.

From the 1st of September 2002 to the 31st of August 2004, 169 newborns with birth weights from 500 to 1000 g were born alive in the south-east district of Poland (Małopolska region). All children were hospitalized in three tertiary care Neonatal Intensive Care Units (NICU) in south-east Poland. Ninety-one infants were discharged home from the NICU. The children who were still alive at the age of 6-7 years were invited to participate in the follow-up study (n=89). Neonatal data used for the study was recorded daily during their hospitalization in the NICU in a prospective manner and stored in computer databases. For the purpose of the study the following data was extracted from the original databases: sex, birthweight, gestational age, intrauterine growth parameters, Apgar score, incidence of preeclampsia, preterm rupture of membranes, chorionamnionitis, presence of respiratory distress syndrome (RDS), need for mechanical ventilation, surfactant administration, use of ibuprofen for patent ductus arteriosus (PDA), PDA ligation, early-and late-onset septic episodes, prevalence of intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), bronchopulmonary dysplasia (BPD)—defined as at least 28 days of oxygen therapy, moderate and severe BPD defined as oxygen therapy at 36 weeks post menstrual age (PMA), weight gain during NICU stay and length of hospitalization.

The control group included age-matched children from one general practitioners (GP) office. 42 children in total fulfilled the qualifying criteria of the study. The majority of parents agreed to let their children participate in the study (n=40), only 2 declined.

After signing an informed consent, parents were asked to complete two questionnaires: 1/ including demographic variables, family characteristics (education level, health status, place of residence (city/rural area), parental atopy status), nutrition during the first year of life (breast-feeding/formula feeding), environmental risk factors of allergy (parental smoking habits, siblings, day care attendance, home pets), history of treatment and hospitalizations due to respiratory problems; 2/ validated, standardized ISAAC (International Study of Asthma and Allergies in Child- hood) questionnaire assessing allergic disorders.[11] All questions were verified by a physician during face-to-face discussion. Afterwards, all children were examined by an investigator for the presence of atopic eczema, (rhino) conjunctivitis, wheezing, and other clinical signs of allergy.

Laboratory evaluation: After the examination, a venous blood sample (3 ml) was taken for the assessment of absolute eosinophil count and serum total IgE (tIgE). tIgE levels were measured using the immunofluorometric method (Immuno-CAP, Phadia AB, Sweden) with an assay sensitivity range of 2-5000 kU/L. Serum tIgE levels above the upper limit for age of the patient were recognized as a positive result. Absolute eosinophil counts were calculated according to standard hospital laboratory methods.

During the same visit skin prick tests (SPT) were performed in a typical manner, for the following 10 allergens

Table 1 Comparison of selected demographic and clinical variables between ELBW newborns and the control group[a]

	ELBW group (n=81)	Control group (n=40)	p value
Birth weight (g), mean (SD)	845 (130)	3554 (512)	<0.001[b]
Gestational age (weeks), mean (SD)	27.2 (2.1)	39.9 (1.4)	<0.001[b]
Female	52 (64)	21 (53)	0.15[c]
Vaginal delivery	17 (21)	34 (85)	<0.001[c]
Multiple pregnancy	10 (12)	0 (0)	<0.001[c]
Small for gestational age	24 (30)	2 (5)	0.003[c]
5th min. Apgar score, Me; (25th -75th percentile)	6 (5–7)	10 (9–10)	<0.001[d]
Siblings	47 (58%)	27 (67.5%)	0.33[c]
School attendance	71 (88%)	40 (100%)	0.03[c]
Paternal history of atopy	14 (17%)	3 (7.5%)	0.17[c]
Pets at home	32 (39.5%)	13 (32.5%)	0.7[c]
Passive smoking			
None	64	32	
History	9	1	0.16[c]
Current	8	7	
Place of residence			
City area	31	18	0.56[c]
Rural area	50	22	

[a]expressed as a number (percentage) of patients unless otherwise indicated.
p value for ANOVA[b], chi square test[c], and Kruskal-Wallis test[d].
ELBW – extremely low birth weight.

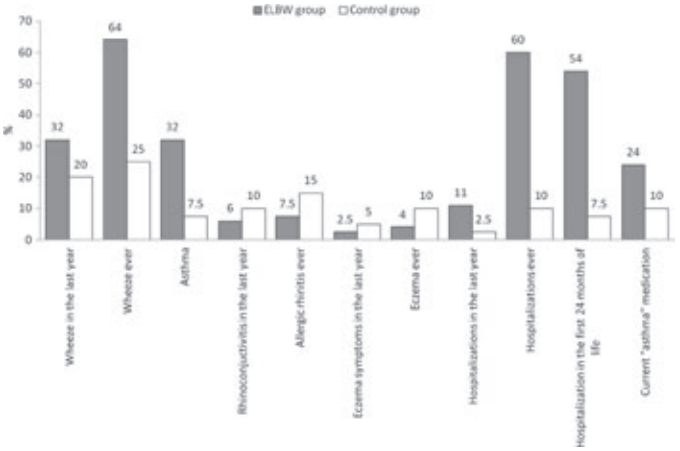

Figure 1 Comparison of the presence of respiratory and atopic problems between the groups at 6–7 years of age.

(Allergopharma, Germany): indoor allergens—house dust mites (D. pteronyssimus, D. farine), dog, cat, molds (Alternaria, Aspergillus, Cladosporium), outdoor allergens—grasses, trees, weeds. A reaction to an allergen was regarded positive if the mean wheal diameter was at least 3 mm. Atopy was defined as a positive SPT to at least one of the aeroallergens.

Exhaled nitric oxide: Exhaled nitric oxide (FeNO) was measured in concordance with published standards,[12] using an electrochemical hand-held device—NIOX MINO[W] (Airway Inflammation Monitor/NIOX MINO/, Aerocrine AB, Solna, Sweden), following the producer's instructions, with exhaled air flows equal to 50±5 ml/s. Measurements of FeNO were performed prior to all other study procedures.

FeNO results were evaluated according to the guidelines by Taylor et al. in which—levels equal or below 20 ppb were regarded as normal.[13]

Lung function: Spirometry was performed using a Lungtest 1000 spirometer with a pneumotachometer-based system (MES, Kraków, Poland). The forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), ratio of FEV_1/FVC and the forced expiratory flow at 50% of FVC (FEF_{50}) was measured before and after the inhalation of 400 ug of salbutamol, according to the recommendations of ATS/ ERS.[14] Results are presented as percent of predicted values with reference values of Zapletal et al.[15] Bronchodilator response was estimated and expressed as the percentage of FEV_1, FEF_{50} increase after salbutamol inhalation ($\Delta\%FEV_1$, $\Delta\%FEF_{50}$). A Δ%FEV1 of more than >12% was considered a significant bronchodilator response.

Outcome variables: The primary outcomes at the age of 7 years were the presence of respiratory and allergic problems defined as a positive response to the ISAAC questionnaire pertaining to: 1) wheezing in the last year, 2) sneezing or a runny or blocked nose with itchy-watery eyes without cold or flu in the last year (rhinoconjuctivitis in the last year), 3) itchy rash in the last year with any flexural involvement or located around the neck, ears or eyes (eczema symptoms in the last year), 4) any wheezing episode in the past (wheeze ever), 5) the diagnosis of asthma (asthma) 6) hay fever/allergic rhinitis (allergic rhinitis), or 7) eczema by a doctor in the past (eczema). Moreover, we also asked: Has your child ever been hospitalized due to respiratory problems? (hospitalizations ever), Was your child hospitalized due to respiratory problems in the its first 24 months of life? (hospitalization in the first 24 months of life), Was your child hospitalized for respiratory problems in the last year? (hospitalizations in the last year), Is your child taking any respiratory or allergic medications? (current medications).

Secondary outcome variables were positive results of serum tIgE or SPT and the subject's respiratory status determined by spirometry results and FeNO.

Statistical methods: In order to draw comparisons between the groups, the following tests were utilized as were deemed appropriate: Student's t-test, ANOVA, Kruskal-Wallis test, chi square test or Fisher's exact test. Odds ratio (OR) and 95% confidence interval (CI) were calculated for the risk of respiratory and atopic problems. Statistical significance was defined for two sided test at the p=0.05 level. Data was analyzed using SAS Software (2006 by SAS Institute Inc., Cary, NC, USA).

Sample-size estimations were based on the assumption that the follow-up rate among ELBW children would be as high as 90% (80 ELBW children). The frequency of primary endpoints was adopted on the basis of an ISAAC study, in which the incidence of wheeze in the last year, rhinoconjuctivitis in the last year, and eczema symptoms in the last year ranged from 15 to 30%. Assuming that the risk of type I error equaled to 5% (two-sided test) and the control group would include 40 children, a study with the power of 80% might demonstrate a 15% difference in the incidence of primary endpoints between ELBW and control group subjects. Sample-size calculation was performed using PS Power and Sample Size Calculations software (Version 2.1.30, February 2003, http://www.mc.vanderbilt.edu/prevmed/ ps/index.htm).

Results

Eighty-one children born as ELBW infants (91% of the available cohort) with a mean birthweight of 849 g (SD: 131 g) and a mean gestational age of 27.2 weeks (SD: 2.1 weeks) were evaluated at a mean age of 6.7 years (SD: 0.4). The control group included 40 full-term children. The comparison of selected demographic variables between the studied groups is shown in Table 1. Vaginal delivery was more frequent in the control group. ELBW children were more frequently small for gestational age than children from the control group (about 30% of them). The groups were similar with respect to age and gender.

The comparison of factors which could have an impact on the respiratory system in the studied groups is shown in Table 1. There were no differences in number of siblings, family history of atopy, history of passive smoking, presence of any pets at home and place of residence. Breast feeding after 1 month of life was less common in the ELBW group, in addition 12% of them did not attend school.

The results of the questionnaire relating to respiratory and atopic problems are presented in Figure 1. Wheeze ever was reported more frequently in the ELBW group (64% of the ELBW vs 25% of control group, OR 5.38, 95% CI: 2.14-13.8), although in the last year that difference had decreased and was no longer statistically significant (32% vs 20%). Asthma was diagnosed in a large number of ELBW children (32% of ELBW vs. 7.5% of the control group, OR 5.83, 95% CI: 1.52-26). The majority of ELBW children required hospitalization due to respiratory problems (hospitalization ever: 60% of ELBW vs 10% of control, OR 13.8, 95% CI: 4.13-51). The hospitalization rate had decreased in the last year, nevertheless it was still four times higher in ELBW than

Table 2 Laboratory tests results in the studied groups

	ELBW group N=22	Control group N=20	p value
Spirometry and bronchial responsiveness (expressed as mean ± SD)			
FEV_1 (%)	81.3±13	95.8±8	<0.001[a]
FVC (%)	79±13	89±7	<0.001[a]
MEF_{50} (%)	62±19	87±26	<0.001[a]
Δ%FEV_1 (%)	6.8±12.3	3.6±5.9	0.3[a]
Δ%MEF_{50} (%)	31±32	19±17	0.15[a]
FEV_1 < 80% predicted value	10 (45%)	0	0.001[b]
Δ%FEV_1 >12%	4 (18%)	1 (5%)	0.3[b]
FeNO (ppb)			
Median (25^{th}-75^{th} percentile)	8 (8–13)	10 (8–14)	0.2[c]
Normal (≤20 ppb)	22	15	0.02[b]
Intermediate (20–35 ppb)	0	3	
High (>35 ppb)	0	2	
	N=81	**N=40**	
serum tIgE (kU/L)			
Geometric mean (± SD)	32±4	56±4	0.002[a]
High (>upper limit for age)	10 (12%)	12 (32%)	0.02[b]
Others			
Absolute eosinophil count per uL)	265±202	225±185	0.3[a]
Positive SPT	8 (11%)	9 (24%)	0.09[b]

p value for ANOVA[a], chi square test[b], and Kruskal-Wallis test.
ELBW – extremely low birth weight.
SPT – skin prick test.

in the control group. The current use of anti-allergic and anti-asthmatic medications (inhaled or nasal steroids, antihistamines, leukotriene antagonists) was 2 times higher in the ELBW group in comparison to the control group (although this difference was not statistically significant). There was no difference between the groups in the occurrence of other allergic diseases or symptoms such as: allergic rhinitis or eczema ever, rhinoconjuctivitis, eczema symptoms in the last year (all symptoms were less frequent in the ELBW group). The results of laboratory tests in the studied groups are presented in Table 2.

Spirometry was performed in 56% (45/81) of ELBW children and in 80% (32/40) of children in the control group (Figure 2). In 44% of ELBW children it was not possible to perform the spirometry because of their neurological complications or lack of child's cooperation. A quarter of the ELBW group (22/81) and half of the control group (20/40) were able to perform acceptable and repeatable spirometry that conformed to ATS/ERS standards for this age group of children. The ELBW children had a significantly lower FEV1 (Figure 3), FVC and FEF50 compared to control subjects. FEV1 lower than 80% of the predicted value was observed in up to half of the ELBW group (10/22) and not in the control group. The values of Δ%FEV1 and Δ%FEF50 were similar in both groups. A significant bronchodilator response was observed in 4/22 of ELBW and in 1/20 of control group subjects (difference between groups was not statistically significant).

FeNO: Appropriate maneuvers for FeNO measurements were obtained in 22 ELBW children and in 20 of the controls. All of the ELBW participants had normal FeNO levels (≤20 ppb). Five children from the control group had abnormal results: 3 had results ranging from 20-35 ppb and 2 above 35 ppb.

Atopy: Serum tIgE (geometric mean) and the number of children with positive results of tIgE levels were more frequent in the control group. Children from the control group also more frequently had positive SPT, however this data was not statistically significant. There was no difference in absolute eosinophil counts between studied groups.

ELBW children with vs. without wheeze: Comparison of selected factors in ELBW children with or without wheezing in the last year is presented in Table 3. There were no differences between groups due to: birth weight, gestational age, gender, length of mechanical ventilation, length of oxygen therapy and indicators of bronchopulmonary dysplasia—oxygen therapy at least 28 days and oxygen therapy at 36 weeks postmenstrual age. The group of ELBW with wheezing in the last year was characterized by more frequent wheezing in the first 24 months of life and more hospitalizations due to respiratory tract infections in that time period. There was no difference regarding: family history of atopy, passive smoking, pets at home, tIgE and positive SPT. The difference in the frequency of hospitalizations in last year, as well as current medication use—were more frequent in the group with wheeze in the last year. The spirometry revealed no difference in FEV_1 between both groups, but a higher Δ%FEV_1 in the group with wheeze in the last year. Only in that group half of the children had an increase in Δ%FEV_1 greater than 12%.

AGA vs SGA infants: Furthermore we compared the incidence of complications in ELBW infants based on intrauterine growth parameters, dividing the subjects into two groups: small for gestational age (SGA) and appropriate for gestational age (AGA). No significant differences were found in the incidence of respiratory symptoms such as wheeze ever or wheeze in the last year in SGA compared to AGA subjects. The diagnosis of asthma was less common in SGA subjects (25% compared to 35%) although this result was not statistically significant. The occurrence of allergic symptoms in both groups were comparable (data available on request). According to laboratory tests we found a higher incidence of positive SPT and positive results of tIgE levels in SGA compared to AGA participants although this was not statistically significant as well (p=0.1).

Discussion

In this study we presented respiratory and allergic problems in the geographically based cohort of ELBW children at the mean age of 6.7 years.

