TREATMENT STRATEGIES
PAEDIATRICS

Volume 3 Issue 1

- **Asthma**
- **Haematological Disorders**
- **Pain Management**
- **Premature Infancy**
- **Respiratory**

Articles include:

New Trends in Surfactant Replacement Therapy in Premature Infants with Respiratory Distress Syndrome

Update on Non-invasive Respiratory Support (NRS) in Children with Acute Respiratory Failure

Treatment of Asthma in Children

Red Blood Cell Transfusion Therapy in Critically Ill Children

Current Practice Guidelines for Procedural Sedation, Pain Management and Anaesthesia in the Paediatric Intensive Care Unit

Metabolic Outcomes of Adults Born Preterm

Includes a review of the 4th Congress of the EAPS and National Conference of the AAP

The hydrolysate in NAN H.A. has been providing scientically proven protection against allergies for 25 years

NAN H.A. 25 years experience in allergy prevention

- Extensively clinically tested and reduces the risk of atopic dermatitis in the first year of life by up to 50 %
- Protective effect confirmed until the age of 6 years
- Protective effect confirmed by the GINI study, 2 meta-analyses and further clinical studies
- Good acceptance due to less bitter taste*

IMPORTANT NOTICE: The World Health Organisation (WHO*) has recommended that pregnant women and new mothers be informed on the beneits and superiority of breast-feeding – in particular the fact that it provides the best nutrition and protection from illness for babies.

Mothers should be given guidance on the preparation for, and maintenance of lactation, with special emphasis on the importance of a well-balanced diet both during pregnancy and after delivery. Unnecessary introduction of partial bottle-feeding or other foods and drinks should be discouraged since it will have a negative effect on breast-feeding. Similarly, mothers should be warned of the difficulty of reversing a decision not to breast-feed.

Before advising a mother to use an infant formula, she should be advised of the social and financial implications of her decisionzfor example, if a baby is exclusively bottle-fed, more that one can (450 g) per week will be needed, so the family circumstances and costs should be kept in mind. Mothers should be reminded that breast-milk is not only the best, but also the most economical food for babies.

If a decision to use an infant formula is taken, it is important to give instructions on correct preparation methods, emphasizing that unboiled water, unsterilized bottles or incorrect dilution can all lead to illness.

* See: International Code of Marketing of Breast Milk Substitutes, adopted by the World Health Assembly in Resolution WHA 34.22, May 1981.

Infant starter formula should only be given following advice from independent experts. Advise parents regarding formulapreparation taking into account the instructions on the packaging. Incorrect preparation of infant starter formulas can lead to adverse health effects.

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Active allergy prevention

TREATMENT STRATEGIES PAEDIATRICS

Treatment Strategies - Diabetes
The Cambridge Research Centre
Coppergate House
16 Brune Street
London
E1 7NJ

Editorial Assistant **Lauran Elsden**
lauran.elsden@treatmentstrategies.co.uk
Editorial Assistant **Hannah Corby**
hannah.corby@treatmentstrategies.co.uk
Business Development **Daniel Healy**
dan@treatmentstrategies.co.uk
Director **Spencer Gore**
spencer@thecambridgeresearchcentre.co.uk
Director **Nigel Lloyd**
nigel@treatmentstrategies.co.uk

Published by The Cambridge Research Centre
info@thecambridgeresearchcentre.co.uk
www.thecambridgeresearchcentre.co.uk
T: +44 (0) 20 7953 8490

Printed by Printech (Europe) Limited

Welcome...

I am very pleased to welcome you to the third edition of *Treatment Strategies – Paediatrics*. This edition of *Treatment Strategies – Paediatrics* includes an independent review of the 4th Congress of the European Academy of Paediatric Societies (EAPS) which took place in Istanbul and the American Association of Pediatrics (AAP) National Conference and Exhibition which was held in New Orleans. At both Congresses, paediatricians from across the globe gathered to examine new technologies and network with like-minded individuals on topics of interest.

This year's EAPS Congress was committed to providing an opportunity for participants to interact and to discuss current and future issues related to paediatrics so that all can learn from the opportunity. It attracted 3,000 prominent experts from around the world, with a goal to advance research and promote the exchange of ideas whilst collaborating across the various fields of paediatrics. The EAPS is the prime meeting platform for the profession.

The American Association of Pediatrics (AAP) National Conference and Exhibition presented the latest clinical data in all areas of paediatrics, with major sessions including Obesity Prevention and Treatment, Bariatric Surgery, the Paediatrician's Role in Promoting Active Commuting for Children and Paediatric Dentistry and Oral Health to name a few. The Congress drew attendees from right across the medical spectrum and indeed the globe, creating a unique and diverse audience.

We hope that this publication will be useful for the readers and especially those involved with ESPNIC, ESPR, EAP and AAP. We hope that the publication and dedicated website acts as a forum for you to present and share your findings and ideas. Our content is continually being updated and the eBook format is constantly evolving to endeavour to become your number one online resource in the field of paediatrics.

Following on from previous successful events, we very much look forward to meeting you again next year at the Annual Congress of the European Society for Paediatric Research (ESPR) in Porto, Portugal, where the three societies, ESPNIC, ESPR and EAP join forces to produce one truly magnificent Congress.

Nigel Lloyd, Editorial Director

The Cambridge Research Centre wishes to thank the following societies for their assistance and involvement in this publication.

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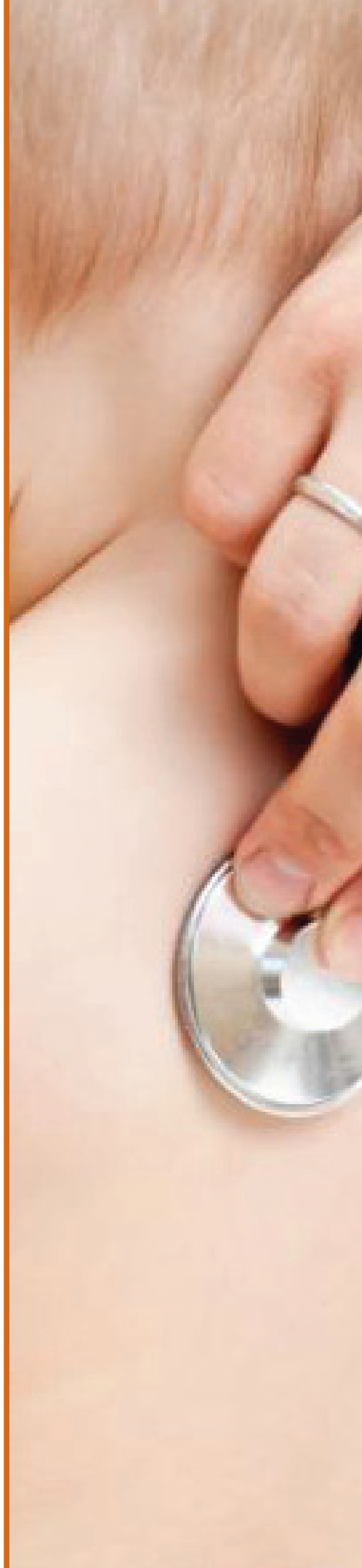

EDITORIAL ADVISORY PANEL

Foreword

Deniz Ertem
Marmara University School of Medicine, Department of Paediatric, Division of Paediatric Gastroenterology, Hepatology and Nutrition, Istanbul

Proper nutrition is integral for disease prevention as well as a treatment startegy *per se*, particularly in childhood. Childhood malnutrition (both under-nutrition and over-nutrition) adversely affects the overall lifelong health of individuals by affecting growth and development. Globally, malnutrition contributes to more than half of the deaths in children younger than five years of age, and is associated with a predisposition to infections, short stature and reduced cognitive capacity. Obesity which is the other extreme point of malnutrition is increasing in prevalence and is directly correlated with heart diseases, diabetes, metabolic syndrome, liver disease, and cancer.

There is a discrepancy between the demand for nutrition counselling and actual physician practice. In adult practice, only one-third of the physicians routinely discussed nutrition with their patients when they were dealing with chronic diseases. In spite of these good intentions, most of the physicians and paediatricians do not feel adequately equipped to deal with nutritional problems in chronic diseases and obese patients.

Surveys regarding the continuing medical education in nutrition have shown that interest and perceived relevance of nutrition declines throughout medical school and it extends into clinical practice as well. Hence, a renewed emphasis on nutrition education and a more comprehensive curriculum, integrating nutrition education into medical training needs to be done. Although perception of the importance of nutrition in preventing disease is satisfactory among paediatricians, inability to address nutritional requirements during the life cycle, inadequate knowledge regarding the role of diet in chronic diseases, and special feeding requirements in certain conditions are the major concerns.
It seems that insufficient time dedication, not only to nutriton training, but also to the practice of nutrition in clinical settings, are the main obstacles.

Treatment Strategies – Paediatrics is an important source and open access for providing up-to-date knowledge on a variety of topics concerning paediatrics. I hope I have raised awareness on the issues concerning basic nutrition which can include nutritional requirements, the assessment of nutrition in clinical setting, and advanced topics on nutrition such as nutritional therapy of diseases such as Crohn's disease, glycogen storage diseases, obesity, and diabetes. These issues will be a primary feature of the next edition to provide enlightment on this basic and very important subject to paediatricans.

The publication also offers extensive reviews of both the 4th Congress European Association of Paediatric Societies, held this year in Istanbul and the American Association of Pediatrics National Conference and Exhibition, which was held in New Orleans.

We do hope you will thoroughly enjoy the latest edition of *Treatment Strategies - Paediatrics* that we have put together and the papers we have carefully selected. Paediatrics continues to be one of the most rewarding areas of medicine, with advancements and developments being made on regularly. We hope that the publication gives an in-depth overview of some of the most interesting and important topics within the field today.

Deniz Ertem is a graduate of Marmara University School of Medicine, and did her residency and fellowship in the same institution. She is currently Professor of paediatric gastroenterology and still working at Marmara University School of Medicine, division of Paediatric Gastroenterrology, Hepatology and Nutrition, in Istanbul, Turkey. Professor Ertem is also an active member of the European Society of Paediatric Gastroenterrology, Hepatology and Nutrition (ESPGHAN).

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TREATMENT STRATEGIES SERIES

www.treatmentstrategies.co.uk

EAPS 2012 Congress Review

05 - 09 October 2012 - Istanbul

4th Congress of the European Academy of Paediatric Societies

Lauran Elsden, *Treatment Strategies*, takes a look over a number of key sessions, as well as spotlighting several stands and products being demonstrated at the exhibition. We then follow with papers and reviews which give a brief insight from a number of sessions highlighting findings that will have direct repercussions on clinical practise that are still very much being discussed.

The 4th Congress of the EAPS builds on the success of the three previous congresses. The EAPS is a partnership between the European Academy of Paediatrics (EAP), the European Society for Paediatric and Neonatal Intensive Care (ESPNIC) and the European Society for Paediatric Research (ESPR).

EAP

Is the specialist section of paediatrics of the European Union of Medical Specialists (UEMS) of the member countries of the European Union (EU) and the European Free Trade Association (EFTA). It is governed by the provisions of these statutes, grouping together paediatricians without regard to their field, their mode of practice or their legal situation. The EAP exists to promote the health of children and young people in Europe. It aims to improve standards in training, service and research in the EU.
www.EAPaediatrics.eu

Introduction *continues on page R2*

Istanbul Congress Centre was the host to this year's exciting Congress.

INSIDE...

ESPNIC

The European Society of Paediatric and Neonatal Intensive Care (ESPNIC), is a non-for- profit organisation dedicated to the care of the critically ill children and newborns throughout Europe. The society is comprised of Nurses and Doctors who are committed to share knowledge and improve the quality of paediatric and neonatal intensive care at the European and international level, and devoted to highly promoting multidisciplinary collaboration among paediatric, neonatal and adult intensivists as we all as nurses and meeting the needs of members, giving them a voice within the European and international context. It aims to raise awareness and increase visibility and credibility in the field.

www.espnic.org

ESPR

The ESPR unifies paediatric research in Europe. Since 1958 it has evolved into the current dynamic grouping of researchers into childhood and its associated conditions, with a successful premier Journal. The Society now numbers about 500 members, mostly clinicians caring for children, oriented towards research aimed at improving the health of all children.

www.espr.info

The EAPS is committed to providing an opportunity for participants to interact and to discuss current and future issues related to paediatrics so that all can learn from the opportunity. It attracts 3,000 prominent experts from around the world, with a goal to advance research and promote the exchange of ideas whilst collaborating across the various fields of paediatrics. The EAPS is the prime meeting platform for the profession.

This year there were 8 State-of-the-Art Sessions in topics as diverse as: Epigenetics, Adolescent Health, Economics & Child Health, Child Physiology, Mental Health in Childhood, Nutrition & Diabetes, Childhood Environment and Genetics, including the prestigious IPRF plenary which brings distinguished scientists to the paediatric community, this year with the topic of Mirror Neurons in Autism and the Molecular Basis of the Master Clock. Attendees were presented with all the new emerging tools in studying health and disease such as optogenetics, the use of stem cells, but were also brought up-to-date on the role of environment in childhood health and disease and our understanding of the impact of health and disease on economic growth. The 2012 programme included sessions ranging from investigations at the bench, to advocacy and translation at the bedside, followed by outcome measures of interventions or changes in clinical practice from the newborn to the adolescent.

During its long history, Istanbul has served as the Capital of many empires, including the Roman Empire, Byzantine Empire and the Latin Empire. Located in the centre of the old world, this exotic city is famous for its historical monuments and scenic views. It is the only city in the world which spreads over two continents: Asia and Europe.

Istanbul is adorned with the masterpieces of Turkish art, the great mosques of the Sultans that crown the hills. The city presents an exquisite, majestic and serene silhouette from all directions. The Golden Horn, which is a very secure natural harbour, has played a significant role in the development of the city. The historic city of Istanbul is situated on a peninsula flanked on three sides by the Sea of Marmara, the Bosphorus and the Golden Horn.

While in Istanbul, you may want to discover the Grand Bazaar which is a teeming indoor maze of jewelry, carpets, leather, textiles, and antiques that dates back 500 years. Its sheer size—65 alleys and more than 4,000 shops—is not for the faint of heart. Get oriented by finding the Old Bedestan, the original marketplace, in the center of the bazaar, and remember that haggling is part of the culture.

The EAPS meeting is the largest of its kind in Europe and special efforts were made to make the format attractive for delegates who participated. Interactive sessions with topics presented as controversies, where participants were able to express their opinions, not only in discussions, but with voting systems, were amongst the congress' attractions.

There were also hands-on teaching workshops and of course the popular poster sessions and symposia to give as much exposure as possible to peers. For the first time the programme also featured topic related Symposia proposed directly by members, thus allowing the sharing of experiences in research and clinical care. The programme was organised in specific tracks and included a specific nursing care oriented track and master classes.

EAPS Satellite Symposium Overview:

Fever and Pain Management in Children - New Objectives in Diagnosis and Treatment

On Sunday 7 October, from 13:30 to 14:30 the satellite symposium *Fever and Pain Management in Children - New Objectives in Diagnosis and Treatment* was presented, starting with a welcome from chairperson, Holger Lode of the Ernst Moritz Arndt University of Greifswald, Germany. Prof. Dr. Lode addressed his colleagues on a topic that is of particular importance to medical professionals in the paediatric area. Febrile illness in young children indicates an underlying infection and is often a cause of concern for parents and carers. Consequently, fever is one of the most common reasons for a child to be taken to the doctor and is the second most common reason for a child to be admitted to the hospital.

The challenge of healthcare professionals is to identify patients whose elevated temperature indicates a severe bacterial infection with potential life-threatening consequences such as pneumonia or meningitis. However, in most cases, the illness is due to a self-limiting viral infection, and a significant number of children have no obvious cause of fever despite careful assessment. These children are of particular concern because it is especially difficult to distinguish between simple viral illnesses and life-threatening bacterial infections in this group. Guidelines based on age, clinical signs and symptoms using a diagnostic tool known as the 'traffic light system' are helpful to improve the recognition, assessment and immediate treatment of patients at risk of severe bacterial infection.

Dr. Edward Prussell of Kings College London, UK, presented his session *Antipyrectic Therapy: Maximising Comfort while Supporting Recovery* which aimed to review recommendations that antipyretic therapy should be used to maximise comfort in febrile children. This can be done by reviewing these recommendations, considering what is meant by the term 'comfort' ad discussing the risks and benefits of antipyretic use. Prof. Dr. Rimantas Kevalas of Kaunas University Clinic, Lithuania, regarded the usefulness of guidelines based on care reports in his session *Paediatric Fever and Pain Management: The Usefulness of Guidelines Based on Case Reports*. He concluded that the purpose of implementing pain-assessment and management guidelines if to provide for the comfort of a children, regardless of whether they are cared for in the emergency setting or in other environments.

The satellite symposium was sponsored by Berlin-Chemie. Berlin-Chemie is a German subsidiary of the Menarini Group, which has been occupying a leading position in the Italian pharmaceutical market for many years. The company, which was formed in 1886, is headquartered in Florence, Italy. Menarini pursues two strategic objectives: research and internationalisation. Both endeavours enable innovative products to be used successfully to the satisfaction of patients throughout the world. The Menarini Group enjoys an outstanding reputation worldwide as an efficient and reliable partner. This applies both to the development of new drugs and to the communication of scientific insights.

Fever is one of the most common reasons for a child to be taken to the doctor and is the second most common reason for a child to be admitted to the hospital.

Prof. Dr. Holger Lode, Chairperson of the EAPS Satellite Symposium

For more information, please visit www.berlin-chemie.com

Uscom Exhibit USCOM 1A: Hemodynamic Monitor

Uscom exhibited at the European Academy of Pediatrics (EAPS) this year held in Istanbul October 2012. There was a tremendous interest from the attendees for the monitoring of stroke volume and cardiac output in both neonatal and pediatric patients. Uscom was represented by Mesut Ugur from Beymed, their Turkish distributor.

Attendees visiting the USCOM booth came from over 20 different countries. All were offered the opportunity to experience the USCOM first-hand and have their flow hemodynamics measured non-invasively.

USCOM 1A: Hemodynamic Monitor
USCOM is a specialised ultrasound device designed for non invasive, high fidelity measurement of cardiovascular function. These measurements can be used to assess and manage hemodynamics. USCOM is a safe, rapid, accurate and cost effective method for managing circulation. USCOM takes advanced hemodynamics beyond the ICU.

The USCOM 1A offers real-time, beat-to-beat measurements of 20 parameters of cardiovascular function including cardiac output, stroke volume and systemic vascular resistance with additional parameters such as cardiac power, stroke work and oxygen delivery.

The USCOM 1A is unique in being completely non-invasive, validated across a wide range of cardiac outputs in neonates, infants, children and adults, and is soundly patent protected. USCOM provides many benefits to patients, which include:

→Non invasive and safe
→All ages and all outputs - neonates to geriatrics from 0.12l/min to 18.5l/min
→Most accurate clinical method of monitoring hemodynamics
→Right and left sided Cardiac Output
→Easy to use - Physician, nurse, paramedic or patient operated
→Advanced hemodynamics in or beyond the ICU
→Real time Stroke Volume resuscitation
→Improves management - objective Early Goal Directed Therapy
→Reduces time and cost
→Many clinical uses - anywhere you'd take a blood pressure
→Simple and quick to set up
→Portable

USCOM uses specialised Doppler Ultrasound for measuring and monitoring hemodynamics. It provides non invasive, accurate, real time, beat to beat, quantitative measures of cardiovascular function.

Uscom Ltd is an Australian medical device company focused on non-invasive, high fidelity measurement of cardiovascular function. These measurements can be used to assess and manage hemodynamics. Optimising circulation saves lives. USCOM provides for safe, rapid, accurate and cost effective optimisation of circulation. USCOM takes advanced hemodynamics beyond the ICU.

