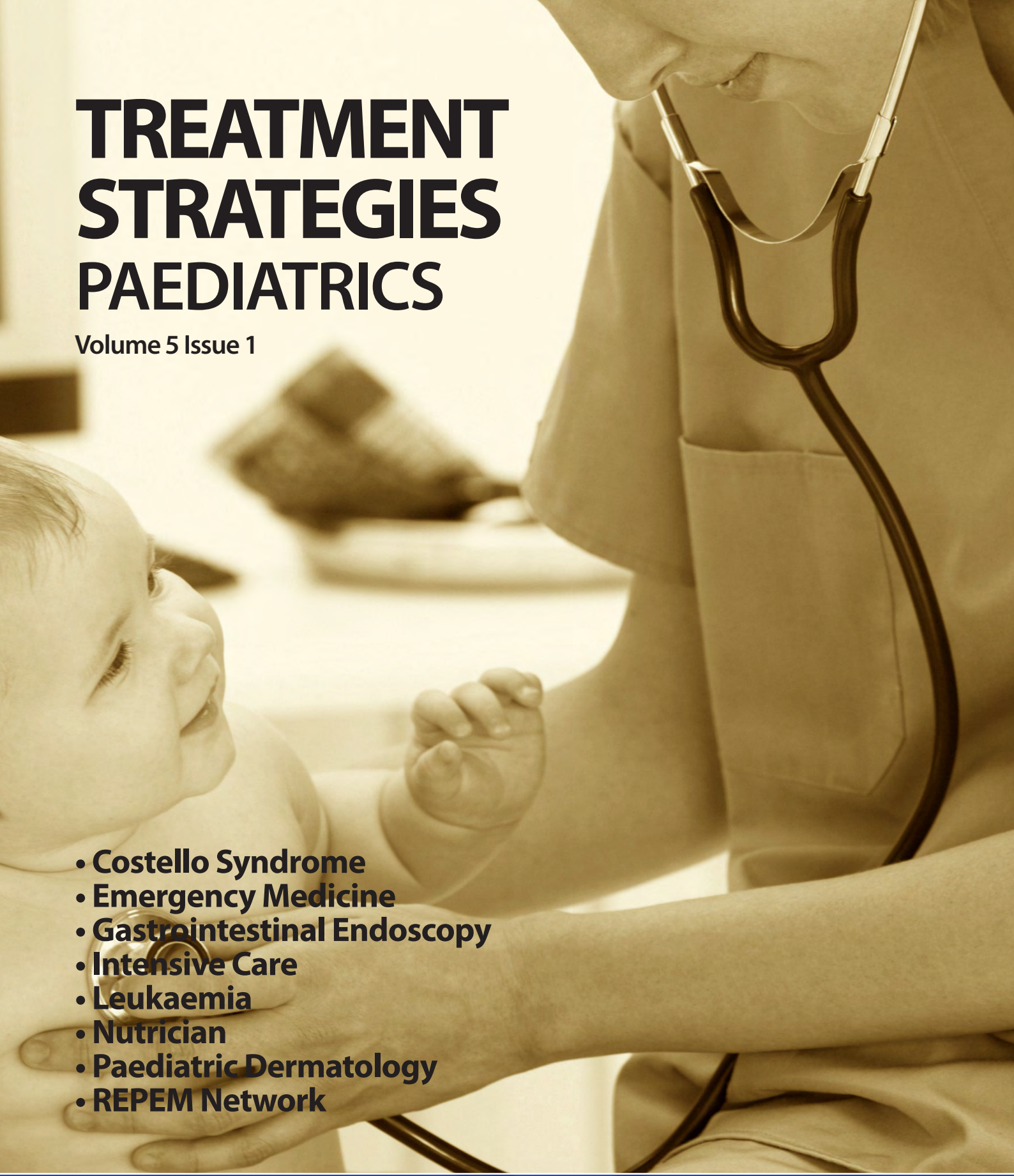
TREATMENT STRATEGIES
PAEDIATRICS

Volume 5 Issue 1



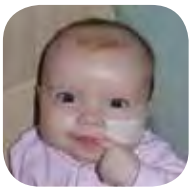
- Costello Syndrome
- Emergency Medicine
- Gastrointestinal Endoscopy
- Intensive Care
- Leukaemia
- Nutrician
- Paediatric Dermatology
- REPEM Network

Includes a Review of the 5th EAPS Congress 2014 - Barcelona

The Gauchers Association is the only organisation in the United Kingdom that provides information and support to those with Gaucher disease, their families and health-care professionals.








The Association:

supports families and carers to ensure all individuals with Gaucher disease have access to best practice in diagnosis, treatment and care.

provides information on Gaucher disease and raises awareness of this rare disease.

promotes research into the causes, effects and treatments of Gaucher disease.

represents the interests of Gaucher patients at all times to ensure that the voice of the Gaucher patient is heard.

www.gaucher.org.uk

Gauchers ASSOCIATION

Registered Charity No 1066407

TREATMENT STRATEGIES PAEDIATRICS

TREATMENT STRATEGIES -
- PAEDIATRICS -
Volume 5 Issue 1
November 2014

The Cambridge Research Centre

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Welcome... to the latest edition of *Treatment Strategies - Paediatrics*.

This edition will address the key topical areas in the paediatrics field and features an exciting collection of papers from esteemed paediatricians.

Treatment Strategies - Paediatrics includes papers on topics such as:

- Costello Syndrome
- Emergency Medicine
- Gastrointestinal Endoscopy
- Intensive Care
- Leukaemia
- Nutrician
- Paediatric Dermatology
- REPEM Network

We hope that this publication will provide you with a comprehensive review of the latest updates and technological advances in medicine.

Following on from a successful visit to Barcelona, we have also included a review of the latest news and developments from this year's EAPS Congress.

So far, 2014 is proving to be a fantastic year for The Cambridge Research Centre, with some exciting changes including Treatment Strategies TV, where you can find footage from the most important scientific conferences, meetings and congresses, as well as interviews, symposia proceedings, roundtable events and much more. We also launched our range of interactive eBooks on iBooks, which is a great new way to read and download our content to your devices. Have you liked our new Facebook page? Here you can find all of the latest news about new projects and upcoming releases, and the Treatment Strategies' team are also all active on Twitter and LinkedIn.
See you in Oslo for EAPS 2015.

Nigel Lloyd, Managing Director

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

Joint Annual Conference
October 7 – 10, 2015

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The International Liver Cancer Association Announces its 9th Annual Conference

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www.ilca2015.org

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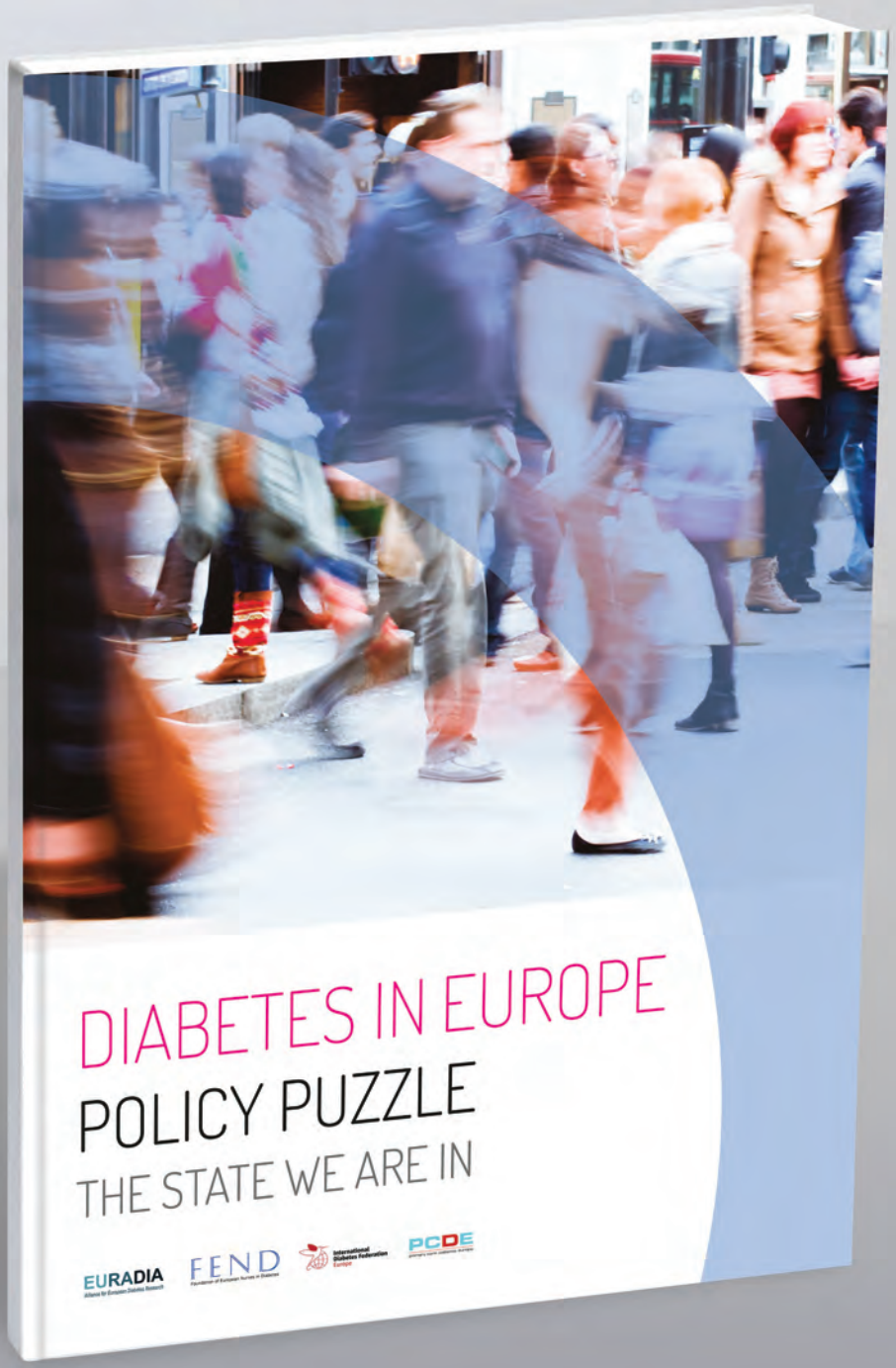

EURADIA Alliance for European Diabetes Research
FEND Federation of European Nurses in Diabetes
International Diabetes Federation Europe
PCDE primary care diabetes europe

5th Congress of the EAPS

17th - 21st October, Barcelona

5th European Academy of Paediatric Societies Congress Review

The Congress

News from EAPS 2014

The EAPS Organising Committee welcomed attendees to the 5th Congress of the European Academic Paediatric Societies (EAPS) 2014 in Barcelona, Spain.

Providing a wealth of knowledge from three leading paediatric societies, the 5th Congress of the European Academy of Paediatric Societies (EAPS 2014) built on the reputation of previous highly successful meetings. Paediatric professionals from around the world will gain unparalleled access to the best scientific research programmes.

The EAPS congress brought together Europe's leading paediatric societies to create a truly state-of-the-art Congress. The combined efforts and talents of the best and brightest minds in paediatrics have turned this biannual event into a major educational platform, attracting high quality presentations that have appeared in leading publications following the event.

The Congress was organised by the three societies which included European Academy of Paediatrics (EAP), European Society for Paediatric Research (ESPR) and European Society of Paediatric and Neonatal Intensive Care (ESPNIC) including the Nurses Section of ESPNIC.

With the largest scientific programme to date the 5th EAPS congress had over 200 contributing top-faculty and experts attending from all over the world.

Six other important European paediatric societies joined as collaborating societies for this year's EAPS congress.

The societies included: European Paediatric Neurology Society (EPNS), the Paediatric Assembly of European Respiratory Society (ERS), the Association for European Paediatric and Congenital Cardiology (AEPC), The Union of European Neonatal & Perinatal Societies (UENPS), the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), and the European Society for Paediatric Infectious Diseases (ESPID).

This year the EAPS congress returned to the beautiful and thriving city of Barcelona. The selection of Barcelona, Spain as the location for EAPS 2014 was not coincidental. Barcelona, more than just a single city, is really a collection of multi-faceted and diverse cities. The weather in October is usually very comfortable, and the cultural and gastronomic virtues need no extra comments.

Firmly established yet dedicated to thinking outside the box, EAPS 2014 aims to engage the world's best in a hearty exchange of experiences and expertise in research and clinical care. Europe's foremost paediatrics subspecialty societies EAP, ESPNIC and ESPR have dedicated their time and formidable talents into organising a stellar educational/research forum that will celebrate outstanding science in all areas of paediatrics.

With the largest scientific programme to date the 5th EAPS congress had over 200 contributing top-faculty and experts attending from all over the world. The Congress included a number of technically advanced tools to help attendees navigate their attendance and to encourage participation. These included a mobile website for smartphones and tablets as well as an electronic programme book.

As always the Congress' most important content was the provision of free papers. Submitted abstracts to EAPS 2014 are guaranteed to facilitate robust debates, thoughtful conversations and fruitful collaborations, with the future of paediatrics being greatly enhanced as a result.

There were of course plenary talks given by world-class authorities with broad paediatric relevance. The Congress programme has been designed with everyone in mind in that it will have something to all attendees. The promotion and advancement of quality paediatric care and training worldwide has a powerful advocate in EAPS 2014. Its compelling and comprehensive scientific programme will unveil the latest research and analysis in the field, as presented by a renowned international faculty.

The organising committee encouraged attendees to attend the EAPS 2014 Networking Event on Monday, October 20th, 2014, which took place at Barcelona's chic and contemporary venue - Opium Mar. Here everyone had the opportunity to meet and make new friends and build professional connections from around the world, make lasting academic relationships, and experience the unique beauty Barcelona has to offer.

The congress also provided important pre-congress courses on Thursday 16th October and Friday 17th October. During these courses the organising societies offered training courses and courses for continuing professional development or education.

Barcelona Spain

As the capital of Catalonia and the second largest city in Spain, Barcelona was well-prepared to welcome ESC Congress attendees to the shores of the Mediterranean. Barcelona is a city of culture, knowledge, creativity and innovation, and delegates had plenty of opportunities to enjoy this beautiful city.

In addition to its culture, Barcelona is the home of several world-renowned universities and hospitals, including the University of Barcelona, Hospital del Mar, University Hospital Clínic de Barcelona and the Centre for Research in Environmental Epidemiology (CREAL), which has research programmes relevant to lung physicians, including their programmes on respiratory, cancer, childhood and air pollution. The city's academic excellence makes Barcelona the perfect location to drive forward science and healthcare.

Barcelona is also a key transport hub. Barcelona international airport handles over 35 million passengers per year, and the city has an extensive motorway network and high-speed rail connections. These networks ensured that congress delegates could quickly and efficiently travel to the city for 5 days of active discussion and lively interaction.

Treatement Strategies Photo Gallery

Awards Presented During the 2014 EAPS Congress

The following awards were presented during the 2014 EAPS Congress:

EAP Investigator Award

The requirements for this award included a request for consideration that was indicated in the abstract submission form at the time of submission. It was also necessary for the content of the abstract to be original work and that the name of the author presenting this work matched that of the applicant.

The work for this award was judged on its scientific content, structure of the abstract, presentation and the presenter's ability to defend the paper and or results during question time from the audience.

The prize awarded for the EAP Investigator Award was EUR 1,500.

Winner: C.N. Van der Veere
"POORER COGNITIVE AND GROSS MOTOR OUTCOME AT AGE 2.5 YEARS AFTER INTRAUTERINE EXPOSURE TO SSRI. PROCEEDINGS FROM THE DUTCH SMOK TRIA"

ESPR Bengt Robertson Award for Research Concerning The Neonatal Lung

The abstracts submitted for consideration of this award were on research concerning the neonatal lung and each abstract submission had to indicate a request for consideration in the form at the time of submission.

The content itslef had to have been original work and the author presenting < 35 years of age and match the name of the applicant.

The Winner was chosen based on the scientific content, structure of the abstract, presentation and the presenter's ability to defend the paper and or results discussed during the question time from the audience.

The prize awarded for the ESPR BENGT ROBERTSON AWARD FOR RESEARCH CONCERNING THE NEONATAL LUNG was EUR 3,000, complimentary registration to the next ESPR Annual Meeting as well as accommodation and travel expenses.

Winner: M.A. Möbius
"MESENCHYMAL STEM- OR STROMAL CELLS FROM THE DEVELOPING HUMAN LUNG ARE PERTURBED BY HYPEROXIA"

ESPR Young Investigators Award

Up to two prizes were awarded to young investigators which at the time of submission requested consideration for this award of their original work.

The presenting author must have been < 35 years of age and made the application. The winners were chosen based on the paper's scientific content, structure of the abstract, the presentation, the presenter's ability to defend the paper and or results during the question time from the audience.

For the First Prize the winner was awarded EUR 600, complimentary registration and free travel to the next ESPR Annual Meeting.

The Second Prize winner was awarded EUR 400, complimentary registration to the next ESPR Annual Meeting.

Winners:
1st prize: M.A.E. Jansen
"GROWTH TRAJECTORIES AND BONE MINERAL DENSITY IN CHILDREN WITH SUBCLINICAL CELIAC DISEASE:THE GENERATION R STUDY"

2nd Prize: J.V. Kraaijeng
"THE EFFECT OF CAFFEINE ON DIAPHRAGMATIC ACTIVITY IN PRETERM INFANTS"

ESPNIC Young Investigators Award

This award supports the development of research activities undertaken with the active contribution of the applicant. The specific intent is to provide support for young and talented physicians in their early career in the field of paediatric and neonatal intensive care to present their research topic of their choice in front of a designated jury during an oral session at the Congress.

Two awards were granted to ESPNIC members presenting original work not presented and or published.

The winner was based on the paper's scientific content, the presentation of the paper, and the presenter's ability to defend the paper and or results during the question time from the audience.

The First Prize given was for the sum of EUR 1,200, complimentary registration and free travel to the next ESPNIC Annual Meeting (up to 500 EUR), one year complimentary membership.

The Second Prize winner was awarded EUR 800, one year complimentary membership, complimentary registration to the next ESPNIC Annual Meeting.

Winner:
M. Cetinkaya
"ASSOCIATION OF E-NOS GENE POLYMORPHISM IN DEVELOPMENT OF BRONCHOPULMONARY DYSPLASIA"

Master Classes at the EAPS

The EAPS offered a number of master classes for participants looking to advance their skills. Master classes gave delegates the opportunity to ask questions and get answers from some of the world's leading experts in the field.

Saturday 18th October 2014

Master Class I -The Psychological Impact of ICU Admission on the Child and Parents. The faculty included Gillain Colville, Head of the Paediatric Psychology Service at St George's Hospital in London in the UK.

In this master class, the main findings of Gillani Colville's research into children's experiences on PICU and the psychological symptoms they and their parents report in the longer term were outlined. The presentation also provided specific examples of the clinical work in this setting.

George Damhuis, The Netherlands and Andre Kroon, The Netherlands also presented Master Class II - Basic Neonatal Chest X-ray Interpretation.

Interpretation of an X-ray is a highly skilled task done by a radiologist. However, neonatal x-rays are generally taken as an emergency procedure outside official working hours. In such situations skills to make rational decisions about immediate interventions, such as intubation, insertions of chest drains or changing ventilation settings, are essential.

The learning objectives of this master class were to schematically read and describe a neonatal chest X-ray and to identify the typical radiologic features of causes of respiratory distress.
Helmut Küster, Germany, presented Master Class III - Structuring Presentations and Posters.

Sunday 19th October 2014

Diego Van Esso, Spain and Zachi Grossman, Israel presented Master Class IV -Fever, Cough and Other Symptoms - Best Treatment Evidence.

Common symptoms like fever, cough, otalgia or the crying fussy baby, are often treated according to traditions, family experience or paediatric recommendations based on experience rather than evidence. Nevertheless there are evidence-based recommendations, which may help the primary care paediatrician to manage these symptoms in an optimal way.