In our opinion, the study has significant value because: 1/ the study group included almost all newborns from the whole Malopolska region born in a period of 2 years that reached the age of 6-7 years. The data in our multi-center study comes from all the tertiary referral centers from the Malopolska region. It is a complete group of patients with a high percentage of observation (91%). 2/ The assessment of the past and current health status of the child was based on a validated, standardized ISAAC questionnaire and all responses were verified by a physician. Moreover, all children were examined by an investigator for the presence of symptoms characteristic of eczema,

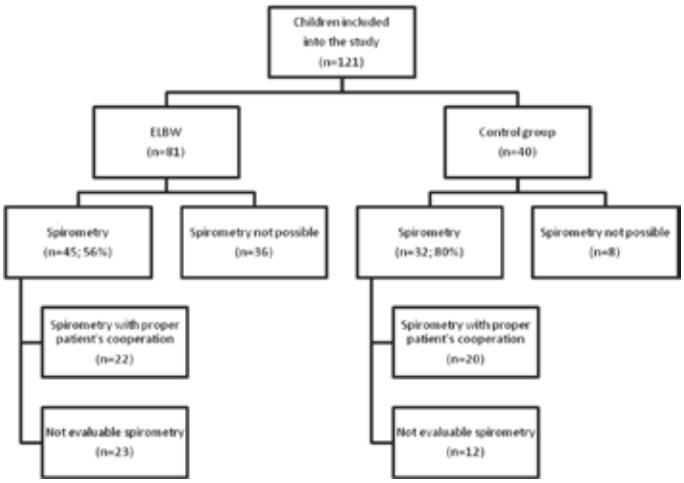

Figure 2 Study flow-chart.

rhinoconjunctivitis, wheezing, and other clinical signs of allergic disorders. 3/ The current study limited the study group to ELBW children, most of the previous studies included VLBW infants. 4/ Lung function was evaluated by spirometry according to the recommendations of ATS/ERS published in 2005.[14] 5/ In addition, FeNO measurements which are a marker of eosinophilic airway inflammation were done as well.

One of the major limitations of the study was the fact that the spirometry results suitable for evaluation were completed by only a quarter of the ELBW participants (22/81) and half of the control group (20/40). Considering the fact that VLBW infants are at a greater risk of neurodevelopmental delay, cerebral palsy, hearing impairment and cognitive and emotional problems later in life,[16] cooperation in this group of children is a challenge and the achievement of reproducible spirometric efforts is extremely difficult. Not to mention the fact that this task can be sometimes difficult among term born children as well.

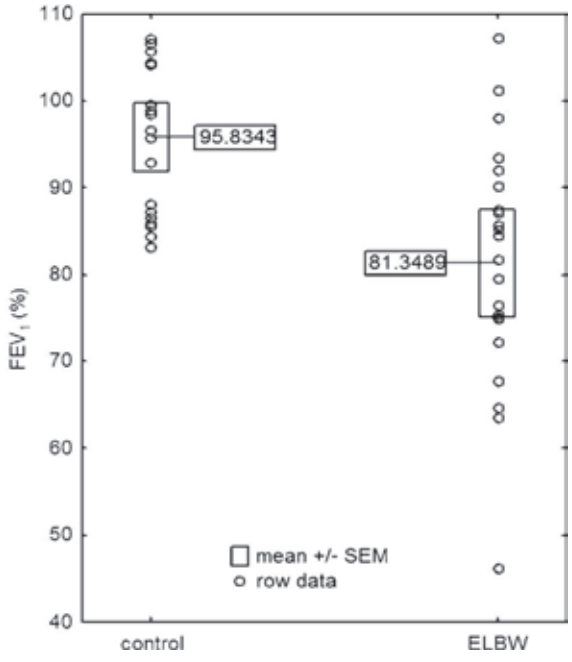

Figure 3 Comparison of forced expiratory volume measurements between the group of extremely low birthweight children and the group of full-term peers.

One of the major results of this study was the observation that among ELBW subjects, the children with wheezing episodes in the last year more often had the need for hospitalization in the first 2 years of life compared to other (non-wheeze in the last year) ELBW children. Surprisingly we found no difference in birth weight, gestational age, length of mechanical ventilation, oxygen therapy in the first 28 days of life or at 36 weeks PMA between ELBW children with and without wheeze in last year. There was no significant difference in family history of atopy, pets at home between ELBW children with and without wheeze in last year. Furthermore those children were not exposed more often to passive smoking. Interestingly enough, positive SPT were not more frequent and serum tIgE levels were not greater in the ELBW population with wheeze in last year. Thus there was no evidence of atopy contributing to persistent respiratory problems in those children. The baseline FEV_1 values were similar, but $\%FEV_1$ values were greater in the ELBW children with wheeze in last year and in half of them there was a significant bronchodilator response.

Our results suggest that symptoms of asthma observed in the ELBW population correlated more strongly with respiratory morbidity in infancy rather than perinatal problems or atopic factors. We have shown that the need for re-hospitalization in the first 2 years of life was a more important risk factor of respiratory problems at the age of 7 than perinatal factors or the diagnosis of bronchopulmonary dysplasia. Furman et al.[17] who followed 98 out of 124 VLBW infants with BPD up to the age of 2 years also showed that the severity of BPD correlated with the duration of neonatal hospital stay and total hospital stay during the first 2 years of life. A similar finding was also mentioned in another study by Ballow et al.[18] which followed 43 VLBW preterm infants until 10 months chronological age and found that they had a considerably higher incidence of infections (especially lower respiratory tract infections) than term infants. What's more is none of them turned out to be bacterial infections. Among lower respiratory tract infections RSV has been shown to be the most common cause in high risk infants such as prematurely born infants.[19] In addition it has been shown preterm infants are more likely to have a more severe clinical course of the disease than term infants (more prolonged hospital stays, requiring oxygen for longer periods of time, more frequent usage of nasal continuous positive airway pressure, CPAP, or mechanical ventilation).[20]

In light of these facts it is highly probable that the increased hospitalization rate in ELBW infants is not only due to the immaturity of the lungs, not fully recovered from the morbidity of the perinatal period but also due to the damage to the lungs that is incurred with each subsequent infection and also through the use of respiratory support (volutrauma, barotrauma, oxygen toxicity) causing a state of chronic inflammation and lung injury.

Our study confirmed previous observations that ELBW children had more frequent respiratory problems at the age of 6-7 years compared to children born at term. In ELBW children, wheeze in the last year or ever in the past and an established diagnosis of asthma were observed more frequently in these subjects than in their peers. The need for hospitalization due to respiratory disease at any time was significantly higher in the ELBW population. This tendency was also present in the last year, however it did not have full statistic significance. However the results of the pulmonary function tests were significantly poorer in ELBW subjects than in controls. This explains why the use of

Table 3 Comparison of selected factors between the group of ELBW infants with and without wheeze in the last year

	Without wheeze in last year (n=55)	Wheeze in the last year (n=26)	p value
Perinatal factors			
Birth weight (g), mean (SD)	853±139	830±159	0.8[a]
Gestational age (weeks), mean (SD)	27.3±2.1	27.3±2.6	0.9[a]
Female	37 (67%)	15 (58%)	0.5[b]
Length of mechanical ventilation (Me; 25-75th percentile) (days)	17 (2–48)	24 (6–39)	0.8[c]
Length of oxygen therapy (Me; 25-75th percentile) (days)	44 (13–77)	55 (34–74)	0.9[c]
Oxygen therapy at least 28 days	34 (62%)	19 (73%)	0.5[b]
Oxygen therapy at the 36 PMA	21 (38%)	10 (38%)	1.0[b]
Infancy			
Wheeze in the first 24 months of life	29 (53%)	21 (81%)	0.03[b]
Hospitalization in the first 24 months of life	25 (45%)	19 (73%)	0.03[b]
Immunoprophylaxis with palimivizumab	8 (15%)	2 (8%)	0.5[b]
Atopy			
Parental history of atopy	9 (17%)	5 (22%)	0.8[b]
Passive smoking	4 (7%)	4 (15%)	0.26[b]
Pets at home	21 (40%)	11 (48%)	0.7[b]
serum tIgE (Me; 25-75th percentile)	22 (12–68)	34 (12–73)	0.3[c]
Absoulte eosinophil count (eos/uL	230±137	338±275	0.03[a]
Positive SPT	4 (7%)	4 (15%)	0.26[b]
Recent status			
Hospitalization in the last year	2 (4%)	12 (46%)	<0.01[b]
Current medications	11 (20%)	15 (58%)	0.002[b]
FEV_1 (%)	80±13	83±16	0.61[a]
Δ%FEV_1 (%)	1±7	16±13	0.002[a]
Δ%FEV_1 >12%	0/14	4/8 (50%)	0.01[b]

p value for ANOVA[a], chi square test[b], and Kruskal-Wallis test.
ELBW – extremely low birth weight.

medications—first and foremost—inhaled steroids were more common in the ELBW group. The need for hospital admissions also suggested that the severity of respiratory disease was greater in ELBW children. Fortunately there has been a decrease in the need for hospitalization in the last year.

Similar observations have been noted in others studies. McLeod et al studied a group of very low birth weight (VLBW) children who were evaluated at the age of 8-9 years and reported that they used inhaled drugs and were admitted to hospital more often than their classroom Peers.[21] Siltanen et al reported an increased prevalence of wheezing in preterm infants (43%) at the age of 10 years compared to term-born subjects (17%).[22] A reduction in the number of hospital admissions after the second year of life, including children with BPD, was reported in another study.[23]

Martinez et al reported that children who started wheezing early in life and continued to wheeze at the age of six years were more likely to have a family history of asthma and elevated serum tIgE. However, the gestational age of the subjects was not revealed in that study.[24] In our population the ELBW children did not present with: allergic rhinitis, rhinoconjunctivitis or eczema more frequently than their term born peers. Buhrer et al also showed a decreased prevalence of atopic eczema in VLBW infants compared to term and near-term infants in the first year of life suggesting that early antigen exposure in VLBW infants could lead to tolerance and a decreased risk of sensitization.[25]

Risk factors of allergy development such as: family history of atopy, exposure to tobacco smoke, contact with animals (pets at home, indoor allergens), place of residence, presence of siblings at home were similar in both groups. The only differentiating factor was duration of breast feeding, which in ELBW children frequently lasted less than one month, meanwhile breast feeding lasting more than 4 months has been proven to reduce the risk of asthma at the age of 6 years.[26]

Asthma was diagnosed more often in the ELBW group (32%) than in the control group (7.5%). In other reports, asthma was also diagnosed more frequently in ELBW children (24.7%) than in controls (13.9%) at the age of 8-9 years[27] and 28% vs 14% at the age of 10 years, respectively.[28] Large-scale analysis conducted by Brooks et al confirmed a strong independent association between low birth weight and asthma, diagnosed by a physician at the age of 3 years.[29] It is important to note, that the prevalence of asthma in our controls corresponded with the results of the ISAAC survey of 6-7 year old children in a proper geographic region.[11]

Siltanen et al reported that atopy was more frequent in term than in the ELBW infants, and reduced pulmonary function in that group was not related to atopy.[9,10,22] Mieskonen et al showed that atopy was less common in VLBW children with BPD than without BPD, furthermore atopic children had higher birth weights, a shorter need for ventilator and oxygen therapy than non-atopic children born prematurely.[30] In our study the

serum tIgE was higher and its level more frequently above the upper limits for age in the control group. The SPT were also more frequently positive in the control group, but the difference was not statistically significant. Thus, we can conclude that symptoms of asthma in our cohort of ELBW children were not associated with atopy.

In our study FEV_1 below 80% of predicted value was observed in the nearly half of ELBW children and not in the control subjects. Similar observations were made in children with symptoms suggestive of asthma and bronchopulmonary dysplasia.[31]

Doyle et al. reported that all respiratory function variables reflecting airflow were diminished in the ELBW group compared to term-born controls at the age of 8-9 years (reduction in FEV_1 below 75% was observed in 19.7% ELBW children vs. 2.4% in control subjects).[27] Mieskonen et al reported that BPD and non-BPD VLBW children had significantly lower FVC, FEV_1, FEF_{50} than controls, but the BPD VLBW children had significantly lower values than non-BPD VLBW at 8 years of age.[30] Mai et al. evaluated VLBW compared to term children at the age of 12 years, a history of asthma was more frequently noted in VLBW children and the only significant risk factor was prolonged oxygen therapy. Spirometric values were similar among VLBW and term children.[8] The improvement in spirometry results (FEV_1) obtained in VLBW subjects between 6 and 12 years of age indicated that there was an acceleration of the lung development, although they did not catch up with their peers in weight and height.[8,28]

Eosinophilic airway inflammation was assessed by measurement of FeNO. Atopy and atopic asthma leads to the increase in FeNO levels.[30,32] Diminished levels of FeNO were observed in children with virus-associated acute wheezy bronchitis.[33] The level of FeNO correlated with BAL fluid or sputum eosinophil percentage, but not with other inflammatory cells, and is considered to be a marker of eosinophilic inflammation.[34,35] A relationship between FeNO and blood eosinophils was also confirmed.[32] In our study, the FeNO levels were not higher in the ELBW population (particularly not greater than 20 ppb), which can indicate the absence of an eosinophilic inflammatory process in their respiratory tract. However, we could not exclude the effect of inhaled steroids on FeNO levels in some patients. Glucocorticosteroids decrease FeNO in asthmatic, but not healthy subjects.[31] Baraldi et al. showed that FeNO was significantly lower in VLBW children with BPD than in VLBW without BPD (however, all results were below 11 ppb).[7] Mieskonen et al. found no significant differences in FeNO levels between BPD and non-BPD non-atopic subjects.[30] Both authors revealed no difference in FeNO between VLBW children and healthy controls. The atopic VLBW children had significantly higher FeNO levels (mean 14.8 ppb) than non-atopic prematurely born subjects (mean 6.3 ppb), although it was not significantly higher than healthy term controls (mean 6.4 ppb).[30] These authors found that flow limitation was not associated with increased NO production and lack of reversibility of airflow limitation and low FeNO values suggested different than asthma mechanism of lower forced expiratory flows. We had similar observations.

Conclusions

In summary we demonstrated that respiratory problems were more frequent in ELBW children at the age of 6-7 years compared to children born at term. ELBW children had more episodes of wheezing, were more frequently diagnosed with asthma and had decreased spirometry parameters compared to their peers. The need for hospital admissions due to respiratory problems was also greater in the ELBW population (although it had decreased in the last year) as was the use of medications, especially inhaled steroids.

However the occurrence of other allergic diseases such as allergic rhinitis, or eczema was not observed more frequently in the ELBW population, nor were symptoms of rhinoconjunctivitis, eczema in the last year. We also did not show an elevation of FeNO in ELBW children which can be assumed as a surrogate of eosinophilic airway inflammation. Mean serum tIgE levels were higher and the number of children with positive results of tIgE levels were more frequent in the control group. Children from the control group also more frequently had positive SPT, however this data was not statistically significant.

On the other hand we found that the need for re-hospitalization in the first 2 years of life was the most important risk factor for the occurrence of respiratory problems at the age of 6-7 years, even more relevant than perinatal factors and the diagnosis of bronchopulmunonary dysplasia. A lot of the studies mentioned in the discussion as well as our own results have shown a decreasing tendency of respiratory problems in ELBW children as they grow up. Longitudinal follow up studies are needed to determine whether this trend will continue but also whether these subjects will be more susceptible to developing pulmonary disease later in life such as COPD (Chronic obstructive pulmonary disease).