For more information, please visit www.uscom.com

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Infatrini is a Food for Special Medical Purposes for use under medical supervision, after full consideration of all the feeding options, including breastfeeding. Infatrini is a nutritionally complete, energy dense, ready to use feed for the dietary management of infants (from birth up to 18 months or 9kg in body weight) with faltering growth, or who have increased nutritional requirements and/or require fluid restriction.

Atom Medical Corporation Showcase Latest Generation of Infant Incubator - The Dual Incu i

At this year's EAPS Atom Medical Corporation showcased their latest generation of infant incubator, the Dual Incu i. The new generation infant incubator has inherited the highest quality features and state-of-the-art technology, meeting the various requirements of the healthcare professional. The Dual Incu i can perform in a wider range of hospital settings through the incubator mode and the infant warmer mode. There are many benefits associated with the new infant incubator which include:

The Dual Incu i: Incubator mode (L) and Infant Warmer mode (R).

→Open care
Superior performance as an infant warmer enables better medical treatment.

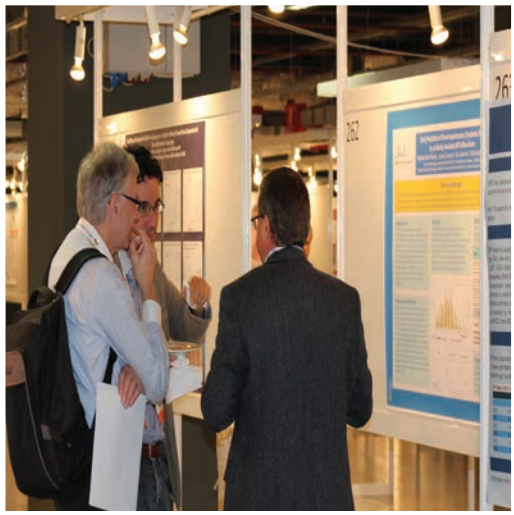
→Transport
The same environment in the NICU can be provided even during the transportation.

→Closed-care
The Dual Incu i reduces the infant's stress and supports daily care giving.

→Developmental care
The Dual Incu i ensures noise levels are kept to a minimum, maintaining a quiet environment to minimise the infant's stress.

Ever since the founding of the company, Atom Medical Corporation has been focused on observing and supporting the birth of obstetrics and gynecology in medical care for neonatal and premature babies.

For more information on the Dual Incu i, please visit www.atom-ami.co.jp



25 Years of Scientific Research Confirm the Effectiveness of NAN HA

More than 15 clinical studies and 3 meta-analyses have scientifically proven: NAN HA reduces the risk of atopic dermatitis in the first year of life by 50% in non-breastfeeding infants with a positive family history for allergy. The protective effect remains significant at the age of 6 years. When developing NAN HA 25 years ago, allergy prevention through the development of oral tolerance was already at the heart of the project.

Breastfeeding provides infant with the best nutrition and is the best and easiest way to prevent the early massive exposure of infants to potential food allergens. But how to avoid a massive exposure to allergens when there is no, or not enough breast milk? Dietary protein is vital. Even though extensive hydrolysates were available for the dietary treatment of infants with cow's milk allergy 25 years ago, they were not an option for generalised use as a preventative measure due to their high manufacturing costs and bitter taste.

Scientists at the Nestle Research Centre developed a new type of hyrolysate: a partial whey hydrolysate. The lesser degree of hydrolysis ensured a better taste and reduced the cost of production. This new type of hydrolysate thereby fulfilled the conditions for a generalised use as a preventative measure.

The results of the German Infant Nutritional Intervention (GINI) Study, the world's largest allergy prevention study with more than 2,000 newborns with familial risk of allergy showed that Nestles partial whey hyrolysate (NAN HA) significantly reduced the risk of atopic dermatitis from birth to 1 year of age and from birth to 3 years of age compared to a standard infant formula.

NAN HA is now not only the best-tested but also the best-tasting hydrolysate on the market. Their process of hydrolysis itself, has remained unchanged since the launch of HAN HA in 1987, as they feel it cannot be improved!

For more information, please visit www.nestlebaby.com

New Technologies Help Raise Awareness of the Niemann-Pick type C disease (NP-C)

This year's EAPS Congress provided a valuable opportunity to raise awareness of the rare inherited disease, Niemann-Pick type C disease (NP-C), which is predominately found to affect children and adolescents. NP-C is a neurovisceral lysosomal lipid storage disorder. It has a broad clinical spectrum that ranges from a rapidly fatal disorder in neonates, to an adult onset chronic neurodegenerative disease.

Presentation of NP-C symptoms consists of a mix of visceral, neurological, and psychiatric symptoms including prolonged unexplained neonatal jaundice/cholestasis, vertical supranuclear gaze palsy, clumsiness, limb and gait ataxia, dysarthria, dysphagia and cognitive decline or dementia.2 Gradual deterioration is observed in daily activities such as walking, talking, swallowing and manipulation, leading to patients being unable to interact with their environment.

NP-C is an autosomal recessive rare genetic disease with an estimated incidence of 1:120,000 live births. The general awareness of this disease is quite low. Because of its extremely heterogeneous clinical presentation characterised by a wide range of non-specific symptoms, the diagnosis is complicated and is likely to be an important factor in the under-detection of NP-C and in some cases, its misdiagnosis.

The prognosis of NP-C disease is strongly influenced by the age of onset of the neurological manifestations. Due to the fast and irreversible deterioration rate of the disease, experts defined treatment goals for symptomatic and disease-specific therapies through consensus guidelines and recommend initiation of the disease-specific therapy approved for NP-C* at the first appearance of neurological symptoms. Early diagnosis is crucial for timely intervention and treatment outcome optimization.

In order to raise awareness of NP-C Actelion were showcasing their range of applications which can help identify the various symptoms associated with the disease.

The NP-C Suspicion Index iPad application has been designed to be compatible with iPad 1 and 2. Please ensure that your device runs iOS5. This iPad application is available as a free version.

What is the NP-C Suspicion Index iPad application?
Niemann-Pick type C is a rare genetic disorder which is often misdiagnosed or goes undetected altogether due to its heterogeneous clinical presentation.

The NP-C Suspicion Index iPad application has been developed to provide an easy access to the index without internet connection. It has been designed to allow healthcare professionals unfamiliar with NP-C to:
• Understand the typical signs and symptoms of NP-C
• Assess the likelihood of a patient having NP-C by calculating the NP-C risk prediction score
• Take the appropriate actions according to the results
• Email the results (Internet connection needed)
• Learn about the visceral, neurological and psychiatric symptoms, including patient videos
Access the scientific poster of the NP-C Suspicion Index

The NP-C Suspicion Index iPhone application has been designed to be compatible with iPhone 1 and 2. Please ensure that your device runs iOS4 and above. This iPhone application is available as a free version.

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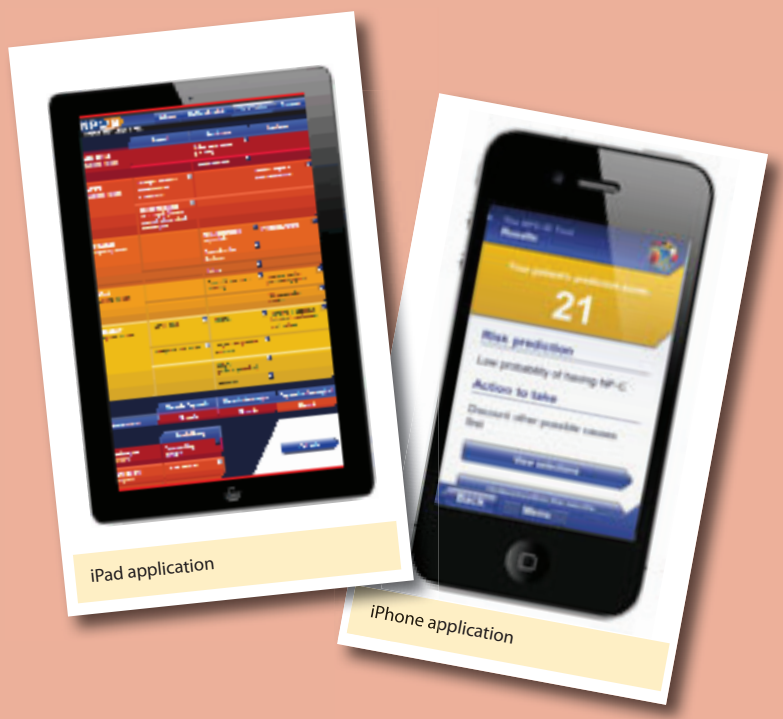


For more information, please visit www.npc-si.com

Thermo Scientific Raise Awareness on Sepsis Diagnosis and Monitoring with their Guide for the Clinical Use of Procalcitonin

Thermo Scientific were in attendance at the EAPS Congress, raising awareness on sepsis diagnosis and monitoring with their *Guide for the Clinical Use of Procalcitonin.*

Sepsis with acute organ dysfunction (severe sepsis) is the number one cause of death in the non-coronary intensive care unit and one of the most significant challenges in critical care:
· More than 750,000 cases of severe sepsis occur annually in the US*.
· The hospital cost of treating patients with severe sepsis in the US is approximately $17 billion each year*.
· Severe sepsis causes 215,000 deaths in the US each year-more than AMI, lung cancer, and other commonly known causes of death in the hospital*.

Cases of severe sepsis are expected to rise in the future due to the increased awareness and sensitivity for the diagnosis, number of immune-compromised patients, use of invasive procedures, number of resistant microorganisms, and the growth of the elderly population. Despite the enormous investment in critical care resources, severe sepsis mortality ranges from 28% to 50% or greater. Progression of sepsis can lead to organ dysfunction and ultimately death.

Severe sepsis consumes an increasing share of healthcare resources and leads to higher total hospital costs due to:
· higher mortality
· significantly increased ventilator use,
· longer lengths of stay. The early recognition and diagnosis of severe sepsis is a crucial part to improve outcome.

Among the newest biomarkers for sepsis, Procalcitonin (PCT) has the highest diagnostic accuracy. PCT levels rise rapidly (within 6-12 hours) after an infectious insult with systemic consequences. Since the outcome in patients with sepsis can significantly be improved if adequate therapy is started early, the measurement of PCT for an early and effective diagnosis is recommended in all patients in whom sepsis and a systemic inflammatory response is suspected. Beyond its value for the diagnosis of sepsis, PCT has also proved to be useful in monitoring the course and severity of the systemic inflammatory response. Daily changes of plasma PCT levels give an indication on the course of the disease and the prognosis of the septic patient. Persistently elevated of PCT are associated with poor outcome and are now viewed as a failure of therapy or the lack of appropriate clearance of the source of the infection.

Whilst in attendance Thermo Scientific aimed to promote and distribute their brochure that intends to provide guidance for the utilisation of PCT and to introduce PCT as a routine tool for improved diagnosis and treatment of sepsis.

For more information please visit www.procalcitonin.com

GETEMED Showcase VitaGuard® Monitors at EAPS

At this year's EAPS Congress GETMED showcased their range of medical products. GETEMED AG has been developing, manufacturing and selling medical products for cardiological diagnostics and ambulatory monitoring of vital signs in high-risk patients for over 25 years. The company, based in Teltow, Brandenburg, has consistently and successfully expanded its market position and is now market leader in Europe in these niche areas.

Improved Safety for High-Risk Patients: Monitoring Systems

GETEMED's VitaGuard® monitors are small, lightweight, portable devices designed to monitor physiological parameters such as heart rate, respiration and oxygen saturation. The devices are mainly used in outpatient services but can just as well be used for monitoring vital signs in clinical environments.

Each of the three VitaGuard® models is highly complex and yet easy to use, not only for trained clinical personnel but also for caregivers without previous medical or technical training. They trigger an acoustic and visual alarm if the patient's vital signs exceed or fall below set limits. All data and waveforms are recorded before, during and after an event and can be viewed on the VitaGuard® display directly or on a PC using the VitaWin® evaluation software.

Efficient Diagnostics: CardioDay® Holter ECG System

GETEMED offers the CardioDay® Holter ECG analysis software together with the CardioMem® series of recorders for acquiring, detecting and analysing cardiac arrhythmia.

When developing new products, GETEMED always focuses on the needs of the potential users. The newly developed CardioMem® CM 4000 recorder underlines this philosophy by providing a high resolution color display with touch screen functionality for the user interface, thereby making it extremely easy to use. As a result, measurement and other device parameters can be changed intuitively.

Telemonitoring: Improved Quality of Life, Best Support

It is GETEMED's strategic goal to develop customised solutions and innovative treatments for telemedical applications by merging the core expertise from the two fields of cardiological diagnostics and vital signs monitoring. Although GETEMED's initial focus was on ambulatory monitoring of newborns, the company has progressed to become a specialist in telemonitoring applications for high-risk patients from all age groups.

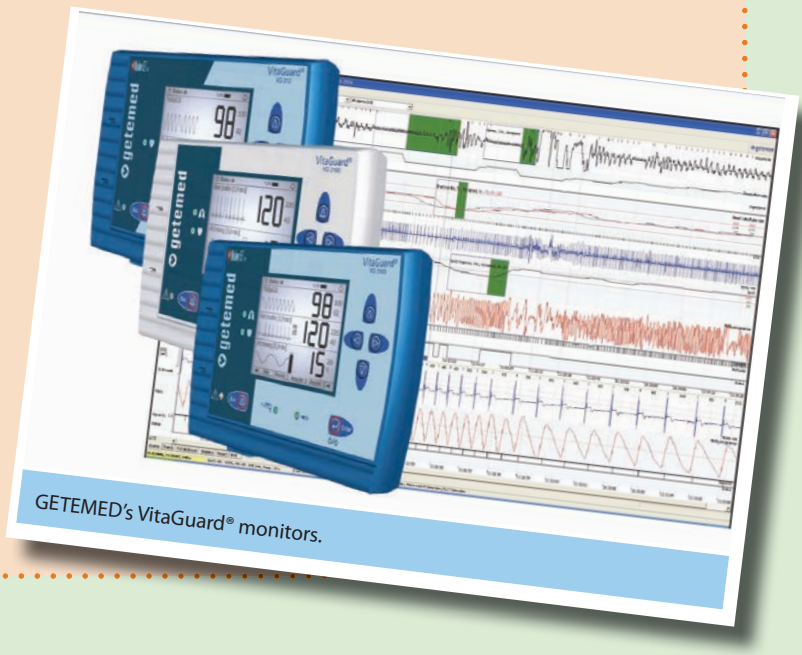
GETEMED has participated in renowned telemedical study and research projects since 2003. Currently the company belongs to the FONTANE project consortium, which won the Federal Ministry of Education and Research (BMBF) competition "Health Regions of the Future" in May 2009 with its project for the North Brandenburg health region. Within this context, a new support model for treating both elderly patients suffering from heart related illnesses and young women during risk pregnancies is currently being put into place for this rural, structurally weak area.

The latest innovations include the first nationwide telemonitoring network which was developed in cooperation with the Deutsche Telekom AG. It spans the complete data chain, from measurement equipment used by the patients at home to the patient's files located in a telemonitoring centre, hospital or doctor's practice. In this project high risk patients suffering from congestive heart failure are supported by two telemonitoring centers located in Cottbus and Brandenburg/Havel.

Pooled Expertise

The company works together with experts from different scientific disciplines so that medical needs can be better understood when developing new products. The Berlin-Brandenburg region offers good conditions and an ideal infrastructure for close collaboration with clinics, universities and other scientific institutions.

Please visit www.getemed.net for further information



GETEMED's VitaGuard® monitors.

Neocate Exhibit at EAPS

Nutricia were amongst the various paediatric exhibitors generating interest at the EAPS Congress in Istanbul. Nutricia showcased, along with others, their Neocate dietary range., now with a new, improved nutrient profile.

The Neocate hypoallergenic product range has been designed for infants and children with cow's milk allergy, multiple food protein intolerance, and a range of food allergy induced disorders. The formulas are based on 100% free amino acids and are formulated without cow's milk protein in order to reduce the possibility of a food allergic reaction.

Neocate is an amino acid based formula that has a specialised age-adapted range. In Europe Neocate is a food for special medical purposes and should be used in consultation with a healthcare professional.

Since its launch in the 1980's Neocate has developed along with our increasing understanding of food allergies and other complex gastro-enteropathies. Its successful use in multiple food allergy-related conditions in infancy has led to the development of an age-adapted range to meet nutritional requirements needed for growth and development in infants and children (from infancy to 10 years of age). Neocate now consists of a family of products for both infants and older children, including both nutritionally complete and supplemental feeds, as well as a semi-solid weaning product.

Neocate is ideal for use where
– Complex CMA symptoms exist
– Symptoms are unresolved on an eHF
– Food allergy related GI symptoms are present

For more information, please visit www.nutricia.com

Airon Present pNeuton Mini Ventilator at EAPS 2012

Airon generated a lot of excitement at this year's EAPS with their latest technological advancement in neonatal paediatric ventilaition, the pNeutron Mini Ventilator.

pNeuton mini Ventilator for infant critical life support anywhere

The new pNeuton mini ventilator, a whole new approach to neonatal, infant and pediatric ventilation. A purely pneumatic ventilator that can support patients non-invasively using nasal prongs or masks with CPAP or ventilation + CPAP. The ventilator can also be used with endo-tracheal tubes for full support.

Operates with no electricity – no batteries – just compressed oxygen and air

With a built-in oxygen blender and precise timing and pressure controls that ventilator will do everything standard infant ventilators do, but without the need for electricity or batteries. The ventilator is ideal for transporting patients both with-in the hospital and via air or ground ambulance. It is fully MRI compatible and can be placed right next to the MRI.

Mini, the newest ventilator to expand your care of the most fragile patients from 400 grams to 25 kilograms.

Benefits for the patient

- A wide range of continuous flow settings to provide the right ventilation for the size of your patient with the least amount of expiratory flow resistance
- Adjustable oxygen delivery from 21% to 100% to precisely match patient oxygen requirements
- Switch from CPAP nasal prongs, face mask to invasive ventilation seamlessly and without interruption
- One ventilator with no change in patient circuit wherever patient care and diagnostic procedures are needed

Benefits for the healthcare provider

- Calibrated controls for precise and easy operation
- Night visible manometer to monitor patient pressure and effort
- Patient disconnect and high pressure alarms that work during non-invasive and invasive ventilation
- MRI conditional – place right next to the scanner with remote alarm output for the control room
- Oxygen powered – no batteries

Rugged and RTCA certified with everything built-in – no accessories needed

Benefits for your budget

Switch from invasive ventilatory support to non-invasive with just a simple change of the patient interface
Lightweight and portable with attachment to any patient care incubator / bed
Minimal oxygen consumption to maximize transport times
No batteries or electronics decrease preventative maintenance costs.

PNeuton mini ventilator.

For more information on critical care ventilation, please visit www.aironusa.com

EAPS Satellite Symposium Overview:

Orphan Europe Raises Awareness About Hyperammonaemia

During this year's EAPS, Orphan Europe organised an interactive satellite symposium entitled "Hyperammonaemia- a true medical emergency", where around 250 physicians and healthcare professionals were actively participating.

Hyperammonaemia is an acute medical emergency with potentially catastrophic effects if the child is not treated quickly and effectively. Although it is not a new problem, clinical presentation is rare increasing the likelihood of misdiagnosis. In addition, the debate about optimal treatment is ongoing. This symposium aimed to increase awareness of this unusual disorder.

Prof. Marshall Summar, the chairman, came all the way from Washington DC where he is Chief of the Division of Genetics and Metabolism and the Margaret O'Malley Chair of Molecular Genetics at the Children's National Medical Centre. He is as well the Director for the NIH sponsored Clinical Research Centre at Children's National.