In this master class the participants received up-to-date information on the best management options for these symptoms which account for a significant time of their daily practice.

Master Class V - How To Do a Systematic Review was presented by Agnes van den Hoogen, The Netherlands.

In this master class participants got a brief overview of how to perform a systematic review. A systematic review aims to provide an exhaustive summary of current literature relevant to a research question. Participants were guided step by step through the process of the systematic review.

The first step is a thorough search of the literature for relevant papers. Secondly, in the methodology section of the review, the databases and citation indexes searched will be listed; as well as any hand searched individual journals. Next, titles and abstracts of the identified articles are checked against pre-determined criteria for eligibility and relevance, depending on the research question.

Each included study may be assigned an objective assessment of methodological quality preferably using a method conforming to PRISMA or the high quality standards of Cochrane collaboration.

Further describing and analysing of the studies included in the review will be performed as data syntheses, combining the results. A systematic review uses an objective and transparent approach for research synthesis, with the aim of minimising bias. Systematic reviews often, but not always, use statistical techniques (meta-analysis) to combine results of the eligible studies, or at least use scoring of the levels of evidence depending on the methodology used. Both quantitative meta-analysis of available data, and qualitative reviews that adhere to the standards for gathering, analysing and reporting evidence will be discussed.

Peter Rimensberger, Switzerland and Andre Kroon, The Netherlands presented Master Class VI - HFO a Practical Approach.

In the neonatal care high frequency oscillation (HFO) is an important mode of respiratory support. For successful use of HFO it is important to achieve and maintain optimal lung volume.

This master class emphasised the practical aspects of HFO by means of a demonstration on site and discussion of clinical scenarios (interactive).

Paul Baines, UK presented Master Class VII - The Ethics of Parental and Decision-Making for Children – Whose Best Interests?

Monday 20th October 2014

Master Class VIII - Lieven Lagae, Belgium presented How to get your paper published

Jonas Nordquist, Sweden presented Master Class IX - How to make a good specialist

Joan Sanchez de Toledo, Spain presented Master Class X - Ultrasound in the cardiac ICU: looking outside the heart

Tuesday 21st October 2014

Linda de Vries, The Netherlands, presented Master Class XI - Neonatal Stroke.

Neonatal stroke may be defined as cerebrovascular injury, which occurs around birth. Injury may be focal or multifocal and may include both ischemic and haemorrhagic injury. Neonatal stroke is most often referred to as perinatal cerebral injury of ischemic origin. The incidence has come down in recent years from 1/4000 to 1/2300 live births.

The learning objectives included; recognition of presenting symptoms, be aware of the risk factors in preterm and full-term infants, which neuro-imaging techniques are best used, how best predict outcome, early and late intervention

Nick Evans, Australia, presented Master Class XII - Functional Echocardiography.

Learning objectives included the historical perspective of point of care neonatologist performed cardiac ultrasound (NPCU), illustrated by case examples

The best strategies for teaching and learning cardiac ultrasound in the NICU.

The European Academy of Paediatrics

The European Academy of Paediatrics (EAP) exists to promote the health of children and young people in Europe. It incorporates the section of paediatrics of the European Union of Medical Specialists (member countries of the European Union (EU)) and the European Free Trade Association (EFTA) and therefore has influence in the political arena to advocate for children and young people as well as for the profession.

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 objectives of the EAP include:

- To study, promote and guarantee a comparably high quality of paediatric care, that is the medical care of children and adolescents up to the completion of growth and development.
- To improve standards in training, service and research and to represent the professional interests of paediatricians in the member countries.
- To provide practical assistance in assuring that the physicians who will be taking care of children will be competent to do so.
- To establish closer bonds between the national professional paediatric organisations, grouping together paediatricians in all fields, to support and coordinate their actions.
- To contribute to the creation or maintenance of solidarity between European paediatricians incorporating in particular paediatric sub-specialists.
- To spread information to medical bodies, professional organisations, paediatric scientific societies as well as to national governments and supranationals as part of the EU.
- To organise exchanges of information by whatever means are adequate on professional subjects concerning paediatrics and paediatric subspecialities.

The European Society of Paediatric and Neonatal Intensive Care (ESPNIC), is a not-for-profit organisation

dedicated to the care of the critically ill children and new-borns. This society is comprised of nurses, doctors and Allied health professionals who are committed to share knowledge, improve the quality of paediatric and neonatal intensive care; and devoted to highly promoting multidisciplinary collaboration at the European and International level and meeting the members' needs giving them a voice at the European and International level.

In this endeavour, ESPNIC is dedicated to promoting and advancing the art and science of paediatric and neonatal intensive care and raising awareness amongst professionals of the field, European and International organisations through a wide range of activities including annual congresses, training programmes, teaching courses and network opportunities with the leading experts in the fields of PICU & NICU.

The European Society for Paediatric Research (ESPR) was founded in 1958 and is one of the oldest European Societies. From then the ESPR has evolved into the current dynamic and vibrant grouping of researchers into childhood and its associated conditions.

Through its successful premier Journal and evolving responsibilities, ESPR aims at promoting paediatric research in Europe and encouraging collaboration between different fields of paediatrics to maintain paediatrics as a unified, scientifically orientated discipline. The Society now numbers > 500 members.

The society encourages collaboration between different specialised fields of paediatrics to maintain paediatrics as a unified, scientifically orientated discipline.

The European Society for Neonatology (ESN) represents neonatology in Europe. ESN works to improve the care and treatment of the new-born infant by facilitating and harmonising education of neonatologists, accrediting training centres and organising annual training courses. ESN has a close partnership with the Neonatal Online Training in Europe (NOTE) program. NOTE collaborates with the University of Southampton.

ESN aims at strengthening its role by increasing the number of members and to further our collaborations with other organisations and societies to improve the care and treatment of the new-born infant, such as EFCNI, UENPS and EAPM.

For more information, please visit
http://espnic-online.org
www.espr.info
www.eapaediatrics.eu

Sponsors of the EAPS 2014

The EAPS had numerous sponsors and exhibitors this year including Chiesi Group and Nestlé as its gold sponsors.

The Chiesi Group was founded in 1935, and it is today an international company focused on respiratory, neonatal and rare diseases. Chiesi's w® is the world leading surfactant for the treatment of respiratory distress syndrome (RDS) in premature neonates, and today is available in 80 countries worldwide. In 2011 Chiesi launched Peyona®, a pharmaceutical standard caffeine citrate which is a stimulant of the central nervous system, belonging to a group of medicines called methylxanthines.

Peyona has been specifically formulated for preterm infants, for the treatment of apnea of prematurity (AOP). These short periods when premature babies stop breathing are due to the baby's breathing centres not being fully developed. This medicine has been shown to reduce the number of episodes of interrupted breathing in premature newborns.

For more information, please visit :
www.chiesi-cee.com

The other gold sponsor was Nestlé Nutrition who shared leading science-based information and education with health professionals, scientists and nutritionists, in an interactive way.

Nestlé Nutrition helps children to develop their full potential and live healthier lives by providing high quality, innovative, science-proven nutrition solutions and education for mothers and infants in the crucial first 1000 Days' of life, nurturing a healthier generation.

The Nestlé Nutrition Institute (NNI), is the world's largest private publisher of nutritional information with more than 3000 publications. All of these resources are available on the NNI website for free to registered members.

The Nestlé Nutrition Institute shares leading science-based information and education with health professionals, scientists and nutrition communities and stakeholders, in an interactive way.

As well as being the world's largest publisher of nutritional papers and journals, the NNI organises and hosts internationally acclaimed workshops and symposia, making their findings available worldwide – often making the most of new technology to do so. It provides accredited continuing education programmes for a wide range of healthcare professionals including doctors, nurses and dietitians. The NNI also offers grants to young clinicians and scientists globally, with a particular focus on the developing world.

For more information, please visit:
www.nestlenutrition-institute.org

Four companies were silver sponsors of the EAPS Congress, including Actelion Pharmaceuticals Ltd, Kellogg Company and Berlin-Chemie AG

Actelion is a biopharmaceutical company headquartered in Switzerland, focusing on the discovery, development and commercialisation of innovative treatments to serve high unmet medical needs.

Zavesca® (miglustat) is indicated for the oral treatment of adult patients with mild to moderate type 1 Gaucher disease. Zavesca may be used only in the treatment of patients for whom enzyme replacement therapy is unsuitable. Zavesca® is indicated for the treatment of progressive neurological manifestations in adult patients and paediatric patients with Niemann-Pick type C disease.

For more information, please visit:
www.actelion.com

Berlin-Chemie AG develops, produces and sells pharmaceutical products. 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 has become a global, owner managed pharmaceutical company.

Berlin-Chemie/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. BERLIN-CHEMIE offers a range of paediatric medication and is an established partner to paediatricians,GPs and pharmacists.

For more information, please visit:
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Through our Breakfasts for Better Days® initiative, the Kellogg Company is providing one billion servings of cereal and snacks – more than half of which are breakfasts – to children and families in need around the world by the end of 2016.

For more information, please visit:
www.kelloggcompany.com

For more than 140 years Schwabe Pharmaceuticals has been committed to improving people's health and quality of life. Today Dr. Willmar Schwabe Pharmaceuticals has reached a position as global leader in the development and manufacture of phytopharmaceuticals.

Result of years of state-of-the art research, experience and clinical evidence with plant-based medicines, Willmar Schwabe products guarantee consistent efficacy, high safety and good tolerability.

By influencing several target systems in the body at the same time, they may be more appropriate for patients suffering from complex or age-related diseases than is the "silver bullet" approach of synthetic medicines.

For more information, please visit:
www.schwabepharma.com

The bronze sponsors oof this congress are as follows; Drägerwerk AG & Co. KGaA; Maquet; Octapharma; and SenTec AG.

Technology for Life Dräger is an international leader in the fields of medical and safety technology. Dräger products protect, support and save lives. The current product range of the medical division includes anaesthesia workstations, medical ventilation, patient monitoring as well as neonatal care for premature babies and newborns. With ceiling supply units, IT solutions for the OR, and gas management systems the company is at the customer's side throughout the entire hospital.

Dräger's approach towards neonatal care is designed to promote a continuous flow of information and includes an open system architecture, as well as innovative and non-invasive technologies that keep pace with the baby´s changing needs. Dräger are amongst the few who continue to maintain a strong commitment to the field of neonatology.

Dräger offers a comprehensive range of products to meet the complex needs of infants, families, and caregivers, from innovative neonatal ventilation systems and specialised incubators to mobile monitors and state-of-the-art IT systems.

For more information, please visit:
www.draeger.com

Maquet has been a trusted partner for hospitals and physicians for more than 175 years and is a global leader in medical systems. As a trusted partner for hospitals and clinicians, Maquet is a global leader in medical systems that advance surgical interventions, cardiovascular procedures and critical care. The company offers innovative therapy solutions and infrastructure capabilities for high-acuity areas within the hospital, including the operating room (OR), hybrid OR/cath lab, and intensive care unit (ICU), as well as intra- and inter-hospital patient transport.

Additionally, Maquet develops intelligent and sustainable room concepts that exceed the expectations of modern hospitals, working in close cooperation with customers, production engineers and architects to integrate high quality products and services.

Cardiovascular specialities include coronary artery bypass surgery; aortic and peripheral vascular surgery; extracorporeal circulation, the Critical Care portfolio includes market-leading intensive care ventilators and anaesthesia machines. Maquet also equips Surgical Work places with infrastructures such as flexible room design for OR and ICU.

For more information, please visit:
www.maquet.com

Octapharma AG is one of the largest human protein products manufacturers in the world and has been committed to patient care and medical innovation for over 30 years. Its core business is the development, production and sale of human proteins from human plasma and human cell-lines. Patients in over 100 countries are treated with products in the following therapeutic areas:

- Haematology (coagulation disorders) - These plasma derived products are produced to the highest standards, using the latest technology, in state-of-the-art manufacturing facilities to ensure the most advanced therapies are available to patients globally.
- Immunotherapy (immune disorders) - Immunotherapy is a therapeutic principal that aims to treat immune-mediated diseases and deficiencies by inducing, enhancing, or suppressing an immune response through immunomodulation or immunoglobulin replacement therapy. These products form the lifeline to health and hope for countless patients and their families around the globe.
- Intensive Care and Emergency Medicine - Our Critical Care products are used by emergency medicine physicians and paramedics around the world, every day they are helping to save lives and improve long-term patient outcome.

For more information, please visit:
www.octapharma.com

SenTec is an innovative Swiss company, manufacturing and developing systems for noninvasive patient monitoring.

The SDMS provides a complete transcutaneous solution for continuous ventilation and oxygenation monitoring. The SDMS allows continuous monitoring of transcutaneous carbon dioxide tension (tcPCO2) in neonates. Versatile sensor application (thorax, abdomen, back, low on forehead, inner or anterior aspect of tight) facilitates continuous measurement in virtually all clinical situations.

SenTec's revolutionary digital sensors combine transcutaneous capnometry (tcPCO2), oxygenation (tcPO2) monitoring and pulse oximetry in ONE sensor suitable for neonatal, paediatric and adult patients. Accurate technology, relevant safety features, multiple connectivity options, and customised system settings help to guide therapy on-line.

To complete the SDMS, V-STATS™ offers sophisticated data management and remote patient monitoring (V-CareNeT™).

All in all SenTec pursues its company mission to improve patient outcome and to reduce cost of care.

For more information, please visit:
www.sentec.ch

Hotel Novotel Genève Centre


Hotel Novotel Genève Centre


Hotel Novotel Genève Centre

EAPS 2016...

The 6th EAPS Congress will take place in Geneva between 21st to 25th October 2016.

Treatment Strategies takes a look at one of the finest hotels Geneva has to offer...

Hotel Novotel Genève Centre
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Costello Syndrome - An Overview

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RASopathy Syndromes

In the last years progress in the field of medical genetics led to detection of a group of congenital disorders caused by germline mutations in the RAS signaling pathway genes. These so-called RASopathy syndromes include Costello syndrome, Noonan syndrome, capillary malformation-AV malformation syndrome, Legius syndrome, LEOPARD syndrome, neurofibromatosis 1 and the cardio-facio-cutaneous syndrome. These syndromes are characterised by developmental delay, facial dysmorphism, short stature, cutaneous and skeletal abnormalities, and various cardiac defects.

The RAS (rat sarcoma) protoongogen plays an important role in cellular growth, differentiation, regulation of the cell cycle and cellular senescence. This RAS pathway is well-studied and somatic RAS pathway mutations have been found in various cancers. Therefore it is hardly surprising that these RASopathy syndromes share a predisposition for benign and malignant tumors. Although clinical signs and symptoms are overlapping each syndrome has unique features. Today advances in molecular genetic testing allow a clear differentiation of each syndrome.

Costello Syndrome

Costello syndrome is one of the less frequent RASopathy syndromes. According to the National Organization for Rare Disorders (NORD) about 350 persons are affected around the world. Jack Costello, a New Zealand paediatrician first described Costello syndrome in 1971 featuring a distinctive facial appearance, mental retardation, growth deficit and cardiomyopathy.[1] 34 years later Aoki *et al*. found that this autosomal dominant syndrome is caused by a de novo missense mutation in the HRAS gene in chromosome 11.[2] This mutation leads to multiple chances in various organ systems and tissues.

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Diagnosis

In some cases Costello syndrome might be suspected prenatally, but also in the postnatal period diagnosis can be challenging due to initially uncharacteristic craniofacial features. Usually the complete clinical picture evolves in the course of time.[3]

Prenatally Costello syndrome should be suspected in the presence of fetal atrial tachycardia, especially when being accomplished by nuchal thicking, polyhydramnios, hydrops, shortened long bones, abnormal hand posture, ventriculomegaly and macrocephaly.[4] The search items "fetal tachycardia" and "polyhydramnios" inserted in PUBmed lead to Costello syndrome in the first place (this led to early diagnosis in one case we published 2014). In one child with Costello syndrome we found an intracardiac echogenic focus ("white spot") at prenatal ultrasound.[5] This intracardiac echogenic focus is not specific for Costello syndrome, but as been described to occur cumulative in patients with Down syndrome.[6] In Costello syndrome preterm delivery is common and generalised oedema may result in increased birth weight.[4]

The typical facial appearance in Costello syndrome includes a prominent forehead, epicantal folds, prominent lips and a wide mouth.[7] Although as mentioned these characteristics may not be that clear in the neonatal period. The facial appearance has also been described as coarse and reminiscent to a storage disease, which may cause diagnostic difficulties.[8] In infants with Costello syndrome the voice is typically described as hoarse.[7]

In the neonatal period abnormal glucose homeostasis may lead to

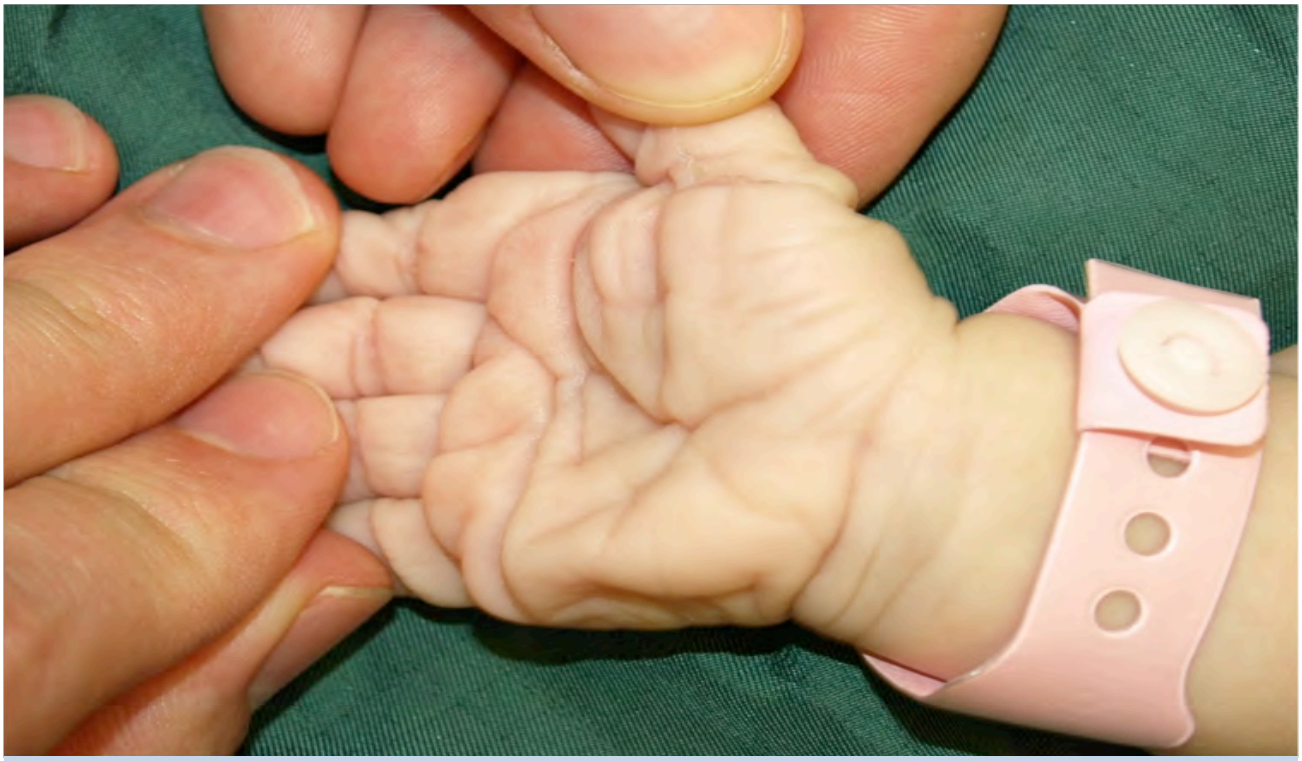

Figure 1. Loose palmar skin creating deep creases.

Figure 2. Ulnar dviation of the fingers.

transient neonatal hypoglycemia.[7,8] By birth the main problems are severe feeding difficulties and failure to thrive.[7] This combined with other abnormalities may already lead to correct diagnosis.