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The Impact of Staffing on Central Venous Catheter-associated Bloodstream Infections in Preterm Neonates – results of nation-wide cohort study in Germany

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Abstract

Background: Very low birth weight (VLBW) newborns on neonatal intensive care units (NICU) are at increased risk for developing central venous catheter-associated bloodstream infections (CVC BSI). In addition to the established intrinsic risk factors of VLBW newborns, it is still not clear which process and structure parameters within NICUs influence the prevalence of CVC BSI.

Methods: The study population consisted of VLBW newborns from NICUs that participated in the German nosocomial infection surveillance system for preterm infants (NEO-KISS) from January 2008 to June 2009. Structure and process parameters of NICUs were obtained by a questionnaire-based enquiry. Patient based date and the occurrence of BSI derived from the NEO-KISS database. The association between the requested parameters and the occurrence of CVC BSI and laboratory-confirmed BSI was analyzed by generalized estimating equations.

Results: We analyzed data on 5,586 VLBW infants from 108 NICUs and found 954 BSI cases in 847 infants. Of all BSI cases, 414 (43%) were CVC-associated. The pooled incidence density of CVC BSI was 8.3 per 1,000 CVC days. The pooled CVC utilization ratio was 24.3 CVC-days per 100 patient days. A low realized staffing rate led to an increased risk of CVC BSI (OR 1.47; p=0.008) and also of laboratory-confirmed CVC BSI (OR 1.78; p=0.028).

Conclusions: Our findings show that low levels of realized staffing are associated with increased rates of CVC BSI on NICUs. Further studies are necessary to determine a threshold that should not be undercut.

Background

Newborns with very low birth weight (VLBW) are at increased risk for developing healthcare-associated blood stream infections (BSI).[1-3] The BSIs mostly occur on neonatal intensive care units (NICU) and are associated with the use of central venous catheters (CVC). To prevent these potentially lethal infections, consistent high quality of care is critical. Process and structure parameter on NICUs are suspected to influence the quality of care and therefore indirectly the incidence of CVC BSI. Until now it is not clear which parameters have the highest impact. Concerning this topic there have been only few studies on structure and process parameters on NICU that also include NICU staffing.[4-6] Analyzing data from the German nation-wide nosocomial infection surveillance system for preterm infants on neonatology departments and ICUs (NEO-KISS), we are able to estimate the situation for a large part of Germany's NICUs.

Methods

Setting and patient population: In January 2000, NEO-KISS was started as a prospective national surveillance system for the most relevant nosocomial infections in VLBW infants (birth weight < 1500 g) in Germany.[7] By January 2008, 213 neonatology departments participated in KISS surveillance. In NEO-KISS, all VLBW infants admitted to the participating NICUs are kept under surveillance from admission to discharge, transfer or death, and all healthcare-associated infections are recorded.

Data collection: We collected data on the structure characteristics of the neonatological departments and on the working processes of their NICUs with two separate point questionnaires. The first enquiry took place in August 2008, the second in April 2009. Information requested about NICU structure included data on number of wards and beds of the concerning departments, VLBW patient days in 2007, the existence of handover and/or infectious diseases rounds, and existence of microbiological screening, among other items. The NICU processes assessed included infusion preparation, CVC and incubator hygiene management, unit-level hand hygiene performance and infusion system use. The "realized staffing" for each unit was defined as realized number of nurses at the time of the questionnaire enquiry divided by the (individual hospital based) planned number of nurses. This ratio was multiplied by 100 and is displayed in the results section as "percentage of realized staffing." Patient data was obtained from the NEO-KISS database for the departments that took part in our enquiry. The data from January 1st 2008 to June 31st 2009 were analyzed. In the NEO-KISS surveillance database, basic demographic data on patients (eg birth weight, sex, way of childbirth, device-days) is collected. Length of stay is defined as the number of

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days between birth or admission and until a weight of 1,800 g has been reached, the patient's discharge or death. The pooled CVC utilization ratio was obtained as number of device-days per 100 patient-days. The pooled incidence density was defined as number of BSI cases per 1,000 patient days.

Definitions of healthcare-associated infections: NEO-KISS focuses on bloodstream infections, pneumonia and necrotizing enterocolitis. Infection is classified as healthcare associated if arised in hospital after the first 72 h of life or 72 h after admission. NEO-KISS uses modified definitions from the Center for Disease Control and Prevention (CDC) for healthcare-associated infections. They are already thoroughly described in former publications.[1,8] A healthcare-associated BSI was considered central venous catheter-associated if the catheter was present within 48 hours before the infection occurred or if the catheter was still present at infection onset. According to the modified definitions of the CDC for primary sepsis, we stratified the cases in clinically-diagnosed BSI and laboratory-confirmed diagnosis (LCD) of BSI.[1,8] The LCD BSI cases were further classified by proven pathogens in the two groups coagulase negative staphylococci only (CoNS) or other than CoNS.

Statistical analysis: In the descriptive analysis, we calculated numbers and percentages and/or median and inter-quartile range (IQR; 25% percentile - 75% percentile). In the multivariable analysis, we used logistic regression models to investigate the association between occurrence of CVC BSI and various patient, structure and process parameters. We investigated two different endpoints: CVC BSI and CVC BSI cases with laboratory confirmed (LCD) diagnosis other than CoNS. Since observations within one neonatology department are not statistically independent due to department-dependent policies, adjusted incidence rate ratios with 95% confidence intervals (CI) were estimated based on generalized estimating equation (GEE) models which account for this clustering effect by using an exchangeable correlation structure.[9,10] The log number of patient days was treated as an offset in the model. For the occurrence of bloodstream infection, the multivariable model building strategy was performed in 3 steps. First step: All patient-based parameters were considered in a logistic regression model by stepwise forward variable selection with the significance level p=0.09 for including a parameter in the model and p=0.10 for excluding a parameter. Second step: All process and structure parameters were considered in the resulting model from

Table 1 Parameters of the analyzed NEO-KISS departments (N=108)

Parameter	Category	N (%) / †median (IQR)
Departments total		108 (100)
Size of department	Beds	†20 (16–29)
	ICU beds	†8 (6–12)
Patients in 2007	Total	†384 (298–529)
	< 1 500 g birthweight	†35 (20–55)
Patients January 2008- June 2009	< 1 500 g birthweight	†44 (28–65)
Level	Level III* (Neonatal critical care) departments	89 (82)
	Level II* (Step down neonatal nursery) departments	14 (13)
	Level I* (healthy baby nursery) departments	2 (2)
	other Level	3 (3)
Realized staffing percentage	Staffing	†99.6% (94.0% - 100.0%)
	Staffing (min-max)	87.0% - 117.0%
	Staffing ≥ 95%	72 (67)
	Staffing < 95%	27 (25)
	Missing	9 (8)
Daily handover rounds and/or regular infectious diseases rounds	No	2 (2)
	Yes	106 (98)
Standards for indication of hand hygiene	No	2 (2)
	Yes	104 (96)
	Missing	2 (2)
Daily disinfection of the buttons of the ventilation systems	No	6 (6)
	Yes	102 (94)
Routine microbiological screening	No	26 (24)
	Yes	82 (76)
Cleaning inside the incubator	No	25 (23)
	Yes	83 (77)
Infusion preparation	In the pharmacy OR on wards with laminar-flow bench	93 (86)
	On wards without laminar-flow bench	15 (14)

*Care level classification is based on the definitions by the National Healthcare Safety Network (NHSN).
IQR, inter-quartile range. Realized staffing percentage, ratio of realized staffing / planned staffing * 100.

Table 2 Basic patient characteristics of 5,586 analyzed VLBW neonates recorded in NEO-KISS between January 2008 and June 2009

Parameter	N (%) overall	Median (IQR)
VLBW neonates	5,586 (100)	
Sex male	2,836 (51)	
Birthweight in g		1,150 (869–1370)
Gestational age in days		205 (190–217)
Patient-days	206,459	33 (23–48)
Cesarean section	4,584 (82)	
Multiple birth	1,735 (31)	
VLBW neonates with ≥ 1 BSI	847 (15)	
CVC-days	50,113	5 (0–14)
1 CVC-associated BSI	349 (6)	
2 CVC-associated BSI	28 (1)	
3 CVC-associated BSI	3 (0)	
VLBW with ≥ 1 CVC-associated LCD BSI	94 (1.68)	
1 CVC-associated LCD BSI	89 (1.59)	
2 CVC-associated LCD BSI	4 (0.07)	
3 CVC-associated LCD BSI	1 (0.02)	
VLBW died before 1,800 g weight or discharge	358 (6)	
Realized staffing percentage		
Missing	551 (10)	
Staffing < 95%	1,403 (25)	
Staffing ≥ 95%	3,632 (65)	

IQR, inter-quartile range. VLBW, very low birthweight. CVC, central venous catheter. PVC, peripheral venous catheter. CPAP, continuous positive airway pressure. BSI, bloodstream infection. LCD, laboratory confirmed diagnosis. Realized staffing percentage, ratio of realized staffing/planned staffing * 100.

step 1 by stepwise forward variable selection using the same significance levels for including and excluding. Third step: With all parameters included by step 1 and 2, a GEE model was calculated that took cluster effects within a department into account. By stepwise backward selection only significant parameters remained in the final model. Excluding criteria were the smallest Chi-square value and p≥0.05 in the Type III score statistic. The quasi-likelihood information criterion (QIC) as a modification of the Akaike information criterion was used as goodness-of-fit measure in the GEE model. P-values less than 0.05 were considered significant. All analyses were performed using SAS (SAS Institute, Cary, NC, USA).[1-3] In Germany, anonymised secondary data research does not require human research committee review.

Results

Basic characteristics of patients and departments: By January 2008, 213 neonatology departments were registered in NEO-KISS. Thereof 108 (51%) departments took part in our 2008 and 2009 inquiries and provided data on their VLBW-patients to the NEO-KISS database between January 2008 and June 2009 leading to a total of 5,586 patients with 206,459 patient days, and 50,113 CVC days. We found 954 BSIs that occurred in 847 (15.2%) infants. Table 1 shows the parameters of the participating NEO-KISS departments collected by the two questionnaires. Table 2 shows basic demographic data of the patients included. The distribution of realized staffing among the analyzed departments showed the 25% lowest achiever below a maximum level of 95% realized/planned staffing. This breakpoint was chosen as distinction between low level of staffing and not low level of staffing.

Table 3 Risk factors associated with CVC-associated BSI on NEO-KISS NICUs

Parameter	Category	OR	CI 95%	p-value
Realized staffing percentage	Missing	1.25	(0.83-1.88)	0.289
	<95%	1.47	(1.11-1.95)	0.008
	≥95%	1=reference		
Birth weight	<500 g	4.23	(2.46-7.3)	<0.001
	500-749 g	3.17	(1.85-5.45)	<0.001
	750-999 g	2.28	(1.47-3.53)	<0.001
	1000-1249 g	1.36	(0.86-2.14)	0.187
	1250-1499 g	1=reference		
Gestational age (completed weeks)	<27 weeks	3.97	(2.23-7.09)	<0.001
	27-28 weeks	3.04	(1.79-5.16)	<0.001
	29-30 weeks	1.99	(1.05-3.77)	0.035
	>30 weeks	1=reference		
Length of stay	21-34 days	0.44	(0.29-0.69)	0.001
	35-48 days	0.32	(0.21-0.49)	<0.001
	>48 days	0.29	(0.2-0.42)	<0.001
	<21 days	1=reference		
Standards for indication of hand hygiene	Yes	0.61	(0.44-0.84)	0.002
	No	1=reference		
Daily disinfection of the buttons of the ventilation systems	Yes	0.68	(0.5-0.93)	0.014
	No	1=reference		
Disinfection of the application port before medication infusion/connection of an infusion system	Often	0.48	(0.31-0.77)	0.002
	Rarely/no	1=reference		
Infusion preparation	On ward without laminar-flow bench	1.53	(1.02-2.28)	0.039
	In the pharmacy OR on ward with laminar-flow bench	1=reference		

IQR, inter-quartile range. CI 95%, 95% confidence interval. CVC, central venous catheter. BSI, bloodstream infection. Realized staffing percentage, ratio of realized staffing / planned staffing * 100.
Results of the multivariable regression analysis by GEE models.

Frequency of different BSI diagnoses: The pooled incidence of BSI was 15.2 per 100 patients, in median 11.7 (IQR 6.3-19.2). The pooled incidence density of BSI was 4.6 per 1000 patient days (median 3.5; IQR 2.1-5.7). Of the 954 (100%) cases of healthcare-associated BSI, 482 (49%) were laboratory confirmed. Two hundred fifty-eight cases (27%) were due to coagulase negative staphylococci only, 214 (22%) were due to pathogens other than CoNS. Four-hundred fourteen BSIs (43%) were CVC associated. The pooled incidence density was 8.3 per 1,000 CVC days (median 6.8, IQR 1.8-12.2). The pooled CVC utilization ratio was 24.3 per 100 patient days.

Table 4 Risk factors associated with CVC-associated LCD BSI other than CoNS on NEO-KISS NICUs

Parameter	Category	OR	CI 95%	P-value
Realized staffing percentage	Missing	0.71	(0.26-1.94)	0.507
	<95%	1.78	(1.06-2.99)	0.028
	≥95%	1=reference		
Gestational age (completed weeks)	<27 weeks	10.73	(4.25-27.08)	<0.001
	27-28 weeks	2.72	(1.08-6.85)	0.033
	29-30 weeks	1.81	(0.67-4.88)	0.241
	>30 weeks	1=reference		
Mode of delivery	Vaginal	2.10	(1.29-3.43)	0.003
	Emergency cesarean section	1.05	(0.55-2.00)	0.888
	Cesarean section	1=reference		

CI 95%, 95% confidence interval. CVC, central venous catheter. BSI, bloodstream infection. LCD, laboratory confirmed diagnosis. CoNS, coagulase negative staphylococci. Realized staffing percentage, ratio of realized staffing / planned staffing * 100.
Results of the multivariable regression analysis by GEE models.

Risk factors for CVC BSI: To assess the risk factors for a CVC BSI in VLBW new-borns, we analyzed demographic, structure and process characteristics of their NICUs individually for each VLBW newborn. The results of the multivariable analyses are shown in Table 3. A realized staffing below 95% of planned staffing proved to be a significant risk factor for the development of CVC BSI compared to the reference category: realized staffing ≥ 95%.

Risk factors for LCD BSI other than CoNS: The multivariable analysis showed that low realized staffing is a risk factor for the development of laboratory confirmed CVC BSI due to organisms other than CoNS. The results are shown in Table 4.

Discussion

Multiple risk factors have an impact on the prevalence of CVC BSI in preterm neonates. We performed a prospective nation-wide study on the impact of process and structure parameters in the majority of German NICUs.

Our results demonstrate that high staffing levels are associated with a lower incidence of CVC BSI and laboratory-confirmed BSI (with organisms other than coagulase negative staphylococci). The results are congruent with several other studies on staffing.[4,11] A study by Pittet et al demonstrated that an increased workload is associated with diminished hand hygiene compliance.[12] Cho et al. showed that even a small increase in the nurse-per-patient ratio is associated with significantly decreased odds for adverse events.[13] Other studies showed that understaffing as well as over-crowding is associated with a higher risk of outbreaks on NICUs.[14,15] Two other studies did not observe an influence of nurse staffing.[16,17] However, both studies assessed the situation on ICUs rather than NICUs. We did not assess the nurse per patient ratio, but we showed that compliance with the in-house recommendations on staffing levels has the potential to prevent healthcare-associated BSI and is a relevant quality assurance tool. So far, there is no general reference for staffing ratios on NICUs. However, the German Commission on Hospital Hygiene and Infection Prevention suggests at least high levels of appropriately trained nurses.[18]

Birth weight and gestational age have been shown in the literature to be the predominant patient related risk factors for healthcare-associated infections.[2,19-21] We could not fully confirm these findings in our study.