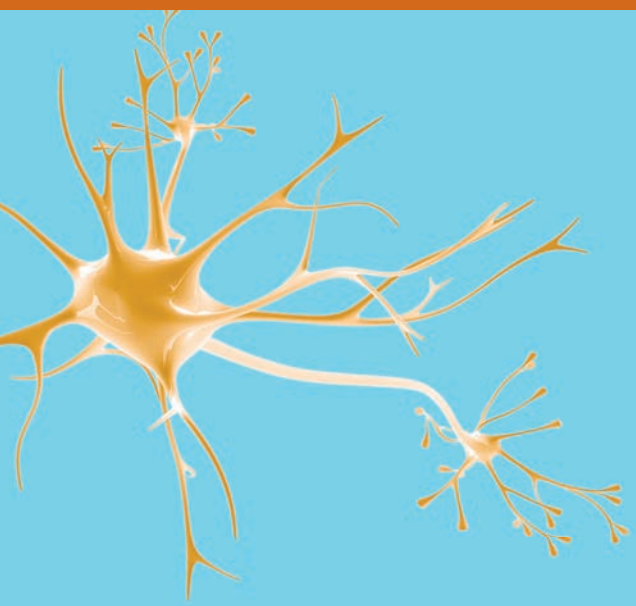
Prof. Summar started with a lecture about the differential diagnosis of hyperammonaemia. The discussion covered the signs, symptoms, recognition and diagnosis, differential diagnoses, and categories of hyperammonaemia. The lecture examined as well the clinical presentation of urea cycle disorders in neonates and adults, and discussed patterns seen in liver failure, organic acidaemia, chemical intoxication, and other causes.

Prof. Johannes Häberle, Senior metabolic consultant at University Children's Hospital Zurich, and Assistant Professor for Paediatrics at the University of Zurich, Switzerland, discussed in the second lecture the management of hyperammonaemic patients. His talk focused on the importance of early diagnosis and immediate initiation of therapy in hyperammonaemia, as confirmed hyperammonaemia should always be treated as an emergency situation. The presentation highlighted as well the central role of the non-specialist physician for patients with hyperammonaemia.

Dr. Mark Sharrard, consultant metabolic paediatrician based at Sheffield Children's Hospital, UK presented a case report entitled: "Neonatal hyperammonaemia with metabolic acidosis – carglumic acid in the treatment of organic acidaemias". The case showed that severe inherited organic acidaemias present neonatally with increasing encephalopathy after a period of normality. Metabolic acidosis, expanded anion gap and hyperammonaemia are hallmarks of organic acidaemias. An early index of suspicion, prompt investigation and initiation of appropriate treatment are essential in preventing deterioration and poor outcome. The administration of a single, large dose of carglumic acid seemed to be effective in treating organic acidaemias while preparations are made for extracorporeal detoxification.

Carbaglu® (Carglumic acid) is a structural analogue of N-acetylglutamate (NAG), which is the naturally occurring activator of carbamoyl phosphate synthetase (CPS), the first enzyme of the urea cycle. Carbaglu® replaces NAG, restores the ureagenesis and diminishes blood ammonia levels.
Carbaglu® is indicated in Europe in the treatment of hyperammonaemia due to:
- Primary NAGS (N-acetylglutamate synthase) deficiency
- Isovaleric acidaemia (IVA), methylmalonic acidaemia (MMA) and proprionic acidaemia (PA)

To watch the webcast, please visit www.orphan-webcast.com



Orphan Europe invites you to watch **the webcast**

Hyperammonaemia

A true medical emergency

Chair: Professor Marshall Summar, Director
Clinical Research Center, Children's National Medical Centre
Washington DC, USA

on www.orphan-webcast.com

Satellite symposium held during the 4th Congress of the European Academy of Paediatric Societies (EAPS)
(Sunday 7 October 2012, Istanbul, Turkey)

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Annual Congress of the European Society for Paediatric Research (ESPR)

11 — 14 October 2013
Porto, Portugal

ESPR 2013 aims to advance paediatric research in Europe and the flow of exchange of information and ideas on new developments in paediatric research.

The program will consist of a mixture of research interaction, training and continuing professional development and will start with pre-congress courses for neonatal trainees and for established clinician scientists. During the congress there will be a track for neonatal continuing professional development in partnership with the Union of European Neonatal and Perinatal Societies (UENPS): world class speakers will cover topics on brain and development, nutrition, epidemiology and circulation.

The scientific program will contain State of the Art plenary lectures along with specialty tracks featuring international experts as keynote speakers, combined with free oral presentations. Poster presentations will receive special attention. We aim to plan enough poster discussion sessions so that all posters can be briefly presented. Young investigator award sessions and post-doc awards, the Bengt Robertson Award for pulmonary research and Robertson Lecture will again be highlights of the conference.

Special topics will include research ethics, large clinical trials, neonatal networks, and basic concepts in paediatrics.

We look forward to seeing you in Porto next year!

For more information, please visit www.espr.info

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AAP 2012 National Conference and Exhibition Review

20 - 23 October 2012 - New Orleans

AAP 2012 Annual Conference of the American Association of Pediatrics

INSIDE...

The Meeting

The Exhibition

Lauran Elsden, *Treatment Strategies*, takes a look over a number of key sessions, as well as spotlighting several stands and products being demonstrated at the exhibition. We then follow with papers and reviews which give a brief insight from a number of sessions highlighting findings that will have direct repercussions on clinical practise that are still very much being discussed.

The AAP experieNCE is the APP National Conference and Exhibition held each fall, typically in October. The AAP is an organisation of 60,000 paediatricians committed to the attainment of optimal physical, mental and social health and well being for all infants, children, adolescents and young adults.

The National Conference is dedicated to keeping healthcare professionals abreast of the latest state-of-the-art practices in paediatrics. Attendees of the Conference represent many specialties and disciplines within paediatrics and the entire healthcare arena. This year saw over 8,000 paediatric healthcare professionals attend to view 1,200 scientific papers, posters and education exhibits, 300 technical exhibitors and 300 scientific sessions.

The AAP Conference faculty represented eight of the top-ten ranked children's hospitals in the United States and nearly

***Introduction** continues on page 26*

The freshly renovated New Orleans Ernest N. Morial Convention Centre.

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200 organisations, including universities, medical institutions, public health offices and government agencies. The 2012 Conference presented the latest clinical data in all areas of paediatrics, with major sessions including Obesity Prevention and Treatment, Bariatric Surgery, the Paediatrician's Role in Promoting Active Commuting for Children and Paediatric Dentistry and Oral Health to name a few. The Congress drew attendees from right across the medical spectrum and indeed the globe, creating a unique and diverse audience.

In addition to their world-renowned speakers, the AAP hosts many complimentary signature events and networking opportunities for conference registrants and their families. These events included the AAP Kid's Camp, the AAP Friends of Children Fund 5K Fun Run and Walk, the President's Reception, District Breakfasts and the Paediatric Bowl to name a few. The AAP experieNCE offered something for everyone.

Delegates were also given the opportunity to tour the world's largest paediatric technical exhibition hall from Saturday through to Monday where all kinds of technologies were showcased. It provided the chance to meet with more than 300 companies, including those specialising in the fields of pharmaceutical, healthcare, infant feeding, nutrition, publications, computer technology and recruiting to learn about their products and services.

This year's Meeting was held in the vibrant city New Orleans. With its unique atmosphere, New Orleans is one of the most popular US destinations. Taking influence from French, Spanish, African and American cultures over the centuries the city has become a unique environment, blending the elegance of the colonial Creoles, the music and cuisine of the peasant Cajuns, the exuberance of Mardi Gras and the sound of jazz playing. Its oldest district, the French Quarter (Vieux Carré), has a wealth of architecture that portrays its colorful history. Most of the original buildings were destroyed in the fire of 1788 and the graceful houses with ornate wrought-iron balconies are actually Spanish in style. In fact, New Orleans has 17 National Historic Districts, with more than 35,000 listed buildings. Music and the city's famous gastronomy attract visitors from all over the world. This is the first return by the Academy to New Orleans since 2005, the same year Hurricane Katrina hit the city. Importantly many venues have now reopened and most have returned to regular operating hours as the city continues its resilient program of recovery. This energetic and exciting city proved to be an excellent host for this dynamic event.

The AAP experieNCE was this year held at the freshly renovated New Orleans Ernest N. Morial Convention Centre, which is an essential component of what makes the city's major business events so successful. With 1.1 million square feet of contiguous exhibit space, the Convention Centre is the sixth largest convention facility in the nation, and it consistently ranks in the country's top ten of facilities that hold the most conventions and tradeshows annually, thus encapsulating all the attributes to constitute a worthy host for such an exciting event.

For this edition of *Treatment Strategies – Paediatrics*, we are looking back over the various sessions that took place across the four-day National Conference, spotlighting exciting findings and research that were presented at the symposiums and poster sessions whilst also bringing you a round-up of the stands found within the lively, dynamic exhibition hall.

"Every conference is as unique as the city we're in, and this year is no different. Moved by our mission, "the health and well-being of all children", this year we'll address child health inequities."

Robert W. Block,
AAP President 2011-2012

Warning Labels Ineffective at Preventing High-Powered Magnet Ingestions

NASPGHAN Releases New Survey Findings

Survey findings released at the AAP Conference by the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) provided compelling evidence that the use of warning labels in marketing and packaging of high-powered magnet sets have not been effective in preventing the ingestion of these magnets by infants, children and teenagers.

In the past 10 years, there have been at least 480 cases of high-powered magnet ingestions, with 204 of those cases occurring in the past 12 months, according to the survey, which provides the first epidemiological evidence of the extent of magnet ingestion injuries in U.S. children. Of the reported cases, 80 percent required endoscopic or surgical intervention. The study found that the majority of magnet ingestions (51 percent) occurred in children 1 to 6 years of age, although ingestions also occurred among adolescents and teenagers, who use the magnets to mimic tongue, lip and nose piercings.

NASPGHAN delivered the survey to 1,747 of its members in August 2012 and received reports of magnet ingestions from 354 paediatric gastroenterologists in response. Survey results may not capture the most severe magnet ingestion cases, which may be sent directly to surgery and are not initially seen or managed by a paediatric gastroenterologist.

The magnet ingestion cases reported involve high-powered magnets commonly sold in sets of 100 or more balls that are often spherical in shape and about 3 to 6 millimeters in size. Most of these magnets are made from an alloy of neodymium, iron and boron and exhibit a strong attractive force. If more than one magnet is swallowed, the magnets will attempt to connect with each other inside the body. When this happens the magnets can tear holes in the stomach and bowel and cause severe, life-threatening complications within hours.

Of the children requiring surgical intervention, in almost all cases, those children also required sedation and single or multiple x-rays. Of the cases requiring surgical intervention, 16 percent resulted in bowel resection – or removal of part of the bowel – which can have long-term health implications. Sixty-two percent of the interventions were for repair of perforation (a hole in the wall at any location in the gastrointestinal tract) or fistula (an abnormal connection or passageway between two parts of the gastrointestinal tract).

"Ingesting two or more of these super-strength magnets is unlike swallowing a marble or other small foreign body," said Athos Bousvaros, MD, NASPGHAN president. "Damage from these magnets begins soon after ingestion. When the intestinal wall separates two or more magnets that attract each other, holes in the bowel can occur. Time is of the essence with a high-powered magnet ingestion. Yet, bowel damage can be difficult to diagnose, especially in toddlers who can't convey they have swallowed magnets."

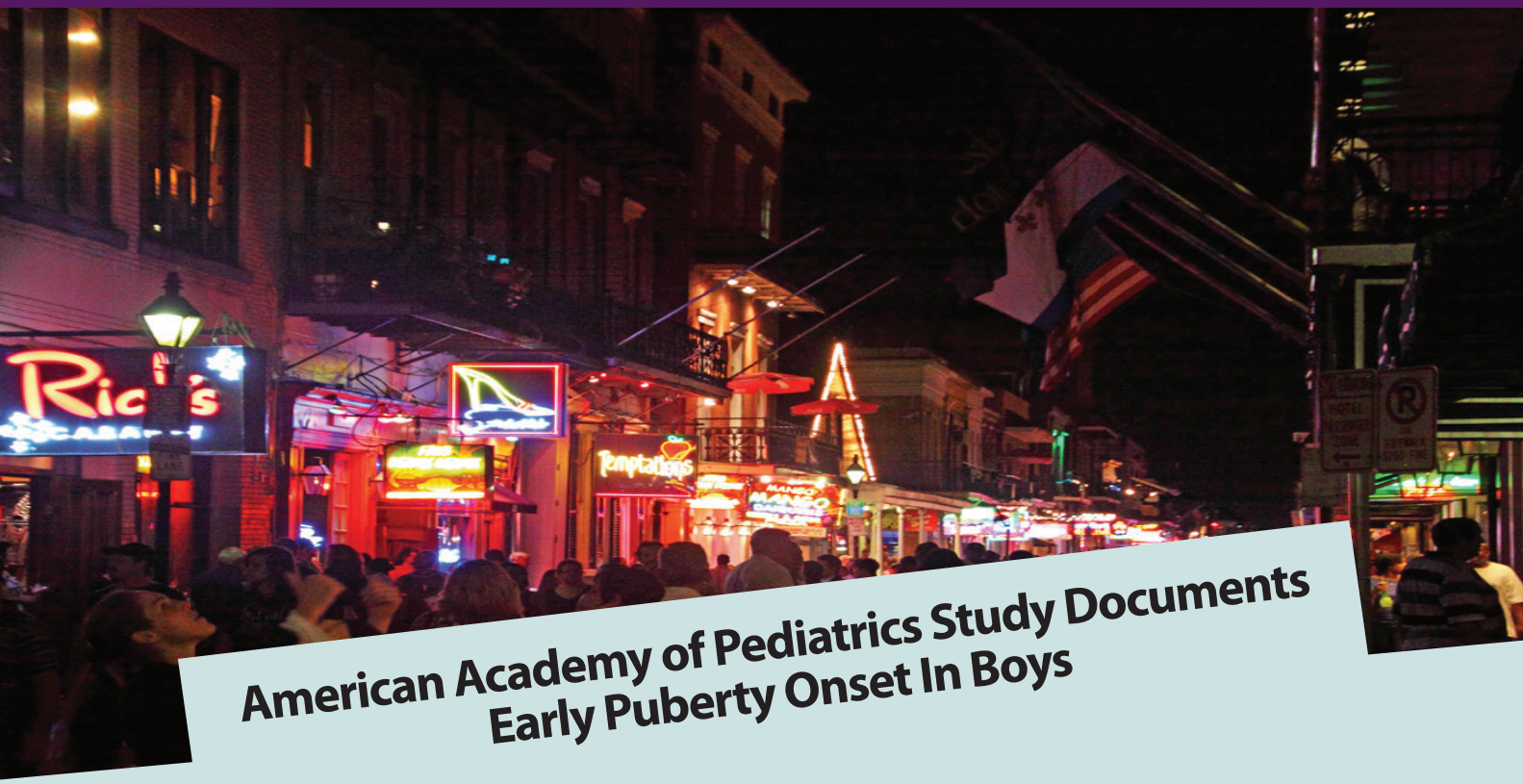
In 2008, high-powered magnet sets were introduced in the consumer market and generally marketed as adult desk toys. The product was initially labeled for use by children 13 years of age and older. Since 2010, high-powered magnet sets have been labeled for consumers 14 years of age and older, and most include warnings to keep the product away from children. The survey results confirm that magnet ingestions and resulting injuries to children continue despite labels and warnings. "Despite improved warnings, the prevalence of high-powered magnet ingestions is increasing, which tells us that warnings are ineffective at preventing ingestions," said Robert Noel, MD, a paediatric gastroenterologist and lead author of the study. "The most effective way to prevent ingestions is to ban the sale of high-powered magnet sets."

The U.S. Consumer Product Safety Commission has proposed a ban on certain high-powered magnet sets, a move strongly supported by NASPGHAN and the American Academy of Pediatrics (AAP).

"Young children naturally put things in their mouths as part of their development, and paediatricians counsel parents to be aware of this risk and keep dangerous items out of their child's reach. But no parent can be vigilant 100 percent of the time," said AAP President Thomas McInerny, MD, FAAP. "The Consumer Product Safety Commission's ban is the decisive action needed to protect young children from potentially severe injuries. For years, the federal government has taken action to educate the public, and to change marketing practices and labeling. Still, these products remain a serious risk to children and teens."

NASPGHAN's mission is to advance understanding of normal development, physiology and pathophysiology of diseases of the gastrointestinal tract and liver in children, improve quality of care by fostering the dissemination of this knowledge through scientific meetings, professional and public education, and policy development, and serve as an effective voice for members and the profession.

For more information, please visit www.naspghan.org



American Academy of Pediatrics Study Documents Early Puberty Onset In Boys

A study conducted by the American Academy of Pediatrics (AAP) has documented that boys in the U.S. are experiencing the onset of puberty six months to two years earlier than reported in previous research.

The study, "Secondary Sexual Characteristics in Boys: Data from the Pediatric Research in Office Settings Network," will be published in the November 2012 *Pediatrics* and published online Oct. 20 to coincide with the AAP National Conference & Exhibition in New Orleans.

The trend toward earlier onset of puberty in girls is now generally accepted and supported by extensive research. Until now, little research was available on the age of onset of puberty in boys in contemporary times.

The study was designed and conducted through the AAP Pediatric Research in Office Settings (PROS) practice-based research network, a system of hundreds of paediatricians nationwide who contribute data to AAP-led scientific studies on children's health. A 1997 PROS study was the first large study to document earlier pubertal onset in US girls. For the study of pubertal characteristics in boys, 212 practitioners in 144 paediatric offices in 41 states recorded information on more than 4,100 boys.

This new research found that the observed mean ages of stage 2 genital and pubic hair growth, and early testicular enlargement - standard indications of pubertal onset - were six months to two years earlier than documented by data several decades earlier. Paediatricians recorded the earliest stage of puberty as occurring in non-Hispanic white boys at age 10.14 years; in non-Hispanic African-American boy at age 9.14 years, and in Hispanic boys at age 10.4.

"Contemporary data on the ages of pubertal characteristics in U.S. boys from onset to maturity, lacking until now, are needed by paediatricians, public health scientists, and parents. Following changes in growth and development is an important part of assessing the health of the nation's children. I am grateful to the paediatricians and the boys who participated in this exciting study."

Marcia E. Herman-Giddens,
Study author

Overall, African-American boys were more likely to start puberty earlier than white or Hispanic boys. Study authors say the causes and public health implications of an apparent shift toward a lower age of puberty onset for boys is unclear and warrants further research.

All parents need to know whether their sons are maturing within the contemporary age range, but, until now, this has not been known for U.S. boys," said PROS Director Richard C. Wasserman, MD, MPH, FAAP. "The PROS study provides 21st century standards."

"The landmark PROS study of the 1990s provided contemporary data for girls' puberty," Dr. Wasserman said. "A study on boys puberty was a logical follow-up. Our paediatric endocrinologist colleagues now use the PROS puberty assessment training materials in their own studies and fellowship training."

Many Grandparent Caregivers Unaware of Newer Safety Guidelines

The number of grandparent caregivers continues to grow, and while these older adults may be experienced in caring for young children, many are unaware of more recent safety and other recommendations – including those related to appropriate child sleep position, crib safety, car seat and walker use, according to research presented Oct. 21 at the American Academy of Pediatrics (AAP) National Conference and Exhibition in New Orleans.

According to the 2011 American Community Survey, an estimated 2.87 million grandparents are the primary caregivers to their grandchildren – a nearly 20 percent increase since the year 2000. In the study, "Grandparent Caregiver Knowledge of Anticipatory Guidance Topics," researchers attended regularly scheduled Grandparent/ Kinship Care support groups. Forty-nine participants completed a 15-question survey that addressed common paediatric safety and anticipatory guidance topics for children of all ages.