Individuals with Costello syndrome show characteristic abnormalities of hands and feet: Fingers and wrists show ulnar deviation, deep palmar and plantar creases go along with loose skin.[9,10] This characteristic "Costello-hand" may be regarded as pathognomic (see Figures 1 and 2). Not by chance the logo of the parent-to-parent support group Costello kids (www.costellokids.com) shows a picture of this typical hand deformity with ulnar deviated fingers.

Finally sequence analysis of HRAS gene will ensure the diagnosis of Costello syndrome.[11]

Feeding Difficulties

All children with Costello syndrome have severe feeding difficulties. To assure appropriate growth and thriving infants with Costello syndrome require feeding via nasogastric tube or gastrostomy in the majority of the cases.[7] Although nasogastric tube is problematic for long time feeding one should not underestimate the frequency of complications of gastrostomy.[12] Gastrostomy creation, often considered as a "minor" surgical procedure, can cause severe morbidity. In the case of necessary gastrostomy we recommend laparoscopic gastrostomy. To our experience this procedure has less complications compared with percutaneous endoscopic gastrostomy (PEG). Severe gastroesophageal reflux disease in infants with Costello syndrome might necessitate fundoplication in some cases.[7] Children with Costello syndrome usually tolerate full oral feedings between the age of 2 and 4 years. Interestingly Lin *et al*. described a trend towards strong tastes (e.g. ketchup and crisps).[7]

Additionally to feeding difficulties chronic constipation is also a frequent finding. Therefore children with Costello syndrome may require livelong bowel management. In the neonatal period this constipation may resemble Hirschsprungs disease.[5] Because of expectable feeding difficulties growthrate has to be monitored carefully in all patients with Costello syndrome.

Developmental, Intellectual and Neurological Characteristics

All children with Costello syndrome show developmental delay or intellectual disability.[13] Axelrad *et al.* found that IQ ranged from severe mental retardation to the average range in a series of 18 individuals with Costello syndrome.[14] They reported a trend towards more problematic behavioral in males. Social skills are constantly described as a relative strength. Because of their often very friendly demeanor Costello syndrome has been described by the acronym AMICABLE syndrome in 1990 (amicable personality, mental retardation, impaired swallowing, cardiomyopathy, aortic defects, bulk, large lips and lobules, ectodermal defects).[15]

Cerebral anomalies, especially ventriculomegaly , are frequently found but they may not be static. Progressive cerebellar enlargement has been described resulting in Arnold Chiari Malformation with Syrinx formation and hydrocephaly.[16] About 20% of all patients with Costello syndrome suffer from seizures.[17]

Musculoskeletal Abnormalities

All children suffering from Costello syndrome present with muscular hypotony in the neonatal period. Muscular hypotony, occuring in all RASopthy syndromes, may be due to a true myopathy in Costello syndrome.[18]

Patients with Costello syndrome show an impaired bone homeostasis. In a small cohort decreased bone mineral density and Vitamin D levels were found.[19] These findings correspond to the occurrence of pathologic fractures reported in adult individuals with Costello syndrome. Generally orthopaedic problems are frequently found in patients with Costello syndrome: ligamentous laxity, scoliosis, kyphosis, elbow and shoulder contractures, tight Achilles tendon, hip dysplasia, pes planus and other foot deformities may even require surgical correction.[20]

Dermatologic Features

Cutaneous papilloma are frequent findings in patients with Costello syndrome. They occur especially in the perinasal region. Although often described, these papilloma are not pathognomic for Costello syndrome as they may also occur in cardio-facio-cutaneous syndrome.[9] Cutaneous papilloma usually develop beyond infancy.

General hyperpigmentation as seen in cardio-facio-cutaneous syndrome has been described and acanthosis nigricans, especially on neck and axilla can be found.[10] However the most striking dermatologic feature is the loose skin on hands and feet (cutis laxa), often resulting in deep creases.

Cardiac Defects

Besides the development of malignancies cardiac involvement is the crucial determinant for prognosis in Costello syndrome. Cardiac abnormalities affect about 87% of infants with genetically proven Costello syndrome and consist in arrhythmia, congenital heart defects and hypertrophic cardiomyopathy.[21] Fetal tachyarrhythmia although rare may lead to cardiac insufficiency followed by hydrops, neurological damage or even fetal death.[21,22] The most frequent congenital heart defects are atrial or ventricular septal defects, pulmonary stenosis and congenital mitral valve abnormalities.[21] Hypertrophic cardiomyopathy in Costello syndrome may develop with time and is suggested to be a dynamic disease: spontaneous regression as well as fatal progression has been described.[23] Therefore close cardiac follow up is mandatory.

Cancer Susceptibility

Costello syndrome goes along with a higher risk for developing benign and malignant tumors: the cumulative incidence of cancer in individuals with Costello syndrome at the age of 20 years is 15%.[24]

In early childhood neuroblastoma and rhabdomyosarkoma have

been described. The age at presentation of these malignancies is the same as in infants without RAS germline mutations. Transitional cell tumor of the bladder has been described in three patients with Costello syndrome at the age of ten, 11 and 16 years.[25] This is remarkable because transitional cell tumor of the bladder typically affects elder men and is exceedingly rare in children or adolescents.

This cancer susceptibility necessitates early tumor screening although a clear benefit of cancer screening in Costello syndrome has not been proven yet. Unfortunately screening programs have some limits: Urine analysis for catecholamine metabolites as a screening for neuroblastoma is not helpful in children with Costello syndrome as these patients have an increased excretion of catecholamine metabolites in urine in the absence of an identifiable catecholamine secreting tumor.[26] The most frequent tumor in Costello syndrome - rhabdomyosarcoma - may occur in variable localisations complicating early detection via ultrasound screening. Nevertheless regular clinical examination and abdominal ultrasound should be performed twice a year since birth until the age of ten years. Urine check for hematuria is necessary yearly at the age of ten years to allow early detection of transitional cell tumor of the bladder.[25]

Conclusion

Being aware of the typical features early diagnosis of Costello syndrome is possible. Feeding difficulties, complex cardiac problems and a cancer susceptibility make Costello syndrome a challenging disease. An interdisciplinary approach is mandatory; various subspecialties must be involved into care of these patients.

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Research in Paediatric Emergency Medicine in Europe: Perspective from a Paediatric Emergency Department in the Basque Country of Spain

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Introduction

Paediatric Emergency Medicine (PEM) is a relatively new and evolving discipline with the aim of providing the best emergency care for children. Such care is delivered in all European countries, with over 100 million attendances to emergency departments (EDs) by children and young people every year. However PEM has been fully established and recognised as a specialty in only a few European countries including the UK, Switzerland and Turkey.[1]

Similar to what has happened in other European countries, paediatric emergency services in Spain have experienced a continuous transformation over the past 20 years. This is due in part to increased volumes of patients in the emergency departments[2] as well as more standardised training of providers in paediatric emergency medicine. In the year 2004, there were 23,654,303 visits to emergency departments throughout different hospitals in Spain (a 45.4% increase over past 10 years).[3] Paediatric emergency services have also experience similar growth. For example, the emergency department at the Hospital Universitario Cruces in Vizcaya, has doubled the number of visits since 1995, reaching a total of 63,000 in 2010.

With the purpose of offering a more specialised and satisfactory experience in the paediatric emergency departments, several teams were developed to work specifically in PEM, as well as plans of expansion of units in different hospitals with focus in paediatric care. The development of such teams has increased the demands for specialised training, knowledge and technical skills in the field. Also, the need for exchange of scientific and organisational knowledge has increased dramatically as the field continues to evolve.

Research is an integral part of any high quality medical discipline.[4-6] However, similar to the status of PEM as a clinical specialty, PEM research is still far from being fully developed in Europe. However some good research has been published relating to the emergency care of children, mostly in single centres. Our paediatric emergency department (PED) has a good tradition in research, as evidenced by the number of publications in high impact factor journals over the past 20 years (see Figure 1). We will present a summary of our main lines of research and the most relevant results thereof.

Infectious Diseases

Our research in this area has been mainly focused in the management of febrile infants. The introduction of conjugated vaccines and other preventive measures as prophylaxis against perinatal group B Streptococcal disease has produced changes in the epidemiology of severe bacterial infections. On the other hand new biomarkers of bacterial infection as C-reactive protein and procalcitonin have merged in the last 10 years. Through our

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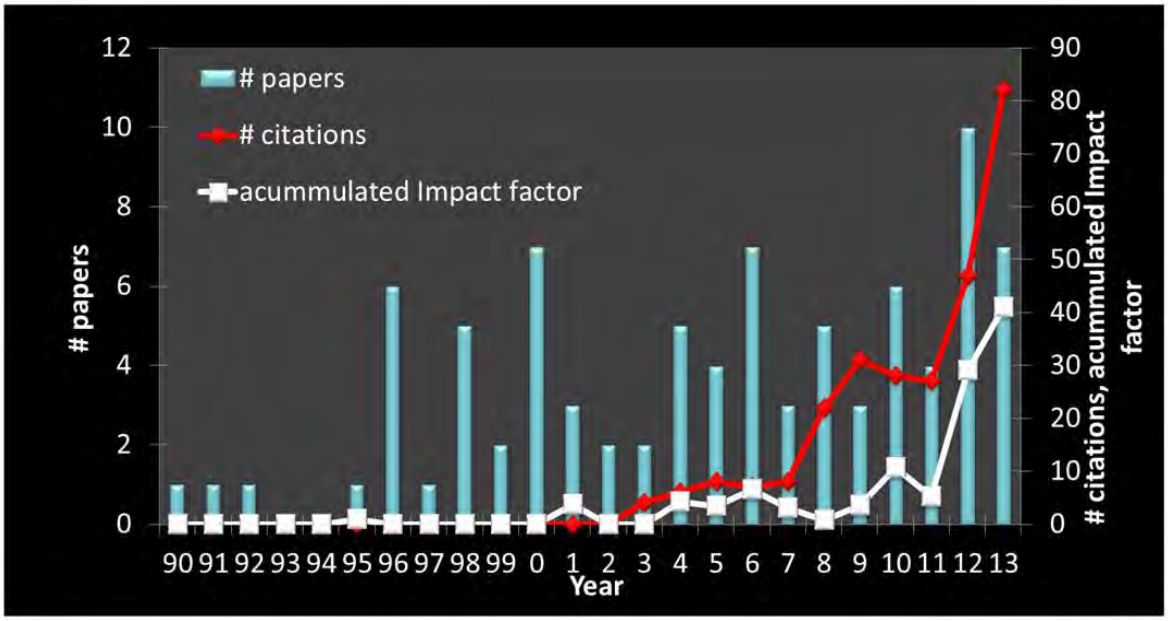

Figure 1. Accumulated impact factor of PED Cruces University Hospital (1995 – 2012).

research we have tried to find a more adapted approach to these patients in this new time.

Epidemiology of Severe Bacterial Infection in our Area

The introduction of vaccination with the 7-valent pneumococcal conjugate vaccine (PCV7) produced an important decrease in the incidence of Streptococcus pneumoniae occult bacteremia (OB) in USA. In Spain, PCV7 became available in the last months of 2001, but it was not included in the official vaccination schedule of the public health system. This led to the vaccination coverage in our area were irregular and not more than 70%. We decided to investigate the impact of this vaccine on the epidemiology of invasive pneumococcal infections in our area.

In the first study[7] we found that after PCV7 introduction in our area, rates of S. pneumoniae OB caused by vaccine serotypes decreased significantly despite only moderate use of the vaccine in our population. A new study performed 5 years later[8] shown that this effect remained 8 years after the vaccine introduction with no evidence of an OB rate increase caused by non-PCV7 serotypes.

In a more recent study[9] we found that despite the decrease observed in the overall incidence of invasive pneumococcal infections following the introduction of PVC7, pneumococcus continued being the leading cause of invasive bacterial infection (IBI) in our area. Considering the pneumococcus serotypes causing IBI we proposed that the introduction of PCV13 could lead to a very significant decrease in the IBI rate and meningococcus could become the leading cause of IBI.

Management of Young Febrile Infants

The rate of serious bacterial infection (SBI) is higher among febrile infants, 3 months of age than among older children, with a prevalence varying from 10% to 20%. As in older children, urinary tract infections (UTIs) account for the great majority of SBIs. However, young infants more often develop invasive bacterial infections (IBIs), that is, bacteremia, sepsis, and meningitis. Thus, these patients are managed more aggressively, and several laboratory tests are usually performed systematically in an attempt to identify patients at higher risk of SBI and especially IBI.

Many efforts have been done in the past years to create and assess accurate tools for the management of young febrile infants. However no optimal strategy has been so far identified. To obtain a good quality of data a registry of febrile infants younger than 3 months of age was created in our PED in 2005. From this registry we have been able to bring in question some of the aspects in the classic approach to these patients.

Febrile infants < 3 months of age have a greater risk for serious bacterial infection (SBI) and the risk is inversely correlated with age. Most protocols recommend admitting to hospital all febrile

infants <28 days of age. However, as the prevalence of SBI is not homogenous in this age group, some authors have considered decreasing this cut-off age, allowing ambulatory management of patients older than 15 days of age and meeting low-risk criteria. In a 7-year registry-based retrospective study including 1365 patients[10] we found that febrile infants 15 to 21 days of age had a rate of SBI similar to younger infants and higher than older age infants. Based on these findings we proposed that the approach to management of infants with fever based on a cut-off age of 2 weeks was not appropriate. Using the same population we study the value of leukopenia in the management of young febrile infants. Leukopenia has been classically considered a risk factor for IBI in this population. Our study[11] showed that leukopenia, in well-appearing young febrile infants, should not be considered as an SBI risk factor.

Other point of interest of our research in this topic has been to find risk factors of SBI in this population to identify patients with a different approach. We analysed 239 febrile infants <3 months of age with a positive urine culture to examine their characteristics.[12] Patients with altered urine dipstick showed more commonly alterations of the biologic markers for bacterial infection. We conclude that febrile young infants with positive urine culture and negative urine dipstick may not have a urinary tract infection and less aggressive management can be considered. On the other hand, in other study[13] we found that a toxic appearance and a positive dipstick were the best predictor of a positive blood culture in this population. We proposed that a more aggressive management should be considered in these patients.

We have also study the yield of the different biomarkers in the management of these patients. Recent studies have shown that white blood cell (WBC) count has limited value in the diagnosis of bacteremia and other SBIs in this age group. Other biomarkers as C-reactive protein (CRP) and more recently procalcitonin (PCT) have proved more accurate in identifying febrile young infants with bacterial infections. In a recent multicenter study[14] we found that among young infants with FWS, PCT was a better marker than CRP for identifying patients with IBI and also seems to be the best marker for ruling out the presence of IBI, mainly in the subgroup of infants with normal urine dipstick (UD) and early-onset fever. We consider that these are useful findings that should be taken into account in clinical practice.

Finally, as consequence of all these investigations we have recently published a study[15] showing that a sequential approach, evaluating, firstly, the appearance of the infant, secondly, the age and result of the urinanalysis, and, finally, the results of the blood biomarkers, including PCT, may identify low risk febrile infants suitable for outpatient management. In this study we have shown that the sequential approach "Step by step approach" performs better than other prior management strategies as the classical Rochester criteria and Laboratory-Score.

All these investigations are now been tested in two multicentre and prospective studies, necessary for these findings are definitely incorporated into clinical practice.

Management of Older Febrile Infants (3 to 24 Months of Age)

We have mainly study the influence of changes in the prevalence of pneumococcal occult bacteremia caused by pneumococcal conjugated vaccine (PCV-7), on performance of the complete blood count (CBC) and other biomarkers in selected patients at risk of having occult bacteremia (OB). In one study[16] we found that the yield of the CBC is lower than in the pre-PCV-7 era and decisions based on CBC should be reconsidered. However, in other study[17] we shown that the prevalence of occult pneumonia in infants with high fever without source (FWS; temperature, > or =39.0 degrees C) and a white blood cell (WBC) count greater than 20 x 10(9)/L, in the era of PCV7 remains high enough (15%) to justify the practice of this test. In this study incidence of pneumonia increases in infants older than 12 months and with higher ANC and serum CRP level.

With regard to other biomarkers we prospectively studied the reliability of CRP and PCT as predictors of invasive infection in a cohort of 868 infants < 36 months of age with fever and nontoxic appearance.[18] Procalcitonin was a useful biomarker, better than CRP to predict invasive infection in non-toxic-appearing infants with fever without apparent focus, particularly in febrile episodes of < 8 hours duration. We also tested the usefulness of two new biomarkers, midregional pro-adrenomedullin (MR-pro-ADM) and C-pro-endothelin-1 (CT-pro-ET-1), in predicting bacterial infection (BI) and especially invasive bacterial infection (IBI) in the same population.[19] Although baseline MR-pro-ADM and CT-pro-ET-1 levels were significantly elevated in patients with a bacterial infection, their overall performance as diagnostic markers was very poor.

Poisonings

Epidemiology

Poisoning remains a major public health care problem, particularly in children. However, few data about the impact of poisonings in the Pediatric Emergency Departments (PED) and epidemiological data are available. To prevent acute poisoning in children it's very important to know in which circumstances they occur.

Early in our research interests, we focus on the epidemiology of poisoning, making descriptive studies which helped us to understand the circumstances in which children are intoxicated in our area.[20,21] As they had observed other researchers we found

that most of poisoning was accidental and occurred in children under 7 years old. At that time, the main drug involved in poisoning was acetaminophen. With the same propose we conducted a prospective multicentre study in 2001-2002 in 17 Spanish hospitals with similar findings.[22]

Due to some differences observed in the epidemiology and management of poisonings in the Spanish PED, a Toxicology Surveillance System was created by the Intoxications Working Group (IWG) of the Spanish Society of Pediatric Emergencies in 2008. This observatory joined 44 hospitals and their first results were published in 2011. In this study,[23] most frequent poisonings seen in Spanish PED were caused by the accidental ingestion of drugs and household products by children less than 7 years-old at home. They also found that drug poisoning was potentially more risky and proposed that drug and household product storage education, proper drug dosage and administration, and good advice could be the main issues to prevent these poisonings. On the other hand with this surveillance system we have identified changes in the epidemiology of poisoning in our country,[24] as the increase of alcohol as a cause of poisoning in children under 14 years in the last 5 years.[25]

Management of Poisonings in the Emergency Department

Another aspect investigated by our group regarding poisoning has been the quality of care received in the emergency room[26] and the impact of different actions carried out by the (IWG) of Spanish Society of Pediatric Emergencies in the management of acute paediatric intoxications in Spain.[27] Overall we have documented a great variability in the management of poisonings among Spanish PED. However the actions carried out by the IWG have produced an improvement in the indication of certain treatments such as gastric lavage.

Our experience in Spain has led to promote an epidemiological study of the same features but globally. The aim of this initiative is to determine the epidemiology and management differences of acute poisonings in children evaluated in emergency departments (EDs) from 8 different regions of the world. This is a registry-based international multicenter prospective study of children treated for acute intoxication in 110 EDs from 20 countries during a year. Results of this study will be presented this year in the most important paediatrics and emergency medicine scientific meetings and probably published very soon.

Respiratory Diseases

Epidemiology

Acute exacerbations of asthma are the leading cause of emergency department visits in the paediatric patient. We have investigated changes in the epidemiology of acute asthma in our hospital from 1987 to the date. A trend toward decreasing length of hospital stay, a fall in the number of ward and intensive care unit admissions, and an absence of in-hospital deaths have been observed during this time.[28–30] In the same period, the number of emergency visits has remained stable with some fluctuations, increasing the proportion of patients under 5 years old. All these changes have been associated with greater intensity of emergency room treatment with increases in the number of doses of nebulised beta 2-agonists administered and in courses of oral prednisolone given.

Evaluation and Treatment of Acute Asthma Episodes

All efforts of emergency room management of children with asthma, identification of severity of the current exacerbation episode, and intensive treatment of the acute asthma attack have usually been directed at reducing the rates of hospitalisation and the return for medical care.