The preparation of infusions at laminar airflow benches has been recommended to minimize the risk of contamination.[22,23] Thomas et al. demonstrated that the training background of the preparing person can be critical, rather than the preparation site.[24] We did not assess the training background of personnel. Nevertheless, our data confirms the importance of laminar-flow benches in the preparation of intravenous fluids.

There are only few studies on the mode of delivery in VLBW newborns. It was found that cesarean section is associated with BSI in VLBW infants, while other studies reported improved morbidity and mortality.[25-27] Even though our results confirm the potential protection by cesarean section, this might also be an indirect effect of emergency vaginal delivery. Cesarean sections are usually handled in a well-prepared professional environment and more common in preterm infants.[28]

This study has following limitations. It is based on the NEO-KISS database. Even though we thoroughly proofed their reliability, the accuracy of data is dependent on the quality of these data. We furthermore depend on the information we obtained by the inquiries that could be subject of relevant recall bias. We did not assess the nurse patient ratio and therefore cannot provide an exact threshold as benchmark for quality assurance. Nevertheless our results show that the planned numbers of staffing can have an impact on their rate of nosocomial infections. Planned staffing should therefore be strictly realized.

Conclusions

We analyzed the impact of various process and structure parameters on the outcome of healthcare-associated BSI in VLBW neonates. A low level of staffing (realized/planned) on a NICU was associated with an increased risk for CVC-associated BSI. Rather high staffing levels should therefore be implemented and continuously be realized on NICUs. Our results furthermore emphasize the importance of standardization and consistency of medical procedures and hygiene measures on NICUs. We furthermore advocate a high level of communication and cooperation between the staff of the NICU and related fields like infectious diseases and clinical microbiology.

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Changes in Quality of Life into Adulthood after Very Preterm Birth and/or Very Low Birth Weight in the Netherlands

Afra van Lunenburg, Sylvia M. van der Pal, Paula van Dommelen, Karin M. van der Pal-de Bruin, Jack Bennebroek Gravenhorst, Gijsbert H.W. Verrips

Abstract

Background: It is important to know the impact of Very Preterm (VP) birth or Very Low Birth Weight (VLBW). The purpose of this study is to evaluate changes in Health-Related Quality of Life (HRQoL) of adults born VP or with a VLBW, between age 19 and age 28.

Methods: The 1983 nationwide Dutch Project On Preterm and Small for gestational age infants (POPS) cohort of 1338 VP (gestational age <32 weeks) or VLBW (<1500 g) infants, was contacted to complete online questionnaires at age 28. In total, 33.8% of eligible participants completed the Health Utilities Index (HUI3), the London Handicap Scale (LHS) and the WHOQoL-BREF. Multiple imputations were applied to correct for missing data and non-response.

Results: The mean HUI3 and LHS scores did not change significantly from age 19 to age 28. However, after multiple imputations, a significant, though not clinically relevant, increase of 0.02 on the overall HUI3 score was found. The mean HRQoL score measured with the HUI3 increased from 0.83 at age 19 to 0.85 at age 28. The lowest score on the WHOQoL was the psychological domain (74.4).

Conclusions: Overall, no important changes in HRQoL between age 19 and age 28 were found in the POPS cohort. Psychological and emotional problems stand out, from which recommendation for interventions could be derived.

Background

Over the last decades, the number of infants that survive a preterm birth has increased due to the progress in perinatal care. With the increase of surviving preterm infants and Very Low Birth Weight (VLBW) infants, another problem arises: the proportion of disabilities within this group of newborns also increases. In the Netherlands the prevalence of live born preterm (22-37 weeks of gestation) is 7.3%. Within this group, 1.1% is born extremely preterm (22-32 weeks of gestation) and 1.0% has a VLBW (<1500 grams). Most of the infants with a VLBW are also born preterm. Follow-up studies of those born with a VLBW show a wide variety of impairments, such as neurodevelopmental disabilities, blindness, deafness and issues with growth and learning. A study of Tyson and Saigal (2005) shows that 16% of children with a VLBW had major neurosensory impairments, including cerebral palsy, deafness, and blindness. A quarter of the VLBW group had an IQ lower than 85.

It is important to know the impact of Very Preterm (VP) birth or VLBW on health and Health-Related Quality of Life (HRQoL) to be able to provide the right (preventive) care in neonatal care units and later on in life. Next to the medical care, knowing the possible consequences on HRQoL can help professionals and parents in the decision making process of treating those born VP or with a VLBW. In the literature, there is no ultimate definition of the term HRQoL. Several studies choose the definition of health from the World Health Organization: "a state of complete physical, mental, and social well-being and not merely the absence of disease." Others choose HRQoL to be defined as the value individuals assign to a particular health-state. This study focuses more on this second definition. The Dutch "Project On Preterm and Small for gestational age infants" (POPS) nationwide population based cohort of adults who were born VP or with a VLBW in 1983, provides a unique possibility to study the long term effects of VP birth or VLBW on HRQoL of adults. Small for Gestational Age (SGA) is defined as a birth weight below the 10th percentile for gestational age and is associated with, for instance, increased neonatal complications. The POPS study assessed three HRQoL questionnaires in adults aged 28 who were born VP or with a VLBW, giving a broad view on HRQoL. The transition into adulthood is an important stage of life, and important events such as finishing school and integration into work may affect HRQoL. Therefore, the purpose of this study is to evaluate changes in HRQoL of adults born VP or with a VLBW between age 19 and age 28.

Methods

Study population: The POPS cohort included 1,338 live-born, VP (gestational age <32 weeks) and/or VLBW (<1500 grams) infants born in the Netherlands in the year 1983. In total, 381 of these children did not survive to their 28th birthday, and 29 of them were lost to follow-up; 928 adults were eligible to participate in this follow-up study at 28 years of age (Figure 1).

The authors are with TNO, Child Health, Leiden, The Netherlands. The authors would like to thanks all the POPS adults for their participation in this study and in all the previous studies in the last 28 years. Reprinted from BioMed Central, Health and Quality of Life Outcomes, [van Lunenburg et al: Changes in quality of life into adulthood after very preterm birth and/or very low birth weight in the Netherlands. Health and Quality of Life Outcomes 2013 11:51.] This article has been slightly edited for our readers. Please visit BioMed Central and type the title to see the references.

Assessment: In the year they would turn 28, individuals were invited to participate in the online study either through an email or a letter. Most participants filled in the questionnaire online (97.5%), a small group completed the questionnaire on paper on request (2.5%). Previously in the POPS cohort, data were collected at birth and ages two, five, nine, 10, 14 and 19 years. In this present study we use these earlier collected data in addition to the data from the quality of life (QoL) questionnaires assessed at age 28.

Data collection: HUI3 (Health Utilities Index, Mark 3) was used to assess HRQoL both on 19 and 28 years of age. HUI3 includes a summary of a comprehensive health status classification system, encompassing eight attributes of health: vision, hearing, speech, emotion, pain, ambulation, dexterity and cognition. The level of functioning for each attribute is classified into five or six levels, ranging from "perfect function" (level one) to "severe dysfunction" (level five or six). With these levels of functioning, an eight-element health status vector can be established.
To provide a generic scale-score of HRQoL, where dead = 0 and perfect health = 1, a Multi Attribute Utility (MAU) was calculated, as a generic score for the HUI questionnaire. Because Dutch population reference scores are not available, this study uses the reference score for the Canadian population which is 0.85, and is the same for age 16–19 as for age 25–29, standard deviation is 0.18 and 0.17 respectively.

LHS (London Handicap Scale) was also used to assess HRQoL both on 19 and 28 years of age, focusing on the level of disability. LHS includes six dimensions of disability: mobility, physical independence (self-care), occupation (daily activities), social integration, orientation, and economic self-sufficiency; every dimension consists of a six-point hierarchical scale of disadvantages. To provide the generic measure of disability (scale 0–100, where 100 is perfect health), a utility for LHS score was calculated based on the Dutch population preference index. The six dimensions of disability are first recoded into a weighted score. Subsequently, the sum of these weighted scores for each dimension and 50.5 provides the LHS score 0–100.

At 28 years only, the WHOQoL-BREF (WHO Quality of Life instrument, short edition) was also assessed to determine HRQoL. The WHOQoL-BREF produces a quality of life profile divided into four domains: physical health, psychological, social relationships, and environment. Domain scores from the WHOQoL-BREF were computed and transformed into weighted scores between 0–100, where 100 is perfect health.

Analysis: The differences in characteristics of participants and non-participants were tested by chi-square tests in case of categorical variables or student's t-tests in case of continuous variables. Characteristics that were tested: sex (male versus female), birth weight (in grams), origin (Dutch versus non-Dutch), educational level (low, middle or high), SES (low, middle or high), SGA versus appropriate for gestational age, maternal age at time of birth (in years), disabilities at five years of age (non, mild or severe), and disabilities at 10 years of age (non, mild or severe).

To adjust for missing values at age 19 and age 28 we applied multiple imputations by using MICE (Multi-variate Imputation by Chained Equations). This method "fills in" plausible values for the missing data, creating five imputed (completed) data sets. Predictive mean matching was used to create multiple imputations. The imputations are based on a model that uses information from the respondents and other variables to achieve optimal estimates. We pooled the results of the five imputed data sets to obtain data estimates, the precision of the estimates incorporates the uncertainty of the missing values. The original data set used for the multiple imputation contained the variables sex (male versus female), birth weight (in grams), origin (Dutch versus non-Dutch), educational level (low, middle or high), SES (low, middle or high), SGA versus appropriate for gestational age, maternal age at time of birth (in years), disabilities at five

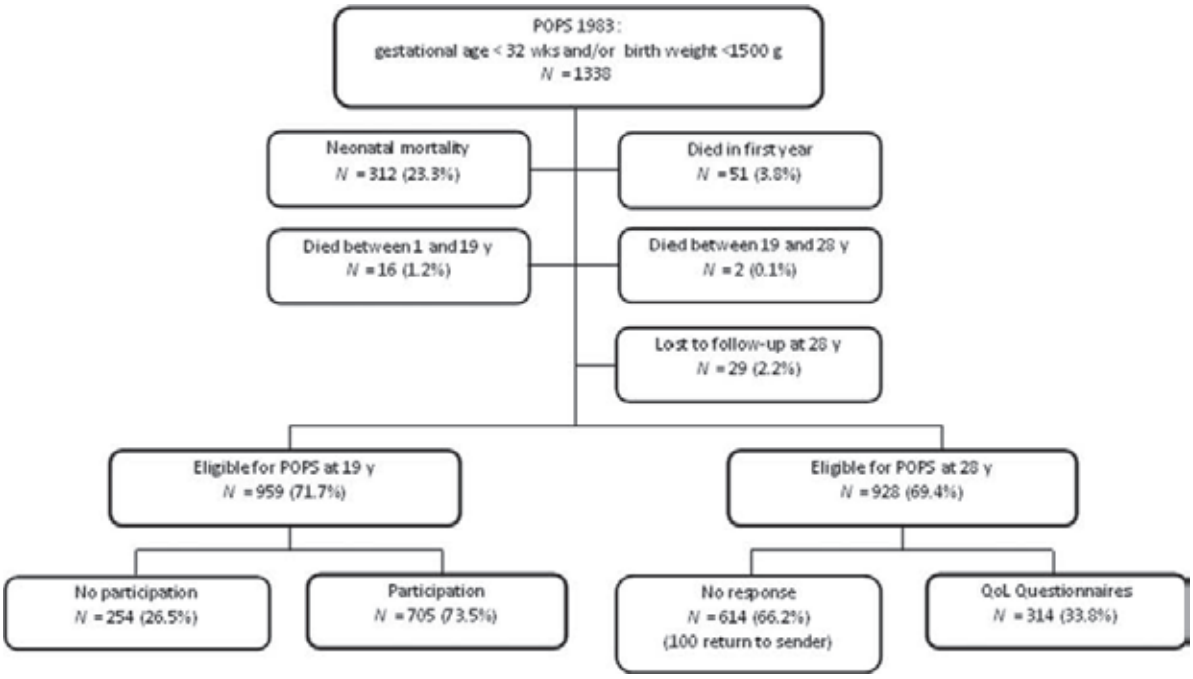

Figure 1 Flow chart inclusion of participants of the POPS study at age 28.

Table 1 Characteristics of participants and non-participants at age 28

		Participants n (%)	Non-participants# n (%)	p-value
Sex*	Male	119 (38)	360 (59)	< 0.001
	Female	195 (62)	254 (41)	
Birth weight (grams)	<=1000	46 (15)	93 (15)	< 0.825
	1001-1250	89 (28)	169 (26)	
	1251-1500	111 (35)	258 (40)	
	>1500	68 (22)	123 (19)	
Origin*	Dutch	293 (94)	500 (82)	<0.001
	Non-Dutch	18 (6)	110 (18)	
Educational level (parents)*	Low	81 (26)	254 (46)	<0.001
	Middle	120 (38)	197 (36)	
	High	113 (36)	103 (18)	
SES (parents)*	Low	97 (31)	292 (48)	<0.001
	Middle	101 (32)	181 (30)	
	High	114 (37)	135 (22)	
Appropriate for gestational age	Yes	189 (60)	390 (64)	0.351
	No, small	124 (40)	224 (36)	
Maternal age at time of birth (years)	<20	11 (4)	54 (8)	0.065
	>=20 and	289 (92)	566 (88)	
	<36	14 (4)	23 (4)	
	>=36			
Disability at age 5*	None	89 (29)	119 (20)	<0.001
	Mild	215 (69)	427 (71)	
	Severe	8 (2)	53 (9)	
Disability at age 10	None	142 (51)	205 (50)	0.058
	Mild	119 (43)	149 (37)	
	Severe	18 (6)	52 (13)	

* $p < 0.05$.
# Survivors of the POPS cohort at age 28 who did not participate in this follow-up study at age 28.

years of age (non, mild or severe), disabilities at 10 years of age (non, mild or severe), the items on HUI3 and LHS at age 19, and the items on HUI3, LHS and WHOQoL- BREF at age 28.

The difference in mean HRQoL scores between age 19 and age 28, both on HUI3 and LHS, was tested with a paired t-test, both on the original and imputed data. The mean WHOQoL score on the "Psychological" domain was tested against the mean score on "Social relationships" with a paired t-test. MAU can be categorized into four levels of disability: none, mild, moderate and severe. Categorization of the MAU score and the eight single attributes score (X) was based on X=1 (none), 1>X>0.90 (mild), 0.90>X>0.70 (moderate) and X<0.70 (severe). Individual changes in MAU and attribute categories from age 19 to age 28 were classified into three categories: better (shift to a more favorable category), stable (no shift), and worse (shift to a less favorable category). MAU score was categorized to see if there was an important shift in disability from age 19 to age 28. To indicate how stable these scores are over time across the whole range of scores, Pearson correlations were calculated. In addition, change in mean weighted scores on the eight attributes of HUI3 and the six dimensions of LHS were tested with a paired t-test from age 19 to age 28.