When asked, "What is the best position for a baby to sleep in?" 33 percent of respondents chose "on the stomach;" 23 percent, "on the side;" and 43.8 percent, "the back." The AAP recommends that infants be placed to sleep on their backs to prevent Sudden Infant Death Syndrome (SIDS). When asked about correct car seat positioning, 24.5 percent responded that a 22 pound, 9 month-old child should be facing forward, and yet the AAP recommends that children remain in a rear-facing car seat until age 2.

Last year, the AAP recommended that bumpers, stuffed animals and blankets be removed from infant cribs, and yet 49 percent of grandparent caregivers thought these items were acceptable. Nearly 74 percent respondents stated that a walker is a good device to help babies learn to walk. The AAP does not recommend walker use, and in fact urges caregivers to dispose of them because of serious safety concerns.

"Paediatric health and safety recommendations are constantly evolving," said study author Kathryn C. Hines, MD, a University of Alabama at Birmingham physician who sees patients at Children's of Alabama. "Many recommendations are likely to have changed since these grandparent caregivers parented their own children."

"Discussion of health and safety recommendations is an essential part of routine well-child care, and paediatricians must recognise knowledge deficits that may exist in grandparent caregivers and be comfortable addressing these deficits," said primary study author Amanda Soong, MD, FAAP, also of UAB.

"Paediatric health and safety recommendations are constantly evolving. Many recommendations are likely to have changed since these grandparent caregivers parented their own children. "

Kathryn C. Hines,
Study author, University of Alabama at Birmingham

American Academy of Pediatrics Weighs In For the First Time on Organic Foods for Children

AAP report cites lower pesticides in organic produce and potentially lower risk of exposure to drug-resistant bacteria, but says the most important thing for children is to eat a wide variety of produce, whether it's conventional or organic.

Parents know it's important for children to eat a wide variety of fruits and vegetables, low-fat dairy products, and whole grains. But it's less clear whether spending the extra money on organic foods will bring a significant benefit to their children's health.

To offer guidance to parents – and the paediatricians caring for their children's health – the American Academy of Pediatrics (AAP) has conducted an extensive analysis of scientific evidence surrounding organic produce, dairy products and meat. The conclusion is mixed: While organic foods have the same vitamins, minerals, antioxidants, proteins, lipids and other nutrients as conventional foods, they also have lower pesticide levels, which may be significant for children. Organically raised animals are also less likely to be contaminated with drug-resistant bacteria because organic farming rules prohibit the non-therapeutic use of antibiotics.

However, in the long term, there is currently no direct evidence that consuming an organic diet leads to improved health or lower risk of disease. However, no large studies in humans have been performed that specifically address this issue.

"What's most important is that children eat a healthy diet rich in fruits, vegetables, whole grains, and low-fat or fat-free dairy products, whether those are conventional or organic foods. This type of diet has proven health benefits," said Janet Silverstein, MD, FAAP, a member of the AAP Committee on Nutrition and one of the lead authors of the report. "Many families have a limited food budget, and we do not want families to choose to consume smaller amounts of more expensive organic foods and thus reduce their overall intake of healthy foods like produce."

The AAP report, "*Organic Foods: Health and Environmental Advantages and Disadvantages,*" was released at a news conference at 1 p.m. CT Monday, Oct. 22 at the AAP National Conference & Exhibition in New Orleans. It will be published in the November 2012 issue of *Pediatrics* (published online Oct. 22).

The report outlines the research that has been conducted on organic foods, including convincing evidence of lower exposure to pesticides and less contamination of livestock with drug-resistant bacteria.

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"At this point, we simply do not have the scientific evidence to know whether the difference in pesticide levels will impact a person's health over a lifetime, though we do know that children – especially young children whose brains are developing – are uniquely vulnerable to chemical exposures," said Joel Forman, MD, FAAP, a member of the AAP Council on Environmental Health and one of the lead authors of the AAP clinical report.

If cost is a factor, families can be selective in choosing organic foods, Dr. Forman said. Some conventionally grown fruits and vegetables tend to have lower pesticide residues. The AAP cites organic shopper's guides like those provided by Consumer Reports and the Environmental Working Group as references for consumers.

The AAP found no individual health benefit from purchasing organic milk, but emphasises that all milk should be pasteurised to reduce the risk of bacterial infections. Raw milk increases the risk of serious infection with bacteria including Salmonella, E. coli, Listeria, Campylobacter and Brucella.

Purchasing meat from organic farms that do not use antibiotics for non-therapeutic uses has the potential to reduce antibiotic resistance in bacteria that infect people. The AAP calls for large, well-designed, prospective cohort studies that directly measure environmental exposures such as estrogen at low levels to understand the impact of hormonal exposure of children through milk and meat.

The AAP report also notes that the motivation to choose organic produce, meat and dairy products may be reasonably based on larger environmental issues, as well as human health impacts like pollution and global climate change.

"Paediatricians want families to have the information they need to make wise food choices," said Dr. Forman. "We hope that additional research will improve our understanding of these issues, including large studies that measure environmental exposures and neurodevelopment."

Off-Label' Use of Meds Routine in Paediatric ICU

But not enough is known about their safety and effectiveness in children, researcher says

The off-label use of drugs is routine in the treatment of children in intensive-care units, a new study finds.

Off-label refers to the use of drugs that do not have U.S. Food and Drug Administration approval for treatment of certain patients or conditions. For example, some drugs are approved for use in adults but used off-label in children.

"Treatment with off-label medications is the rule rather than the exception in the paediatric intensive-care unit," said study author Susan Sorenson, a doctor of pharmacy. "Numerous problems emanate from the lack of drug data in children, including uncertainty about whether a drug is effective in children for a particular disease, questions about the side effect profile, and lack of dosing information."

The study looked at off-label drug use among nearly 500 children, ranging in age from newborn to 17 years, in the paediatric intensive-care unit at Primary Children's Medical Centre in Salt Lake City.

A total of 335 drugs were prescribed to the children and 96 percent of them received at least one off-label drug, including all patients aged 13 to 17, according to the study, which was presented Sunday at the American Academy of Pediatrics' national conference in New Orleans.

Sorenson added that it "is very difficult when you stand at the bedside and want to treat a sick child with a drug and you don't know if the dose or drug you have chosen or recommended will harm the child or help the child."

This study attempted to determine the drugs used most frequently in the sickest paediatric patients that lack dosing information, "with the intent that studies of dosing, safety and efficacy will be carried out on those drugs," Sorenson explained in an academy news release.

"More studies need to be conducted so that prescribing in our youngest and sickest patients can be done based on evidence," she added. Data and conclusions presented at meetings should be considered preliminary until published in a peer-reviewed medical journal.

Children with Mental Health Disorders More Often Identified as Bullies

Children diagnosed with mental health disorders were three times more likely to be identified as bullies, according to new research presented Oct. 22 at the American Academy of Pediatrics (AAP) National Conference and Exhibition in New Orleans.

Bullying is a form of youth violence defined as repetitive, intentional aggression that involves a disparity of power between the victim and perpetrator. A 2011 nationwide survey found 20 percent of U.S. high school students were bullied during the preceding 12 months. And while it is well-established that victims of bullying are at increased risk for mental health illness and suicide, few studies have investigated the mental health status of those who do the bullying.

In the study, "Association Between Mental Health Disorders and Bullying in the United States Among Children Aged 6 to 17 Years," researchers reviewed data provided by parents and guardians on mental health and bullying in the 2007 National Survey of Children's Health, which included nearly 64,000 children.

In 2007, 15.2 percent of U.S. children were identified as bullies by a parent or guardian. Overall, children with mental health disorders were three times more likely to bully other children. A sub-analysis by type of mental health disorder found that children with a diagnosis of depression were three times more likely to bully, while a diagnosis of Oppositional Defiant Disorder (ODD) was associated with a six fold increase in the odds of being identified as a bully.

"These findings highlight the importance of providing psychological support not only to victims of bullying, but to bullies as well," said study author Frances G. Turcotte-Benedict, MD, a Brown University master's of public health student and a fellow at Hasbro Children's Hospital in Providence, RI."

"In order to create successful anti-bullying prevention and intervention programs, there certainly is a need for more research to understand the relationship more thoroughly, and especially, the risk profile of childhood bullies."

> **"These findings highlight the importance of providing psychological support not only to victims of bullying, but to bullies as well."**
>
> **Frances G. Turcotte-Benedict**
> **Brown University & Hasbro Children's Hospital**

Saint Louis Cathedral, situated in the French Quarter of New Orleans

In Vitro Fertilisation Linked to Increased Risk for Birth Defects

In vitro fertilisation (IVF) may significantly increase the risk of birth defects, particularly those of the eye, heart, reproductive organs and urinary systems, according to new research presented Saturday, Oct. 20, at the American Academy of Pediatrics (AAP) National Conference and Exhibition in New Orleans.

According to the study, despite increasing use of IVF in the United States, associations between birth defects and IVF are poorly understood. Management of birth defects comprises a large part of paediatric surgical care and demands significant health care resources.

According to the Centers for Disease Control, California has the highest rate of IVF usage in the United States. In the abstract, "Congenital Malformations Associated with Assisted Reproductive Technology: A California Statewide Analysis," researchers examined infants born in California from 2006-2007 after IVF and other treatments such as fertility-enhancing drugs or artificial insemination. Researchers examined maternal age, race, the number of times the mother had given birth, infant gender, year of birth and presence of major birth defects.

"Our findings included a significant association between the use of assisted reproductive technology, such as certain types of in vitro fertilisation, and an increased risk of birth defects," said study author Lorraine Kelley-Quon, MD, a general surgery resident at Ronald Reagan UCLA Medical Center, who conducted the research at Mattel Children's Hospital UCLA.

Overall, 3,463 infants with major birth defects were identified among 4,795 infants born after IVF and 46,025 naturally conceived infants with similar maternal demographics. Birth defects were significantly increased for infants born after IVF – 9 percent versus 6.6 percent for naturally conceived infants, even after controlling for maternal factors. Specifically, malformations of the eye (0.3 percent versus 0.2 percent), heart (5 percent versus 3 percent), and genitourinary system (1.5 percent versus 1 percent) were greater in IVF infants. Overall, an IVF infant's odds of birth defects were 1.25 times greater than that of a naturally conceived infant with similar maternal characteristics. Risk of birth defects after other fertility treatments such as artificial insemination or ovulation induction alone were not significant.

"For parents considering in vitro fertilisation or other forms of assisted reproductive technology, it is important that they understand and discuss with their doctor the potential risks of the procedure before making a decision."

Lorraine Kelley-Quon,
Ronald Reagan UCLA Medical Centre

Crosscare Inc Showcase their New Colic Campaign

Crosscare Inc., the makers of Colief® Infant Drops, were in attendance at the American Academy of Pediatrics (AAP) conference in New Orleans. Crosscare Inc were showcasing their new campaign which aims to educate paediatricians and nurses about an emerging theory in the diagnosis and treatment of colic.

Affecting up to 20 percent of infants, colic is one of the top newborn conditions of most concern to parents. Characterised by hour-long crying spells and extreme discomfort for babies, colic has also been associated with stress, fatigue, anger, and feelings of inadequacy in parents.

Colief® Infant Drops for the treatment of Colic.

Professionals are invited to learn more about a new theory on the diagnosis of colic, transient lactase deficiency (TLD), by joining a webinar and be entered to win a trip for two to Ireland, where Colief Infant Drops and Crosscare Inc. originate.

"We are committed to providing education and information to the professional community as their patient continues to seek a solution to their baby's discomfort. Colic can be extremely difficult for parents and babies, but with a new way to diagnose and treat this condition, families can get back to less crying time, more we time," says Sharon Skelton, marketing manager for Crosscare Inc.

Despite the condition's prevalence, the precise cause of colic has historically been uncertain. Research suggests, however, that 38 percent of colic cases can be attributed to transient lactase deficiency, a condition causing an inability to digest lactose sugar, leading to severe intestinal pain and bloating. Developed to relieve symptoms of this condition, Colief is a lactase enzyme which eases the digestion of lactose in both formula-fed and breastfed infants.

New to the U.S., Colief Infant Drops have been clinically proven to reduce crying time in colicky babies and have been trusted by families in the United Kingdom for over 15 years. Colief is added to breastmilk or formula at the beginning of every feeding until the infant's intestinal system begins producing more lactase on his or her own, around three to four months.

"We are committed to providing education and information to the professional community as their patient continues to seek a solution to their baby's discomfort. Colic can be extremely difficult for parents and babies, but with a new way to diagnose and treat this condition, families can get back to less crying time, more we time."

Sharon Skelton, Crosscare Inc

For additional information, please visit www.colief.com

Children's Physicians Honored by American Academy Of Pediatrics

Robert Wood and Tina Cheng were recently honored by the American Academy of Pediatrics (AAP) at the organisation's national conference in New Orleans, Oct. 20-23.

Wood received the 2012 Bret Ratner Paediatric Allergy and Immunology Research Award, given every two years to an outstanding paediatric allergist-immunologist for contributions in basic and/or clinical research in allergy.

Cheng received the AAP's Job Lewis Smith Award for lifetime achievement and outstanding service in community paediatrics through clinical care, teaching, advocacy and innovations in patient care.

Wood, who directs the Division of Paediatric Allergy and Immunology at Johns Hopkins, is one of the world's foremost experts on food allergies and is conducting both clinical and translational research to unravel the underpinnings of food allergy.

Wood's current work focuses on oral immunotherapy for the treatment of several food allergies, including egg, milk and peanut. The method involves treating children with increasingly high doses of the very food they are allergic to, thereby training their immune systems to adapt. Wood has published a series of scientific studies on the subject over the last several years, the latest of which appeared this summer in *The New England Journal of Medicine*.

"***Dr. Wood's relentless pursuit of therapies for food allergies has brought us closer than ever to a real treatment for a disease that affects millions of children***," said Johns Hopkins Children's Centre Director George Dover, M.D. "I am confident that in the next 20 years, we will have a mainstream frontline therapy for food allergies, in great part thanks to Dr. Wood's research."

Tina Cheng , Winner of the Job Lewis Smith Award

Robert Wood, Winner of the Bret Ratner Pediatric Allergy and Immunology Research Award

Cheng, professor of paediatrics at Johns Hopkins and director of its Division of General Paediatrics and Adolescent Medicine, has been a relentless and outspoken advocate on reducing health disparities and violence prevention in children. Her research interests include injury prevention, positive youth development and access to care, among other areas. Her commitment to improving child health starts at the individual level, with patients and families and extends all the way to the federal level through her work to promote health policies designed to improve paediatric care and health outcomes. She has conducted randomised trials of community-based violence prevention programs with adolescents in the emergency department and with high-risk sixth graders in persistently violent schools, and has led primary care programs to reduce health disparities.

"***Dr. Cheng's passion and tireless efforts to reduce teen violence, close gaps in access and care, and improve child health have had wide and far-reaching effects that extend well beyond the local community and have informed policies on regional and national levels***," Dover said.

Cheng is a principal investigator on the NIH-funded D.C. Baltimore Research Center on Child Health Disparities with Howard University and Children's National Medical Center. She currently leads three randomised trials of youth development and prevention with disadvantaged children, teens and their families. Cheng is the author of more than 100 original articles. She is past president of the Academic Pediatric Association and currently chairs the AAP's Committee on Paediatric Research and is associate editor of *Pediatrics in Review*.

UV Skinz Continue their Mission to Raise Awareness about Sun Protection

UV Skinz, a leading provider and internationally distributed brand of sun protective clothing, who were proud to be in attendance at the American Academy of Pediatrics 2012 National Conference & Exhibition (2012 NCE) in New Orleans.

UV Skinz encouraged attendees of the 2012 NCE to visit booth #1247 to learn about UV Skinz' wide array of sun protective wear and accessories and to understand just how easy it is to live sun safe while having fun outdoors.

UV Skinz' continued attendance at the 2012 NCE marks another step forward in its mission to protect children from the damaging effects of the sun's UV radiation. "Most people don't realise that one severe sunburn as a child more than doubles the risk of getting cancer as an adult," explains Rhonda Sparks, Chief Executive Officer and President of UV Skinz. Rhonda adds, "The growth trend in sun protection and the fight against melanoma and skin cancer is more prevalent today than ever before. Consumers are not only trying to become educated in the prevention of skin cancer but are incorporating sun protection into their everyday life."

According to a 2011 report from the American Academy of Dermatology, more than 2 million cases of skin cancer will be diagnosed this year. UV Skinz hopes to change these statistics as 98% of skin cancers are preventable. "By attending the 2012 AAP National Conference, we hope to meet new partners who will help us spread the word about sun safety and effective sun protection," states Rhonda Sparks. "We want our products to work as a preventative to these skin diseases like toothpaste does to cavities."

UV Skinz is a leading provider of UV protective wear, swim shirts and accessories for the entire family. By providing the highest quality and hippest designs at competitive prices, UV Skinz aims to make sun protection effortless.

For more information, please visit www.uvskinz.com

AAP At a Glance...

The 2012 American Academy of Pediatrics National Conference and Exhibition (AAP NCE) proved to be the definitive meeting place for professionals in the field of paediatrics. The AAP is committed to the attainment of optimal physical, mental, and social health and well being for all infants, children, adolescents, and young adults. With over 60,000 members from across the globe, and 8,000 attendees, the AAP NCE is their most widely attended event.

The scientific program lived up to expectations and presented the latest clinical data in all areas of paediatrics. The AAP Conference faculty represented eight of the top-ten ranked children's hospitals in the US and they truly did put together a program of challenging and exciting content to appeal to members from all paediatric disciplines.

The American Academy of Pediatrics National Conference and Exhibition once again proved to be the event that no one in the paediatrics community could afford to miss out on. Held in the remarkable Ernest N. Morial Convention Centre, a venue perfectly suited to the enormity of the congress, the National Conference and Exhibition provided the opportunity for efficient networking and the chance to further advance scientific knowledge and, consequently, patient care.

We throughly enjoyed this year's event and very much look forward to attending and meeting you at next year's conference, which will this time be held in Orlando, Florida.

AAP National Conference & Exhibition 2013

October 26-29, 2013
Orlando, Florida

The AAP National Conference & Exhibition (AAP Experience) is the forum for AAP member and non-member physicians, residents, medical students, nurses and allied health members to convene for practical updates and reviews of paediatric practice, research, and advocacy. The conference is the premier paediatric educational event, providing approximately 350 sessions in nearly 60 content areas in varying educational formats. The exhibit hall features the latest paediatric medical and pharmacologic products, services, resources, and technology.

Next year's Conference will be held in sunny Orlando, Florida and promises to be an exciting event for all those in attendance!

For more information please visit
www.aap.org

Treatment of Asthma in Children

Gunilla Hedlin[1] and **Göran Wennergren**[2]

1. Centre for Allergy Research, Department of Women's and Children's Health, Astrid Lindgren Children's Hospital, Karolinska Institutet, Stockholm; 2. Department of Paediatrics, University of Gothenburg, Queen Silvia Children's Hospital, Göteborg

Infants and Pre-school Children

Many infants and young children have asthmatic symptoms with wheezing, usually with colds.[1] However, the pathogenesis of wheezing disorder in the young age group is heterogeneous, and this heterogeneity is reflected by the varied effectiveness of the medication.