With this aim we have performed several studies to identify factors associated with the severity of acute asthma and patient's hospitalisation and the effectiveness of different treatment strategies. Shortly after the introduction of oxygen saturation in the management of children with acute respiratory disease, we showed that this parameter and the peak expiratory flow (PEF) rate could satisfactorily assess the severity of acute asthma in children and the patient's outcome.[31]

Regarding to the treatment of acute asthma in the emergency department, in one study[32] we found that co-administration of ipratropium bromide and repeat doses of nebulised salbutamol produced a small beneficial clinical effect compared with administration of nebulised salbutamol alone. This beneficial effect was related to a decrease in the hospitalisation rate, particularly in patients with severe asthma attacks. On the other hand, through the research in this field we have contributed to show that the administration of bronchodilators using a metered-dose inhaler with spacer is an effective alternative to nebulisers for the treatment of children with acute asthma exacerbations in the emergency department.[33,34]

New Strategies to Improve Short Outcome of Children with an Asthma Exacerbation

Similar to the findings in other studies we have found that children treated at the emergency department because of an asthma-related event present a high morbidity at 7 and 15 days after discharge, mainly associated with symptom persistence, need for rescue bronchodilator medication, and absenteeism from school or day nursery.[35,36] All these studies pose that according to reported

data on short-term morbidity, it would be necessary to define therapeutic and follow-up strategies after treatment for acute asthma and emergency department discharge.

The most important expert consensus on asthma have recently proposed that besides standard treatment for an acute asthma exacerbation in the paediatric emergency department, action plans should include a review of the maintenance treatment of asthma to improve underlying disease control. Considering this recommendation, we conducted a study to assess the impact of improving long-term control medications on quality of life in children with persistent asthma symptoms attended in our PED.[37] The results were encouraging, with an improvement in quality of life in children where maintenance treatment were initiated or stepped up. These findings have led to changes in our routine management of children with asthma, recommending changes in long-term control treatment in patients with persistent asthma criteria.

The Future

An increasing number of young investigators are joining to our team and more than 20 projects in different research lines are currently in progress. Our goals for the near future are to improve the quality of our research through collaboration with other research groups and networks. Two recent initiatives, the Spanish Pediatric Emergency Research Group (SPERG)[38] and the Research in European Pediatric Emergency Medicine (REPEM)[39] are the best example of research collaboration and the way to obtain more generalised and meaningful research results.

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Dillemas Concerning the Person Performing Procedural Sedation and Analgesia (PSA) for Gastrointestinal Endoscopy (GE) in Children

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Introduction

Gastrointestinal endoscopy (GE) practice in childhood, performed under procedural sedation and analgesia (PSA) has increased in the last two decades. Cooperation between endoscopist and anesthesiologist should be focused on the level of safety and minimising the risk of adverse according to the announcement of the Helsinki Declaration on Patient Safety in Anesthesiology in 2010. There is still open question, whether some patients can be managed using minimal or moderate sedation, and, if not, for the others sedation or anesthesia could be much better. The next issue is who might undertake PSA - pediatrician or anesthesiologist.

Children present a group of patients with potential problems that differ greatly from those of adults. According to published data, the frequency of anesthesia-related cardiac arrests in children is 0.014%, and mortality or post-resuscitation irreversible neurological disability is still high: 24% and 15-30% respectively. Providing sedation one must have the skills to rescue the patient even though this technique seems to be safe when used by non-anaesthesiologists. Cote showed that safety during PSA is determined by the professional skills of the provider, rather than by particular medications.

This review presents considerations concerning safe performance of pediatric gastrointestinal endoscopy under PSA, and distinguishing which personnel should perform PSA for this procedure in children.

Alicja Bartkowska-Sniatkowska studied at Poznan University of Medical Sciences, qualified as medical doctor (MD) in 1988. In 1997 completed an internship in anaesthesiology and intensive care, in 2003 in emergency medicine. PhD theses, based on the dynamics of IL-6, TNF-α and lactates in patients with severe multiple trauma, completed in 2001. From 2006 working as Head of Department of Paediatric Anaesthesiology and Intensive Care in University Children's Hospital in Poznan. Member of PSAIC, ESA, ESPA, PRC. Currently conducting research on pharmacokinetics and pharmacodynamics of drugs administered in critically ill children in PICU and in daily anaesthesia practice.

PSA

Procedural sedation and analgesia has been defined from many years as a state that allows patients to tolerate unpleasant and painful procedures. Depths of sedation has been assessed by a continuum differentiating PSA into Minimal Sedation (MS), Moderate Sedation (MDS), Deep Sedation (DS) and at last General Anesthesia (GA). During minimal sedation, cognitive function is suppressed following by reduced anxiety and fear. In moderate sedation the maintenance of respiratory function may be compromised and drug-induced depression of consciousness, what is sometimes unpredictable, could change from "moderate" to "deep" without any particular symptoms. For this reason the presence of a trained person who is at least competent to provide pediatric advanced life support (ALS), airway management and/or cardiopulmonary resuscitation (CPR) could be essential for the patient's safety. Generally, when performing procedure of PSA the risk of loss of both spontaneous breathing and protection of the airway can be lost observed, particularly in infants and smaller children, necessitating support of the airway and/or ventilation. The rate of respiratory complications during PSA depends on factors such as higher ASA classifications as well as the use of multiple sedation agents.

Pediatric Management

Routine pediatric assessment before PSA should predict more obvious risks, namely: younger child's age (under 1 yr), and the presence of co-existing morbidity. The state of health is routinely assessed by ASA (American Society of Anesthesiologists) higher ratio seems to be and strictly correlating with higher risk of complications e.g. greater ASA grade (ASA≥III), although even 33% of children with reported cardiac arrest were previously categorised as ASA I-II. Pre-procedural assessment should also identify potential airway and breathing problems. Assessment

of the risk of laryngeal spasm is extremely important in babies and would include recent upper respiratory tract infections, asthma, exposition to tobacco inhalation and coexistence of gastroesophageal reflux. Even though laryngospasm is infrequent (0.4%), it's classified as a life-threatening complication and pediatric recommendations suggest delay of any medical procedure at least 15 days after severe respiratory infection.

Laboratory assessment prior to gastrointestinal endoscopic procedures in children depends on the individual conditions. Healthy children (ASA I or II) can be sedated without any laboratory tests, while with children categorised as ASA ≥III, or when the endoscopist anticipates any bleeding or complication, it would be necessary to check a minimum of blood type, blood count, electrolytes and/or coagulation parameters. Children with severe chronic diseases could be assessed by appropriate consultant.

Vaccinations

Current recommendations for sedation/ and anesthesia strategy in relation to routine vaccination in childhood are not yet settled. According to the principles of good practice to suggestion of different time intervals between PSA and vaccinations, depending on the type of vaccine was given. Procedures for children just inoculated should be postponed 3 days for nonlive vaccines and 3 weeks for live vaccines, to help to differentiate between adverse events following immunisation (AEFI) and procedural complications per se. The presence of or contact with patients with contagious diseases should be dealt with by postponement of the procedure for 2-3 weeks.

Fasting

Fasting before PSA and endoscopy would be important both for the quality of the endoscopic procedure (essential for endoscopist) and for the patient's safety (essential for provider of sedation). However fasting too long is not beneficial. According to the latest recommendations published by European Society of Anaesthesiology (2011) children should be encouraged to drink clear fluids up to 2 hours before the procedure. Infants can be given breast milk up to 4 hours before. Solid food and other types of milk should be prohibited for 6 hours independently of the age of infant or child.

Pharmacological Premedication

In younger (< 5yr) and non-cooperative children effective premedication could promote anxiolysis, and what is important in gastroenterological practice, a decrease in autonomic reflexes. Some recommend oral administration of midazolam as following: children aged 1-6yr – 0.25-0.50 mg/kg, children >6yr - 0.25-0.30 mg/kg. Prolonged presence of drug residues in the stomach may compromise gastroscopy and alternative routes be used instead. The newest drug option during premedication among the pediatric patients, could be alpha-2 agonists such as dexmedetomidine (dex) and clonidine (clo) is promoting anxiolysis and pain reduction without respiratory and circulatory depression, which is a unique feature. The oral doses for dexmedetomidine and clonidine are 2.5 mcg/kg and 4.5 – 5.0 mcg/kg respectively, while intranasal dosing of 1 mcg/kg is recommended.

PSA Drugs

Midazolam, short acting imidazobenzodiazepine, seems to be safe in the hands of non-anaesthesiologists for PSA in infants and children from many years. The average T1/2 is short (2.5 – 4 hours), in particular that its metabolite, hydroxymidazolam, has minimal clinical activity. Published data recommend intravenous administration for gastrointestinal endoscopies. According to the recommendations doses of 0.05-01 mg/kg for infants (>6m) and children (<5 yr) are preferred, for children aged 5-12 yr – 0.025-0.05 mg/kg, and for older loading single dose of 1.5-2.5 mg midazolam could be essential. Diazepam has longer T1/2 (0.8 -2.25 day), and this is even longer in neonates, infants and obese patients (up to 3.9 days). Additionally, its metabolites are also active, precluding disqualify this drug from day-case procedural practice in pediatrics. Lorazepam, is also less useful during PSA in view of slow onset of action (15-20 min.) and long duration (6 – 8 hours).

Recent data increasingly concern the use of hypnotic agents, such propofol, ketamine or etomidate by non-anesthesiologists for sedation during endoscopy. Guidelines published in the European Journal of Anaesthesiology in December 2010 generated significant debate among both proponents and opponents about propofol usage by non-anesthesiologists. Propofol as an "ideal intravenous short-acting hypnotic agent" can usually be administered in a single dose, lower for older children (0.5-1.5 mg/kg) and higher for children younger than 8 years (1.5 – 3.0 mg/kg), as well as continuous infusion with a fast recovery time. The most important disadvantage of propofol is its narrow therapeutic range. The US Food and Drug Administration (FDA) denied the petition of the American College of Gastroenterologists to change the registration for this drug allowing to use propofol by non-anesthesiologists. In contrast to adult patients, the practice of non-anesthesiologist administration of propofol in children is uncommon but data are limited. Many authors agree that propofol administration does, in fact, qualify as monitored anaesthesia care (MAC), requiring standards and competences applicable to anesthesia. Published reports have evaluated the incidence of complications during pediatric propofol sedation. The most common respiratory adverse event was desaturation 9.3%, apnea 1.9%, assisted ventilation 1.4% with unplanned intubation 0.02%. Hypotension (15.4%) and bradycardia (0.1%) seemed to be

also important during propofol administration. Critical incident analysis of those adverse events demonstrates that 80% of events present initially as respiratory compromise and, it is rather due to lack of clinical knowledge, poor monitoring standards rather than the type of the drug itself.

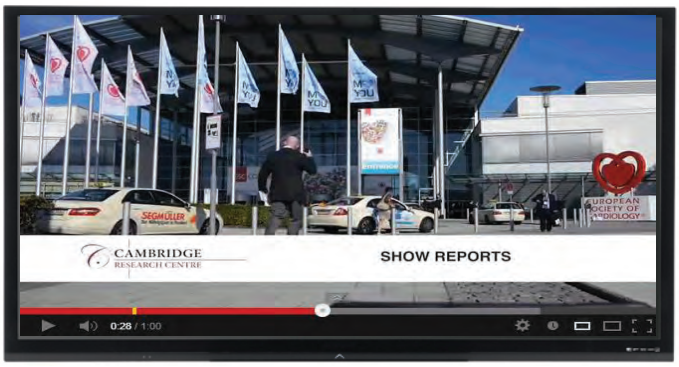
Dexmedetomidine, in contrast to propofol, may offer advantages in sedation for a population of pediatric patients with "difficult airways" due to the lower incidence of respiratory depression. Nevertheless, dexmedetomidine should be carefully used in patients with pre-existent bradycardia, hypovolemia, hypotension. Side effects of dex can be antagonised by the antagonist - atipamezole. Based on adult data, the recommended loading dose of 0.5-1 mcg/kg given over 10 minutes, following by infusion with 0.2 to 0.7 mcg/kg/h may also be used in children, even some authors suggest omitting the loading dose to avoid cardiovascular instability.

Conclusions

There are still ambiguous opinions concerning PSA in pediatric endoscopic practice, confounding by variables influencing the likelihood of adverse events. The exact delineation between what could or should be done by pediatric endoscopists or pediatric anesthesiologists is still not agreed.

The main issue is a good classification scheme for patients who could be provided for by a non-anesthesiologists versus those who should not. This scheme should comply procedural factors such as anticipated discomfort or pain and prolonged procedure; patient's factors like age (e.g. infancy), airway compromise, cardio-respiratory conditions, hepatic and renal insufficiencies and finally patient/parent preferences.

The next issue should concern the drugs used for procedural sedation. Benzodiazepins such a midazolam have a wide margin of safety, but are typically weak and do not always guarantee success. Anesthetic drugs, in contrast, have more favorable potency and short duration of action, ensuring successful performance of procedure. However, on the other hand, they have a smaller therapeutic window and so, in untrained hands, may increase the risk of complications. For this reason, according to the American Society of Anesthesiologists (2010) to provide deep sedation safely, certain provisos like education and training with assessment of competencies that might lead to some form of the licensure should exist: generally anesthesiologists performed anesthesia while the endoscopists performed sedation. In pediatric practice, only collaborative cooperation between pediatricians and anesthesiologists should guarantee successful procedure.



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Treatment Advances in the Neonatal Intensive Care Unit with a Neonatal Neurologist

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Introduction to Neonatal Neurology

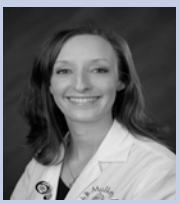
Given the large number of neurologic problems encountered in the neonatal intensive care unit in both premature and term newborns, the need for a neurologist with special interest in neonatal neurology is large and growing.[1,2] Some paediatric centers now have a dedicated neonatal neurologist or even a neonatal neurocritical care unit with nurses that have advanced training in neurologic focused care.[2-4] In this setting, the neurologist works with the neonatologists to deliver the most advanced neurologic treatments available. Hypoxic-ischaemic encephalopathy of the newborn is one example of a neurologic condition that benefits greatly by having a neurologist involved throughout the newborn's care.[2] Other neurologic conditions seen in the neonatal intensive care unit that benefit by having a neonatal neurologist include seizures, neuromuscular disorders such as cases of hypotonia, genetic conditions, cerebral malformations, stroke, and neurologic complications of prematurity (intraventricular haemorrhage and periventricular leukomalacia).

Neonatal Seizures and Electroencephalography

The identification and treatment of neonatal seizures represents a challenge in the neonatal intensive care unit. Newborns can have seizures due to a variety of conditions and seizures have varied semiology making them potentially hard to recognise. Infants may have vital sign changes or movements that are suspicious for seizures including apnea, episodes of tachycardia or even bradycardia, repetitive focal body movements, or eye deviation. One thing that makes seizures particularly challenging to recognise and treat in neonates is the high incidence of subclinical seizures (seizures without a visible clinical sign).[1] In an electroencephalogram (EEG) study of neonatal seizures, only 20% of the total electrographic seizure burden was clinical, so continuous EEG monitoring is essential in order to properly identify and treat neonatal seizures.[5] In addition, this same study showed that only about 1/3rd of the clinical seizure events were correctly recognised by trained neonatal providers.[5] Short routine EEG studies of about one hour in duration are therefore typically not sufficient to properly diagnose and treat neonatal seizures. Consultation by a neurologist early in the evaluation can help direct the investigation for seizures with EEG, the diagnostic evaluation to determine the underlying etiology, and most importantly the urgent treatment with anti-epileptic medications (see Figure 1).[2] Not unexpectedly, long-term video EEG monitoring use is increased by having a neonatal neurologist.[2]

The American Clinical Neurophysiology Society recommends continuous EEG monitoring for infants at a high risk of seizures which include infants with hypoxic-ischaemic encephalopathy, central nervous system infection, stroke, sinovenous thrombosis, cerebral malformation, metabolic conditions, and other forms of brain injury such as intraventricular haemorrhage that can be associated with prematurity.[6] EEG monitoring should be initiated when these conditions are suspected or when the infant is having clinical signs concerning for seizure. The event of concern can then be captured on EEG to confirm that it is a seizure ensuring proper treatment with anti-epileptic medications. The EEG is then used to ensure adequate seizure treatment and is typically continued until the infant has been free of seizures for 24 hours.[6]

Two main types of EEG are used for continuous EEG monitoring



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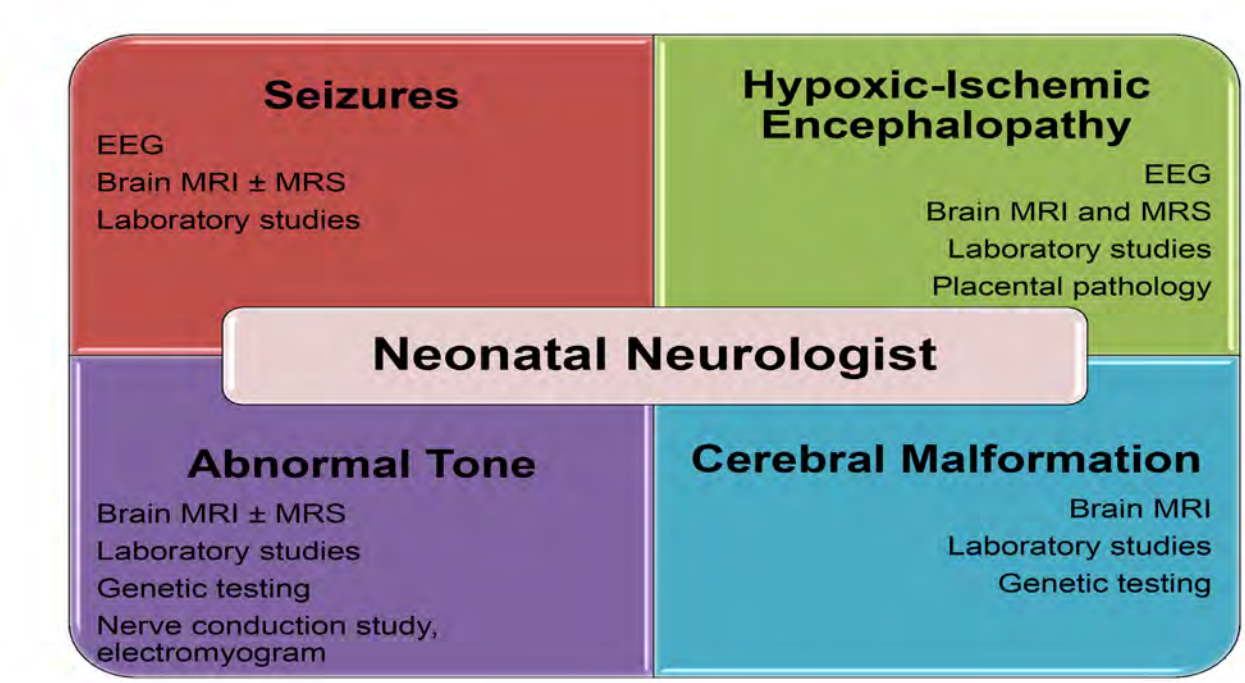

Figure 1. Common Neurologic Diagnoses and Testing by a Neonatal Neurologist.

in the neonatal intensive care unit; conventional EEG, which is the gold standard used for long-term EEG monitoring by neurophysiologists and amplitude-integrated EEG (aEEG). An aEEG is different from a conventional EEG because it is a time compressed EEG recording using a limited number of channels that has been well studied in infants with hypoxic-ischaemic encephalopathy.[7-9] The advantages of aEEG are that it can function as a bedside brain monitor and can more easily be interpreted by non-neurologists since it can be read using pattern recognition. The aEEG however, has lower sensitivity for seizure detection compared to full-channel EEG.[10,11] Both full-channel EEG and aEEG can also be used simultaneously.[6,12] This method enables the neonatal neurologist to have the full-channel EEG for complete evaluation of seizures and background activity and the aEEG can be a bedside tool for the neonatologists and trained nursing staff.