Results

Participant characteristics and non-response: Non-participants were more often male and non-Dutch, had a lower educational level and SES, and had more severe disabilities at age five than participants (Table 1).

Overall (scale) scores HUI, LHS, WHOQoL: Table 2 shows that overall HRQoL on the HUI3, LHS and WHQoL were close to the optimal HRQoL score of 1 (HUI3) or 100 (LHS and WHOQoL-BREF). The WHOQoL "Psychological" domain score was lowest and significantly lower compared to the next-lowest WHOQoL domain score ("Social relationships").

Changes in HUI and LHS score from age 19 to age 28: Table 2 shows that both the mean HRQoL score measured with HUI3 and LHS did not change significantly from age 19 to age 28 in the original data. After multiple imputations, a significant increase was found in the mean MAU score from 0.83 at age 19 to 0.85 at age 28 (p=0.002). The mean individual MAU difference was 0.02 (sd=0.17; 95% CI −0.03 to −0.01). LHS showed no significant change after multiple imputations.

Individual HUI scores, when divided into four levels of disability (none, mild, moderate, severe), improved in 28%, was stable in 48% and worsened within 24% of participants. Figure 2 shows this distribution of MAU-change scores and the change scores on its eight single attributes on HUI3 from age 19 to age 28 after multiple imputation; the physical attributes are more stable than

Table 2 Outcome in assessed 19 and 28-year-olds compared with outcome in all survivors at age 28

Questionnaire		Assessed outcome n=314 Mean (sd)	MI[#] Outcome n=957 Mean (sd)
Health Utilies Index 3 (Multi Attribute Utility)	19y	0.89 (0.16)	0.83 (0.22)
	28y	0.88 (0.16)	0.85 (0.20)
	Change 28y-19y	- 0.01 (0.15)	0.02 (0.17)*
London Handicap Scale (Utility)	19y	96.5 (8.3)	93.9 (12.4)
	28y	95.9 (8.0)	94.6 (9.8)
	Change 28y-19y	- 0.57 (7.5)	0.71 (9.0)
WHOQoL-BREF[$] (Recoded into score 0–100)	Psychological	73.9 (14.7)*	74.4 (13.5)*
	Social	79.0 (17.3)	78.2 (16.9)
	Relationships	85.6 (12.9)	85.0 (12.8)
	Environment	85.8 (14.1)	85.8 (13.1)
	Physical health		

* $p < 0.05$.
[#] MI: After multiple imputation.
[$] Mean WHOQoL scores and standard deviations at age 28.

the psychological attributes. Hearing and dexterity were both stable in 96% of participants, ambulation in 95%, and vision and speech were stable in 77% of participants. The psychological attributes pain, cognition and emotion show a bigger proportion of participants shifting to a better or worse category. Pain improved in 17% of participants, cognition in 22%, and emotion in 21%, respectively 15%, 14% and 14% shifted to a worse category. Pearson correlation scores over time on the eight single attributes on HUI3 show a positive correlation between cases at age 19 and cases at age 28: hearing r=0.468, dexterity r=0.916, ambulation r=0.906, vision r=0.478, speech r=0.332, pain r=0.390, cognition r=0.366, and emotion r=0.388. Dexterity and ambulation have the highest correlation, indicating the least change between the two ages. MAU score also showed a positive correlation (r=0.684).

Figure 3 shows the mean weighted scores on the eight attributes of HUI3 at age 19 and age 28 after multiple imputations. A significant decrease in mean weighted score on ambulation and dexterity from age 19 to age 28 is shown. Ambulation decreased from 0.9895 to 0.9869 and dexterity decreased from 0.9905 to 0.9884. Speech, emotion and cognition significantly improved from age 19 to age 28. The mean weighted score for speech increased from 0.9849 to 0.9885, for emotion from 0.9652 to 0.9735, and for cognition from 0.9656 to 0.9756. Figure 4 shows the mean weighted scores on the six dimensions on the LHS. The

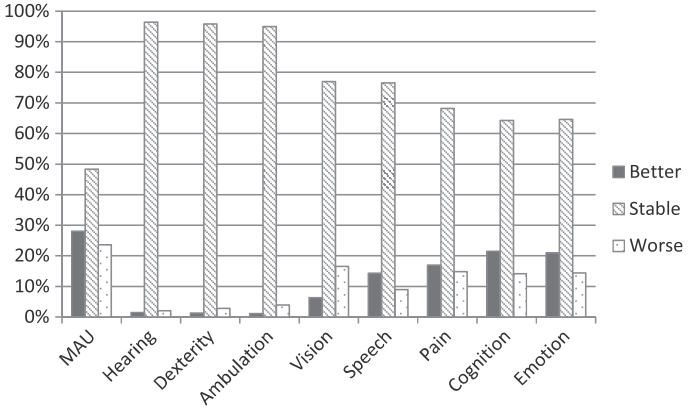

Figure 2. Distribution of MAU- and attribute change scores between ages 19 and 28 after multiple imputation.

mean weighted score on economic self-sufficiency significantly increased from 8.00 at age 19 to 8.31 at age 28.

Discussion

Overall, this study shows positive results in HRQoL scores for adults born VP or with a VLBW. Mean MAU score on the HUI3 decreased non-significantly from 0.89 at age 19 to 0.88 at age 28 in the original data. The imputed results show a significant increase of 0.02 in mean MAU score from 0.83 at age 19 to 0.85 at age 28. The imputed mean MAU scores were adjusted downward (indicating a lower HRQoL) compared to the original results, which can be explained by the higher number of disabilities in the imputed data. According to Horsman et al., a difference of 0.03 is considered to be clinically important. Thus, no important changes in MAU score were found in the transition into adulthood in our population. A previous study by Verrips et al. also showed no change in HUI3 scores from age 14 to age 19 within the POPS cohort. Unfortunately the POPS study has no matched control subjects, therefore a similar international cohort is used for comparison. A Canadian study found similar results on HUI scores in young adults of 23 years of age: 0.85 (n=143 preterm) versus 0.88 controls (n=130). HUI3 reference score of HRQoL for adults aged 25–29 years is 0.85 (sd=0.17). However, due to cultural variations this comparison cannot be interpreted as a main finding and the main aim of this study is to explore the change in HRQoL from age 19 to age 28. HRQoL score on the LHS did not change significantly from 96.5 (19y) to 95.9 (28y) in the original data, nor in the imputed data from 93.9 (19y) to 94.6 (28y). Saigal et al. concluded that the young adults had adopted to their disabilities, which explains the high scores on HRQoL.

The WHOQoL scores at 28 years of age are high compared to the norm population: physical health 85.8 versus 78.8 (norm); social relationships 78.2 versus 72.3 (norm); and environment 85.0 versus 71.2 (norm). It is remarkable that the score on the "Psychological" domain is lower than in the norm population: respectively 74.4 versus 75.9 and lower compared to the scores on the other WHOQoL domains. The facets that are incorporated with the psychological domain are: bodily image and appearance; negative feelings; positive feelings; self-esteem; spirituality/ religion/personal beliefs; thinking, learning, memory and concentration. Verrips et al already highlighted the relationship between psychological problems and HRQoL change from 14

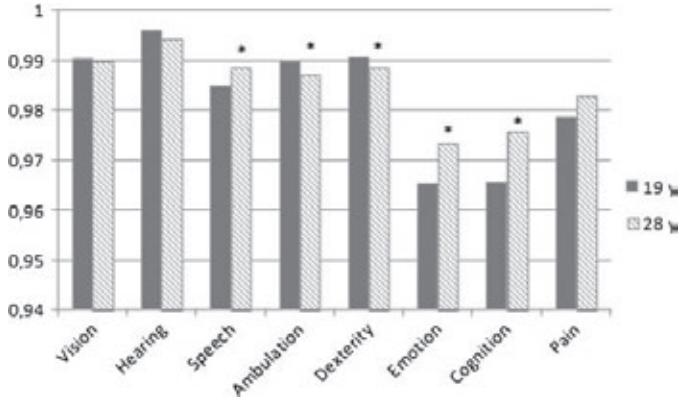

Figure 3. Change in mean weighted scores on the eight attributes of HUI3# after multiple imputation.

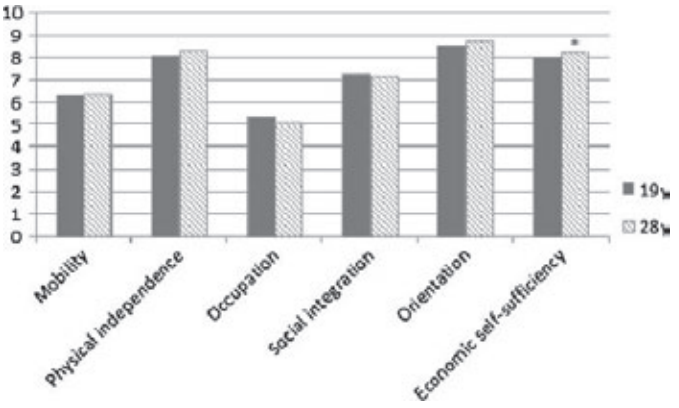

Figure 4. Change in mean weighted scores on the six dimensions of LHS# after multiple imputation.

to 19 years of age. The current study found the same effect in HRQoL change from 19 to 28 years of age. It seems that major health disabilities alone do not always predict one's own perspective on HRQoL, as found in previous studies.

The change in individual MAU score from age 19 to age 28 was stable in 48%, improved in 28%, and worsened in 24% of participants. In comparison, from age 14 to age 19 individual MAU change score was stable in 45%, improved in 25%, and worsened in 30% of participants, nearly the same as in our study. There was a positive correlation over time across all the scores of the single eight attributes and the MAU score. Scores on dexterity and ambulation are high, almost one, indicating that these attributes are most stable over time. The psychological attributes, especially emotion and cognition, were less stable than the physical attributes. A part of the participants shifted to a worse category, but there was even a greater part that shifted to a better category, so there is hope for improvement. It might be of great importance to early monitor emotional well-being in this group. Interventions should be directed at dealing with (potential) disabilities within this group of children at teen age, to prevent later onset of emotional problems and to better manage pain. Especially because emotion, cognition and speech already improved significantly from age 19 to age 28, but overall score on the "Psychological" domain at age 28 were still significantly lower. A great emphasis in future research should be on the psychological problems that seem to be highly represented in adults born VP or with a VLBW. These psychological problems seem to influence changes of HRQoL during the transition into adulthood.

The non-response group in our study represents the same characteristics as found in the follow-up study at 19 years of age: more often male, non-Dutch, lower educational level, lower SES and more severe disabilities. When these characteristics are not taken into account in the analyses, results may show an overestimation of the HRQoL of the POPS cohort. To correct for this selective dropout we applied multiple imputations. A limitation of this method though, is that the power gets artificially high and attention must be paid that two-third of the data at age 28 is imputed rather than actually collected. On the other hand, POPS is a unique cohort with a very long follow-up from birth to 28 years of age, and multiple imputations can be based on the abundance of earlier collected data at birth and ages two, five, nine, 10, 14 and 19 years. Therefore the multiple imputations should give a good correction for non-response bias, resulting in a reliable outcome. Earlier data collected in the POPS study also included disability-status variables of the population. These variables can be used in the multiple imputations to correct for the selective dropout of those who might have been too disabled to be able to complete an Internet survey.

Conclusions

Overall, no important changes in HRQoL between age 19 and age 28 were found in our POPS cohort. Psychological and emotional problems are prominent and interventions should be directed at early detection, monitoring and managing these problems to decrease the negative impact on everyday life.

Adherence to Oxygenation and Ventilation Targets in Mechanically Ventilated Premature and Sick Newborns: a retrospective study

Marianne Trygg Solberg, Ida Torunn Bjørk, Thor Willy R. Hansen

Abstract

Background: Ventilator treatment exposes newborns to both hyperoxemia and hyperventilation. It is not known how common hyperoxemia and hyperventilation are in neonatal intensive care units in Norway. The purpose of this study was to assess the quality of current care by studying deviations from the target range of charted oxygenation and ventilation parameters in newborns receiving mechanical ventilation.

Methods: Single center, retrospective chart review that focused on oxygen and ventilator treatment practices.

Results: The bedside intensive care charts of 138 newborns reflected 4978 hours of ventilator time. Arterial blood gases were charted in 1170 samples. In oxygen-supplemented newborns, high arterial pressure of oxygen (PaO2) values were observed in 87/609 (14%) samples. In extremely premature newborns only 5% of the recorded PaO2 values were high. Low arterial pressure of CO2 (PaCO2) values were recorded in 187/1170 (16%) samples, and 64 (34%) of these were < 4 kPa. Half of all low values were measured in extremely premature newborns. Tidal volumes above the target range were noted in 22% of premature and 20% of full-term newborns.

Conclusions: There was a low prevalence of high PaO2 values in premature newborns, which increased significantly with gestational age (GA). The prevalence of low PaCO2 values was highest among extremely premature newborns and decreased with increasing GA. Further studies are needed to identify whether adherence to oxygenation and ventilation targets can be improved by clearer communication and allocation of responsibilities between nurses and physicians.

Solberg is with Lovisenberg Deaconal University College; Solberg and Bjørk are with the Department of Nursing Science, Faculty of Medicine, University of Oslo; Hansen is with the Department of Neonatal Intensive Care, Women's and Children's Division, Oslo University Hospital; Hansen is also with the Institute of CLinical Medicine, Faculty of Medicine, University of Oslo, Norway. The authors are grateful to Professor Magne Thoresen for his statistical advice. Reprinted from BioMed Central, BMC Pediatrics, [Solberg et al.: Adherence to oxygenation and ventilation targets in mechanically ventilated premature and sick newborns: a retrospective study. BMC Pediatrics 2013 13:126.]

Keywords: Newborn infant, Premature infant, Mechanical ventilation, Oxygenation

Background

Clinical practice with respect to ventilator management, administration of oxygen, and assessment of oxygenation differs greatly among neonatal intensive care units (NICUs).[1,2] Ventilator treatment exposes newborns to both hyperoxemia and hyperventilation. The goal of ventilator treatment is to balance gas exchange while minimizing trauma to the lung tissue.[3] Adjusting oxygenation and ventilator therapy is challenging, and improved strategies are needed to minimize hyperoxemia[4] and hyperventilation with hypocarbia[5,6] in pre-term and full-term newborns. Appropriate oxygenation is achieved by titrating the fraction of inspired oxygen (FiO2) and the mean airway pressure (MAP). The aim of appropriate ventilation is to maintain an arterial pressure of carbon dioxide (PaCO2) of ~5.3 kPa (40 mm Hg).[7]

Nurses need a target range for oxygen saturation (SpO2) in order to titrate FiO2 appropriately. SpO2 in the 85-95% range excludes hyperoxia,[8] but there is no consensus for the optimal saturation target ranges in premature newborns.[9] A collaborative prospective meta-analysis of five ongoing trials in the USA, Australia, United Kingdom, New Zealand and

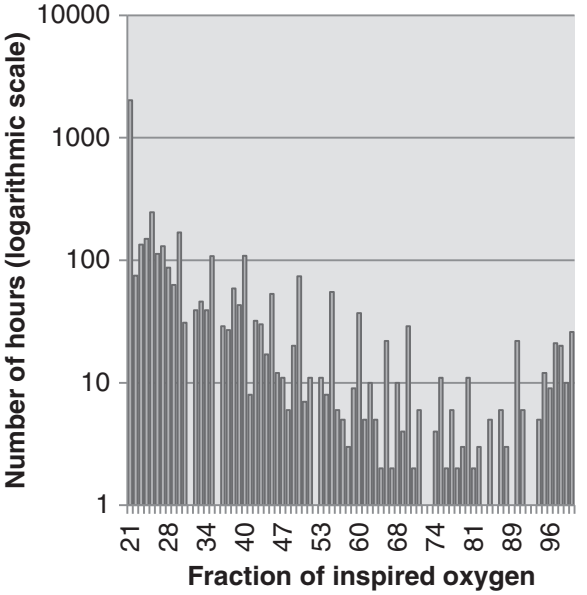

Figure 1 Distribution of FiO_2. *n* = 4428 hours (138 patients).