The majority of the infants and many of the pre-schoolers have "viral wheeze". As a rule, these children have no signs of allergy and they wheeze more or less only when they have colds. This is sometimes called episodic viral wheeze.[1] The pathogenetic mechanisms are not fully established, but they are different eosinophil inflammation. Most of the children with viral wheeze grow out of their wheeze at age 2 to 3 years, although some of them continue to wheeze with colds up to school age.[1]

In children with eczema or allergic sensitisation, the symptoms triggered by colds can be regarded as virus-induced asthma exacerbations. These children often have symptoms also between colds (multiple-trigger wheeze), and are more prone to develop "true" asthma.[1] Differences in terms of inflammatory markers between episodic viral and multiple-trigger wheeze support the more allergic nature of multiple-trigger wheeze.[2] However, it should be recognised that viral wheeze and multiple-trigger wheeze are not sharply delineated entities.[3] For example, a child may have only virally induced symptoms from the beginning but may then also develop allergic symptoms. Furthermore, it should be acknowledged that virus infections are also the most common cause of acute asthma symptoms in children with asthma with allergic sensitisation.

The high percentage of infants and young children with wheeze and asthmatic symptoms means that there is a real need for effective treatment. However, the treatment effect is often modest or unsatisfactory in this young age group.

Possible Treatment Strategies for Pre-school Wheezers

As a group, children with signs of atopy and children who also wheeze between colds respond positively to inhaled corticosteroids (ICS), while the effects of ICS are often unsatisfactory in viral wheeze. Periodic treatment with ICS or with montelukast has been shown to reduce symptoms to some degree in pre-school wheezers with intermittent wheezing in conjunction with viral infections.[4, 5, 6] However, the available data indicate that, as a general rule, the treatment effect in episodic viral wheeze is at best modest.

Early ICS Treatment does not Alter the Natural Course of Asthma

Randomised, controlled trials in pre-school children have been unable to show that early steroid treatment has a disease-modifying effect.[7,8,9] Asthma symptoms return when ICS therapy is discontinued and the prevalence of asthma at school age is not reduced.

Pre-school and School Children

Reason for Differences in Treatment Effects

The reason why the effect of inhaled corticosteroids is usually poorer in episodic viral wheeze than in asthma with eczema or allergic sensitisation, is most likely different airway inflammation. In viral wheeze without eczema or allergic sensitisation, neutrophil leukocytes are usually found in the bronchoalveolar lavage.[10, 11] In contrast, in asthma with allergic sensitisation, eosinophils are found in the bronchoalveolar lavage, even if the symptoms are triggered by a viral

Gunilla Hedlin is Professor of paediatric allergology and co-director of the Centre for Allergy Research at Karolinska Institutet. She is also senior consultant at Astrid Lindgren Children's Hospital and Karolinska University Hospital in Stockholm, Sweden. Her fields of research are severe asthma and allergy in children.

Göran Wennergren is Professor of paediatrics at the University of Gothenburg, Sweden. He is also chairman of the Acta Paediatrica Foundation. His fields of research are asthma in children, paediatric allergy and the sudden infant death syndrome (SIDS).

infection.[10, 11] Corticosteroids effectively down-regulate eosinophil inflammation but have little or no effect on neutrophils and neutrophil-associated cytokines such as IL-8.

In a study of airway pathology, an early increase of airway smooth muscle was shown to be associated with asthma at school age. Thus indicating that early morphological changes are important for the risk of continuing from pre-school wheeze to school aged asthma.[12]

The role of the leukotriene antagonists in the management of asthma in children of different ages is discussed in a recent review. The conclusion by the authors agrees with the current recommendations stated in the GINA guidelines and the updated British Thoracic Society guidelines. LTRA are mainly indicated for mild asthma, viral wheeze and as add on therapy to ICS. We still lack reliable tools to identify those who will respond best to LTRA.[13]

ICS Effect on Linear Growth

The general opinion is that ICS at low or moderate doses rarely affect linear growth, but the height of all children receiving maintenance treatment with ICS should be measured once or twice a year. Signs of retarded growth requires further investigation. From the CAMP study it was recently reported that treatment with ICS reduced final height with on average one centimetre.[14] However, this side effect of ICS treatment has to be evaluated in relation to the beneficial effects on asthma morbidity and quality of life.

Medication Taken and Correct Diagnosis?

In children with an insufficient response to treatment, adherence should be evaluated. A liberal attitude towards re-assessments of the asthma diagnosis is recommended and X-rays and an extended laboratory work-up may be indicated. A foreign body, a vascular ring or a lung malformation, a tumour causing bronchial obstruction, or a disease such as cystic fibrosis may produce respiratory symptoms in the child that may be mistaken for asthma.[15] Parents perception of the severity of the child's asthma has a major impact on the adherence to recommended treatment[16] and education plays an important role in improving appropriate use of asthma therapy.[17]

How to Step-up in Children with Uncontrolled Asthma?

In a study from the CARE Network in the United States 182 children were enrolled who were symptomatic despite being prescribed Fluticasone 100 mcg twice daily.[18] The investigators used a triple crossover, un-blinded design to assess whether additional therapy with high dose ICS, long-acting β-2 agonist (LABA) or leukotriene receptor antagonist (LTRA) was better. The features of the results were (a) that LABA additional therapy performed best for the group, although many children did better with the other alternatives; and (b) the peak of the ICS dose response curve for most of the children was at a low dose fluticasone.

Severe Asthma in School Children

The SMART (Symbicort Maintenance And Reliever Therapy) regiment relies on the use of a single inhaler (budesonide and formoterol) as regular therapy and for exacerbation of symptoms. Since the patient receives an extra dose of inhaled corticosteroid at the same time as the reliever is taken, the steroid dose is automatically increased when a deterioration is approaching, i.e. with a cold.

Studies have shown that the strategy significantly reduces the risk of severe exacerbations,[19] although there are some conflicting data on efficacy and the corticosteroid dose required by those on the SMART regiment.[20]

A trial of the SMART regime using the budesonide 200 mcg/formoterol 6 mcg Turbuhaler, is worth considering in school children and teenagers with severe, therapy resistant asthma in whom severe exacerbations are still a problem.

Anti-IgE immunoglobulin therapy, omalizumab, is expensive but has become popular despite the inconvenience of administration with subcutaneous injections every second to fourth week. It is a logical option in children with true severe, therapy resistant asthma who have been through detailed assessments,[21, 22] and who meet the criteria:

(a) chronic symptoms or severe exacerbations despite high dose medication, or adequate control of asthma only at the cost unacceptable side-effects;

(b) IgE mediated sensitisation to one or more aero-allergens; and

(c) action has been taken to reduce the environmental allergen exposure.

There is sufficient evidence of efficacy in terms of reduction in exacerbations and medication use, and improvement in quality of life[23, 24] for this therapy to be recommended in children with atopic allergic asthma age six years and over if they meet the clinical criteria and have an appropriate level of IgE. However, there are no simple tests which predict who will respond to omalizumab.[25] It was recently reported that the *in vitro* test of basophil response to allergen demonstrated effects of omalizumab to depend on the specific/total IgE ratio and an increase in the intrinsic response of the basophil to IgE mediated stimulation. This test is however neither simple nor possible to perform on a routine bases.[26]

Possible New Treatment Alternatives

Several new treatment alternatives are in the pipeline, including Pitrakinra (IL-4/IL-13 antagonist),[27] Lebrikizumab (IL-13 antagonist),[28] and Reslizumab (antibody against IL-5)[29] all of which predominantly target allergic asthma. As these will probably be expensive treatment alternatives, identifying those most likely to benefit from these interventions will be increasingly important. So

far Mepolizumab (IL-5 antagonist) is the only monoclonal antibody based drug, besides omalizumab, that has been studied in children and with rather promising results in children older than 12 years of age with severe eosinophilic asthma.[30]

Finally a novel marker of potential clinical relevance need to be mentioned, that is periostin, a protein suggested to be a marker of Th2-type inflammation in asthma[31] The effect of Lebrikizumab treatment has been shown to be greater in severe asthmatics with high periostin levels compared to those with low periostin levels, as demonstrated by an improvement in FEV1 and reduction in FeNO[32] thus providing an new example of biomarker guided treatment in severe asthma.[33]

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TREATMENT STRATEGIES

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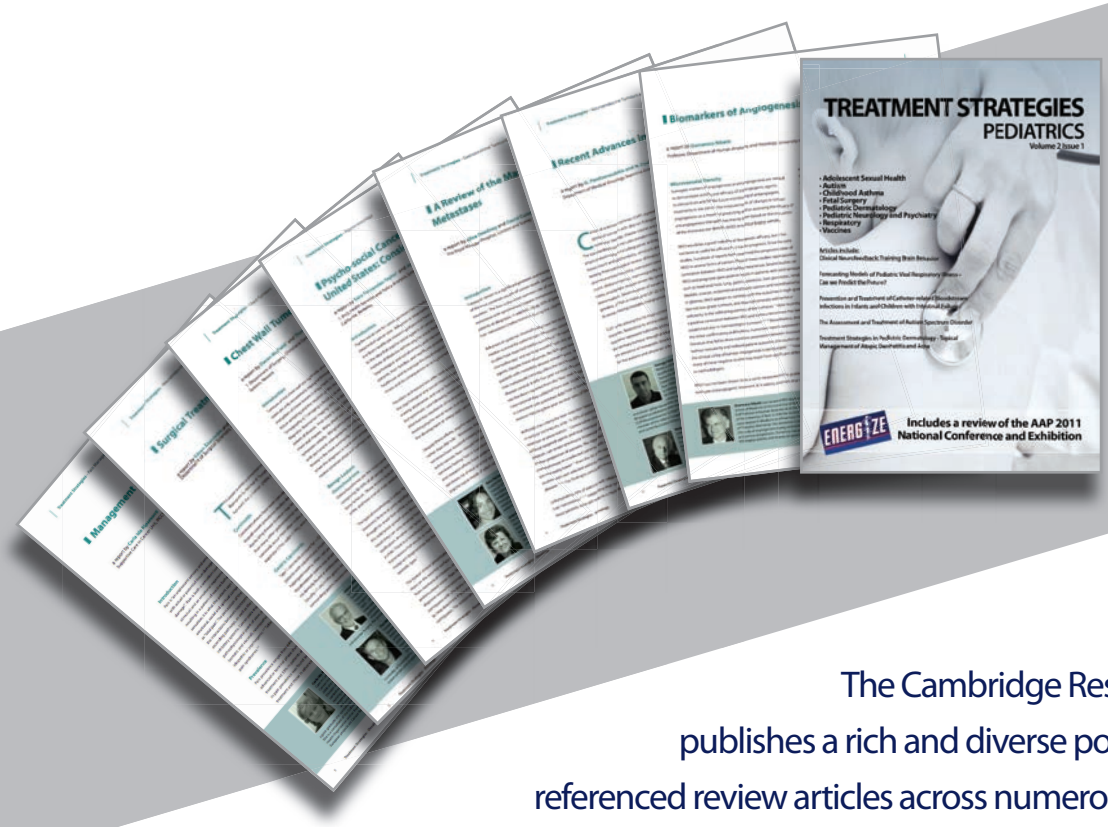

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Red Blood Cell Transfusion Therapy in Critically Ill Children

Sonia Labarinas and **Oliver Karam**
Paediatric Critical Care Unit, Geneva University Hospital, Geneva

Introduction

Humans have to be able to extract oxygen (O_2) from the atmosphere, transport it to their cells, and use it for essential metabolic processes. Whereas some cells can produce energy in absence of oxygen (anaerobic metabolism) for a short time, other organs (such as the brain) are made up of cells that rely on continuous oxygen supply for their metabolism (aerobic metabolism). Nearly all O_2 is transported to the cells thanks to haemoglobin (Hb), as only 0.3% is dissolved in plasma. Therefore, haemoglobin is essential to life.

Critically ill children have a significant risk of developing anaemia during their stay in the intensive care unit.[1-3] The pathogenesis of the anaemia is multifactorial and has been well described in the paediatric and adult literature.[4, 5] It is mostly associated with a decreased production and increased destruction of red blood cells (RBCs), and to blood loss during procedures or during lab exams.

Oxygen Transport

The process of delivering O_2 to the cells is called oxygen delivery (DO_2). DO_2 is dependent on cardiac output (CO) and arterial concentration of O_2 (CaO_2).

$$DO_2 = \text{cardiac output} \times CaO_2$$

Arterial concentration of O_2 (CaO_2) is defined by the formula:

$$CaO_2 \text{ (ml } O_2/100 \text{ ml)} = \{(Hb \times SaO_2 \times 1.34) + (0.003 \times PaO_2)\}$$

Hb level is expressed in g/dL, arterial O_2 saturation (SaO_2) is expressed as a fraction and partial pressure of oxygen in arterial blood (PaO_2) is expressed in mmHg. Therefore, global DO_2 is directly proportionate to Hb concentration.

DO_2 represents the amount of oxygen received by cells. However, only a small proportion is used, which is defined as the oxygen consumption (VO_2).

$$VO_2 = \text{Cardiac Output} \times 1.34 \times Hb \times (SaO_2 - SvO_2)$$

Where arterial and venous saturations in oxygen (SaO_2 and SvO_2) are expressed as a fraction, and Hb concentration is expressed in grams per deciliter (g/dL).

In normal physiological conditions, DO_2 is three to five times greater than VO_2 and VO_2 doesn't depend on DO_2. Nevertheless, if DO_2 drops enough, compensatory mechanisms are overwhelmed and VO_2 falls proportionally. Below this critical point, VO_2 becomes dependent on DO_2 and tissue hypoxaemia occurs. Therefore, in these situations, it is fundamental to improve DO_2 in order to provide enough oxygen for aerobic metabolism and allow for energy requirements to be met.

Intuitively, it might seem that transfusions would increase DO_2 and VO_2 in anaemic critically ill patients. However, many studies have failed to show such an improvement.[6, 7] Furthermore, RBC transfusions are an expensive treatment, as the real cost of each RBC unit is approximately 750$.[8]

Complications of RBC Transfusions

Although RBC transfusion has become increasingly safer (with virtually no risk of viral transmission), there is a growing acceptance that its use isn't devoid of risks and is associated with

Sonia Labarinas is currently a paediatric critical care fellow, at the University Hospital in Geneva, Switzerland. She is a board certified paediatrician, after having completed most of her residency in Switzerland and Spain. She has also trained one year as a paediatric onco-hematology fellow. Her current thesis field consists in determining red blood cell transfusion thresholds in the PICU.

Oliver Karam is a paediatric critical care physician, at the University Hospital in Geneva, Switzerland. His research interests include red blood cell (RBC) transfusion thresholds, clinical and biological effects of RBC length of storage, and plasma transfusion strategies. He is currently a member of the institutional board on transfusion strategies, and leads an international research group on transfusion medicine. He has been invited as a lecturer to national and international meetings worldwide, and is a regular reviewer of research papers for many scientific journals.

complications and unfavourable outcomes.

The most frequent transfusion-related complications in critically ill children are been well documented in 2011 by Istaphanous *et al.*[9]

They included:
- Bacterial infections
- Febrile reactions
- Transfusion associated volume overload (TACO)
- Metabolic anomalies
- Coagulation defects
- Transfusion related acute lung injury (TRALI)
- Immunomodulation
- Necrotising enterocolitis and retinopathy in neonates
- Graft versus host disease

Other paediatric studies also showed increased nosocomial infections, length of mechanical ventilation,[1] and mortality.[5, 10, 11]

Length of Storage and Clinical Impact

RBC units can currently be stored up to 42 days. This has permitted the creation of a blood bank, which is essential to any health system. Nevertheless, stored RBC units suffer from progressive biological alterations such as K+ increase, 2,3-diphosphoglycerate (2,3DPG) decrease, pH fall and ATP depletion, among other variations. RBC morphology also changes, which leads to an impaired function of the red cell itself. Studies have also detected many proinflammatory molecules in RBC units, including cytokines, complement activators, O_2 free radicals, histamine and other bioreactive substances that may initiate, maintain, or enhance an inflammatory process. Therefore, the length of storage seems to alter the composition of transfused RBC units, which might have clinical impacts.

Considering these time-related changes, there is currently some debate about the appropriate storage time. A prospective descriptive study[12] undertaken in critically ill children suggested that the outcome is less favourable when transfusing packed RBC units that have been stored for more than 2 or 3 weeks. On the other hand, a large observational study conducted on the general Swedish and Danish population has not shown any mortality increase.[13] Recently, a neonatal randomised controlled trial has shown that fresh blood (stored for a mean period of 5 days) was not better that the usual blood (stored for a mean period of 14 days).[14] As the clinical impact could be different depending on the severity of the illness and the population, a paediatric and an adult trial are underway.

Current Recommendations

In 1942, 2 anaesthesiologists, Drs. Adams and Lundy, wrote: "When concentration of Hb is < 8 to 10 g per 100 cubic centimeters of whole blood, it is wise to give a blood transfusion before operation." Thereafter, the "10/30" rule (Hb of 10 g/dL or haematocrit of 30%) was standard practice for more than 50 years.

In 2005, Armano *et al.* described in a prospective study the most frequent clinical situations requiring a transfusion: these were an Hb<9.5g/dl, the illness severity upon arrival, cardiac anomalies and multiple organ dysfunction.[2] Two survey of paediatric critical care physicians[11, 15] revealed an Hb threshold range from <7g/dL to <13g/dL for the same clinical scenarios. Therefore, there is a large variability in the current practice of RBC transfusions.

The most common determinant leading to a red blood cell transfusion does not depend exclusively on Hb. Other factors, like age, illness severity, PaO_2, lactic acidosis and active bleeding will also motivate such an approach.

Within the last few years, more subtle recommendations can be made, based on appropriate balance of the risks and benefits of RBC transfusions. Clinical situations requiring RBC transfusions can be divided into five categories: hemorrhagic shock, unstable patients, stabilised patients, patients with cyanotic heart disease, and chronic anaemia.

Clinical situations and their current transfusion recommendations:

Hemorrhagic shock: This specific clinical situation combines erythrocyte loss and hypovolemic shock. Therefore a rapid replacement of RBCs is probably necessary. Nevertheless, no randomised controlled trial has yet evaluated a proper RBC transfusion threshold. As a consequence, physicians generally rely on expert recommendations. These suggest initiating volume resuscitation with 40 to 60 ml/kg of crystalloid solutions before transfusing RBC units.

Unstable patients: Such patients can be defined as hypotensive, or normo-tensive with signs of poor perfusion (lactate level> 3mmol/l, SvO2 <65-75%, prolonged capillary refill, oliguria, abnormal level of consciousness). Based on data extrapolated from an adult trial in septic patients,[16] it seems appropriate to transfuse unstable patients if Hb<10g/dL, after optimisation of the cardiac output.

Stabilised patients: A patient is considered stable or stabilised if the mean systemic arterial pressure is not less than 2 standard deviations below the normal mean for age and if cardiovascular support has not been increased for at least 2 hours. Studies in adults (TRICC) and children (TRIPICU) suggest that most stable critically ill patients can support an Hb concentration> 7g/dL.[17, 18] Sub-group analyses suggest that this is also true for post-op cardiac surgery patients, post-op general surgery patients and septic patients. This threshold is therefore recommended for stabilised patients.

Cyanotic congenital heart disease: These patients will spontaneously compensate their low arterial saturation by increasing their haemoglobin. Consequently, thresholds as high as 13 g/dl and even 16 g/dl are recommended in some textbooks. In 2011, Cholette *et al.* showed in a randomised controlled trial that a more restrictive transfusion strategy (Hb <9g/dL) could be safe for these patients.[19]

Chronic anaemia: Patients with chronic anaemia (i.e. anaemia that is not the result of acute blood loss nor acute haemodilution) have usually increased their cardiac output (to maintain DO_2) or have decreased their VO_2. No randomised controlled trial has evaluated the transfusion threshold for these patients. The only data is from observational studies. In 61 adult Jehovah's Witnesses with an Hb < 8 g/dL, deaths due to anaemia only increased at an Hb below 5 g/dL20. Although such a threshold seems reasonable to many physicians, no recommendation can be made until a proper trial is undertaken.