Neuroprotection

Therapeutic hypothermia has increasingly become a standard of care for term newborns with hypoxic-ischaemic encephalopathy with favorable results in clinical trials.[13-15] Meta-analyses at 18 months of age and of long-term outcome studies demonstrated a reduction in death and severe neurodevelopmental disabilities and an increase in normal neurologic survival for infants with hypoxic-ischaemic encephalopathy that received therapeutic hypothermia, either with whole body cooling or with selective head cooling.[16,17] The care of an infant requiring therapeutic hypothermia is best with the combined expertise of a neonatal neurologist, neonatologist, paediatric neuroradiologist, and experienced nurse.[2,3] It is important for a neurologist to be available to follow the infant from admission to discharge and respond to changes in the neurologic exam, review the EEG and brain magnetic resonance imaging (MRI), and discuss findings and prognosis with the family (see Figure 1).[2] Developing a standardised protocol for therapeutic hypothermia can also help to ensure high quality standardised care.

Unfortunately, some newborns with hypoxic-ischaemic encephalopathy treated with therapeutic hypothermia still have brain injury and impaired neurodevelopmental outcomes. Other neuroprotective agents are activity being studied in clinical trials that may further improve neurologic outcomes when combined with therapeutic hypothermia.[18] Erythropoietin is a medication and naturally occurring hormone that has been used in newborns for a long time to treat anemia, but also has exciting potential as a neuroprotectant. Studies have shown that it can reduce neuronal apoptosis, has antioxidant and anti-inflammatory properties, and increases neuronal regeneration following ischaemic brain injury.[19] A phase I clinical trial in newborns with hypoxic-ischaemic encephalopathy demonstrated safety with adequate plasma concentrations of erythropoeitin.[20] Erythropoietin may also show benefit for reducing brain injury in extremely low birth weight preterm newborns.[21] Certainly it seems that there are some exciting new neuroprotective treatments on the horizon for newborns at risk for brain injury that can be offered by a neonatal neurologist.

Brain Imaging

Brain imaging is an important tool for the neonatal neurologist in evaluating multiple different types of neurologic conditions in the neonatal intensive care unit.[2] A brain MRI is often obtained to

evaluate the etiology of neonatal seizures, brain injury in hypoxic-ischaemic encephalopathy, cerebral malformation associated with genetic or metabolic conditions, and to evaluate central causes of hypotonia (see Figure 1). Techniques can be used to obtain brain MRI in newborns without sedation.[22] Brain magnetic resonance spectroscopy (MRS) should be included for cases of suspected hypoxic-ischaemic encephalopathy since it may show signs of injury earlier than conventional brain MRI.[23] MRS can also be used to evaluate for metabolic encephalopathies such as Zellweger syndrome, which show characteristic changes from the normal spectra.[24] The quantitative brain MRI technique of diffusion tensor imaging, which is not currently included in most clinical brain MRI protocols, provides highly sensitive measures of white matter injury that may not be detected with other types of imaging modalities.[25] Head ultrasound is useful for evaluating the ventricles for developing hydrocephalus or haemorrhage, but does not display the brain parenchyma with enough detail to properly evaluate other types of neurologic conditions. Head computed tomography is used less often, due to radiation from this technique. The neonatal neurologist therefore can determine the best type of brain imaging to evaluate the patient.

Genetic and Neuromuscular Investigations

Neurologists play a critical role in the evaluation of a newborn with genetic, metabolic, and neuromuscular disorders in the neonatal intensive care unit. Newborns can have hypotonia due to a variety of conditions that benefit by having the expertise of a neonatal neurologist along with a geneticist to examine the infant and determine the best route for establishing the underlying diagnosis (see Figure 1).[2] In these infants, brain MRI may show cerebral malformations that would point toward a central cause of hypotonia. Sometimes, however, the evaluation of infants with hypotonia may be prolonged with initial testing negative. The dedicated neurologist in the neonatal intensive care unit, that has followed the infant over time, can help to plan the next stage of diagnostic testing. In addition, having a neurologist that is able to provide continuity of care is often very important for counseling the patients' family about the findings and diagnosis.

Placental Pathology

Evaluation of the placenta by a trained placental pathologist can aid the neonatal neurologist in assessing neurologic conditions in the newborn.[26] In newborns with hypoxic-ischaemic encephalopathy the placenta may show abnormal weight, infarction, infection, and/or inflammation and these findings can have implications for the timing of the brain injury and the infant's response to therapeutic hypothermia.[27,28] Pathology of the placental may help explain the etiology of cases of neonatal encephalopathy and of neonatal stroke in otherwise normal pregnancies, although further study into the relationship between placental findings, brain imaging, and neurodevelopmental outcome is certainly needed.[29,30]

Developing a Neonatal Neurology Service

In a busy neonatal intensive care unit there are often neurology cases that would benefit by having neurology consultation. A child neurologist with special interest in neonatal neurology can perform timely consultations and be part of a multi-disciplinary care team along with the neonatologist.[2] The neurologist can implement protocols for the treatment of neonatal seizures and hypoxic-ischaemic encephalopathy which improve the standard of care. The neurologist can read the EEG studies, determine need for and duration of anti-epileptic drug therapy, and guide evaluation into the etiology of seizures. Given that many newborns with neurologic conditions are in the neonatal intensive care unit for at least several weeks, the neurologist can follow their neurologic exam over time and provide recommendations for outpatient care. In our neonatal intensive care unit that has about 850 admissions per year, about 12% need a neurology consultation.[2] A neurologist may therefore need to spend around 20% time in the neonatal intensive care unit, which could be combined with other inpatient and outpatient responsibilities.

Conclusion

The field of neonatal neurology is growing with new treatments and advances in neurodiagnostic methods. The neurologist is part of the multi-disciplinary team that is needed to care for many types of newborns with neurologic conditions in the neonatal intensive care unit.[2] The development of specialised treatment guidelines by a neonatal neurologist helps to ensure high quality standardised care of the neurologic conditions most often encountered in the neonatal intensive care unit. Improving neurologic care of newborns with a neonatal neurologist will hopefully improve the long-term neurodevelopmental outcomes for the youngest neurology patients.

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Strategies of Prophylaxis and Empirical Treatment of Febrile Neutropenia in Children with Acute Leukaemia: How Can We Perform a Rational/Reasonable Choice?

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Infections represent one of the most important complications of antineoplastic chemotherapy and neutropenia is the most well known risk factor, even if not the only one.[1]

Prophylactic administration of antibiotics in leukaemic patients is frequently advocated as life-saving on the basis of meta-analyses and clinical trials performed mainly in adults.[2] In children with acute leukaemia the efficacy of antibacterial prophylaxis for the prevention of febrile neutropenia has been evaluated in only two randomised, double blind, placebo-controlled trials (RCT)[3,4] that showed a very similar effectiveness (21% vs. 23%) and number of patient to be treated for preventing a febrile episode (5 vs. 4) in spite of the use of drugs with different spectrum of activity, amoxicillin-clavulanate or ciprofloxacin. More recently, a reduction in the incidence of fever and Gram-positive infections, but not in that that due to Gram-negatives, was observed in a large survey performed in children with acute myeloid leukaemia,[5] and similar results were observed in 3 other surveys in children with acute myeloid leukaemia or other aggressively treated haematological malignancies where complex prophylactic schemes, cefepime alone or intravenous vancomycin plus either oral cephalosporin, oral ciprofloxacin, or intravenous cefepime,[6] cefepime/vancomycin or piperacillin-tazobactam[7] or ciprofloxacin/voriconazole or micafungin[8] were adopted. In spite of this potential effectiveness in aggressively treated children, the use of antibacterial prophylaxis can be associated with the selection of resistant strains.[9] Even if results of the major RCTs and meta analyses suggest that administration of antibacterial prophylaxis for febrile neutropenia had no impact on the selection of resistant bacteria,[2,10,11] it must be remembered that 1) RCTs, and meta-analyses derived from these data, cannot be used for epidemiological purposes since RCTS do not collect data on infections occurring after the end of the study and in patients not enrolled in the trial, 2) there are unequivocal data showing that increased resistance may be observed in children who did not receive this prophylaxis, but who were treated by hospital where prophylaxis is used in adults;[12] and 3) the widespread use of fluoroquinolones has been associated with the emergence of bacteria displaying cross-resistance to fluoroquinolones, β-lactams, and aminoglycosides.[13-16] Interestingly, an accurate evaluation of the possible selection of resistant strains during antibacterial prophylaxis has been performed only in recent years, and all studies showed an increase in isolation of resistant pathogens,[4,6,8] mainly associated with changes in enteric microbiota induced by both chemotherapy and antibiotics.[4,17] In any case, the initial recognition of this phenomenon led many international guidelines to recommend to implement a systematic strategy for monitoring rates of vancomycin resistant enterococci, infections due to C. difficile, methicillin-resistant S. aureus and fluoroquinolone-resistant Gram-negatives in or der to adapt prophylactic (and therapeutic) strategies to local epidemiological data.[16,18,19] Another point never deeply analysed in RCTs regards the effectiveness of prophylaxis in preventing fever during all the repeated periods of neutropenia induced by subsequent cycles of chemotherapy. A retrospective analysis of data derived from a prospective survey on the incidence of fever and infections during neutropenic periods in cancer children,[20] showed that aggressiveness of chemotherapy, and no other factor including prophylaxis, determined the probability of fever during subsequent neutropenic periods in children with acute leukaemia. When a prophylaxis program is implemented other questions must be answered that regards the type of the event we want to prevent,

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e.g. fever or bacteraemia, and its frequency in our patients' population.[21] Indeed, only one study evaluated prospectively the incidence of fever and infectious episodes in neutropenic cancer children,[20] and showed that this complication occurred in only 48% of neutropenic periods following aggressive chemotherapy for acute leukaemia/lymphoma, with a 14% incidence of bacteremias. As a consequence, if we consider the actual epidemiology of fever in neutropenic children and the effectiveness of antibacterial prophylaxis observed in paediatric RCTs we can estimate that for every 100-neutropenic patients receiving prophylaxis, 75–80 of them are treated unnecessarily to prevent the remaining 20–25 from developing fever. If we consider that the incidence of Gram-negative bacteraemia, the most feared complication because of high mortality, generally represents no more than 10–15% of all febrile neutropenic episodes, probably we would administer unnecessarily prophylaxis in 96–97 patients to prevent Gram-negative bacteraemia in 3–4 of them. This number could still be considered as acceptable,[22] if antibiotic resistance would not be an emerging problem. In the only paediatric RCT that evaluated also the selection of resistant strains,[4] the proportion of ciprofloxacin resistant Gram-negatives colonising patients after 2 weeks of intervention was 95%, whereas it was 27% in those randomised to receive placebo. From the other hand, we observed 17% (25/145) resistance to ciprofloxacin of Gram-negative organisms causing bacteraemia in our centre in the period 2004- 2011, despite we do not use ciproflaxacin prophylaxis.[23] These proportions of resistance also in patients not receiving ciprofloxacin are worrisome. Stemming from all these considerations it is our opinion that now is the time when antibacterial prophylaxis in neutropenic children with cancer should be abandoned at least during chemotherapeutic regimens. If some benefit could be expected in some single patient or subgroups it should be carefully evaluated in the light of the risk of selecting resistant strains. At this point the correct and systematic application of infection control measures[24] probably represent the best "treatment" strategy to prevent severe infections in neutropenic cancer children without major "adverse events" and preserving antibiotics for future treatments.

The increasing incidence of infections due to antibiotic resistant bacteria, especially extended- spectrum-beta-lactamase producing Enterobacteriaceae and multidrug resistant P.aeruginosa, is becoming a major problem for health care systems,[25-29] and involves also paediatric patients receiving antineoplastic chemotherapy or stem cell transplant,[30-35] even if its geographical distribution is still very different.[25,26] This constitute a major problem for the choice of the better initial, empirical antibacterial therapy of febrile neutropenia.[1] RCTs on empirical treatment of febrile neutropenia with adequate sample size and power have been mainly performed in adults,[1] but the results have been applied also to children,[36] even if the epidemiology of neutropenic fever may be slightly different between these patients populations.[1,20,37] The prompt administration of an appropriate initial empirical antibiotic therapy is critical for the outcome of febrile neutropenic patients[1,38,39] and the use of monotherapy with an anti pseudomonal beta-lactam or a carbapenem is recommended in all the most recent guidelines[19,36,40,41] as an effective and safe strategy. However, in our opinion this recommendation is based on an misconstruction: from one hand it is recommended to use an anti-pseudomonal beta lactam in order to treat a potentially life-threatening Gram-negative bacteraemia, while on the other the selection of drugs and their use as monotherapy is mainly derived by randomised clinical trials were effectiveness of the therapy was measured on the treatment of all febrile episodes, mainly fevers of unknown origin, and not bacteraemias.[1] Noteworthy, three very recent surveys on antibiotic susceptibility of Gram-negative rods isolated in cancer patients (both children and adults) showed that the proportion of strains resistant to at least some of the drugs recommended for monotherapy of febrile neutropenia was ≥10%.[42-44] Therefore, even if monotherapy is clearly effective to treat a patient with fever without any localisation or microbiological documentation, it could be not adequate in a not negligible proportion of cases in presence of a potentially life-threatening Gram-negative infection (due to P. aeruginosa, or to other Gram-negatives). A 20% proportion of resistant strains had been suggested as cut-off to stop fluoroquinolone prophylaxis for febrile neutropenia in cancer patients,[16,18,19] but no indication is available for therapy. Noteworthy, the presence of a 10– 20% proportion of resistant strains is indicated as level to change treatment strategy in community acquired intra-abdominal infections,[45] while this proportion is reduced to 5% to change treatment strategies for gonococcal infection.[46] Clearly these conditions are very different from febrile neutropenia, but we believe reliable, even if arbitrary, to consider this ≥10% proportion of resistant strains observed in epidemiological surveys as an alarming threshold to recommend review of empirical therapy strategies. In fact, an inappropriate initial antibacterial therapy of Gram-negative bacteraemia in a neutropenic patient is associated an increased risk of persistent infection, septic metastasis and death.[34] These considerations seem at least indirectly to support the possible use of a combined therapy with an anti-pseudomonal beta-lactam and an aminoglycoside (single-daily administration) for initial empirical therapy of febrile neutropenia, both drugs chosen on the basis of local susceptibility data,[44] with de-escalation to monotherapy in the case of fever of unknown origin.[47] Significantly, a combination of beta-lactam and aminoglycoside was chosen for initial empirical treatment of febrile neutropenia in 87% of the paediatric centres vs. 16% of the adult centres included in the aforementioned multicentre survey,[43] and in 55-81% of those included in an Italian nationwide paediatric study.[48] Interestingly, a very recent RCT showed that the combination of piperacillin-tazobactam and tigecyclin was more effective than piperacillin-tazobactam alone for the treatment of febrile neutropenia in adults with haematological

malignancies.[49] Even if tigecyclin is not approved for paediatric use, this study currently suggests a possible better effectiveness of a combined therapy with adequate spectrum of activity. Monotherapy could still represent a reasonable choice in absence of specific risk factors or clinical condition at onset of fever, i.e. in those cases we could identify as "low risk".[40,41] Anyway this approach require a strict epidemiological control and could be more acceptable in adults,[41,50] but less in children where no prediction rule has been derived or validated in multicentre studies.[51,52] In spite of the recommendation against empirical use of glycopeptides in initial empirical therapy of febrile neutropenia in absence of specific clinical or microbiological conditions (signs of skin infection, suspect of vascular access-related infection, local epidemiological condition of high frequency of infection due to methicillin-resistant S.aureus or beta-lactam resistant enterococci),[19,36,40,41] and its lack of efficacy in patients with persistent fever without any clinical or microbiological documentation[1] this practice is still quite frequent, especially in paediatrics.[43,48] The increase in vancomycin minimal inhibitory concentration (MIC) for methicillin-resistant S.aureus (the so called vancomycin creep) is now a well-known phenomenon, and guidelines suggest the use of daptomycin or linezolid in these cases[53,54] (by the way both drugs are not approved for paediatric use). Less clear is what to do in presence of infections due to coagulase-negative staphylococci with increased vancomycin MIC that are becoming an increasingly described phenomenon[55-59] and can represent a not life threatening, but a difficult to treat infection in cancer children.[56]

Overall, the problems due to selection of resistant pathogens are particularly worrisome if we considered the quite complete absence of new drugs with the need to administer old, less studied drugs in complex combinations.[47,58,60,61] In any case paediatric pharmacokinetic/pharmacodynamic data[62] as well as significant data of their effectiveness and tolerability frequently lack for many of these old antibiotics (e.g. colistin, fosfomycin), and for the few, new compounds under investigation.[47,63,64] This scenario could have a negative impact on the final prognosis of children undergoing chemotherapy for acute leukaemia in the next future. Therefore it is mandatory to have a careful, clever and science driven use of the available antibiotics especially in populations like leukaemic children that need frequently these drugs as life-saving therapies.

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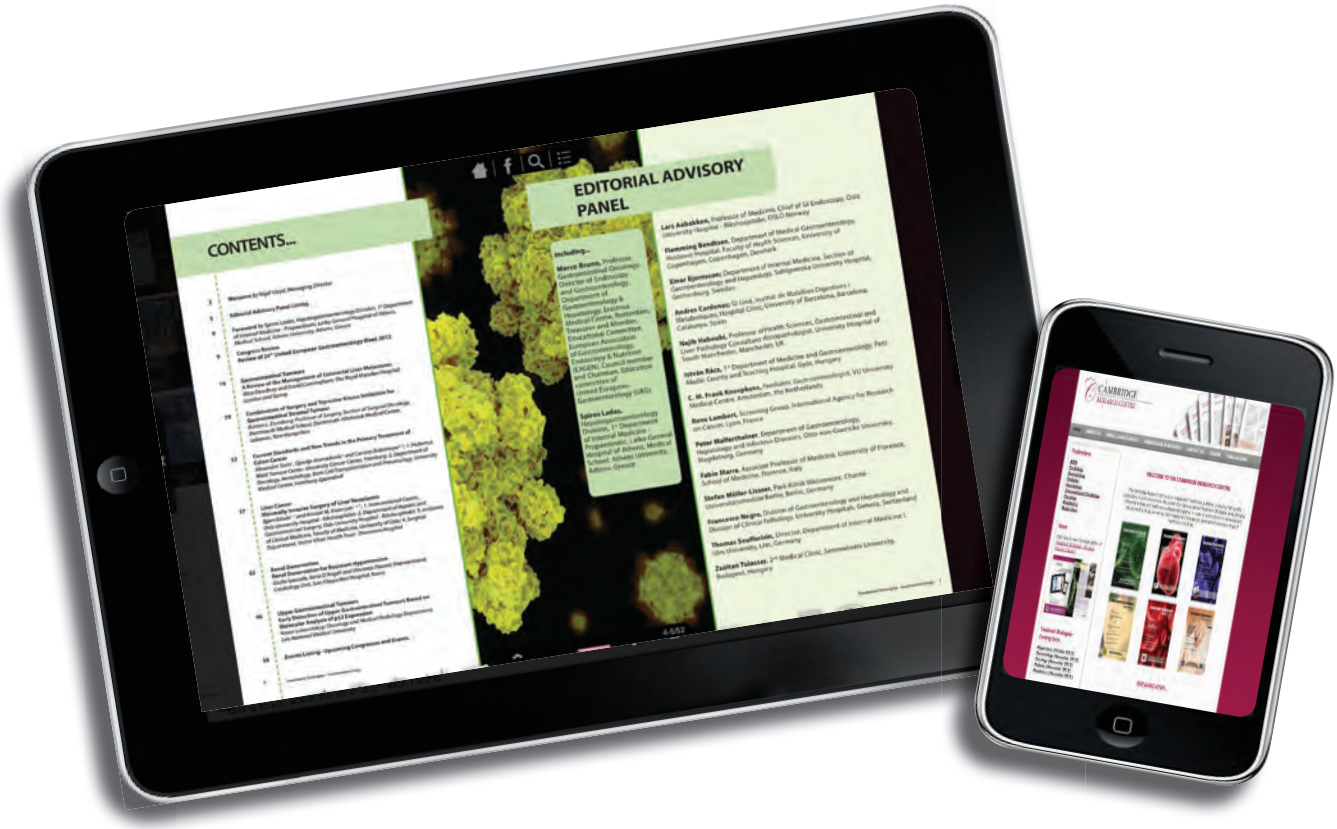

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Cure Rates of Childhood Acute Lymphoblastic Leukaemia in Lithuania and the Benefit of Joining International Treatment Protocol

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Introduction

Childhood acute lymphoblastic leukaemia (ALL) comprises, depending on age, 20–30% of all paediatric malignancies and represents the largest group of childhood cancers.[1,2] The disease was universally fatal fifty years ago. Nowadays, based on risk-adapted antileukaemic therapy and improved supportive care, long-term survival rates of 85-90% could be achieved by the best contemporary treatment protocols. This development reflects international collaboration of large paediatric oncology groups, inclusion of patients in clinical trials, and systematic reporting of trials results.[3-7] It has been shown that clinical trials in children with cancer result in significant improvement in cure rates.[8,9] However, few data on population-based long-term treatment results of childhood ALL with or without international collaboration have been published by paediatric oncology groups in Central or Eastern European countries.[10-12] Treatment results of 208 children with ALL treated in Lithuania from 1986 to 1994 were described in 1995.[13,14]

Due to historical reasons paediatric oncologists in Lithuania did not join international treatment protocols until recently, and because of a population of three million inhabitants conduction of national clinical trials was not possible. Children with cancer in Lithuania were treated according to protocols developed by international study groups that were published or obtained by personal contacts to study chairs. Children with ALL from late 1970s to 2008 were treated according to Berlin-Münster-Frankfurt (BFM)-based protocols. However, we neither prospectively registered patients nor enrolled them into clinical trials.