Table 1 Number of newborns with measurements of arterial blood gases

	GA 23 - 28	GA 29 - 37	GA 38 - 41	GA > 41	Total count
Total number of newborns with recorded arterial blood gases	41	35	29	16	121
Total number of newborns with recorded arterial blood gases who received FiO_2 >21%	33	27	19	14	93
Number of newborns with at least one low PaO_2 (Prem. < 6, full term < 8 kPa)	23	15	15	9	62
Number of newborns with at least one high PaO_2 (Prem. > 10, full term >10.7 kPa)	8	9	7	9	33
Number of newborns with at least one $PaCO_2$ < 4.7 kPa	26	18	18	8	70
Number of newborns with at least one $PaCO_2$ < 4 kPa	15	10	7	3	35

Prem. = premature.

Canada (NeOProM), aimed to establish the optimal SpO2 target ranges for extremely preterm newborns.[9-11] Interim results recommend SpO2 levels > 90% to avoid mortality.[9] Previous recommendations suggested SpO2 levels < 85%.[12,13] There is no evidence or consensus to guide the administration of oxygen in full-term newborns.[14]

The Neovent study group found that time-cycled, pressure-limited ventilation was the most common mode currently used for neonatal ventilation. The tidal volume (TV) was usually targeted to 4-7 ml/kg.[15] The same study group found that hypocarbia was relatively uncommon during neonatal ventilation, and they speculated that hypercarbia was more common because of the practice of permissive hypercarbia.[15]

Few studies relate arterial oxygen tension values to SpO2 targets.[8] It is not known how often the problem of hyperoxemia and hyperventilation occurs in NICUs in Norway. The present retrospective study is the first part of a larger study that aims to discover areas for quality improvement regarding oxygen and ventilator treatment of preterm and sick newborns. The purpose of this study was to investigate the documentation of oxygenation and ventilation among newborns receiving mechanical ventilation in a Norwegian NICU, to report on the following: (1) use of oxygen during ventilator treatment; (2) extent of charted deviations from oxygenation and ventilation targets; and (3) data associated with variations in MAP.

Methods

Patients and study design: The setting of this study was a level 4 NICU at Rikshospitalet, Oslo University Hospital, Norway. We retrospectively studied the documentation of oxygen and ventilator treatment practices between July 2010 and November 2011using intensive care charts. Patients who satisfied the inclusion criteria were identified through the NICU proprietary quality control database. Infants were eligible for inclusion if they had been mechanically ventilated for a minimum of 3 hours, and we chose to limit data collection to a maximum of 48 hours for each patient. The sample was grouped by gestational age (GA) into extremely premature (23-28 weeks GA), moderately premature (29-37 weeks GA), full-term (38-41 weeks GA), and newborns > 41 weeks post-conceptual age (defined as GA plus chronological age).[10] The principal diagnoses were categorized using ICD 10 (KITH-Health Affairs) and were: immature lungs, other lung/respiratory problems, circulatory problems, and infection.

Relevant variables for oxygenation and ventilator treatment were defined according to the literature, clinical practice, and discussion with experts in the field. Variables collected and reported in this study were GA, sex, birth-weight, diagnoses (infection, lung problems, immature lungs and circulatory problems), peak inspiratory pressure (PIP), positive end-expiratory pressure (PEEP), inspiratory time (TI), FiO2, TV, MAP, highest preductal SpO2 value, arterial pressure of oxygen (PaO2), and PaCO2. Data were collected on expiratory TV measured from the ventilator, because this measures the effectiveness of mechanical ventilation.[16] Blood gas analysis was carried out on arterial samples only, because capillary blood gases were deemed to have insufficient reliability for our purposes. This reliability problem relates to newborn infants crying as a reaction to vasopuncture, which frequently presents as rapid changes in PaO2 and PaCO2.[17] Capillary blood gases were therefore analyzed solely for comparison with arterial gases.

The limit of acceptable PaCO2 was set at 4.7-5.9 kPa.[18] Normal limits for PaO2 were 6-10 kPa for premature newborns[19] and 8-10.7 kPa for full-term infants.[18] Appropriate limits for SpO2 for newborns receiving supplemental oxygen were set at 88-93% in premature infants and not above 95% in full-term newborns, according to existing practice guidelines in our unit. The normal limits of TV were considered to be 4-6 ml/kg for premature and 5-8 ml/kg for full-term newborns.[20]

Statistical analyses: Statistical analyses were performed using SPSS version 19.0 (SPSS Inc., Chicago, IL, USA). A research assistant checked data for accuracy. A power analysis resulted in the inclusion of charts from 138 premature and full term newborns. This was based on the assumption that the proportion of newborns with SpO2 outside the recommended limit, was approximately 10%, estimated with an accuracy of ± 5% and calculated with a 95% confidence interval (CI).

Table 2 Arterial blood gas measurements in 1-hour periods

Hours of observation	GA 23 – 28	GA 29 – 37	GA 38 – 41	GA > 41	Total hours observation
	n (%)	n (%)	n (%)	n (%)	n (%)
Total hours of observation	1624 (100)	1480 (100)	1112 (100)	762 (100)	4978 (100)
1-hour blocks with listed arterial blood gases	442 (27)	297 (20)	262 (24)	169 (22)	1170 (24)
1-hour blocks without listed arterial blood gases	182 (73)	183 (80)	850 (76)	593 (78)	3808 (76)

Obtained in 121 patients.

Table 3 PaO_2 values in 1-hour periods when FiO_2 was >21%

	GA 23 – 28	GA 29 – 37	GA 38 – 41	GA > 41	Total count
	n (%)	n (%)	n (%)	n (%)	N (%)
No. of low PaO_2 values (Prem. < 6, full term < 8 kPa)	57 (24)	50 (31)	71 (60)	30 (33)	208 (34)[a]
No. of normal PaO_2 values (Prem. 6–10, full term 8–10.7 kPa)	170 (71)	91 (57)	24 (20)	29 (32)	314 (52)
No. of high PaO_2 values (Prem. > 10, full term >10.7 kPa)	12 (5)	19 (12)	24 (20)	32 (35)	87 (14)[b]
Total count	239 (100)	160 (100)	119 (100)	91 (100)	609 (100)

Obtained in 93 patients.
[a]Data from newborns with circulatory problems were included in the count of low PaO_2 values.
[b]Of the high PaO_2 values, 28 (32%) were >14.6 kPa.

Descriptive statistics and frequencies were calculated for GA, weight, number of newborns with measurements of arterial blood gases, 1-hour periods with and without arterial and capillary blood gas measurements (based on 24 1-hour periods per day), PaO2, PaCO2, and TV. The recorded values for TV were summarized with respect to the two limits that were applicable to premature and full-term newborns in the NICU. Preductal SpO2 values were analyzed for the trend in mean values over time. The cutoff point for defining hypocarbia was PaCO2 < 4.7 kPa, and extreme hypocarbia was defined as PaCO2 < 4.0 kPa. When analyzing the distribution of arterial blood gases, and comparing the prevalence of high versus low PaO2 and PaCO2 between the GA groups, we controlled for possible interdependence due to repeated measurements in each individual by using a generalized linear model and Wald's analysis.[21] We used partial correlation to analyze the correlation between PaCO2 and TV.[22] A mixed linear model with repeated measures was used to analyze variations in MAP. Any p value <0.05 was considered significant.

Ethical approval: Approval by the Regional Committee for Medical Research Ethics in Norway was not required for this study because data collection was anonymous. Permission for the study was obtained from the Data Protection Officer at Oslo University Hospital and from the director of the NICU.

Results

Sample description: The documentation included 4,978 hours of ventilator time for 138 newborns. Ventilator support consisted of 4,702 hours of conventional mechanical ventilation and 276 hours of oscillation. The minimum duration of ventilator treatment was 5 hours and our predetermined maximum period of study was 48 hours. There were 85 male (62%) and 53 female (38%) infants. GA ranged from 23 to 52 weeks and weight at the time of study entry was 426-5345 g. There were 42 (30%) extremely premature, 42 (30%) moderately premature, 34 (25%) full-term and 20 (15%) newborns aged > 41 weeks. The leading diagnoses were lung immaturity [57 (41%)], other lung problems [43 (31%)], circulatory problems (including congenital heart disease) [32 (23%)] and infection [6 (5%)].

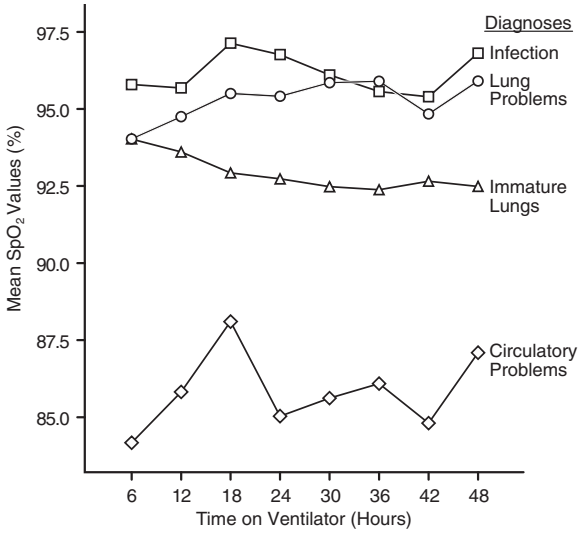

Figure 2 Mean SpO_2 trends by diagnosis.

Use of oxygen during ventilator treatment: Figure 1 summarizes the distribution of oxygen concentrations received by the newborns. In total, newborns received 2020 hours of ventilator support with FiO2 = 21%. Oxygen was given at a median FiO2 of 24% in premature newborns and a median of 21% in full-term newborns. The mean values were respectively 30% (CI 95% = 29.4-30.6) and 32% (CI 95% = 31.1-32.9).

Charting of deviations from oxygenation and ventilation targets: Blood samples were taken for arterial blood gas analysis from once an hour, to every 3 to 4 h. Table 1 shows the number of newborns with measurements of arterial blood gases.

Monitoring and assessment of oxygenation: Table 2 shows the arterial blood gas measurements in 1-hour periods obtained during ventilator treatment.

Capillary blood gas measurements were obtained in 47 patients. There were 226/4978 (5%) 1-hour periods with recorded capillary blood gases: with 39 (17%) in extremely premature, 94 (42%) in moderately premature, 56 (25%) in full-term, and 37 (16%) in newborns > 41 weeks old. Analysis comparing the frequency of capillary and arterial blood gas sampling showed that arterial blood gas sampling was most common. Wald's analysis indicated significant differences between the GA groups in the frequency of using arterial blood gases (p = 0.02). Further analysis showed that samples for arterial blood gas analysis were withdrawn

Table 4 Mixed-model repeated-measures analyses for variations in MAP

	Estimate	95% confidence interval		Sig (p)
		Lower	Upper	
Change over time	6.7	1.87	11.54	0.007
PEEP	- 4.43	- 11.76	2.91	0.237
Hours×PEEP	0.12	- 0.26	0.50	0.546
TI	27.77	12.01	43.52	0.001
Hours×TI	- 0.67	- 1.27	- 0.08	0.026
PIP	23.81	17.68	29.94	0.000
Hours×PIP	- 0.55	- 0.79	- 0.31	0.000

Dependent variable: MAP.

significantly more often from the extremely premature versus moderately premature infants (p = 0.004).

Table 3 shows the distribution of low, normal and high PaO2 values according to GA in newborns who received oxygen supplementation. Although extremely premature infants had relatively few high PaO2 values, the percentage of high value samples increased with GA. There was a significant difference between GA groups with regard to the risk of low versus normal PaO2 values (p < 0.001) and normal versus high values (p < 0.001). Further calculations showed that the odds ratio (OR) of normal PaO2 (compared to high PaO2) in newborns of GA 23-28 weeks was 16 (95% CI = 6.5-40) times greater than that in newborns of GA > 41 weeks. The mean SpO2 trends over time are shown in Figure 2.

Monitoring and assessment of ventilation: Low PaCO2 values were recorded in 187/1170 (16%) samples (70 patients). When the cutoff for low PaCO2 was set at 4-4.7 kPa, there were 42 (34%) low PaCO2 values in extremely premature, 30 (24%) in moderately premature, and 35 (28%) in full-term newborns, and 16 (13%) in newborns aged > 41 weeks. The analysis showed no significant difference in the occurrence of low PaCO2 between GA groups (p = 0.639). However, when the cutoff value was reduced to < 4 kPa (n = 64), there was a significant difference (p = 0.015) between the groups. The OR of PaCO2 < 4 kPa in newborns of GA 23-28 weeks was 5 (95% CI = 1.6-15) times greater than that in newborns of GA > 41 weeks.

For premature infants of GA 23-37 weeks, there were 2374 recorded TV measurements in 1-hour periods, with a median TV of 4.7 ml/kg. Less than half of the measurements (n = 1058) were within the normal reference range of 4-6 ml/kg, and 520 (22%) were > 6 ml/kg. There was no significant correlation between PaCO2 and TV (r = 0.007, p = 0.87). Full-term newborns had a total of 1535 TV measurements in 1-hour periods, with a median TV of 6.1 ml/kg. More than half of all measurements (n = 883) were in the normal range, while 301 (20%) were > 8 ml/kg. There was a significant weak negative correlation between PaCO2 and TV (r = –0.12, p = 0.03).

Data associated with variations in MAP: A linear mixed effects model was used to estimate variations in MAP using the independent variables PEEP, TI and PIP (Table 4). Table 4 shows that there was a significant correlation between MAP variability, TI and PIP, which decreased with the passage of time. There was no significant correlation between MAP variability and PEEP. This suggests that changing PEEP was not used as a strategy to adjust MAP and thereby affect oxygenation. The two groups of premature infants received PEEP with a mean pressure of 4.7 cm H2O (CI 95% = 4.67-4.73), and full-term newborns received PEEP with a mean pressure of 4.9 cm H2O (CI 95% = 4.85-4.95).