Conclusion

Red blood cell transfusions remain the only effective and rapid way to increase haemoglobin level. Despite the high incidence of transfusion in critically ill patients, the benefit of transfusions remains the subject of much controversy. According to current literature, lower transfusion thresholds are well tolerated in critically ill stabilised patients. This could lead gradually to a reduced exposition to blood products and herewith decrease transfusion-related complications among this group of patients. In conclusion, RBC transfusions should be based on individual patient's characteristics and only administered if the benefit outweighs the potential risk.

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Current Practice Guidelines for Procedural Sedation, Pain Management and Anaesthesia in the Paediatric Intensive Care Unit

Rimantas Kevalas,[1] Danguole C. Rugyte[2] and **Birute Petraitiene[1]**

1. Paediatric Intensive Care Unit, Department of Paediatrics and 2. Department of Anaesthesiology, Lithuanian University of Health Sciences, Kaunas

Introduction

The practice guidelines are intended for paediatric intensive care physicians, anaesthesiologists and residents who administer sedation and anaesthesia for diagnostic or therapeutic procedures in the Paediatric Intensive Care Unit (PICU).

Preprocedure Evaluation[1]

A patient's medical history must be obtained (including major organ systems, previous anaesthesia and sedation, medications, allergies, and most recent oral intake); a focused physical examination, including heart, lungs, and airway; and laboratory testing based on underlying condition and it's possible effects on management of the patient. The risks, benefits, limitations, and alternatives of the procedural sedation and analgesia should all be evaluated.

Preprocedure Fasting

For elective procedures, there should be sufficient time allowed for gastric emptying. Four hours after breast milk and 6 hours after formula in infants, and 6-8 hours after solid food in children. Clear fluids are allowed up till 2 hours before procedure.[2]

For urgent or emergent situations, the potential for pulmonary aspiration should be considered when determining target level of sedation (deep sedation or anaesthesia should be avoided). Delay of the procedure or protection of the trachea by intubation should be considered. Non-invasive, painless procedures and invasive procedures, associated with low level of pain could be done under minimal or moderate sedation and local anaesthesia when appropriate.

Equipment

The following equipment should always be available:

- Oxygen
- Airway equipment of appropriate size
- Means of positive-pressure ventilation
- Intravenous equipment
- Suction
- Monitoring: ECG and heart rate, pulse oximetry, blood pressure and end tidal CO2 monitoring
- Pharmacologic antagonists, and medications for cardiovascular resuscitation
- Defibrillator should be immediately available

Dose Titration

Medications should be administered incrementally, allowing sufficient time between doses to assess their effect. If both sedatives and analgesics are used, dose reduction should be considered.

Use of Anaesthetics and Sedatives

- **Midazolam** can be administered orally, intranasally[3] (i.n.), intrabuccaly[4] (i.b.) or intravenously (i.v.). Intranasal or buccal dose is equivalent to the intravenous dose. Dose of midazolam can be safely increased up to 0.5 mg/kg (max. dose 10 mg).

- **Diazepam** dose for sedation 0.1–0.2 mg/kg (max. dose 10 mg).

- **Propofol**[5,6] initial dose for sedation is 1 mg/kg, titration in 0.5 mg/kg increments to the desired effect, and injected slowly.

- **Thiopental** initial i.v. dose for sedation is 2 mg/kg, titration in 1 mg/kg increments to the desired effect, and injected slowly.
Initial i.v dose of thiopental for anaesthesia is 5-8 mg/kg for infants and young children and 5-6 mg/kg for older children and adolescents.
Rectal dose for sedation is 30 mg/kg.

Dilution:

- Standard dilution of thiopental (i.v) for children.: 1 ml - 10 mg (200 mg to 20 ml) or 1 ml - 20 mg (400 mg in 20 ml);
- Standard dilution of thiopental (i.v) for infants over 1 month of age: 1ml -1 mg;
- Standard dilution of rectal thiopental: 1 ml - 100 mg.

- **Ketamine** dose for sedation 1-3 mg/kg i/v. Atropine 0.01 mg/kg administration for premedication should be considered to reduce salivation especially for manipulations in respiratory tract before

Procedure	Analgesia/sedation		
	< 8 years		≥ 8 years
	No IV access	Presence of IV access	
· **Non-invasive (painless)** · CT scan · Magnetic resonance imaging · Echocardiography · Ultrasonography · Electroencephalogram	**< 20 kg**: rectal thiopental 30 mg/kg ± midazolam 0.1–0.2 mg/kg i.n., i.b. **≥ 20 kg**: midazolam 0.5 mg/kg orally. Consider insertion of i.v. catheter and administer accordingly, if necessary.	i.v.: midazolam 0.1–0.2 mg/kg ± ketamine 1–2 mg/kg to effect or i.v propofol 1-2 mg/kg to effect or i.v thiopental 1-2 mg/kg to effect.	If necessary: see column 'presence of IV access".
· Scintigraphy	**Induction**: inhalational + i.v.: fentanyl 1 µg/kg + intermediate or long acting MR. Intubation + mechanical ventilation **Maintenance**: i.v.: thiopental 5 mg/kg/hr. or propofol 9-12 mg/kg/hr ± intermediate or long acting MR.	**Induction**: i.v.: thiopental 5-8 mg/kg or propofol 2.5–3.5 mg/kg + fentanyl 1 µg/kg + intermediate or long acting MR. Intubation + mechanical ventilation **Maintenance**: i.v.: thiopental 5 mg/kg/hr. or propofol 9-12 mg/kg/hr ± intermediate or long acting MR	
· **Invasive (associated with low level of pain)** · Peripheral IV insertion · Straight urethral catheterisation · Wound dressing or suture (minor injuries)	Midazolam 0.2–0.5 mg/kg orally, i.n., i.b. ± local anaesthesia	1) Midazolam 0.2 mg/kg i.v. ± local anaesthesia 2) Morphine 50–100 µg/kg i.v. (bolus) ± local anaesthesia	**If necessary:** 1) Midazolam 0.2 mg/kg i.v. or 0.5 mg orally ± local anaesthesia 2) Morphine 50–100 µg/kg i.v. (bolus) ± local anaesthesia
· **Invasive (average pain)** · Endoscopy (fibrobronchoscopy etc.) · Lumbar puncture · Nasolacrimal duct probing · Anterior fontanelle puncture	**Induction**: inhalational anaesthesia ± i.v.: fentanyl 1 µg/kg **Maintenance**: inhalational anaesthesia ± local anaesthesia	**Induction i.v.:** 1) Midazolam 0.1–0.2 mg/kg ± fentanyl 1 µg/kg ± inhalational anaesthesia 2) Diazepam 0.1–0.2 mg/kg (max. dose 10 mg) or midazolam 0.1–0.2 mg/kg + ketamine 1–2 mg/kg 3) Propofol 1-3.5 mg/kg ± fentanyl 1 µg/kg **Maintenance:** 1) inhalational anaesthesia ± local anaesthesia 2) Ketamine[10] 0.5–1 mg/kg i.v. to effect ± local anaesthesia 3) Propofol[11, 12] 0.5 mg/kg repeat dose i.v. or 5-9 mg/kg/hr ± local anaesthesia	
· Rigid bronchoscopy	**Induction**: inhalational anaesthesia+ i.v.: fentanyl 1 µg/kg + short acting MR **Maintenance**: inhalational anaesthesia ± i.v.: fentanyl 1 µg/kg (max. dose 3 µg/kg) ± short acting MR i.v. (if procedure prolonged)	**Induction i.v.**: 1) Thiopental 5-8 mg/kg + fentanyl 1 µg/kg + short acting MR 2) Propofol 2.5-3.5 mg/kg + fentanyl 1 µg/kg + short acting MR. **Maintenance**: 1) Mask anaesthesia ± fentanyl 1 µg/kg (max. dose 3 µg/kg) i.v. ± short acting MR i.v. (if procedure prolonged) 2) Propofol 9-12 mg/kg/hr anaesthesia or inhalational anaesthesia ± fentanyl 1 µg/kg (max. dose 3 µg/kg) i.v. ± short acting MR i.v. (if procedure prolonged).	
· FEGDS*			See column above (with tracheal intubation) or minimal to moderate sedation with midazolam 0.2 mg/kg i.v. (if short procedure)
· **Invasive (high level of pain)** · Bone marrow puncture · Joint puncture · Renal biopsy · Liver biopsy · Paracentesis · Thoracocentesis and drainage · Central venous catheter insertion · Cardioversion · Burn dressing · Wound dressing (multiple, deep, large, open wounds)	**Induction**: inhalational anaesthesia + i.v.: fentanyl 1 µg/kg **Maintenance**: inhalational anaesthesia ± i.v. fentanyl 1 µg/kg (max.dose 3 µg/kg)	**Induction i.v.**: 1) Thiopental 2–7mg/kg + fentanyl 1 µg/kg 2) Diazepam 0.1–0.2 mg/kg (total dose 10 mg) or midazolam 0.1–0.2 mg/kg + ketamine 1–2 mg/kg 3) Propofol 1–3.5mg/kg + fentanyl 1 µg/kg. **Maintenance**: 1) inhalational anaesthesia 2) Thiopental 1 mg/ kg i.v. to effect ± fentanyl 1 µg/kg (max. dose 3 µg/kg) 3) Ketamine 0.5–1 mg/kg i.v. to effect 4) Propofol 0.5 mg/kg repeat dose i.v. or 5-9 mg/kg/hr ± fentanyl 1 µg/kg (max. dose 3 µg/kg)	
Angiography	**Induction**: inhalational anaesthesia+ i.v.: fentanyl 1 µg/kg + intermediate or long acting MR. Intubation + mechanical ventilation. **Maintenance**: i.v.: thiopental 5 mg/kg/hr. or propofol 9-12 mg/kg/hr.+ 1 µg/kg fentanyl (before puncture) + local anaesthesia ± intermediate or long acting MR i.v.	**Induction**: ¡ v.: thiopental 5-8 mg/kg or propofol 2.5–3.5 mg/kg + fentanyl 1 µg/kg + intermediate or long acting MR. Intubation + mechanical ventilation. **Maintenance**: i.v.: thiopental 5 mg/kg/hr. or propofol 9-12 mg/kg/hr + 1 µg/kg fentanyl (before puncture) + intermediate or long acting MR ± local anaesthesia	**Induction**: i.v.: thiopental 2–7 mg/kg or propofol 1–3.5 mg/kg + fentanyl 1 µg/kg. **Maintenance of sedation**: thiopental (if necessary) 1 mg/kg or propofol 0.5 mg/kg repeat dose or 5-9 mg/kg/hr ± fentanyl 1 µg/kg (max. dose 3 µg/kg) + local anaesthesia.
· **Shock and hypotension**	**Induction**: midazolam 0.1 mg/kg (max. dose 0.3 mg/kg) i.v., i.n., i.b. ± ketamine[13] 1–2 mg/kg i.v. Maintenance: ketamine 0.5–1 mg/kg i.v.		
*FEGDS – fibrooesophagogastroduodenoscopy.			

Table 1. Procedural sedation and analgesia/anaesthesia in the PICU.

administration of ketamine.

• **Fentanyl**[7] administration should be careful and a cumulative dose of 3 µg/kg should be avoided when spontaneous breathing is desirable. For infants less than 18 month of age the opioid should be injected at least per 3-5 min. Muscular relaxants or naloxone should be immediately available if chest wall rigidity syndrome occurs.

• **Morphine** administration should be careful. Titrate to desired effect in 20-50 µg/kg increments. Inject slowly to reduce histamine release and hypotension. Reduce doses by 1/2-2/3 in infants over 1 month of age.

• **Sevoflurane** is a preferable agent for inhalational anaesthesia.

• **Muscular relaxants (MR)** difficult airway and the risk of aspiration in suspected patients should be considered before an appropriate muscle relaxant is used.

• ***Intermediate or long acting MR*** is used for long-lasting procedures. *Atracurii besilas*, initial dose 0.5 mg/kg, repeat dose 0.1-0.2 mg/kg; *Rocuronii bromidum*, initial dose 0.6–1.2 mg/kg, repeat dose 0.1 mg/kg; *Pipecuronii bromidum*, initial dose 0.06–0.08 mg/kg, repeat dose 0.02 mg/kg.

• ***Short acting MR*** is used for short procedures and rapid sequence induction. *Mivacurii chloridum*, initial dose 0.2 mg/kg, repeat dose 0.02 mg/kg. *Succinylcholine* (if there are no contraindications) in a dose of 1-2 mg/kg should be considered in infants and as an alternative for rapid sequence induction.[8] Administer atropine 0.01-0.02 mg/kg to prevent bradycardia in infants before succinylcholine.

• **Local anaesthesia** is performed by 1-2% lidocaine solution (max. dose 5 mg/kg).

Intravenous Access

Sedatives and anaesthetic agents routinely are administered intravenously if there is an intravenous access. For infants and young children without intravenous access, sedatives and anaesthetics are administered by other routes. Intravenous access should be made under deep sedation if deep sedation or anaesthesia is required for procedure management. If minimal to moderate sedation is required, procedure management can be maintained without an intravenous access on a case-by-case decision basis. However, possibility of an intravenous catheter insertion should be evaluated in advance to ensure an IV route to be immediately available.

Recovery

Patients should be observed until they are awake and/or no longer at risk for cardiorespiratory depression.

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Metabolic Outcomes of Adults Born Preterm

James R.C. Parkinson and **Neena Modi**
Section of Neonatal Medicine, Department of Medicine, Imperial College London, Chelsea and Westminster Hospital Campus, London

Introduction

Around 10% of births in the developed world are preterm, below 37 weeks gestational age (GA), and the absolute number is rising globally. Advances in neonatal healthcare have greatly improved the survival rate of these infants, free from major impairment. The population of adults that were born preterm is hence growing rapidly, and their health is a matter of growing importance. A growing body of evidence has identified premature birth as a risk factor for the development of metabolic syndrome associated features in later life, including insulin resistance and high blood pressure. We discuss candidate mechanisms and the potential for therapeutic intervention.

The Metabolic Syndrome and Preterm Birth

The constellation of abdominal adiposity, hypertension, insulin resistance and dyslipidaemia, collectively termed the "metabolic syndrome", imposes a substantial burden upon population health. Despite some two decades of intensive, international research effort, aetiology and prevention remain elusive. These conditions, originally viewed as consequences of a suboptimal adult lifestyle, are now recognised to be influenced by experiences in early life.[1] Preterm infants are part of the "low birth weight" spectrum, and their early neonatal period, corresponding to the third trimester of pregnancy, differs from conditions *in utero*. A number of studies have demonstrated an association between preterm birth and the development of features of the metabolic syndrome in later life. These features include abdominal adiposity, higher blood pressure, insulin resistance and ectopic fat deposition.[2-4] However, other studies suggest no negative long-term impact.[5-7] The aim of this review is to assess the current evidence for an altered metabolic phenotype in adults born preterm, discuss the possible biological trajectories involved, and identify potential interventional strategies to attenuate these effects.

The Phenotype of the Adult Born Preterm

Anthropometry

Individuals born prematurely demonstrate lower weight, body mass index (BMI) and shorter stature throughout infancy and childhood, compared to their term born peers.[8, 9] These differences are attenuated during adolescence, with women born preterm demonstrating faster catch-up growth than men.[9, 10] By adulthood, there are no differences between preterm and term individuals in height, weight or BMI.[11, 12] As with all anthropometric measurements, BMI only offers a proxy measure of body adiposity and metabolic dysfunction.[13]

Body Composition

Measurements of body composition suggest that the reduced weight observed in children and adolescents born preterm is associated with reduced adipose tissue mass, as opposed to reduced lean mass.[14, 15] However, similar to the attenuation in anthropometric differences, these effects are no longer apparent in adulthood.[13, 16-18] Magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS) are techniques that enable a more in-depth assessment of metabolically distinct adipose tissue and ectopic lipid depots. These techniques have revealed greater intra-abdominal adiposity (IAAT) and intrahepatocellular lipid (IHCL) in preterm infants[19] and adult men born preterm[4] in comparison with term-born controls. Intra-abdominal adiposity and IHCL are strongly associated with insulin resistance,[20, 21] with excess lipid deposition in both regions thought to induce cellular stress that initiates and perpetuates an inflammatory cycle, contributing to the development of this key feature of the metabolic syndrome.[22]

Insulin Resistance

Data on the relationship between GA and more established markers of insulin resistance, such as fasting glucose and insulin, have been inconclusive; several studies find no association,[23, 24] while other large cohort analyses demonstrate a clear link between GA and development of diabetes in childhood and later life.[25, 26] Future studies which provide data on glucose homeostasis using a recognised outcome measurement such as HOMA-IR,[27] which is sensitive and combines both glucose and insulin measurements, may elucidate the real effect.

Dyslipidaemia

Hyperlipidaemia is another key cardiovascular risk factor used to

identify the metabolic syndrome.[22] The limited data available examining plasma lipids and cholesterol demonstrate no differences between term and preterm individuals.[4, 28, 29] To-date studies have characterised healthy participants and have involved small numbers. Hence absence of any difference may reflect inadequate power or insufficiently sensitive standard clinical assays. High throughput techniques involving chemical spectroscopy providing a "fingerprint" of metabolites may help to detect areas of altered metabolism in children and adults born preterm individuals and identify biomarkers suitable for longitudinal evaluation.[30] We have shown that young adult men born preterm have significant differences in urinary metabolites associated with increased blood pressure and inflammation, compared to term-born controls.[4]

Appetite Regulation

Perturbation of appetite regulation and adipose tissue sensing are candidate causal mechanisms in early life programming. Determining levels of key metabolic hormones is a means of gauging derangement of hypothalamic circuitry involved in energy homeostasis and surrogate outcome evaluation in nutritional trials. Pre-pubertal children born preterm demonstrate higher circulating concentrations of the appetite stimulating peptide ghrelin.[31] Furthermore, leptin, a central regulator of energy homeostasis, is significantly altered in adolescents born preterm who receive a high compared to low nutrient diet postnatally, even after adjusting for fat mass.[22] Functional MRI also provides a non-invasive means of assessing these physiological pathways.

Hypertension

Hypertension is a major risk factor for heart disease, stroke and renal failure. Systematic reviews and meta-analyses of a large number of independent studies have consistently demonstrated increases in systolic (SBP) and diastolic blood pressure (DBP) of around 3-4 mmHg in ex-preterm children, adolescents and adults.[32-34] Lowering BP by 2 mmHg has been reported to reduce hypertension by 17%, heart attacks by 6% and stroke by 15%,[34] and this increase is therefore of great clinical relevance. With regards to mechanism, the third trimester represents a crucial period for kidney development, with nephrogenesis completed by 36 weeks gestation. However, only a small number of studies have examined renal function in children[36] and adults[37] born preterm, with no consistent differences with full-term counterparts observed.

Disturbance of endothelial function is considered key to the development of vascular disease, and is another potential mediating factor linking preterm birth and increased blood pressure. Dysfunction in microvasculature,[37] autonomic cardiac control,[38] and arterial stiffness have all been observed in preterm infants. However, conflicting data exist on arterial stiffness and endothelial dysfunction in children and adolescents born preterm; with some studies indicate a positive association[5, 38] whereas no association is found in others.[6, 39] Continuous ambulatory monitoring is considered a more reliable approach to assessing blood pressure as it is less affected by the anxiety response that accompanies one-off "office" measurements.[31] A meta-analysis revealed a smaller but significantly increased ambulatory SBP of around 2 mmHg in women but not men.[40] Several additional studies have also demonstrated sex differences in individuals born preterm in relation to susceptibility to adverse outcomes, including adiposity, ectopic fat deposition and metabolic profile.[4, 41] Together, these data suggest a gender specific trajectory following preterm birth.