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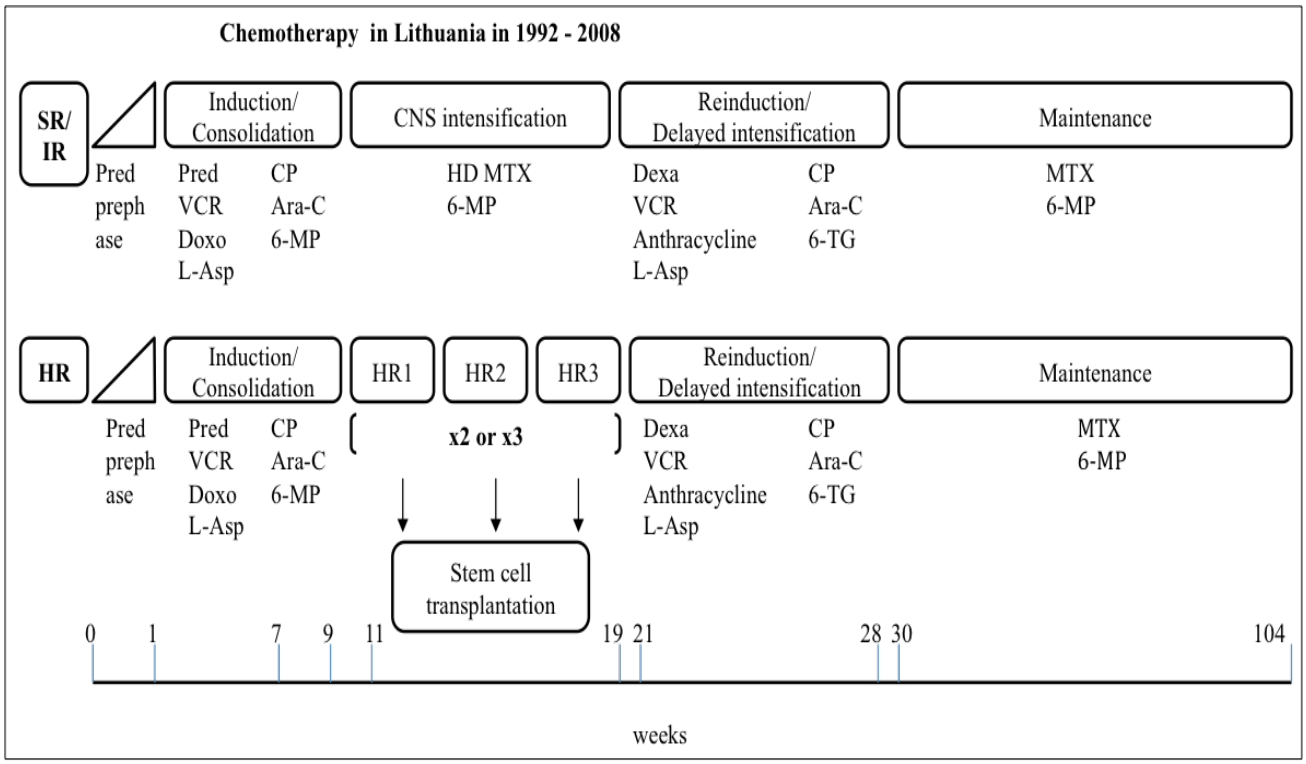
Aim of the Study

There was an obvious need to collect and analyze data on childhood ALL in Lithuania. Furthermore, collaboration with the Nordic Society of Pediatric Hematology and Oncology (NOPHO) developed in recent decade, and Lithuania joined the international NOPHO ALL-2008 treatment protocol which was one of the leading international ALL treatment protocols. To determine long-term treatment results of childhood ALL in Lithuania and to evaluate the benefit of participation in an international treatment protocol, population-based study was developed.

Patients and Methods

We collected the data of all 459 children with ALL that were diagnosed from January 1992 to December 2012 and treated at the Center for Oncology and Hematology, Children's Hospital, Affiliate of Vilnius University Hospital Santariskiu Klinikos, in which all children with ALL in Lithuania were treated. All children with T-lineage ALL (T-ALL) or B-cell precursor ALL (BCP) aged up to 16 years until January 2003 and subsequently aged up to 18 years (reflecting the age limit for patients in paediatric departments in Lithuania), including six patients with Down syndrome, were included into this population-based study. To evaluate progress in treatment results, we divided the study period into four time-periods: 1992–1996 (N=132), 1997–2002 (N=136), 2003–2008 (N=109) and 2009–2012 (N=82) depending on different diagnostic



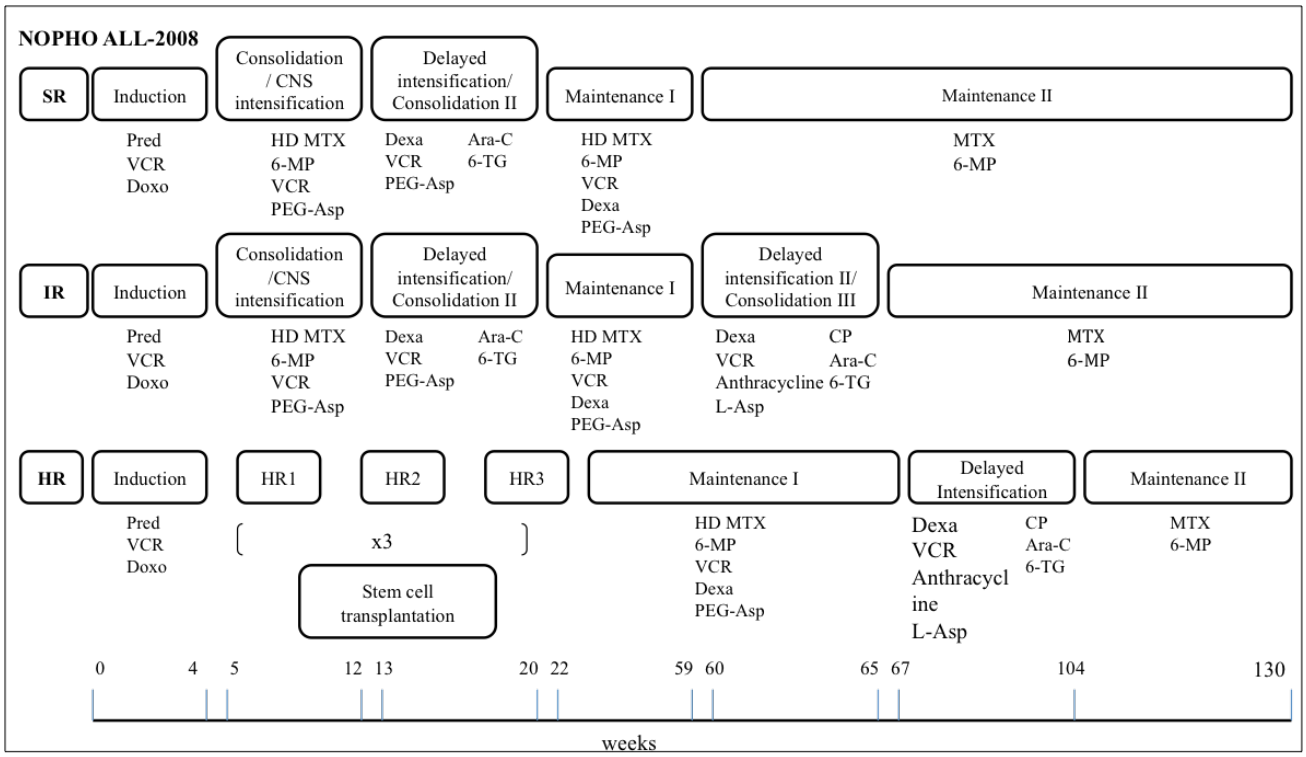


Figure 1. Outline of treatment used for children with ALL in Lithuania and the Nordic countries.

and therapeutic possibilities available.

Median (75% range) follow-up of 314 patients remaining alive on the 1st of April, 2013 was 10.9 (2.5 – 19.0) years (Table 1). Of all 459 patients, 162 patients had a follow-up of ≥10.0 years. Four patients developed a second cancer after a median of 5.9 years from diagnosis of ALL.

Diagnostic Procedures

Diagnostic methods differed among the study time-periods and developed over time. Diagnosis of ALL was established if ≥25% of cells were identified as leukaemic blasts in a diagnostic bone marrow. Smears were evaluated by cytomorphological methods by the year 2001. Since 2001 routine immunophenotyping with

Table 1.

	1992 – 1996, N=132	1997 – 2002, N=136	2003 – 2008, N=109	2009 – 2012, N=82	p
Median (75% range) FU, years for alive patients	19.0 (16.6–20.4), N=71	12.7 (11.3–15.2), N=89	7.5 (4.7-9.5), N=84	2.2 (0.5-3.6), N=70	
Boys, N (%)	82 (62%)	77 (57%)	50 (46%)	47 (57%)	0.086
Girls, N (%)	50 (38%)	59 (43%)	59 (54%)	35 (43%)	
WBC, x 10^9/L median (75% range)	9.9 (2.3 – 56.0)	9.0 (2.8 – 43.8)	9.2 (2.3 – 58.4)	18.2 (3.9 – 101.3)	0.025*
Age, years median (75% range)	4.9 (2.1 – 10.3)	5.3 (2.2 – 10.9)	6.3 (2.5 – 13.1)	5.2 (2.3 – 11.5)	0.14
CNS, N (%)					
CNS 1	95 (72)	125 (92)	100 (92)	78 (95)	
CNS 2/3	7 (5)	8 (6)	8 (7)	4 (5)	0.90
NA	30 (23)	3 (2)	2 (2)	0	
Immunophenotype, N(%)					
BCP	1 (1)	54 (40)	89 (82)	67 (82)	ND
T-ALL	4 (3)	17 (13)	20 (18)	15 (18)	
NA	127 (96)	65 (48)	0	0	
Cytogenetics, N(%)					
Normal karyotype	-	2 (1,5)	11 (10,1)	20 (24,4)	ND
HeH	-	-	19 (17,4)	11 (13,4)	
t(12;21)	-	-	2 (1,8)	19 (23,2)	
t(1;19)	-	-	-	6 (7,3)	
amp(21)	-	-	-	3 (3,7)	
11q23/*MLL*	-	-	-	1 (1,2)	
t(9;22)*[BRL/ABL]*	-	-	3 (2,8)	2 (2,4)	
Hypodiploid	-	-	-	1 (1,2)	
Other	-	-	11 (10,1)	20 (24,4)	
NA	132 (100)	134 (98,5)	63 (57,8)	-	

Table 1. Baseline characteristics and treatment results of the patients treated in different time periods. FU = follow-up period; WBC = white blood cell count in peripheral blood at diagnosis; CNS = central nervous system; BCP = B-cell precursor ALL; T-ALL = T-lineage ALL; NA = not available; HeH = high hyperdiploid karyotype (modal chromosome number >50); hypodiploid karyotype = modal chromosome number <45; 11q23/MLL = 11q23/MLL rearrangement; other = non-stratifying cytogenetic aberrations; p value = determined after comparison of the values among different time-periods.

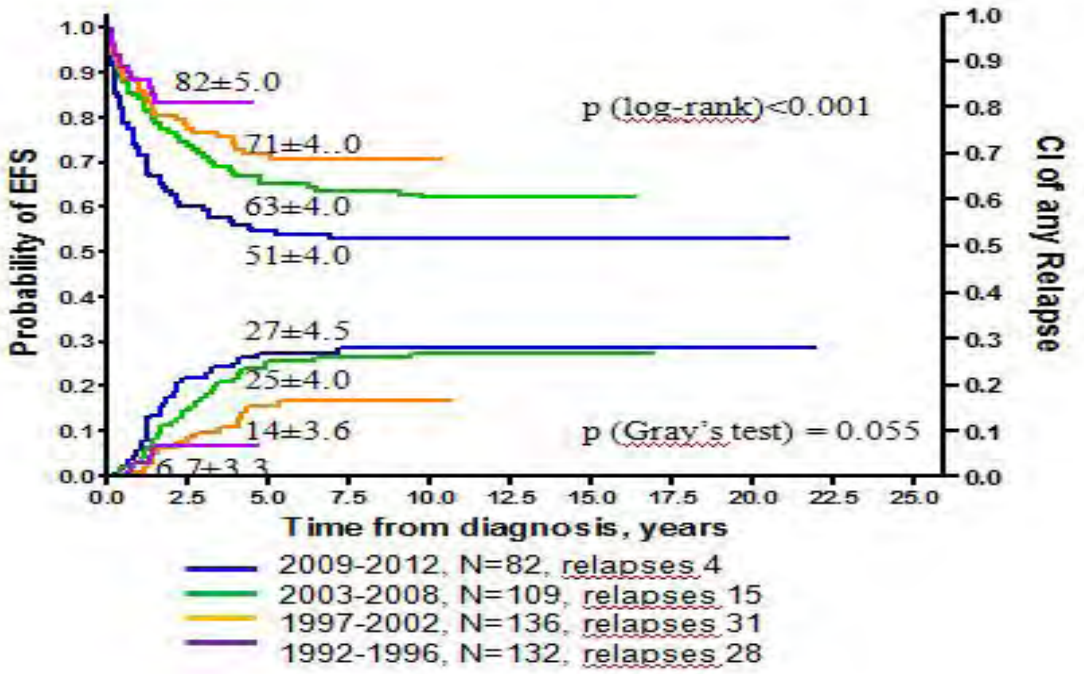


Figure 2A. Probability of event-free survival and cumulative incidence of any relapse in four consecutive time periods.

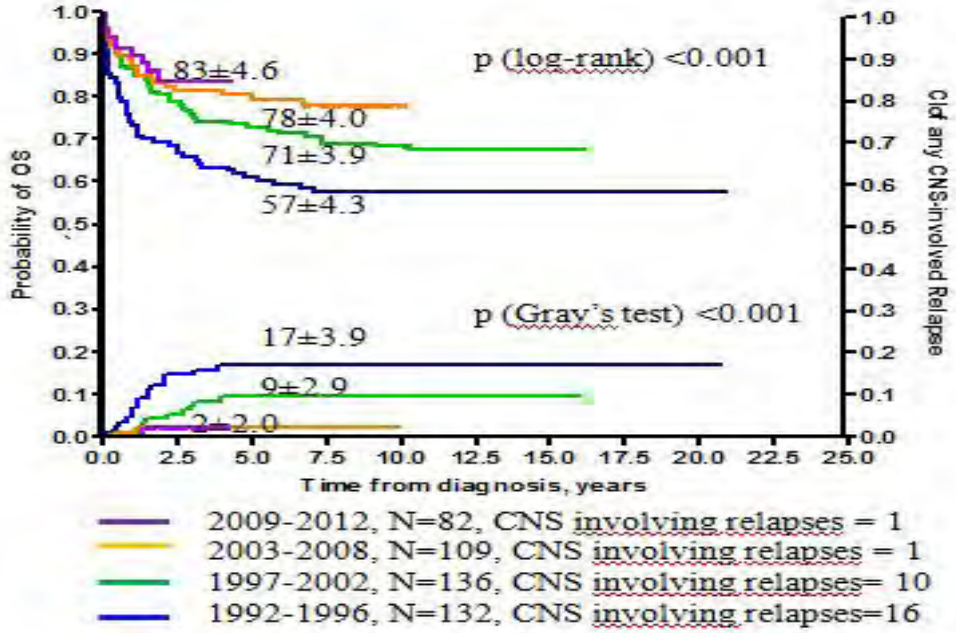


Figure 2B. Probability of overall survival and cumulative incidence of any central nervous system relapse in four consecutive time periods.

panels of monoclonal antibodies directed toward lineage-associated antigens according to well established criteria[15] was introduced. G-band karyotyping became routine in 2007. Since 2009 directed analysis by fluorescence in situ hybridisation (FISH) and/or reverse transcriptase PCR for specific cytogenetic aberrations as well as DNA-index by flow cytometry became mandatory as risk stratifying factors in the NOPHO ALL-2008 protocol. Furthermore, since 2009 all leukaemic samples have been also explored for t(12;21) [ETV6-RUNX1] translocation. The presence of this translocation did not influence treatment stratification except that patients were excluded from dexamethasone induction therapy if white blood cell count (WBC) at diagnosis was at least 100 x 109/L.

In addition, genotyping of thyopurinmethyltransferase by low activity alleles was introduced since joining the NOPHO ALL-2008 protocol as a mandatory test for individual 6-mercaptopurine dose adjustment during consolidation and maintenance therapy.[16]

Central nervous system (CNS) disease was defined by presence of

leukaemic blasts in diagnostic spinal tap and/or peripheral cranial nerve palsy, and/or intracranial leukaemic infiltrates detected by imaging methods. Since 2009, CNS1 was defined as no blasts on cytospin, CNS2 as ≥1 and <5 cells per µl with blasts on cytospin, and CNS3 as ≥5 cells per µl with blasts on cytospin of diagnostic spinal tap.

Treatment

Both in Lithuania and in the Nordic countries which protocol NOPHO ALL-2008 was joined by Lithuania in 2009, children with ALL were treated according to the strategy developed by BFM-group.[17] Consequently, chemotherapeutic drugs and treatment phases were basically the same in all time-periods with some differences in drugs combinations or time-schedules. The outline of treatment used in Lithuania during the 1992 - 2008 period and in the NOPHO ALL-2008 protocol is depicted in Figure 1, and has been in detail described previously.[18]

Before the NOPHO-era remission induction chemotherapy consisted of four drugs: corticosteroid (prednisolone), vincristine, L-asparaginase and anthracycline. Consolidation phase was based on antimetabolites - high dose methotrexate and oral 6-mercaptopurine. Reinduction therapy was designed to eradicate the already present resistant leukaemic sub-clones adding non-cross resistant drugs (cyclophosphamide, cytosine arabinoside and 6-thioguanine). Maintenance phase consisted of small doses of methotrexate and 6-mercaptopurine depending on the protocol up to two to three years from diagnosis.[19] Preventive therapy for overt CNS leukaemia consisted of craniospinal irradiation or intensive intrathecal therapy together with high dose methotrexate.