Discussion

The purpose of oxygen administration in the NICU is to prevent free radical damage.[23] In the present study, the median FiO2 in premature newborns was lower (24%) than in the study by van Kaam et al, who found a median FiO2 value of 28% during conventional mechanical ventilation.[24] Furthermore, we found that newborns achieved acceptable mean SpO2 during the observation period (Figure 2). Targeting saturation to 88-93% in premature newborns and not more than 95% in full-term newborns has been a goal for several years.[25,26] However, these targets have not yet been fully agreed upon, because the results of ongoing randomized trials testing high versus low SpO2 targets are still pending.[9,10,27] Our calculation of mean SpO2 may have masked episodes of hypoxemia or hyperoxia when nurses titrated FiO2. Nevertheless, it suggests that the goal for saturation targets was met to a large extent. Using SpO2 alone to guide decisions concerning oxygen administration is not evidence-based practice. Thus, nurses also have to assess skin color, heart rate, and values from blood gases as well transcutaneous O2 measurements.[28]

Although it has been suggested that entrenched clinical practices and cultures make it difficult to change the use of oxygen,[29] our results showed that extremely premature newborns did not receive excessive amounts of oxygen (Tables 1 and 3). The incidence of hyperoxemia increased with GA. Because of the hemoglobin oxygen dissociation curve,[12] sick newborns with pulmonary hypertension are at higher risk of developing high levels of hyperoxemia when they are treated with an oxygen saturation of ~95%. It is common practice in NICUs that nurses wait until an infant is stable before withdrawing arterial blood for gas analysis, and this practice will affect the results. In addition nurses' workload is an important factor in the achievement of SpO2 goals and appropriate oxygen management in the NICU. There is evidence that compliance with saturation targets is improved with higher nurse: patient ratios.[30] The good results for oxygen management in the NICU in the present study may in part have been due to the practice of having a 1:1 nurse:patient ratio for all infants on mechanical ventilation.

Our study revealed that low PaCO2 values occurred most commonly in extremely premature infants. Hypocarbia may cause cerebral vasoconstriction, resulting in decreased oxygen delivery to the brain.[7,10] Moreover, in extremely preterm infants, PaCO2 in the normal range seems to yield the best electroencephalography activity.[31] PaCO2 can be regulated by controlling the minute ventilation with TV, or the ventilator rate.[3] It is therefore noteworthy that we found high TVs in 22% of preterm infants and 23% of newborns aged >37 weeks. Nevertheless, the median TV of 4.7 ml was lower than the 5.3 ml recorded in the study of van Kaam et al.[24] Mechanical ventilation using high TVs is known to cause lung damage.[32] We did not find any significant correlation between PaCO2 and TV in the premature infants, and only a weak negative correlation in full-term infants. This suggests that the relationship between lung physiology and what happens during respirator treatment may not be simple.

Our results showed that variations in PEEP had no significant effect on MAP variability (Table 4). Changing PEEP is often an effective way to adjust oxygenation[33] and to regulate MAP for experienced clinicians who can accurately assess changes in measured data and calculate the impact of any adjustments.[34] The premature newborns in our study had a PEEP mean value of 4.7 cm H2O which was similar to that observed in the study of van Kaam et al., although they suggested that PEEP values >7 cm H2O might be protective for the lungs.[24]

It is suggested that maintaining appropriate oxygenation is hindered by insufficient communication of unit policies as well as personal bias about the best practice.[35] Control of oxygenation and ventilation is crucial during mechanical ventilation. Therefore, further studies should identify how communication and allocation of responsibilities between nurses and physicians can reduce the incidence of hypocarbia and hyperoxemia.

One limitation of this study was that we had no record of fluctuations in oxygenation levels, nor observations of how soon after blood gas analyses adjustments were made. Regarding the analysis of the mean SaO2, it would have been helpful to include an analysis that indicated the uncertainty in the results. However, because of the volume of repeated measurements for each individual, a standard box plot could not be used. Another weakness of the study was related to the high TV values, which were presented as a general occurrence regardless of how many high values there were from each individual patient.

Conclusions

We showed that, in general, premature newborns were treated within the desired limits of SpO2, and few high PaO2 values were noted. The occurrence of high PaO2 values increased significantly with GA. Many recorded TVs were too high and hypocarbia during ventilation was more common in the extremely premature infants.

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Survey on Retinopathy of Prematurity (ROP) in Italy

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Abstract

Background: This study aims to investigate the incidence and the relative risk factors of retinopathy of prematurity (ROP) and posterior-ROP (P-ROP): ROP in Zone I and posterior Zone II, as well as to analyze the occurrence of surgical treatment of ROP and to evaluate the short term outcome of the disease in Italy.

Methods: It is a prospective multicenter observational study; all infants with a birth weight (BW) ≤ 750 g and/or a gestational age (GA) ≤27 weeks born between January 1st 2008 and December 31st 2009 in 25 III level Italian neonatal intensive care units were eligible for the study.

Results: 421 infants were examined: 265 (62.9%) developed ROP and 102 (24.2%) P-ROP. Following the multivariate analysis erythropoietin-therapy ($p < 0.0001$) and intraventricular hemorrhage (IVH) ($p = 0.003$) were significantly associated with ROP while gestational age ≤24 weeks ($p = 0.011$) and sepsis ($p = 0.002$) were associated with the onset of P-ROP. Eighty-nine infants (34%) required surgical treatment; following the multivariate analysis P-ROP was an independent factor associated with the need of surgical treatment ($p < 0.0001$). A favorable outcome was reported in 251 (94.7%) newborns affected by ROP. Adverse outcome occurred in 14 patients: all of them underwent surgery and showed P-ROP.

Conclusions: P-ROP is the most aggressive type of ROP. It associates with lower GA and sepsis. Obstetricians and Neonatologists must focus on the reduction of severe preterm births and on the prevention of neonatal early and late onset sepsis in order to reduce the incidence of P-ROP.

Background

Retinopathy of prematurity (ROP) is a vasoproliferative disorder of the retina that may result in a significant loss of vision and even blindness. In recent decades the survival rate of extremely preterm infants has improved dramatically.[1] Since extremely preterm infants are at high risk of developing ROP, the number of infants with severe ROP has risen considerably in the last few years. Currently, ROP is one of the most common causes of childhood blindness.[2]

In 1951, Campbell first highlighted the involvement of supplemental oxygen in the pathogenesis of ROP; the role of oxygen was subsequently reconfirmed by other authors.[3,4] During the first stage of the pathogenesis of ROP, hyperoxia suppresses the activity of the vascular endothelial growth factor (VEGF) and alters the normal vascularization of the retina due to vaso-constriction and vaso-obliteration of the existing immature vessels. In the second phase of ROP, up regulation of VEGF and other growth factors, triggered by hypoxia, induces vascular over proliferation. Thus both hypoxia and hyperoxia are involved in the pathogenesis of ROP.[5]

Fifty percent of extremely preterm infants show clinical signs of ROP, although this percentage varies widely. Complete recovery rate is approximately 85%.[6]

Several papers have described the risk factors for ROP and have provided recommendations for the prevention of the disease.[7,8] The American Academy of Pediatrics, the American Academy of Ophthalmology and the American Association of Pediatric Ophthalmology and Strabismus have established the screening instructions that are currently used in neonatal intensive care units (NICUs).[9-12] According to these studies all preterm infants born at less than 30 weeks of gestation and/or with a birth weight less than 1500 g should undergo an indirect ophthalmoscopy of dilated eyes. The ophthalmoscopy should start from the 31st week of post conceptional age or from the 28th day of life. The CRYO-ROP report has defined the criteria of the "threshold ROP"; the ETROP data, published in December 2003, demonstrated a benefit of earlier treatment compared with conventional management; babies who meet ETROP criteria should be considered eligible for surgical treatment (cryo-therapy, argon or diode laser-therapy).[12,13]

The aim of our prospective multicenter cohort study is to investigate the incidence and the relative risk factors of ROP and P-ROP, the incidence of surgical treatment and to evaluate the short-term outcome of the disease in Italy.

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[Borroni et al.: Survey on retinopathy of prematurity (ROP) in Italy. Italian Journal of Pediatrics 2013 39:43.]

Table 1 Population characteristics

Parameters	N° of newborns	%	Parameters	N° of newborns	%
GA (weeks)			RDS	384	99.7%
22–23 - 24	92	22.6%	PDA	251	65.0%
25	102	24.2%	IVH	167	43.5%
26	134	31.8%	LPV	99	26.7%
≥ 27	90	21.4%	Fungal Sepsis	46	11.4%
			Bacterial Sepsis	178	44.2%
BW (g)			BPD	208	54.9%
300–450	9	2.1%	Blood transfusions	357	89.9%
451–600	70	16.6%	EPO therapy	210	55.6%
601–750	167	39.7%	Mechanical ventilation (> 7 days)	258	69.2%
> 750	175	41.6%	NPT (> 7 days)	303	80.6%
Male	182	45.5%	ROP	265	62.9%
Inborn	358	88.0%	P - ROP	102	24.2%
APGAR score 5th minute ≤ 7	176	47.7%	Preplus disease	55	13.1%
PROM	122	31.9%	Plus disease	79	18.8%
Chorioamnionitis	93	27.8%	Laser treatment	89	21.1%
Antenatal steroids	331	84.0%	Adverse outcome	14	3.3%

Methods

This study, promoted by the "Italian ROP study group," involved a cohort of infants born between January 1st 2008 and December 31st 2009 with a birth weight (BW) ≤ 750 g and/or a gestational age (GA) ≤27 weeks, in 25 III level Italian NICUs. Gestational age was confirmed by fetal ultrasound. In order to reduce differences in the neonatal assistance, the newborns admitted to the III level NICUs 6 hours following birth were excluded; newborns who died before discharge and newborns affected by major congenital malformations were also excluded.

The following data for each infants were recorded on a specific database: gender, race, premature rupture of membranes, chorioamnionitis, use of prenatal steroids, place of birth (inborn or outborn), fifth minute Apgar score, days of mechanical ventilation, days of parenteral nutrition, doses of erythropoietin (EPO) and blood transfusions.

The following complications of preterm birth were registered:
- intraventricular hemorrhage (IVH): any grade according to the Volpe classification[14]
- periventricular leukomalacia (PVL): evaluated at any age by ultrasounds (cystic periventricular white matter lesions) or by Magnetic Resonance Imaging (periventricular high-intensity areas on T2-weighted images and atrophy of the cerebral white matter predominantly at the peritrigonal region)
- respiratory distress syndrome (RDS): oxygen requirement increasing during the first 24 hours, typical radiological pattern such as reduced air content, reticulogranular pattern of the lung air and bronchogram
- patent ductus arteriosus (PDA): clinical evidence of left to right PDA shunt or ecocolorDoppler evidence of PDA with evidence of left to right ductal shunting
- early or late onset sepsis:
  - early: bacterial and/or fungal infections, diagnosed by means of a positive culture of blood and/or cerebrospinal fluid, within the first three days of life,
  - late sepsis: if diagnosed, after the third day of life
- moderate or severe BPD, in accordance with the definition of Jobe and Bancalari[15]
  - moderate BPD is determined as the need for < 30% oxygen at 36 week postmenstrual age (PMA) or discharge whichever comes first
  - severe BPD is determined as the need for ≥ 30% oxygen and/or positive pressure (NCPAP or IPPV) at 36 week PMA or discharge whichever comes first

This is a prospective non-interventional survey; the participating neonatal intensive care unit assisted the newborns in accordance with their own protocols; therefore the management and the care of the patients in each center varied one from the other.

Only the eye examinations were standardized: all the participating centers have a staff of pediatric ophthalmologists. Following pupil dilation with cyclopentolate hydrochloride 0.2% and phenylephrine hydrochloride 1%, pediatric ophthalmologists performed indirect ophthalmoscopies using scleral depression, if required, to visualize the retinal periphery, at weekly intervals, starting from the 4th week of life until complete retinal vascularization occurred.[12]

Ophthalmologists diagnosed ROP according to the ICROP report and classified the severity of ROP on the basis of:
Zone:
- Posterior: ROP in Zone I and posterior Zone II (P-ROP)[16]
- other zones: ROP in other Zones (OZ-ROP)

Presence of pre-plus (p-PD) or plus disease (PD):[12] The classification based on Zone and on the presence of plus or pre-plus disease was chosen in order to reduce the variability in the classification of ROP among the various centers participating in the trial.

In case of surgical intervention, ophthalmologists reported the type of intervention carried out (laser therapy, cryotherapy) and the number of ablative surgical treatments performed.

Table 2 Association between ROP and neonatal parameters: logistic univariate analysis

Parameters	ROP	No ROP	Univariate analysis	
	n newborns (%)		OR	p-value
GA ≤ 24 weeks	71 (75%)	24 (25%)	2.01	0.008
BW ≤ 750 g	168 (68%)	78 (32%)	1.73	0.007
Male gender	111 (45%)	71 (46%)	0.96	0.848
Inborn	217 (86%)	141 (90%)	0.68	0.238
APGAR score 5th minute ≤ 7	125 (56%)	72 (49%)	1.31	0.205
PROM	78 (34%)	44 (29%)	1.22	0.380
Chorioamnionitis	60 (31%)	33 (23%)	1.47	0.130
Antenatal steroids	198 (81%)	133 (88%)	0.59	0.085
RDS	234 (100%)	150 (100%)	Not applicable	
PDA	167 (66%)	84 (34%)	1.96	0.002
IVH	118 (71%)	49 (29%)	2.10	0.001
LPV	44 (19%)	55 (38%)	1.22	0.543
Sepsis	134 (70%)	57 (30%)	2.02	0.001
BPD	142 (61%)	66 (45%)	1.94	0.002
Blood transfusions	217 (90%)	140 (90%)	0.93	0.833
EPO therapy	147 (70%)	63 (30%)	2.39	< 0.0001
Mechanical ventilation (>7 days)	157 (71%)	101 (67%)	1.20	0.432
NPT (> 7 days)	185 (83%)	118 (78%)	1.37	0.234

The outcome was defined "adverse" if total or partial retinal detachment or macular fold occurred, while normal anatomy (no detachment or macular fold) was defined as "a favorable outcome."

Univariate and multivariate logistic regression models were used to estimate the odds ratios (ORs) and the p-values for the association between ROP and the clinical parameters of the patients. Initially, the models were used to evaluate the independent predicting factors for developing ROP of any stage; the independent parameters associated with the evolution of the disease were also studied. Moreover, ORs were used to describe the characteristics of the infants that were candidates for the laser treatment. Sample size was calculated to detect a difference equal or greater than 15% in relative frequencies of different groups, with 5% significance level and a power of 80%.

A P value <0.05 was considered significant. All statistical analysis was performed with Stata software 9.0 (Stata Corporation, 1999, Texas).

Table 3 Association between ROP and neonatal parameters: logistic multivariate analysis

Parameters	ROP	No ROP	Multivariate analysis	
	n newborns (%)		OR	p-value
GA ≤ 24 weeks	71 (75%)	24 (25%)	1.58	0.147
BW ≤ 750 g	168 (68%)	78 (32%)	1.63	0.053
PDA	167 (66%)	84 (34%)	1.21	0.455
IVH	118 (71%)	49 (29%)	2.10	0.003
Sepsis	134 (70%)	57 (30%)	1.43	0.135
BPD	142 (68%)	66 (32%)	1.32	0.249
EPO	147 (70%)	63 (30%)	2.93	< 0.0001

Results

The study involved 421 VPI; the spreadsheets were not completed in full for each newborn, with a rate of incompleteness for each parameter between 4% and 15%. Birth weight, gestational age and ROP description were considered mandatory, moreover newborns with more than 10% missing data were not included in the sample. Table 1 shows the distribution of birth weight and gestational age, and the clinical features of the study population.

All infants underwent the eye examinations in accordance with the guidelines. Ophthalmological screening was started at an average of 30 weeks of postmenstrual age. ROP was diagnosed in 265 newborns (62.9%). At the univariate analysis (Table 2) GA (p = 0.008), BW (p = 0.007), PDA (p =0.002), IVH (p = 0.001), early and late onset sepsis (p = 0.001), BPD (p = 0.002) and EPO therapy (p < 0.001), showed a significant association with the occurrence of ROP.