Methodological Considerations

Despite the emerging picture of altered metabolism, a number of methodological aspects must be acknowledged and addressed before the contribution of preterm birth to the development of the metabolic syndrome can be fully determined. Bias, arising from selective publication of smaller studies reporting larger effects,[42] and inappropriate statistical adjustment for confounders such as BMI and adult weight, which lie along the causal pathway between birth weight and blood pressure, may have overestimated the effects of preterm birth.[43] Conversely, the dose-response relationship between prematurity and metabolic syndrome associated outcomes, as suggested by several large cohort studies,[26, 44] suggests the exclusion of extremely preterm individuals that is often observed in study recruitment may result in an underestimation of the association between preterm birth and outcomes.

Intrauterine Growth Restriction and Preterm Birth

A focus on low birth weight as a risk factor for adult blood pressure has also complicated efforts to specifically define the role of preterm birth, as this nomenclature fails to disentangle the overlap with intra-uterine growth restriction. There is an established association between low birth weight and reduced insulin sensitivity, type-2 diabetes, cardiovascular disease and increased central/abdominal adiposity in later life.[45] A small number of publications have attempted to address this confounder by comparing outcomes in preterm infants born with a birthweight appropriate for gestational age (AGA) with those born small for gestational age (SGA). These have identified no significant differences were observed between preterm AGA and SGA groups regarding features of the metabolic syndrome, including blood pressure.[46, 47]

Other Influences

Additional influences, such as socioeconomic status (SES), also appear to contribute to the development of an adverse cardiovascular phenotype.[48] Studies in which preterm subjects were matched for SES[49, 50] or in which outcome data were statistically adjusted for SES, [44, 46, 51, 52] indicate that the increase in blood pressure observed in adults born preterm is independent of this variable.

Accelerated Ageing

The early manifestation of features of the metabolic syndrome seen in preterm individuals is suggestive of accelerated ageing. Telomere length has been postulated as a mechanism of longevity regulation; telomeres from somatic cells shorten with every division and correlate with longevity in many species.[53] As well as shortening with cell division, stress exposure in intrauterine life associated with shorter telomere length in adulthood.[54] However, a study involving a large follow-up of several adult cohorts indicates no association between telomere length and either body size or gestational age at birth.[55] Ageing is inexorably linked to the development of features of the metabolic syndrome and a significant increase in blood pressure in childhood, translates to a greater risk upon reaching adulthood.[56] The predisposition of preterm individuals to develop features of the metabolic syndrome is therefore likely to become more pronounced as they age, particularly in an obesogenic environment.

Neonatal Interventions

With regard to interventional strategies, critical or sensitive periods of early development appear to exist both pre and postnatally, during which time nutrition has long-term implications for disease risk in adulthood.[57] Growth velocity in infancy is a key determinant of body size, adipose tissue mass and body composition, irrespective of birth weight.[58] Low birth weight infants that have rapid postnatal growth are at increased metabolic risk and are the most likely to develop type-2 diabetes, hypertension, abdominal obesity and coronary heart disease.[59, 60] Notably, sensitivity to accelerated growth has been associated with the first week of postnatal life,[61] independent of both birth weight and gestational age.[60, 62] Nutrition is a key determinant of the rate of postnatal growth and represents a potential target for clinical intervention in preterm populations.

Next Steps

To-date there is limited data available on older ex-preterm adults due to the relatively recent advancements in neonatal care and inconsistent and often poor medical record archiving. Few studies have presented data on preterm individuals older than 30 years of age and the full range of effects of early life programming may not emerge until later in life. For example, the benefits of human breast milk feeding for preterm babies on blood pressure were not observed at follow up at 7-8 years but only detected during adolescence.[63]

The range of effects observed in outcome measurements between term and preterm populations recorded at different ages highlights the difficulties inherent in defining an "ex-preterm" phenotype. The true impact of preterm birth on life-long metabolic and cardiovascular health is now a matter of population health and will need to be defined in carefully designed studies with serial assessments of longitudinal outcomes. The extent to which life-style factors may amplify or attenuate biological trajectories is also unknown. Determining the biological pathways responsible and identifying the casual influence of confounders such as low birth weight and neonatal growth rate also remain to be answered. Future studies should be powered to detect gender specific trajectories following preterm birth and designed to elucidate the physiological mechanisms which underpin divergence.

Funding: JRCP is funded by the Chelsea & Westminster NHS Foundation Trust.

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New Trends in Surfactant Replacement Therapy in Premature Infants with Respiratory Distress Syndrome

Filip Cools
Neonatal Intensive Care Unit, Universitair Ziekenhuis Brussels

Introduction

Premature infants frequently suffer from respiratory distress syndrome (RDS) due to pulmonary surfactant deficiency. For infants born before 29 weeks' gestation, the incidence can be as high as 93%.[1] Although the use of mechanical ventilation has strongly improved their outcome, it has also been associated with both acute lung injury, such as pneumothorax and pulmonary interstitial emphysema, as well as chronic lung injury or bronchopulmonary dysplasia.[2] In the 1990s, the administration of exogenous surfactant has been established as an effective and safe treatment for RDS, reducing mortality by more than 30% and the risk of pneumothorax by almost 60%.[3]

Randomised controlled trials performed in those years also showed us that the timing of surfactant administration is of great importance. Prophylactic treatment, i.e. surfactant administration to infants at risk of RDS within the first hour after birth, was associated with less risk of death or pneumothorax compared with selective treatment, i.e. surfactant administration to infants with established signs of RDS.[4] As a result, mechanical ventilation combined with prophylactic surfactant therapy became the recommended strategy for the treatment of RDS.

In the late 1990s, however, an increasing body of evidence indicated that mechanical ventilation could be harmful to the fragile, immature lungs of premature infants through various pathogenetic mechanisms.[5,6] As a result, a shift occurred in the management of RDS towards non-invasive forms of respiratory support, mainly nasal continuous positive airway pressure (CPAP).

Filip Cools currently acts as the Head of the Neonatal Intensive Care Unit at the UZ Brussel in Brussels. Further to this he acts as Associate Professor at the Vrije Universiteit Brussel (VUB). Dr. Cools' other affiliations and duties include secretary of the Board of the Belgian Society for Neonatology (GBN-BVN), staff member of the Belgian Centre for Evidence-Based Medicine (CEBAM) and Director of the Belgian Branch of the Dutch Cochrane Centre.

At the same time, an equally important change occurred in the patient population neonatologists were faced with. On the one hand, the use of antenatal corticosteroids to stimulate foetal lung maturation, had become standard practice,[7] on the other hand, a trend towards an increasing number of extremely premature infants was seen, born at the limits of viability. This resulted in an increasing population of extremely fragile preterm infants with only mild to moderate severe RDS.

These two changes combined have created an interesting challenge for neonatologists in finding the optimal strategy to combine the most appropriate non-invasive respiratory support with the optimal method of surfactant replacement therapy. In the past decade, several strategies have been developed and studied.

1. Early stabilisation with Nasal CPAP; Rescue Intubation, Surfactant Therapy and Mechanical Ventilation if Respiratory Distress Progresses

Although the use of nasal CPAP in the treatment of RDS was already described in 1971,[9] the interest only became strong after the publication in 1987 of a survey of 8 North American neonatal units showing that the center practicing early nasal CPAP instead of initiating mechanical ventilation, had by far the lowest incidence of bronchopulmonary dysplasia.[10] In Scandinavia, stabilisation of very low birth weight infants using early nasal CPAP instead of mechanical ventilation progressively became standard practice in the 1990s. The feasibility and safety of this approach was supported by observational studies.[11] The first large randomised controlled trial (COIN trial, 2008) confirmed that, using early nasal CPAP in infants less than 29 weeks' gestation with signs of respiratory distress at birth, mechanical ventilation could be avoided in 54%.[12] The risk of death or bronchopulmonary dysplasia, however, was comparable in both groups. A concerning finding of the COIN study was that the risk for pneumothorax was significantly increased in infants managed with early nasal CPAP (9% versus 3%). This result has been contributed to the fact that infants in the nasal CPAP group only qualified for intubation

and surfactant therapy if their RDS had progressed to a more severe stage, with a fractional inspired oxygen concentration exceeding 0.60, and to the fact that not all infants, once intubated, necessarily received surfactant.

In the SUPPORT trial, comparing early nasal CPAP with prophylactic intubation and surfactant at birth in infants less than 28 weeks' gestation who are at risk of RDS, a similar reduction in the need for mechanical ventilation was seen.[13] At 7 days of age, significantly more infants were alive and without need for mechanical ventilation in the CPAP group as compared with the prophylactic surfactant group (55% versus 49%). As opposed to the COIN trial, no difference in the risk for pneumothorax was seen. Of notice is the fact that in the SUPPORT trial infants in the CPAP group were intubated earlier in the course of their disease (oxygen requirement greater than 50%), and that all intubated infants received surfactant. In the Vermont Oxford Network trial, finally, infants 26 – 29 weeks' gestation were managed with either prophylactic intubation and surfactant therapy at birth or nasal CPAP and rescue intubation if oxygen requirements exceeded 40%.[14] Eighty-two percent of infants in the CPAP group were managed without intubation.

A recently updated Cochrane systematic review concludes that a strategy of immediate intubation and prophylactic surfactant therapy at birth of infants who are at risk of RDS, is associated with an increased risk of death or bronchopulmonary dysplasia (relative risk 1.12, 95% confidence interval 1.02 – 1.24) compared with an approach of initial stabilisation with nasal CPAP and selective surfactant administration to infants showing evidence of RDS.[15]

2. INtubation-SURfactant-Extubation (INSURE)

Because of the concern that, using an approach of initial stabilisation with nasal CPAP, the optimal window for early surfactant therapy would be missed, and that therefore a possibly beneficial treatment would be withheld from infants who need it, a new strategy was developed in Scandinavia in the early 1990s.

This strategy consisted of surfactant administration by transient intubation followed by rapid extubation and continuation of nasal CPAP, and was called the INSURE technique (INtubation – SURfactant – Extubation).[16] In a first randomised trial, Verder and coworkers showed that, in preterm infants less than 72 hours old with established signs of RDS (ratio of arterial to alveolar oxygen tension of less than 0.22) who are on nasal CPAP, the INSURE procedure could reduce the need for mechanical ventilation from 85% to 43%.[17] In the following years several trials were performed to investigate the effectiveness of this intervention both in infants who are at risk of RDS (prophylactic INSURE) as well as in infants with established signs of RDS (early selective INSURE).

Early INSURE in Infants with Established Signs of RDS:

In a Cochrane systematic review, early INSURE (surfactant administration with brief mechanical ventilation within one hour after birth) in spontaneously breathing infants with signs of RDS who were stabilised on nasal CPAP, was compared with later selective intubation and surfactant administration followed by continued mechanical ventilation.[18] Early INSURE was associated with a significantly reduced need for mechanical ventilation (6 trials, relative risk reduction of 33%) and risk of need for oxygen at 28 days of age (4 trials, relative risk reduction of 49%). However, both the risks of death (6 trials) or BPD at 36 weeks gestational age (3 trials) were comparable in both groups. Verder and colleagues compared the same procedure in a population of preterm infants with moderately severe RDS (arterial to alveolar oxygen tension ratio between 0.35 and 0.22), with a late rescue INSURE procedure, i.e. when their RDS had progressed to a more severe stage (arterial to alveolar oxygen tension ratio between 0.21 and 0.15).[19] Significantly more infants were alive and without need for mechanical ventilation on day 7 of life in the early INSURE group (79% versus 37%). Whether it has any longer term benefit, for example on the risk of BPD, is difficult to say since only 2 of the 60 included infants developed BPD at 36 weeks' gestation. In conclusion, compared with rescue intubation and surfactant therapy or with late rescue INSURE, early INSURE in infants with established signs of RDS significantly reduces the need for mechanical ventilation, but whether or not it offers any benefit in terms of prevention of death or BPD, is less clear.

Prophylactic INSURE in Infants at Risk of RDS:

Two randomised trials investigated whether a prophylactic INSURE procedure, i.e. INSURE performed within the first minutes after birth in preterm infants who are at risk of RDS, would offer any benefit over a strategy of early therapeutic surfactant therapy, i.e. once signs of RDS have become apparent. In the Vermont Oxford Network trial, which included preterm infants from 26 up to 29 weeks' gestation, both prophylactic INSURE as well as nasal CPAP and early rescue intubation and surfactant treatment if RDS deteriorates, were compared with prophylactic intubation and surfactant therapy at birth.[20] In the INSURE group, 83% of infants were successfully extubated after the procedure, and 41% was managed without mechanical ventilation. In the CPAP group, a similar percentage of infants (48%) were able to avoid mechanical ventilation. Compared with prophylactic intubation and surfactant therapy, both prophylactic INSURE as well as CPAP with early rescue surfactant therapy showed a clear trend, though not statistically significant, towards a decreased risk of death or BPD at 36 weeks' gestation: relative risk 0.78 (95% confidence interval 0.59 – 1.03) for INSURE, and 0.83 (95% confidence interval 0.64 – 1.09) for CPAP and rescue surfactant. The incidence of death and BPD at 36 weeks' gestation was very similar in both groups (28% in the INSURE group

and 30% in the CPAP group). In the CURPAP trial, where slightly more immature infants were included (from 25 up to 28 weeks' gestation), prophylactic INSURE was compared with early selective INSURE (i.e. when fractional inspired oxygen concentration exceeded 0.40).[21] For the INSURE procedure, mechanical ventilation was allowed to continue for a time period up to one hour after surfactant administration. In the prophylactic INSURE group, 90% of infants could be successfully extubated after the procedure, whereas in the early selective INSURE group, the success rate was only 62%. The need for mechanical ventilation within the first 5 days was comparable in both groups: 31% and 33% for the prophylactic group and early selective group, respectively. Also, a similar number of infants survived in room air at 36 weeks' gestation in both groups: 78% and 79% for the prophylactic group and early selective group, respectively. In conclusion, the currently available evidence suggests that INSURE performed prophylactically in infants at risk of RDS, does not offer any advantages over an early selective INSURE in infants with established signs of RDS or an approach of initial stabilisation with nasal CPAP and early selective intubation with surfactant administration when RDS deteriorates.

3. Intratracheal Surfactant Administration to Spontaneously Breathing Infants

The INSURE technique still has two potential disadvantages. First, infants need to be intubated intratracheally. This can be a hazardous procedure for a preterm infant,[22] and is often associated with the use of premedication, which itself might have adverse effects such as hypotension or changes in electrical brain activity.[23, 24] Second, a brief episode of positive pressure ventilation cannot be avoided. Animal experiments have not only shown that even a few large positive pressure breaths can be injurious to surfactant deficient lungs,[25, 26] but also that surfactant deposition in lung tissue is better when it is administered under spontaneous breathing than under mechanical ventilation.[27] Therefore, alternative methods of surfactant administration, where endotracheal intubation and positive pressure ventilation can completely be avoided, have been investigated. A few methods have only been tested in small, observational studies, such as the pharyngeal deposition of surfactant before the first spontaneous breath,[28] or the application of surfactant via a laryngeal mask.[29] Other methods, such as the aerosolisation of surfactant are very promising, but still have to overcome important technical challenges.[30] A method that has been developed in Germany and that recently has found its way into clinical practice, however, is the intratracheal instillation of surfactant in spontaneously breathing infants.[31] While the infants is on nCPAP, a thin catheter (e.g. feeding tube) is placed in the trachea under direct laryngoscopy and using Magill forceps. Then, surfactant is instilled for 1 to 3 minutes while the infant continues to breathe spontaneously. Positive pressure breaths are applied over the CPAP system only in case of apnea or desaturation. After surfactant has been instilled, the catheter is removed immediately.

The first randomised controlled trial (the AMV or Avoiding Mechanical Ventilation trial) comparing this new technique with the "standard approach" of initial stabilisation with nCPAP and rescue intubation and surfactant in infants 26-28 weeks' gestation, demonstrated that the need for mechanical ventilation could significantly be reduced from 73% to 33%.[32] The procedure was successful from the first attempt in 95% of the patients and was well tolerated. Unfortunately, the study was not powered to detect differences in longer term outcomes, such as death or BPD at 36 weeks' gestation. Although this new method of surfactant administration is promising, it still faces a few challenges. First, the difficulty of performing the procedure should not be underestimated and it requires a considerable period to train all the staff members of a neonatal unit before it can be used safely.[33] Second, what the optimal technique for intratracheal insertion of the catheter is, is still uncertain. Because of the difficulty of manipulating Magill forceps in the pharynx of an extremely low birth weight infant, an alternative method has been studied in a pilot study using a more rigid vascular catheter which can be introduced into the trachea without the use of Magill forceps.[34] Finally, since INSURE has now been widely adopted as standard practice in many neonatal units, clinicians need to know whether this less invasive method of surfactant administration is superior to INSURE in terms of outcomes such as death or BPD. In order to address that question, a study comparing both techniques directly would be required.

Conclusion

Non-invasive respiratory support is increasingly used in the early management of RDS in preterm infants. This has moved neonatologists to re-evaluate surfactant replacement therapy trying to find the optimal combination in terms of timing and route of administration. Early selective INSURE definitely has proven to be a valid alternative. Intratracheal instillation of surfactant during spontaneous breathing might have an additional advantage because it is less invasive, but still needs further investigation. In the future, even less invasive methods such as aerosolisation of surfactant will gain more interest.

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Update on Non-invasive Respiratory Support (NRS) in Children with Acute Respiratory Failure

Edoardo Calderini,[1] Giovanna Chidini,[1] Marco Ellena[2] and **Cesare Gregoretti[3]**

1. Paediatric Intensive Care Unit, Department of Anesthesia and Critical Care, Fondazione IRCCS Cà Granda, Ospedale Maggiore Policlinico, Milan; 2. Department of Anaesthesia and Intensive Care, Ospedale Molinette University of Turin; 3. Department of Emergency and Intensive Care, CTO, M. Adelaide Hospital, Turin

Introduction

Endotracheal intubation and mechanical ventilation represent the conventional treatment of acute respiratory failure (ARF). However a potential number of serious complications such as ventilator-associated pneumonia, subglottic and tracheal injury and ineffective clearance of secretions can significantly add to morbidity and mortality.[1,2]

Non-invasive respiratory support (NRS) is an alternative respiratory treatment without the need for endotracheal and tracheostomy tubes. NRS could be delivered as non-invasive continuous positive airway pressure (nCPAP) or non-invasive positive pressure ventilation (nPPV) via an interface (nasal/facial mask or helmet).

A high pressure free-flow gas circuit and turbine or piston-driven ventilators are widely employed to deliver nCPAP and nPPV, respectively. It has been shown that NRS improves alveolar ventilation and oxygenation reducing the work of breathing. A number of controlled studies and meta-analysis have demonstrated its efficacy in adult patients but experience in paediatric population is still scarce. Despite this, the use of NRS in paediatric intensive care units (PICUs) is rapidly growing to avoid intubation and prevent extubation failure.

The aim of this paper is to update a recently published review by Chidini *et al.*[3] on NRS in children with ARF by adding articles available in the literature since July, 2010 to November, 2011.

We searched Medline, EmBase, and the Cochrane database, using the keywords "non-invasive" or "non-invasive (mechanical) ventilation", or "non-invasive respiratory support" for all reports of children with ARF. Papers on neonates were excluded.

Technical Issues

The presence of leaks through the interface may impair the correct functioning of the ventilator, thus causing asynchrony, patient discomfort and NRS failure.

Ueno and co-workers[4] in a bench study, investigated how ventilators cope by varying the amounts of leakage during NRS. The authors tested three "home" ventilators (Respironics® Vision, Trilogy100,and Drager® Carina) and two "ICU" ventilators (Puritan Bennett® 840 and Drager® Evita XL).