Since April 2009, all BCP and T-ALL patients were enrolled into prospective NOPHO ALL-2008 protocol which had been described in detail previously.[3,20] Main differences in therapy compared with previous periods were: (i) cranial radiotherapy was omitted for all patients; (ii) L-asparaginase, i.v. was replaced by pegylated asparaginase (Oncaspar®), i.m.; (iii) treatment with L-asparaginase was delayed until Consolidation phase (starting from d. 29); (iv) anthracyclines in Induction were reduced to two doses of 40 mg/m2; (v) individual starting doses of 6-MP dependent on genotype of enzyme thiopurine methyltransferase; (vi) treatment duration was extended up to 2.5 years from diagnosis.

Haematopoietic Stem Cell Transplantation (HSCT)

Allogeneic haematopoietic stem cell transplantation (HSCT) for children in Lithuania became available in 2002. No strict criteria for HSCT existed before NOPHO-era. In the NOPHO ALL-2008 protocol, recommendations for HSCT were based on treatment response criteria only. Overall, 20 patients received allogeneic HSCT during the study period in Lithuania in CR1 (N=8) or ≥CR2 (N=12). One patient was alive from the latter group while six patients out of eight who were transplanted in CR1, were alive without disease at the time of the study was carried out with a median (range) follow-up of 2.0 (0.2-9.0) years.

Results of the Study

Characteristics of all 459 study patients are presented in Table 1. Incidence of childhood ALL in Lithuania was 3.2-3.6 cases per 100 000 of children per year during the study period with the dominance of boys (56%) vs. girls (44%). Age, white blood cell count (median (75% range): 9.2 (2.6 – 46.4) x 109/L for 211 BCP patients, and 90.7 (12.5 – 382.5) x 109/L for 55 T-ALL patients, respectively), and distribution of immunophenotype and cytogenetic aberrations, when the latter two characteristics were available, were in consistence with the findings of other childhood ALL study groups.[21-23]

Progressive improvement in pEFS and pOS was observed over time (see Figure 2A and 2B). The 5-year pEFS improved from 50±4% in 1992-1996 to 71±4% in 2003-2008 (pooled p<0.001), and the 5-year pOS improved from 57±4% to 78±4%, respectively (pooled p<0.001). There was a trend for further survival improvement in 2009-2012, however, follow-up time for these patients was relatively short (see Figure 2A and 2B).

Five-year cumulative incidence of relapses reduced from 27±4.5% in 1992-1996 to 14±3.6% in 2003-2008 (p=0.042) (Figure 2A). In 2009-2012, four patients out of 82 developed early relapses so far (5%) after 0.6–1.4 years from diagnosis. One of them (IR, BCP) developed an isolated bone marrow relapse after parents abandoned the treatment. Another patient (IR, T-ALL) developed an isolated CNS relapse. The remaining two isolated bone marrow relapses occurred for HR ALL patients (T-ALL with hyperleukocytosis and BCP with MLL- rearrangement).

Incidence of CNS disease at diagnosis remained stable during the study period (see Table 1), while the 5-year cumulative incidence of CNS involving relapses decreased from 17±3.9% in 1992-1996 to 9±2.9% in 1997-2002 (p=0.077), and decreased further down to 1±1.0% in 2003-2008, after high dose MTX of 5 g/m2 was introduced (p <0.001) (Figure 2B). Importantly, cumulative incidence of CNS involving relapses did not increase in 2009-2012 period (3-year cumulative incidence 2%) after cranial irradiation was omitted for all patients. However, follow-up was short for the recent period.

The most common cause of deaths in remission (61%) was treatment-related septic complications during myelosuppression (N=30), followed by profuse bleeding (N=4), high dose MTX induced gastroenteritis (N=2), haemorrhagic pancreatitis (N=1), or cerebral venous sinus thrombosis (N=1). The exact reason was difficult to

identify with certainty for 11 patients.

Discussion

Not surprisingly, survival rates of childhood ALL in Lithuania during all time-periods were inferior to those reported by large international paediatric oncology study groups.[3-5,7,23,24] However, the gap was decreasing over time from approximately 20% in the earliest period to almost approaching the rates reported by large international groups during the recent NOPHO-era. EFS rate has improved due to a decrease in rates of relapses and induction failures. Cumulative incidence of induction failure or death in remission still remained high, however, was decreasing over time. These findings have several implications.

First, total health care expenditure per capita in US dollars in Lithuania in 1990 was only 10% of that in the European Union countries.[25] In 1992-2002 there was a lack of both the supportive care measures such as broad spectrum antibacterial or antifungal drugs, and of antileukaemic therapy. Due to health care reforms, health care expenditure per capita in 2011 increased to 1 292 $ US, i.e. 35% of that in Western European countries.[26] Furthermore, since the year 2000, approximately Litas 2 mln (Euro 580 thousand) was additionally assigned on annual basis by the State for the treatment of children with cancer in Lithuania. This allowed the necessary antileukaemic and supportive care drugs to be available for all childhood ALL patients and to perform all required diagnostic procedures in spite of increasing costs.[27]

Second, Lithuania's health care system used to be characterised by inefficiency, poor health care and a lack of universal access.[25] The restricted access to internationally available research information and international collaboration led Lithuanian physicians to stay behind in the rapidly developing paediatric oncology. Supportive care and nursing practice was also inferior. However, the curriculum is now close to the Western European standards.[28]

Third, the study indicated a further trend towards survival improval in the 2009-2012 period compared with 2003-2008 period despite the fact that neither financial nor human resorces had improved significantly. International collaboration and finally joining of the NOPHO ALL-2008 treatment protocol could have played a significant role in several ways: (i) internal resources had to be found for implementing new laboratory methods in Lithuania for diagnostic work-up, risk grouping and monitoring of MRD in consistence with protocol requirements. These measures led to improved diagnostics and to better risk stratification of children with ALL; (ii) careful monitoring and data registration in the NOPHO leukaemia register enabled to analyze the efficacy of supportive care measures; (iii) discussions in the NOPHO ALL-2008 protocol working groups allowed direct comparison of treatment results among different centers. All the features listed above led to a steadily increasing understanding of the biology of childhood ALL which in turn may have improved clinical decisions.

Conclusions

Cure rates of childhood ALL in Lithuania are steadily improving and are now approaching those reported by the largest international study groups. The reasons for positive effect are both a better financial support for treatment of childhood cancer in Lithuania and international collaboration with joining international treatment protocol.

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IV Nutrition-time to Reconsider the Risk/Benefit Ratio and What is Needed for Improvements

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Advances in medicine through continued research and clinical experience do not always support current practice, often finding instead an increasing number of complications. Such is the case with intravenous nutrition (IVN), often called total parenteral nutrition (TPN), even though it has never been "total" in the sense of providing all essential as well as all valuable nutrients. IVN has proven fundamental and lifesaving when enteral nutrition is not possible. But it clearly is not without risks and complications, some of which are coming to light from recent research. Examples in infants, children, and adults help illustrate this point.

In preterm and very low birth weight newborn infants, IVN has proven essential for sustaining metabolism, contributing to positive nitrogen balance, and promoting growth, as well as reducing morbidity and mortality. IVN also has advanced growth rates of lean body mass and head circumference, which have been correlated with improved developmental outcomes, even as late as 18 to 22 months after birth.[1,2]

Use of IVN in newborn infants has not been without complications, however. Most infuse dextrose at unnecessarily high rates, which all too commonly produces excessive hyperglycaemia by adding glucose to persistent hepatic glucose production.[3] This is compounded by the effects of endogenous and infused catecholamines and glucocorticoids that suppress insulin production and inhibit insulin action.[4,5] Such hyperglycaemia also usually is highly variable, which induces its own set of complications.[6] High rates of IV lipid infusion also contribute to hyperglycaemia[7,8] by competing with glucose for oxidation and by promoting gluconeogenesis. Metabolic complications of hyperglycaemia, which occur when the maximal glucose oxidative capacity is exceeded, are not insignificant, including increased energy expenditure, oxygen consumption, carbon dioxide production, respiratory distress, fat deposition out of proportion to lean mass, fatty infiltration of heart and liver, and intracellular production of reactive oxygen species (ROS).[9] Insulin treatment of hyperglycaemia only worsens toxicity of ROS from hyperglycaemia and perhaps contributes to the association of hyperglycaemia with retinopathy of prematurity (ROP).[10] Aggressive glucose and insulin treatments along with cortisol and catecholamines also induce an increased mitochondrial allostatic load via increased cell glucose uptake. This leads to a variety of adverse cellular effects, including mitochondrial fragmentation, oxidative stress through increased ROS production, mitochondrial DNA damage, decreased energy production, apoptosis, and increased susceptibility to cell death.[11]

Excessive glucose and insulin also induce fatty infiltration of the liver and hepatic steatosis.[12] This problem is compounded by IV lipid products that contain potentially toxic phytosterols and/or insufficient polyunsaturated fatty acids, primarily docosahexaenoic acid (DHA).[13,14] The critical role of these substances in IV lipid emulsions has been corroborated by reversal of hepatic steatosis with newer IV lipid emulsions that contain DHA and not phytosterols.[15,16] Use of AA solutions not designed specifically for the very preterm infant has resulted in very high plasma concentrations of certain AAs and urea nitrogen.[17] More commonly, current IV AA solutions, even at reasonable infusion rates of 2-3 g/kg/d, have produced plasma concentrations of some of the essential amino acids that are less than those of the normally growing human fetus of the same gestational age, which naturally would preclude the capacity for achieving "normal" fetal rates of protein accretion and growth of lean body mass and brain.[18,19] These observations also illustrate the increasing concern that appropriate IV AA solutions and infusion rates of specific AAs for infants who are sick and physiologically unstable still are relatively unknown.

The use of IVN in older children and adults has become even more controversial. As with preterm infants, adults who cannot take sufficient nutrition enterally to maintain normal metabolism develop worse outcomes from under nutrition unless IVN is provided.[20,21] Such complications include increased morbidity and mortality, impaired immunity, increased infection, poor wound healing, suppressed autophagy, reduced cellular repair and organ recovery, and loss of skeletal and cardiac muscle. Such problems have been difficult to dissociate from other pathophysiology in treated patients, however, and have been aggravated by hyperglycaemia from excessive IV dextrose infusion, just as in newborn infants. Addition of insulin in children and adults with hyperglycaemia met with initial success in reducing the incidence and severity of hyperglycaemia and its complications using "tight glucose control" protocols.[22,23] Subsequent trials failed to demonstrate benefits from tight glucose control, however, and actually demonstrated significant excess mortality.[24] Adverse outcomes have been noted in infants and children as well, including more frequent episodes of hypoglycaemia and even shorter leg length in preterm infants when insulin was used to prevent hyperglycaemia.[25,26,27,28]

Recent studies in adults in ICUs have only added to the confusion of risks vs. benefits of IVN in ICU patients, reporting variable outcomes with some benefits but also worse outcomes with IV nutrition.[29,30,31] Unfortunately, none of these studies was done in the same way as the others, different outcomes were used for primary research aims, each included a different mix of patients and disorders from the others, and evidence of balanced IV nutrition as well as total nutrition was variable or unclear.[32] Such differences among studies only compound problems generated by the complexity of differences among ICU patients regarding prior nutritional status, degree of illness and pathophysiology, presence or not of surgical and traumatic conditions, and treatments with drugs and hormones.

Among most studies, under fed and malnourished patients appear to benefit the most from IVN. Sufficient protein, IV and enteral, has been associated with improved nitrogen balance,[33] increased insulin and insulin sensitivity, reduced infections, muscle preservation and strength, and, among preterm infants, improved neurodevelopment. Infusion of glucose and lipids that meet but do not exceed energy requirements appear beneficial, especially in the malnourished patient. IV amino acid and lipid solutions have a long way to go, however, to provide the right balance of essential amino acids and fatty acids, especially among patients with specific requirements. In some cases, unique requirements (e.g., the extremely preterm infant) dictate infusion rates of specific nutrients to reduce adverse conditions as well as promote more normal growth and development. In other cases, adverse conditions (e.g., hypoxia-ischemia, sepsis, hepatic injury, hypotension, poor circulation, etc). impose need for unique infusion rates of IV nutrients. Furthermore, nearly all patients benefit from enteral nutrition even when IV nutrition is considered essential. Clearly, use of IV nutrition in critically ill humans, from infants to adults, deserves continued research and evaluation. IV nutrition may be essential, but it is not total, not complete, and not without risks.

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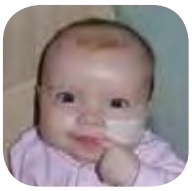
The Gauchers Association is the only organisation in the United Kingdom that provides information and support to those with Gaucher disease, their families and health-care professionals.





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supports families and carers to ensure all individuals with Gaucher disease have access to best practice in diagnosis, treatment and care.

provides information on Gaucher disease and raises awareness of this rare disease.

promotes research into the causes, effects and treatments of Gaucher disease.

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Dermoscopy: a Critical Tool for the Paediatric Dermatologist

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Introduction

Dermoscopy allows for the non-invasive visualisation of structures not visible to the unaided eye. It has been shown to improve clinicians' diagnostic accuracy while improving confidence in clinical diagnosis.[1,2] Because treating paediatric patients requires an additional degree of sensitivity towards minimising patient discomfort and reducing emotional distress, the dermatoscope could be viewed as an ideal tool to efficiently evaluate paediatric skin lesions.[3] Dermoscopy has been proven beneficial in diagnosing a myriad of different conditions ranging from infectious and inflammatory lesions to benign and malignant neoplasms. The focus of this review will be the dermoscopic examination of skin infestations (entodermoscopy) and infections, inflammatory skin conditions, and hair disorders (trichoscopy).

Shirin Bajaj is a medical student at Northwestern University Feinberg School of Medicine in Chicago. After her third year of medical school, she returned home to New York to pursue her interest in oncology and clinical research through a cutaneous oncology research fellowship program at Memorial Sloan Kettering Cancer Center. She hopes that through her research she can contribute to the field by increasing early detection of malignancy with the ultimate goal to improve outcomes. Serving on her school's curriculum comittee and by founding volunteer initatives at local high schools, she also has a strong interest in improving medical education and in mentoring young students interested in science.

Cristián Navarrete-Dechent is a third year Dermatology Resident at the Department of Dermatology of the Pontificia Universidad Católica de Chile in Santiago, Chile. He has clinical and research interest in cutaneous oncology and dermoscopy. He has published more than 10 peer-reviewed articles in both national and international journals. At the time this article was written, Dr. Navarrete-Dechent was doing a Clinical Observership at the Department of Dermatology of the Memorial Sloan-Kettering Cancer Center, New York, NY, USA.

Ashfaq A. Marghoob is a board-certified dermatologist specializing in the diagnosis and treatment of cancers of the skin. He is director of Memorial Sloan Kettering's regional skin cancer clinic in Hauppauge, Long Island. He continuously explores the importance and significance of the clinical and dermoscopic morphology of lesions. He has published numerous papers on topics related to skin cancer with an emphasis on melanoma, atypical/dysplastic nevi, and congenital melanocytic nevi. His research interests are focused on the use of imaging instruments such as photography, dermoscopy, and confocal laser microscopy to recognize skin cancer early in its development. He hopes that educating physicians and the public about the importance of early skin cancer detection will help save lives.

Infestations

Scabies

Scabies is a skin condition caused by the mite *sarcoptes scabiei var homonis* and almost one third of affected patients seen by dermatologists are younger than 16 years old.[4] In children, scabies usually manifests as a pruritic generalised eruption and the primary morphology consists of small, erythematous papules and burrows. The signs and symptoms often mimic other conditions including insect bites, folliculitis, contact dermatitis, viral exanthema, atopic dermatitis, and papular urticaria, among others.[3,5,6]

The definitive diagnosis of scabies is made with the visualisation of the mite, its eggs or faeces under the microscope *ex vivo*. This has classically been performed with a superficial skin scraping using a scalpel. However, scraping of the skin can result in inadvertent superficial lacerations or erosions that in a paediatric patient could make the subsequent examination difficult. Skin trauma can be avoided by using a dermatoscope to make the diagnosis of scabies.

Examination of the burrow with dermoscopy (which conventionally is at 10x magnification) will result in the visualisation of a small, dark-brown, triangular-shaped structure that corresponds with the pigmented anterior third of the adult mite (mouth parts and two anterior pairs of legs).[7] The burrow is observed as a shiny whitish keratotic thin tract under dermoscopy. This dark triangle together with the shiny hyperkeratotic furrow has been coined the "delta-jet airplane with contrail". (see Figure 1).

The sensitivity of the dermoscopic "delta sign" has been evaluated and has been shown to be equivalent to that of the classic skin-scraping test. Dupuy *et al* found a sensitivity of 91% for dermoscopy, as compared to a sensitivity of 90% for skin scraping.[8]

Head Lice (Paediculosis Capitis)

Head lice is caused by infestation by the louse *paediculosis humanus var capitis* and is a disease not uncommonly seen in children between

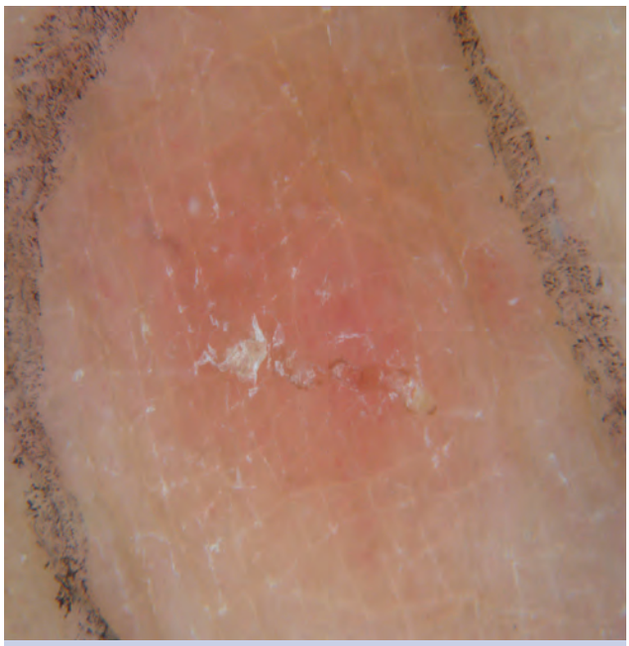

Figure 1. Scabies. There is a serpiginous hyperkeratotic burrow with a small dark triangular-shaped structure at the end. This characteristic structure, known as the "delta-jet airplane with contrail" is pathognomonic for scabies.

the ages of 3 and 12 years.[9] Children often present with an itchy scalp. The differential diagnosis of an itchy scalp in a child also includes the following: tinea capitis, atopic dermatitis, seborrheic dermatitis, and contact dermatitis.

The visualisation of the adult louse is difficult because it sheepishly avoids light and can scurry away from visible light at a rate of 6 to 20 cm per minute.[9,10] However, the eggs (nits) are firmly attached to the hair shafts with a glue-like substance and are easily visible with a dermatoscope. If nits are within 0.6 cm of the scalp, active infection is more likely.[11]

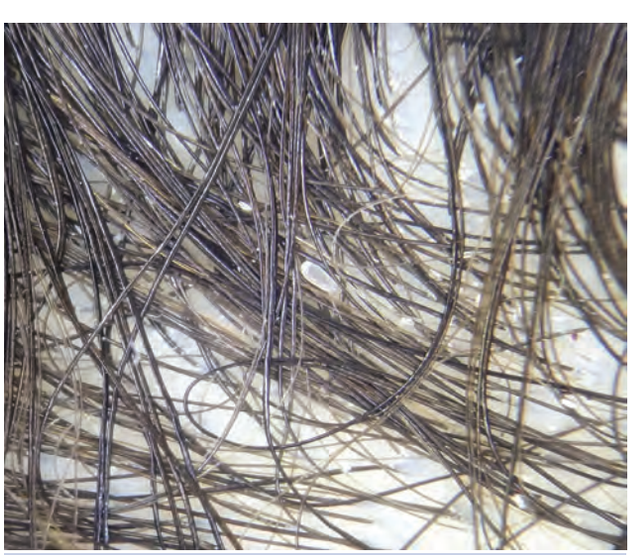

Figure 2. Empty nit attached to hair shaft. In the center of the image the empty nit can be identified by its translucent appearance and flattened free-end.