Following the multivariate analysis only EPO-therapy (p < 0.0001) and IVH (p = 0.003) were significantly associated with ROP (Table 3). P-ROP was diagnosed in 102 cases (24.2%); the ROP Zone was not reported in 10 cases; 7 of these infants underwent surgical treatment and all of them had a favorable outcome (Figure 1).

Gestational age (p = 0.002), sepsis (p = 0.002) and BPD (p = 0.02) were significantly associated with P-ROP. At the multivariate analysis, gestational age ≤ 24 weeks (p = 0.011) and sepsis (p =0.002) appeared to be independent factors leading to P-ROP (Table 4). PD was diagnosed in 79 newborns; 56 of them were affected by P-ROP (55%) and 19 were affected by OZ-ROP, (in 4 infants ROP Zone was not reported) (Figure 1). p-PD was diagnosed in 17 newborns with P-ROP, in 33 infants with OZ-ROP and in 5 patients the zone of ROP was unknown (Figure 1). These differences were statistically significant (p < 0.0001).

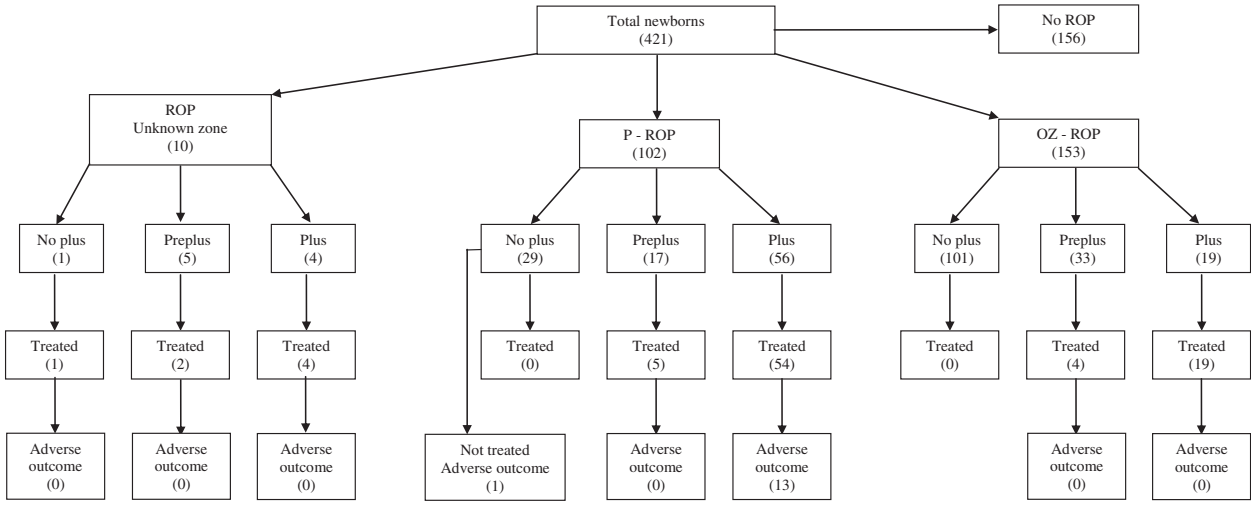

Figure 1 Outcomes of the enrolled newborns.

Eighty-nine infants underwent surgery (34% of the 265 newborns with ROP); 59 of them (66.3%) showed a P-ROP and 23 (25.8%) an OZ-ROP (Figure 1). This difference was statistically significant ($p < 0.0001$).

Zone of ROP, gestational age, birth weight and sepsis were significantly associated with need of surgery at the univariate analysis; following the multivariate analysis only P-ROP was an independent factor associated with the need for surgical treatment ($p < 0.0001$). Birth weight below 750 g showed a borderline significance ($p = 0.054$), while gestational age ($p = 0.946$) and sepsis ($p = 0.188$) were not statistically related to the requirement of laser therapy. The use of EPO was not associated with surgical treatment: 54% of the surgically treated infants and 68.2% of the non-treated infants received EPO.

PD was diagnosed in 87.5% of the surgically treated infants and p-PD in 12.5% of cases. None of the newborns without PD or p-PD underwent surgery. One hundred seventy newborns with ROP were not surgically treated: PD was diagnosed in only 2 and p-PD in 41 (21.1%)(Figure 1).

Ophthalmologists performed surgical therapy between the 32nd and 34th weeks of gestation: laser-therapy, argon laser 532 nm or diode laser 810 nm, and cryotherapy. In all cases the laser-therapy was performed; in 8 cases cryotherapy was attempted as additional treatment. Four newborns with P-ROP required vitrectomy following laser and cryotherapy (1.5% of all newborn with ROP). All patients showed P-ROP in Zone 1. The outcome was evaluated as favorable in 251 non-treated infants (94%) and in 68 (86.7%) of surgically treated infants. Adverse outcomes occurred in 14 patients (3.3% of total population, 5.3% of infants with ROP and 14.6% of surgically treated infants): 11 had bilateral and 3 unilateral retinal detachment. All 14 had P-ROP and underwent surgery (Figure 1).

Discussion

ROP widely affected extremely premature infants: the occurrence of P-ROP represented the main risk factor for surgical treatment. A considerable number of newborns required surgery; laser therapy was mostly effective and adverse outcomes were rare.

Our incidence data differ from those of the Cryotherapy for Retinopathy of Prematurity Cooperative Group trial and from those of the ETROP study;[9,17] these studies reported a higher incidence of ROP but they were conducted prior to the introduction of the current guidelines to prevent ROP.[18]

Table 4 Association between P-ROP or treated newborn and neonatal parameters: logistic univariate and multivariate analysis

Parameters	P - ROP	OZ - ROP	Univariate analysis		Multivariate analysis	
	n newborns (%)		OR	p-value	OR	p-value
GA ≤ 24 weeks	37/71 (52.1%)	29/71 (40.8%)	2.43	0.002	2.30	0.011
Sepsis	60/134 (44.8%)	68/134 (50.7%)	2.35	0.002	2.64	0.002
BPD	57/142 (40.1%)	79/142 (55.6%)	2.01	0.020	1.53	0.182
Association between zones and significant neonatal parameters: univariate and multivariate logistic analysis						
Parameters	**Treatment**	**No treatment**	**Univariate analysis**		**Multivariate analysis**	
	n newborns (%)		**OR**	**p-value**	**OR**	**p-value**
P - ROP	59/89 (66.3%)	35/142 (24.6%)	7.84	< 0.0001	7.30	< 0.0001
EG ≤24 weeks	33/89 (37.1%)	33/142 (23.2%)	1.95	0.024	0.97	0.946
BW ≤ 750 g	69/89 (77.5%)	79/142 (55.6%)	2.75	0.001	2.07	0.054
Sepsis	54/89 (60.7%)	61/142 (42.9%)	2.36	0.003	1.58	0.188
Association between laser treatment and significant neonatal parameters: univariate and multivariate logistic analysis						

Other studies showed results similar to ours.[19-21] The 2009 Vermont-Oxford Network Report showed an incidence of ROP superimposable on our results.[22]

In the multivariate analysis EPO therapy and IVH significantly associated with the incidence of ROP; birth weight showed only a borderline association. EPO therapy was a risk factor for ROP, but not for P-ROP. Shah et al did not find any significant difference between EPO therapy and the presence or severity of ROP.[23] Before the "EPO era," blood transfusions were more common in NICUs and some researchers considered them as a risk factor for developing ROP.[24,25] Suk et al in a multiple regression model found that blood transfusions were a significant independent risk factor for the development of ROP. Currently it is not clear if the therapy with EPO is advantageous compared to the blood transfusions in treating anemic preterm infants.[26] Schneider et al. showed that EPO therapy does not increase the number and the severity of ROP cases, while it may reduce the number of blood transfusions.[27] Recently, in a mouse model of proliferative retinopathy, Chen et al. studied the role of EPO in suppression of retinal neovascularization; they proposed the hypothetic intravitreal use of EPO in proliferative retinopathy.[28]

In our study EPO administration was a factor involved in the development of ROP, while it was not a factor related to the severity of the disease: it was not significantly associated to P-ROP and to the necessity of surgical intervention. GA ≤ 24 weeks and sepsis were significant risk factors for developing P-ROP. Even though gestational age was not directly related to the ROP, it triggered P-ROP and therefore was one of the main causes of the more severe type of the disease.[29]

It is noteworthy that BPD was not associated with the ROP, nor with the more aggressive kind of ROP, even though the use of oxygen is particularly involved in ROP pathogenesis. This may arise from the use of more accurate targets of oxygen saturation during oxygen-therapy, both in the first weeks of life, when hyperoxia is dangerous, and also during the following weeks, when hypoxia induces neovascularization. Some authors recommend monitoring oxygen therapy on the basis of gestational age and postnatal age: low-oxygen levels during early phases of life and high levels in the later phases.[30]

Our data on the risk factors for P-ROP are consistent with the pathogenetic model recently proposed by Lee and Damman: in their review they concluded that exposure to perinatal infection/inflammation is associated with an increased risk for ROP. Circulating products of infection and/or inflammation might directly damage the developing retina; moreover inflammation and/or oxidative stress might increase the risk of oxygen-associated ROP. This means that prenatal, perinatal, and postnatal systemic inflammation could sensitize the pre-ROP retina for subsequent results, setting the stage for what is now called phase I and phase II of ROP pathogenesis. The authors concluded that strategies for targeting inflammatory responses might help in reducing the risk for ROP in extremely preterm infants.[31]

In our study laser therapy was performed in all infants requiring surgery; most of these infants had a P-ROP. PD represented the main indicator for surgical intervention as also reported in the ICROP study.[11]

In almost all cases, the infants with ROP associated with PD underwent surgical intervention; only 2 out of 75 newborns with PD were not treated with laser therapy. Moreover, occurrence of p-PD represented an indication for surgical intervention; although it was more evident in the newborns affected by P-ROP than in OZ-ROP there was probably an overtreatment in some cases. PD was significantly higher in P-ROP than in OZ-ROP; therefore infants with P-ROP underwent surgery more frequently than infants with OZ-ROP. These observations confirm the severity of P-ROP.

The percentage of children treated with laser therapy in our population was equal to the percentage reported in a Malaysian study and double the number reported in a Swedish paper.[20,21] This variability of data may be due to the differences of the populations involved. As Darlow et al in the Australian and New Zealand Neonatal Network argued, the discrepancy between the data reported in scientific literature may be attributed to a wide variability in the classification of ROP.[32] For this reason we classified the severity of ROP on the basis of zone and presence of PD or p-PD. Our protocol allowed us to classify ROP disease more clearly without the inter-individual differences of ophthalmologists.

Treatment was performed between the 32nd and the 34th weeks of gestation. The majority of surgically treated infants had a favorable outcome; this is encouraging even though Ruth Axer-Siegel and coll. reported 92.3% favorable outcomes following laser therapy in a cohort of 100 neonates, which is slightly better than our data.[33] It is important to underline that all 14 infants with an adverse outcome were ≤24 weeks gestation, each one underwent almost one episode of sepsis and was affected by P-ROP: this confirms once more that P-ROP represents the most severe form of ROP and it is associated with the worst short term outcome.

Conclusion

In order to prevent severe ROP in very preterm infants, a multidisciplinary strategy is necessary: obstetricians should prevent preterm births and intrauterine infections; neonatologists should reduce the occurrence of septic diseases and should carefully monitor infant oxygen exposure. In all NICUs, a pediatric ophthalmologist should periodically evaluate all very preterm infants from the 28th day of postnatal age. The follow-up of infants with Zone I and Zone II posterior ROP needs to be particularly scrupulous since these infants are at high risk of surgical intervention and adverse outcome.

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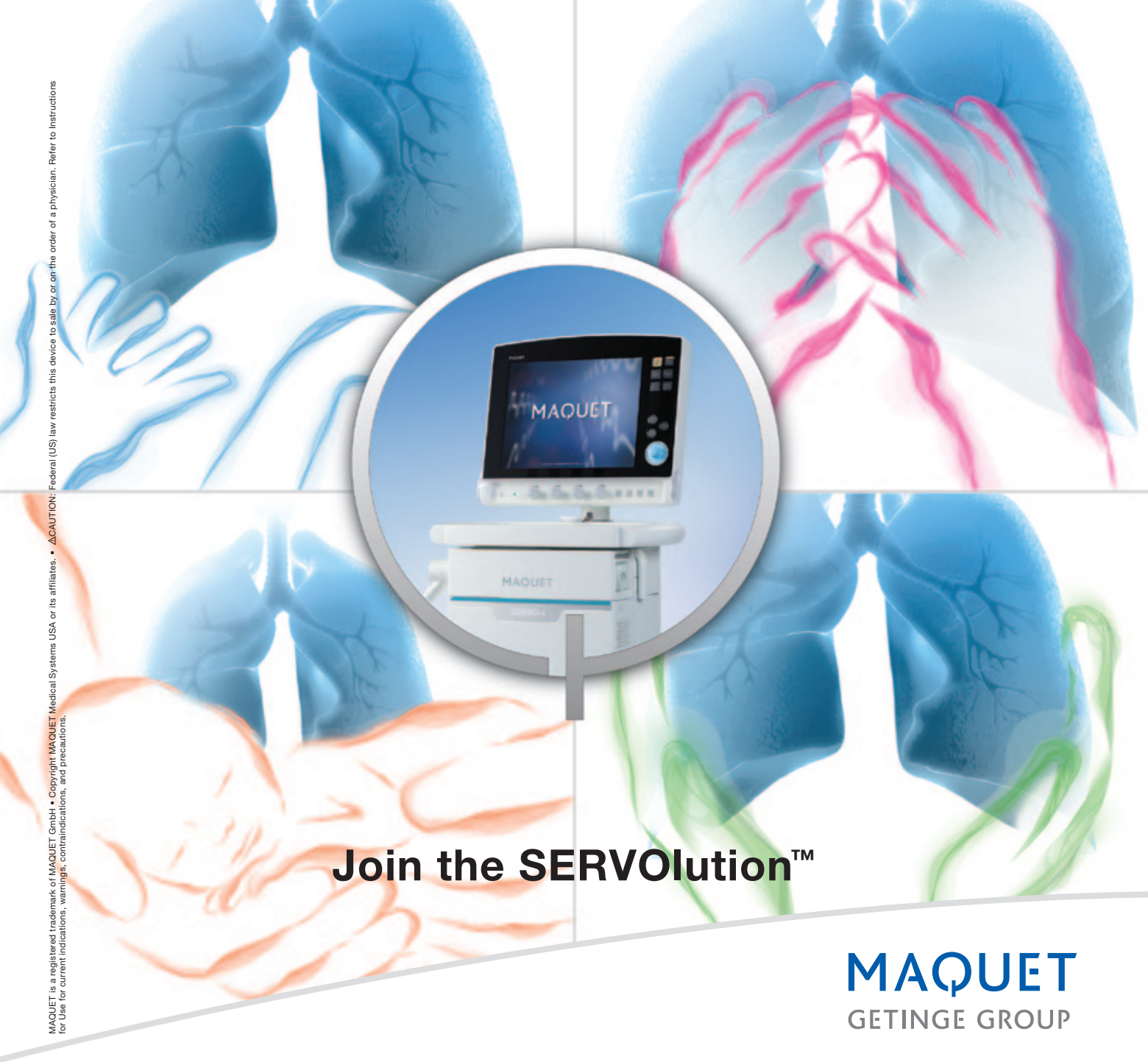

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