At pressure support (PS) of 0 and 10 cmH_2O and PEEP of 5 and 10 cmH_2O, spontaneous breathing was simulated using a model lung. By opening different-size holes, defined as medium and large, leaks were produced (28 L/min and 52 L/min at PS 10 cmH_2O, respectively). With medium leak, Vision and Carina were the only ventilators able to maintain the set PEEP and PS levels. With greater leakage, no ventilators reached the preset PEEP and PS levels. This paper suggest that "home" ventilators perform better in the presence of leaks than "ICU" ventilators. Large leaks are not yet well compensated by any machine.

Muñoz-Bonet *et al.*[5] completed a survey, in a prospective observational three years study, to evaluate whether a conventional "ICU" volumetric ventilator with an automatic air-leak compensation software could be successfully applied to infants and children with ARF of different origin. Thirty-two episodes of ARF were observed in twenty-six patients (mean age: 7.9 years, SD 5.2) during the study period. A Drager® Evita 2 Dura ventilator was used in CPAP + PS mode in post-extubation failure and in mild to moderate *ex-novo* ARF, while Bilevel Positive Airway Pressure (BiPAP®) + PS mode in the rest of cases. In all modes a non-invasive ventilation software was used and all subjects were connected to non-vented facial masks. Sedatives were given to all patients and none of them required NRS withdrawal. A significant improvement in respiratory rate, peripheral oxygen saturation and heart rate was rapidly obtained and maintained throughout the first twenty-four hours. Only four patients needed tracheal intubation. No severe complications were reported. The authors concluded that conventional "ICU" ventilators equipped with air-leak compensation module are suitable for non-invasive respiratory treatment in a large population of infants and children with ARF of various etiologies.

Obstructive Condition

Severe viral bronchiolitis is one of the first causes of epidemic lower respiratory tract infection among infants and represents 2%-6% of all

admissions to PICUs in developed countries.

In a prospective physiological study, Essouri *et al*.[6] aimed to determine the optimal level of nasal CPAP in ten infants with severe hypercapnic viral bronchiolitis as assessed by the maximal unloading of the respiratory muscles, and improvement of breathing pattern and gas exchange. The median value of intrinsic PEEP (PEEPi) was 6 cmH_2O (range 3,9-9,2 cmH_2O). Spontaneous breathing and three increasing levels of CPAP (4,7 and 10 cmH_2O) delivered by a neonatal ventilator coupled with adapted nasal prongs were compared. Nasal CPAP was associated with an immediate amelioration of breathing pattern, gas exchange and respiratory effort. The comparison between the three different level of nasal CPAP showed the greatest reduction in respiratory effort at CPAP 7 cm H_2O, as expressed by the decrease in oesophageal and diaphragmatic pressure swings (-48% and -46%, respectively) and pressure time product per minute (-56% and -54%, respectively).

The authors concluded that in infants with hypercapnic respiratory failure due to acute viral bronchiolitis, a CPAP level of 7 cmH_2O was associated with the greatest unloading of the respiratory muscles and improvement of breathing pattern, as well as a favourable short-term clinical outcome. This CPAP level is explained by the level of the threshold load represented by PEEPi that has to be overcome at the beginning of inspiration.

The prevalence of asthma in young children is continuously increasing. When conventional therapies are insufficient, Bilevel Positive Airway Pressure (BiPAP) has been found to be a safe and effective therapeutic intervention in the paediatric emergency department (PED) and PICUs. Williams *et al*.[7] in a retrospective (from January 2005 to July 2009) and prospective (from August 2009 to November 2010) descriptive analysis of 165 enrolled subjects aged 0.6-8.27 years (mean 3.7, SD 1.6) with moderate and severe asthma, went to investigate safety and clinical findings of BiPAP via facial mask. Overall, subjects on BiPAP showed improvement in Paediatric Asthma Score (PAS). Only four children needed tracheal intubation after significant period on BiPAP and three of them were extubated within the first 24 hours. Mean PAS at BiPAP initiation was 12.1 (SD 1.6) and quickly decreased to 6.3 (SD 2.2) at four hours (or at end of trial). Seventy-one children had trial off BiPAP in paediatric emergency department (PED) for clinical improvement while seven were restarted.

BiPAP mean application time in PED was 210 minutes (SD 158, range 30-720). Ninety-nine (60%) subjects were admitted to the PICU and continued BiPAP for 0-47 hours (mean 6.6, SD 8.6). Fifty-seven (35%) required ward admission and nine (5%) were discharged home from the PED; none returned within 72 hours. No mortality, pneumothoraces, aspirations or morbidity were demonstrated. The authors concluded that BiPAP application in moderate to severe asthmatic exacerbation for children 20 kg or less, is safe and may improve clinical outcomes. However, they emphasised the need for further prospective and randomised investigations to confirm BiPAP efficacy in paediatric asthma patients.

In selected sub-glottic stenosis (SGS), NRS may represent a valuable tool to treat obstructive symptoms, improving the breathing pattern and reducing respiratory efforts in younger infants with severe upper airway obstruction.

Rossetti *et al*.[8] described a case report on the use of NRS in one patient aged 10-months affected by severe SGS secondary to previous prolonged tracheal intubation. Fiberoptic laryngoscopy revealed a SGS III, i.e. from 71% to 99% laryngeal obstruction. An emergency tracheal intubation was performed using a 2,5-mm uncuffed tube and then dilated with progressive wider tube up to 4-mm. After 48 hours of deep sedation to prevent vertical up-and-down movements of the tube through the lesion, the stenosis was successfully treated by radial dilation with angioplasty balloon catheter. During the following five days, non-invasive PS mode and medical therapy resulted in complete respiratory comfort, improved nutritional status and discharge of the patient to the ward. The authors concluded that the association between radial dilation and NRS represents an interesting alternative to tracheostomy in the treatment of severe SGS in children.

Predictive Factors of NRS Failure

NRS constitutes an alternative treatment for paediatric ARF. However, tracheal intubation should not be delayed when considered necessary. One of the major challenge during NRS is to identify early prognostic signs of treatment failure. Muñoz-Bonet and coworkers[9] surveyed predictive factors of NRS in children aged from one month to sixteen years with moderate-to-severe ARF during a four-year study period. NRS failure was defined as the need for tracheal intubation. NRS was applied in thirty-seven patients and failed in nine (19.1%) due to the progression of ARF. Small babies population, diagnosis of ARDS and chest x-ray worsening at twenty-four hours, were linked to treatment failure. They also demonstrated that the association of mean airway pressure >11.5 cmH_2O and inspired oxygen fraction (FiO2) > 0.6, were able to predict NRS failure in nearly 80% of children.

Lum *et al*.[10] in a prospective observational study determined the factors that predict outcome of NRS in critically ill children in a multidisciplinary PICU of a university hospital in Kuala Lumpur, Malaysia. Out of 278 children (average age 8.7 months) with ARF and treated with NRS, 129 received NRS as unique ventilatory support, 98 were treated with NRS to facilitate extubation and 48 because of postextubation ARF. Interestingly, 71.2% of children had underlying chronic disease, probably reflecting a typical PICU population of a developing country. Overall, NRS avoided intubation in more than 75% of children. During this study, a high paediatric risk of mortality (PRISM) II score, the presence of sepsis, an abnormal respiratory rate and high requirement of FiO2 at start of NRS, were found to be independent predictive factors of NRS failure. Worsening respiratory failure and septic shock were the two main causes of failure of NRS.

The authors concluded that in a large population of children admitted to PICU in a middle income country with limited resources, NRS represents an effective strategy to prevent tracheal intubation and to rapid discharge to the ward where respiratory treatment can be continued. High PRISM II score, respiratory rate, the need of oxygen and the presence of sepsis at initiation of NRS should suggest closer monitoring to prevent NRS failure.

At the Great Ormond Street Children's Hospital in London, 163 patients aged between 1 month to 18 years who received NRS during the 7-year study period, were evaluated to determine whether physiological parameters and underlying condition predict NRS success.[11] Eighty-three children received NRS as first-line intervention to avoid intubation and 64% succeeded. Those who failed showed higher FiO2 (0.56 vs. 0.47, p = 0.038), higher respiratory rate (53.3 vs.43.3 breaths/min, p = 0.012) and lower pH (7.26 vs. 7.34, p = 0.032) before NRS was started and required a higher FiO2 once NRS was applied. Eighty patient were started on NRS to prevent post-extubation failure and 60% had a successful treatment. Those individuals who failed showed significantly higher systolic and diastolic blood pressure two hours after NRS was applied (104 vs. 77.9 mmHg, p = 0.001 and 64.5 vs. 54.1 mmHg, p = 0.037), probably representing a stress response in the failing child.

Interestingly, patients on CPAP were more likely to avoid intubation when compared with those on BIPAP in both groups (first line elective and post-extubation NRS). Looking at underlying condition, the authors demonstrated that children with a primary respiratory disease who were treated with NRS as first-line treatment, avoided intubation in 30/36 cases (83%) while those with an underlying oncological disease showed a much lower success rate (35%, 8/23 cases). The presence of sepsis further decreased the rate of success in the oncological group (20%, 3/15 cases). Primary respiratory illness were also more likely to avoid re-intubation after extubation (27/33 cases, 82%). The authors concluded that tachypnoea and acidosis prior to establishing NRS and oxygen requirement pre and post NRS, are the strongest predictive factors for treatment failure when NRS is used as first-line treatment to prevent intubation. In contrast, when NRS is used to avoid re-intubation, the most important predictive factor for re-intubation is persistent hypertension after NRS is established.

Conclusions

The use of NRS is rapidly growing in PICUs both as a means to prevent intubation in the early stage of ARF and for the prevention and treatment of post-extubation respiratory distress. In general, the evidence supporting the use of NRS in children is still limited as well as the criteria for identifying the right patient, the appropriate setting and the right time of application. Unlikely, no new randomised controlled studies were published in the last year and a half.

From a technical point of view, it has been shown that new turbine ventilators are very effective in compensating air leaks through the interface thus facilitating patient comfort. On the other hand conventional "ICU" ventilators , equipped with a non-invasive software with automatic air leak compensation, performed very well and were able to guarantee good patient-machine interaction.

Many recently published observational studies on large paediatric populations confirmed that NRS is safe and effective in terms of gas exchange amelioration, unloading of the respiratory muscles and intubation rate in mild to moderate respiratory failure of different etiologies. To our knowledge, no trial has so far evaluated the use of NRS in hypoxemic children considered sufficiently ill to require immediate ventilatory assistance.

The outcome of NRS in early to moderate ARF depends primarily on the type and evolution of the underlying disease. Lower rate of NRS success was noticed with pneumonia and ARDS suggesting for these patients a cautious approach and very strict monitoring. Interestingly, in infants with severe hypercapnic viral bronchiolitis it has been shown that 7 cmH_2O is probably the optimal CPAP level to reduce the work of breathing by counteracting PEEPi. Encouraging results were also obtained in moderate to severe asthmatic children with BiPAP by facial mask with quick clinical improvement and very low rate of intubation. Moreover, NRS has been shown to be very flexible as it could be delivered both in the PICUs as well as in the ward according to the severity of the disease, provided that the ward team has the necessary skills.

The failure of NRS relies on several negative predictive factors: the type of ARF, with pneumonia and ARDS having the worst rate of success; the underlying disease with sepsis and malignancies playing a major role in affecting the outcome, the severity at admission as expressed by higher severity scores and high oxygen requirement. Moreover, recent data confirm previous evidence that parameters relating to respiratory and cardiovascular status can determine which patients will avoid intubation or re-intubation when placed on NRS. The effect of NRS on more complex outcomes requires further investigation.

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Upcoming Congresses and Meetings

39th Annual Meeting of the British Paediatric Neurology Association 2013

23 – 25 Jan 2013

Manchester, UK

The BPNA is a professional organisation for doctors who specialise in the care of children with neurological disorders. This year a variety of oral presentations will be given on topics such as narcolepsy in children, chronic childhood ataxia, multiple sclerosis in children and genetic testing. There will also be a number of keynote speakers giving interesting and thought-provoking lectures including Dr Simon Jones, Consultant in Paediatric Inherited Metabolic Disease who will be presenting on 'Emerging treatments for inborn errors of metabolism' and Professor Hugh Piggins, Professor of Neuroscience, Manchester University who will speak on 'Daily rhythms in electrical activity in the brain'. This year's meeting will be held at the Manchester Conference Centre.

32nd Annual Meeting of the European Paediatric Orthopaedic Society (EPOS)

17 – 20 April 2013

Athens, Greece

Having been held annually for more than 30 years, EPOS meetings have always been one of the most important meeting environments for world paediatric orthopaedics. 2013 will mark the 32nd of these Annual Meetings, which have received accolades from attendees for advanced scientific programs coupled with a warm and friendly social setting, in Athens, Greece. The EPOS program committee is working hard on a highly challenging scientific meeting. Their local committee, led by John Dimtriou, is looking forward to organising an unforgettable social program in one of Southern Europe's most important beautiful and historic destinations.

24th Congress of the European Society for Paediatric Urology

24 - 27 April 2013

Genoa, Italy

The European Society for Paediatric Urology is a non-profit society whose main purpose is to promote paediatric urology, appropriate practice, education as well as exchanges between practitioners involved in the treatment of genito urinary disorders in children. The congress venue is in Genoa's ancient, medieval harbour, in a unique position, close to the Acquarium, one of the largest in Europe and at a walking distance from the historicalcenter, the Cathedral and most of the ancient palaces.

46th European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)

08 – 11 May 2013

London, UK

The 46th Annual Meeting will take place in the East of London at the International Conference Centre, (ICC) London ExCeL, located close to the Royal Victoria Dock and London City Airport using the DLR and alighting at the Prince Regent stop for the ICC London ExCeL. The scientific programme promises to offer the most recent updates in scientific and clinical research within the fields of paediatric gastroenterology, hepatology and nutrition. With stimulating key note lectures and symposia, sessions for post graduates and allied health professionals combined with diverse satellite symposia from key industry partners, it promises to be a popular and exciting meeting. The theme for the Meeting is 'Research for a Better Future' which will include interesting topics such as emerging concepts in parenteral nutrition, Coeliac disease and autoimmunity and perinatal liver disease.

Annual Meeting for the Society of Pediatric Radiology

14 - 18 May 2013

Texas, USA

The 2013 program builds on the creativity and innovative spirit of prior years. Thanks to the tremendous efforts of the program committee members, you will find that the postgraduate course offers a diverse and robust agenda. Eight sunrise sessions provide additional educational opportunities to start the day. In addition, the protocol sessions have been expanded to include ultrasound in addition to the popular body and neuro CT and MR sessions, five special half-day sessions Saturday morning, and a multi-vendor session providing hands-on workstation exposure in 3D Read With the Experts.

31st Annual Meeting for the European Society of Paediatric Infectious Diseases (ESPID)

28 May – 01 June 2013

Milan, Italy

ESPID Annual Meetings are distinguishable by their innovative scientific programmes, interactive case sessions, platform presentations, educational workshops, and ESPID 2013 in Milan will be no different! Focusing on Paediatric Infectious Diseases: Future Prospectives, ESPID 2013 will provide clinical practitioners, researchers and industry professionals' unparalleled access to the latest findings and analysis in the field of paediatric infectious diseases.

24th Annual Congress of the European Society of Paediatric and Neonatal Intensive Care (ESPNIC)

12-15 June 2013

Rotterdam, The Netherlands

Every year ESPNIC organises a European

paediatric intensive care and neonatal intensive care congress, presenting the latest developments of technology, treatment and care, and giving priority to scientific research and creative solutions of paediatric and neonatal intensive care; to a large audience of health professionals working in the field. Representatives from all professional groups, working in the paediatric and neonatal intensive care field are invited to participate.

XI World Congress of Perinatal Medicine

18 - 21 June 2013

Moscow, Russia

The congress organising committee has been hard at work to welcome delegates and to make this Congress unforgettable not only from a scientific point of view but also to reinforce friendship ties, make new friends and try to help underdeveloped countries. An exceptional scientific and social program has been prepared to welcome attendees to Moscow. The city is splendid during the summer. Not only is there the opportunity to enjoy the medical and scientific events of the Congress, but also to experience world-renowned sights such as the Kremlin, Tretyakov Gallery, St. Basil's Cathedral, Bolshoi Theatre, Tolstoy House Museum and many other unique attractions.

7th Congress on Pediatric Transplantation

13 - 16 July 2013

Warsaw, Poland

The International Pediatric Transplant Association (IPTA) is a professional organisation of individuals in the field of paediatric transplantation. The purpose of the Association is to advance the science and practice of paediatric transplantation worldwide in order to improve the health of all children who require such treatment.

The Association is dedicated to promoting technical and scientific advances in paediatric transplantation and to advocating for the rights of all children who need transplantation. this year's congress will be held in Warsaw, Poland.

British Association of Paediatric Surgeons (BAPS) Annual Conference

16 - 19 July 2013

Bournemouth, UK

2013 marks the BAPS' Diamond Anniversary. BAPS holds their annual congress at which there are free paper scientific sessions, meet-the-experts seminars, keynote lectures and associated meetings. BAPS was founded in 1953. Its objects are the advancement of study, practice and research in surgery for children to cultivate professional relations with paediatric surgeons overseas. The forthcoming congress will be held in the coastal town of Bournemouth and promises to be an exciting event.

9th Joint Meeting of Paediatric Endocrinology

19 - 22 Sept 2013

Milan, Italy

This prestigious occasion will reunite the European Society for Paediatric Endocrinology (ESPE) with the Pediatric Endocrine Society (PES), Australasian Paediatric Endocrine Group (APEG), Asia Pacific Paediatric Endocrine Society (APPES), Japanese Society for Pediatric Endocrinology (JSPE), and the Sociedade Latino-Americana de Endocrinologia Pediátrica (SLEP).

European Paediatric Neurology Society (EPNS) Annual Congress

25 - 28 Sept 2013

Brussels, Belgium

The EPNS is a Society of paediatric neurologists and members of allied disciplines from all parts of Europe and the world and is dedicated to promoting clinical care, training and scientific researchin the field of paediatric neurology. The congress will next be held in Brussels' Square Meeting Centre.

54th Annual Meeting of the European Soceity of Paediatric Research (ESPR)

10 - 14 Oct 2013

Porto, Portugal

ESPR 2013 aims to advance paediatric research in Europe, help exchange of information, and spread ideas on new developments in paediatric research and to serve the European Society of Neonatology members and European neonatology by a focus on training and accreditation. The program will consist of a mixture of research interaction, training and continuing professional development.

41st Meeting of the British Society for Paediatric Endocrinology and Diabetes (BSPED)

13–15 Nov 2013

Brighton, UK

The BSPED aims to improve the care of children and young people with endocrine disorders and diabetes mellitus by bringing together professionals from a range of disciplines including tertiary paediatric endocrinologists and diabetologists, general paediatricians with an interest in endocrinology and/or diabetes, researchers, nurses and other healthcare professionals. The society (BSPED) was formally constituted and named at the Annual General meeting in Liverpool in 1979. The annual meeting has been an exciting event and 2013 hopes to be no exception. Brighton promises to be an exciting host for the upcoming meeting!

European Society of Pediatric Otorhinolaryngology (ESPO) Conference

31 May - 03 June 2014

Dublin, Ireland

We are pleased to announce that the next ESPO Conference will be held in Dublin. The theme will be "Decision Making" in Paediatric Otorhinolaryngology. Dublin is one of Europe's most poplar destinations. It is a vibrant, cosmopolitan city, steeped in history and tradition, with plenty to see and do. Many historical areas have been rejuvenated and restored, with new shopping centres, restaurants and bars. This combined with the world famous Irish charm and friendly hospitality makes Dublin an enjoyable city to visit for all people.

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