Dermoscopy can further enlighten the examination by exposing the morphology of the nit.[12-15] Viable nits are brown and oval-shaped whereas empty nits are translucent, with a flattened free edge (see Figure 2). Dead nymphs also contain an air pocket visible as a translucent focal zone.[12] The presence of vital nits with dermoscopy can guide the initiation of treatment.[14]

One common error that occurs in the clinical examination is that hair casts and other pseudonits (hair spray, debris, gel) can be confused for nits. Clinically, one can distinguish hair casts from pseudonits by pulling at the hair shaft; hair casts by be pulled away whereas nits cannot.[12] Close-up visualisation using a dermatoscope can easily help to make this distinction with minimal discomfort.[12,14]

Pubic Lice (Phitiriasis)

Phthirus pubis, or pubic lice are short, broad, blood-sucking insects with a pincer adaptation in the first pair of legs. While pubic lice are usually found in the coarse hair-bearing areas of the genitals they can occasionally be found in the eyelashes and axilla because these hair shafts are both spaced far enough and are thick enough in diameter for their pincers to grasp.[16] Although infestation is uncommon in children, when children are infested, lice typically dwell in their eyelashes.

Dermoscopy can instantaneously diagnose this condition by identifying the crab by its characteristic louse morphology and by its prominent thick claws that are usually seen grasping hair shafts.[17-19]

Tungiasis

Tungiasis is caused by infestation with the hematogenous gravid female flea *tunga penetrans*.[20,21] While it originated in Central and South America, it was subsequently carried by ship to Africa and from there to Asia, and it can be seen in children in endemic areas. Clinically, it presents as a yellow to brown nodule(s) with a small dark-brown to black central opening. It most commonly presents on the toe.

Dermoscopy will show a whitish nodule with a dark-brown central pore, which corresponds to the faecal-genital opening of the flea. A peripheral pigmented ring can be seen which corresponds to the flea's posterior abdomen. In addition, blood in the gastrointestinal tract may be visualised as blue-black blotches.[22,23]

Larva Migrans (Creeping Eruption)

Animal hookworms are usually acquired via direct inoculation from contaminated soil with cat or dog faeces. The most common parasite is *ancylostoma brazilensis*. On physical examination, the characteristic finding is an erythematous, serpiginous eruption.[24,25] The parasite typically enters the host via the skin on the foot. Dermoscopy reveals translucent, brownish structureless areas in a segmental arrangement

that corresponds to the body of the larva.[26]

Infectious Lesions

Molluscum Contagiosum

Molluscum contagiosum (MC) is a benign, usually self-limited infectious process that can be seen in the paediatric population. It is caused by the family of DNA poxviruses. Clinically, MC is characterised by small, discrete, flesh-colored, dome-shaped, umbilicated papules.[27] The diagnosis is typically straightforward based on the aforementioned features, however in some cases it can be difficult to make the diagnosis based on the clinical morphology alone. Dermoscopy can help by revealing the characteristic morphology.

Under dermoscopy MC has central umbilication surrounded by polylobular, white to yellow amorphous structures. The central umbilication is usually surrounded by thin peripheral vessels that display a "crown pattern", also known as the red corona or crown vessels. These vessels emanate from the periphery towards the center and do not cross the midline (see Figure 3).[3,28]

Warts

Cutaneous warts are benign epidermal proliferations caused by the human papilloma virus.[29] They are frequently encountered problem in children of all ages. Warts are usually classified as verruca vulgaris, flat warts, verruca plantaris or palmaris, or genital warts (condilomas). On clinical examination, warts can often be difficult to distinguish from other skin lesions such as corns, calluses, squamous cell carcinoma, and even amelanotic melanoma.[3,30] Dermoscopy can help in rendering the correct diagnosis. On dermoscopy corns have a translucent core, while calluses have homogenous yellowish opacities.[3]

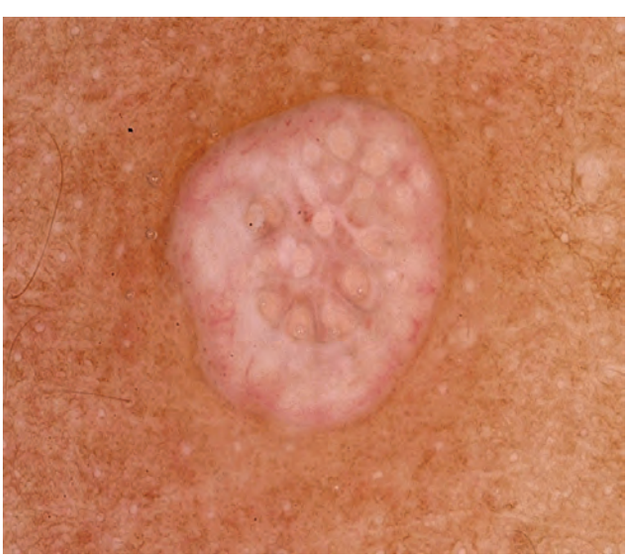

Figure 3. *Molluscum contagiosum*. Pink papule with central umbilication, polylobular white to yellow structures, and crown vessels.

In comparison, verruca vulgaris under dermoscopic view reveals, "multiple densely packed papilla, each containing a central red or black dot surrounded by a whitish halo".[7] These red and black dots correspond to normal or thrombosed capillaries, respectively. Flat warts display dotted vessels over a yellowish to brown background. Plantar/palmar warts have dark brown to red dots that correspond to thrombosed vessels and the wart usually causes interruption of the dermatoglyphs.[31] The dermoscopic morphology of genital warts consists of mosaic, knob-like, finger-like or nonspecific patterns with a variety of associated vascular patterns including hairpin, glomerular, and dotted vessels.[32]

Dermoscopy can also help to guide the need for further treatment with cryotherapy, as while some lesions may look completely resolved to the naked eye, dermoscopy may reveal small papilliform surfaces indicative of persistent disease.[30]

Inflammatory Lesions

Psoriasis

Thirty-one to forty-five percent of adults with psoriasis have their first outbreak during the first two decades of life.[33] The diagnosis can typically be made clinically, however dermoscopic examination can help to differentiate psoriasis from other erythemato-squamous disorders.

The classic dermoscopic findings are dotted vessels regularly distributed on a pink background with overlying white scale (see Figure 4).[34] While dotted vessels are considered characteristic of psoriasis, they are not a specific finding, as other inflammatory skin conditions can present similarly. However this vascular morphology in combination with other features including pink background and diffuse white scale together gives a sensitivity of 84.9% and a specificity of 88.0% in coming to an accurate diagnosis of psoriasis as opposed to other inflammatory skin conditions.[35] Other vascular patterns associated with psoriasis are globular rings and hairpin vessels. Red globular rings (red globules arranged in a circular or ring-like pattern) are a highly specific feature for psoriasis. Its histologic correlate is tortuous elongated capillaries that reside within the dermal papillae; this is considered the vascular basis of the Auspitz sign.[35,36]

Psoriasis is conventionally treated with topical corticosteroids. Dermoscopy can be used to assess treatment response and overuse of treatment. The overuse of topical corticosteroids can cause skin atrophy that may be clinically undetectable to the unaided eye in early stages. Vazquez-Lopez *et al*. found that dermoscopic assessment of patients' with the disease can detect steroid-induced impending skin atrophy, within the window when skin changes are still reversible.[37] Overuse of topical steroids thins the epidermis and rete ridges, which exposes subpapillary vessels that appear on dermoscopy to be "red lines". While such red lines are not specific to overuse of

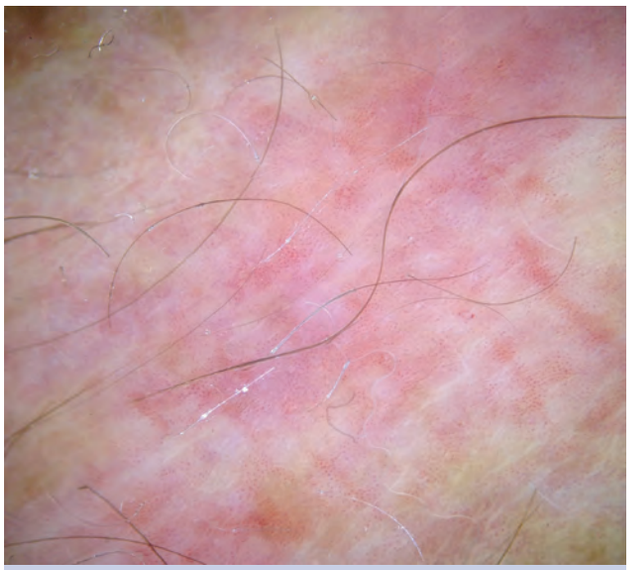

Figure 4. Plaque psoriasis. Dotted vessels on a pink background.

topical steroids, they are not characteristic of plaque psoriasis, and therefore can be a clinically useful way to make the timely decision to discontinue treatment if necessary.

Lichen Planus

While *lichen planus* is usually diagnosed in adults over 30, up to 11% of cases initially present in children and adolescents.[33] Wickham's striae (WS) are pathognomonic gray to whitish lines in a network-like pattern on the surface of papules. While WS are not always apparent clinically, dermoscopically they are much more conspicuous.

Dermoscopy can also add clinically useful information about active vs. resolving lesions, as well as duration of disease. In active lesions, dermoscopy will reveal rounded, arboriform, reticular or annular "pearly-white" lines (Wickham's striae) that are typically surrounded by linear vessels (radial capillaries) on a violaceous background.[38] In comparison, regressing lesions will present with one of two patterns. They will either present with diffuse brown structureless areas corresponding to pigment limited to the epidermis, or with multiple blue-gray dots and globules corresponding to pigment deposits deeper within dermal melanophages.[3,39] The morphology of the lesion can also help to predict time to resolution. In a study by Vazquez-Lopez *et al* authors followed 50 hyperpigmented biopsy-proven lichen planus lesions with dermoscopy and found that lesions with a greater number of blue dots on dermoscopy tended to be more persistent and slower to resolve.[39]

Hair Disorders

Alopecia Areata

Alopecia areata (AA) is a non-scarring alopecia and is considered an autoimmune disorder with genetic basis and environmental triggers.[40] Dermoscopic signs of AA are present in 59.3% of patients and include "exclamation mark" hairs and black dots; both are signs of fragmented or destroyed hair shafts and are associated with disease severity.[41] Yellow folliculocentric dots are also seen in AA and appear as polycyclic to round yellowish to pink dots that histologically correspond to distended follicular infundibula filled with sebum, cadaverised hairs, and keratin debris. While black dots and exclamation mark hairs on dermoscopy can also be seen in trichotillomania and telogen effluvium, yellow folliculocentric dots are more specific for AA.[42]

Dermoscopy in patients with AA can additionally help in monitoring treatment response to corticosteroids as it may allow for the visualisation of newly growing vellus hairs.[43,44] The value of this subtle sign is largely emotional in nature as evidence of treatment response, albeit not visible to the naked eye, can help to motivate patients and their parents to continue treatment.

Trichotillomania

Trichotillomania is another cause of alopecia in children, and it must be differentiated from alopecia areata as the etiology and prognosis is quite different. Trichotillomania is also known as "hair puller syndrome," and is characterised by irresistible pulling of one's hair. In early childhood it can be a transient habit that children outgrow.[45] Differentiating from AA clinically can be challenging, as patients will usually deny the habit, but evaluation with dermoscopy can help.[46] Under dermoscopy, the presence of hairs with longitudinal splitting (trichoptilosis), flame hairs (wavy hairs resembling a fire-flame), and coiled hairs (irregularly coiled hairs with a jagged end), are associated with this disorder.[3,47] Bleeding and scratching secondary to trauma have also been reported.[46] While black dots and exclamation point hairs can been seen in both AA and Trichotillomania,[48] the presence of coiled hairs is more specific for Trichotillomania.[47]

Tinea Capitis

Tinea capitis (TC) can cause alopecia in children and adolescents.[49] While the gold standard for diagnosis is culture, confirmation of results can take weeks, and instantaneous diagnosis with dermoscopy offers the option of immediate treatment.[48] The main differential for TC is AA, and the use of trichoscopy can allow for its accurate identification as a separate clinical entity.

TC is associated with the presence of comma and corkscrew hairs under dermoscopy. Comma hairs are short C- shaped hairs that are curved and have uniform thickness.[3,48] Corkscrew hairs, which have a coiled appearance, were previously thought to be a marker of TC in African American children; however there are case reports of corkscrew hairs in patients with TC of different racial backgrounds.[50,51] The presence of corkscrew vs. comma hairs in TC has also been thought to differ based on offending organism.[50] Other non-specific additional features that may be visualised in patients with TC include black dots,

zig-zag hairs, broken hairs, and Morse code hairs, which are hairs with multiple thin white bands across the hair shaft.[47,48]

Hair Shaft Disorders

In the past, hair shaft disorders were diagnosed by pulling hairs from the scalp and subsequently examining them under the microscope. With dermoscopy, one can avoid this painful process and examine the hair *in vivo*. The morphology of the hair shaft can be visualised and it is fairly easy to diagnose the following disorders: Monilethrix, Pili torti, Pili trianguli, Pili annulati, and Trichorrexis nodosa.

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Real Time Paediatric Community-acquired Septic Shock : a Snapshot by the REPEM Network

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Introduction

Even in an era of immunisation and virtually open access to primary health services, paediatric sepsis still causes significant morbidity and mortality in high-income countries, especially when shock is present.[1] Recent research even demonstrates an increase in prevalence of severe sepsis in the U.S. due to a significant increase in the prevalence of severe sepsis in newborns.[2]

Conducting research in this field, it seems important to focus on the first hours of the disease, including the pre-hospital phase and the (as most often) entry point to the paediatric hospital: the emergency department (ED). Indeed It's already been over 10 years since Han *et al*. demonstrated increased survival due to early intervention by community hospital physicians in their benchmark paper.[3] Early goal-directed therapy, targeting normal mixed venous saturations and adequate hemoglobin levels, was by then considered as state-of-the-art treatment in adults.[4] Few years later the positive impact of this strategy was identified in children as well.[5] The latest guidelines published by the American College of Critical Care Medicine, incorporating all current evidence, already dates from 2007.[6] These guidelines are the result of expert consensus and are developed to promote standardisation of care. A recent survey amongst paediatric intensivists demonstrates high adherence to these guidelines in the paediatric intensive care department.[7] However little is known regarding adherence in the pre-PICU timeframe.

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Current Community-acquired Sepsis-related Morbidity in Europe

This was the background against which the REPEM network [Research in Paediatric Emergency Medicine] decided to set up a research initiative. In a first phase we wanted to collect current data regarding all aspects of community-acquired sepsis in children including presentation and management on the different platforms where children with sepsis can be expected to be treated during the initial hours of their disease.[8] The REPEM network includes physicians at the capacity of researcher, medical director, research director, consultant or director of medical education who work in a European paediatric emergency department. The network was established in October 2006, as an extension of the paediatric section of the European Society of Emergency medicine (EUSEM). Its mission is to improve emergency care for children through high standard national, multinational and multicentre research.

Study Cohort

We conducted a retrospective observational study in 16 ED from 12 countries. Participating centres were most often tertiary referral centres, the entry point to their hospital varied significantly (either retrieval from district hospitals -10.8% for the total cohort- either local emergency department). Patients bypassing the ED or the retrieval service (for example chronic patients who were admitted via the outpatient department or directly from home) were not included. Each centre obtained approval by their institutional ethical committee. Each centre screened their patient database retrospectively in a backward way for a 6- to 12-month period, with a starting date between May 2010 and September 2011 and selected up to 20 consecutive cases to be included in the analysis. Patients were selected applying a screening tool. Only cases in which the patient was referred to the participating centre within the first 6 hours after the first healthcare contact were included, this to avoid

including hospital-acquired sepsis.[8] The CRFs were appraised by the principle investigator (PVDV), only high-quality data were included in the study, any ambiguous case was excluded. This resulted in a total of 176 well documented case report forms, on which statistical analysis was performed.

Findings

Disease Severity in Community-acquired Sepsis

The nomenclature of sepsis/septic shock offers a quite artificial framework and covers a range of moderately severe to acute life-threatening conditions.[9,10] The disease severity can be indirectly assessed by the need for certain treatments. All patients in our cohort had signs of decreased perfusion and all were given IV fluids with a median of 30 ml/kg during the first 6 hours. A significant proportion required mechanical ventilation (25.9%) and/or vasoactive medication (42.9%), but also less severely ill patients (16.9% required < 10 ml/kg IV volume-expansion) were included. In most of the patients (79.6%) shock reversal was noted quite early as they did not require any further fluid resuscitation after the first 6 hours. Indeed in only 65.7% of the cases patients were deemed to require transfer to a HDU or PICU environment, in the other patients circulation was restored very early and they could be admitted to the paediatric ward. This disease spectre is also reflected in the range of length of stay in hospital (0 to 71 days – median 4 days). Blood products were required in 22.7% of the cases and colloids were administered in 18.2%. As stated in the guidelines corticosteroids might be indicated in catecholamine-resistant shock and these were given in 14.9%.[6] A diagnosis of toxic shock syndrome was put forward in 7.2% of the cases, which is reflected in the administration of IVIG in 5.7% of the patients.

Of note: significant comorbidity was high (35.8%) with moderate to severe a priori disability of 10.7%. These numbers are comparable with previous studies.[11] In these cases, true classification as 'community-acquired' rather than 'healthcare-associated' sepsis can be discussed.

Outcome of Community-acquired Sepsis

Ten out of 176 patients had poor outcome, either death (n=8), either a reduction of POPC of 2 or more (n=2). Of the eight patients who died, three had severe comorbidity. Three patients required CPR during the first hour after admission, all of whom died; another three patients suffered an in-hospital cardiac arrest requiring CPR later on, two out of three of them had good outcome. Two deaths were not included in the analysis since they were referred more than 6 hours after presentation before transfer to the participating centre.

None of the patient characteristics, including associated morbidity, was significantly correlated with outcome. Neither was the causative organism. This is probably explained by overall low mortality.

The very low mortality figures in our study sample, especially if compared to previous landmark papers[3,4,5] may partially reflect quality of care and good availability of efficient health services, but may also be caused by inclusion of less severe cases. Indeed definitions of sepsis and septic shock are very aspecific and do not take into account the highly variable hemodynamic patterns associated with paediatric sepsis.[12] It also predicts that any research project involving sepsis and outcome may be dependent on very large study populations.[6] Low mortality numbers may also be affected by a selection bias which is inherent to our study design since only centres with firm data collections, who as such are more likely to have efficient facilities to treat critically ill children in accordance with guidelines, could participate in it.

Etiology of Sepsis

Frequently, causative organisms could be identified. The majority of isolated microorganisms were either gram-positive (n=37) or gram-negative (n=61) bacteriae, with the single most frequent still being Neisseria Meningitidis (n=25). Viral causes are confirmed in 19 cases. Of the 70 cases with unknown etiology, the majority is presumed to be bacterial on a clinical base. Adherence to guidelines supporting early administration of antibiotics seemed fairly good in our population with adequate antibiotic treatment started within three hours in 96.6% of the cases.

Considerations on Future Research

Considering results from the ARISE study, current evidence suggests that 'Early goal-directed therapy' as described initially, most likely does not offer outcome benefit in patients with early shock.[4,13] In children this approach is further hampered by technical and organisational barriers. It is however clear that early recognition and a structured approach has saved and will further save lives. It is also clear that not every patient with sepsis and/or decreased perfusion should be treated in a similar way.[14] Identifying which intervention offer the most benefit, for different subgroups of patients, should be the main focus of future research.

Because the rarity of bad outcome, in a randomised controlled trial, very large numbers of patients will be needed to significantly demonstrate benefit of a certain approach or treatment. More stringent inclusion criteria may be a solution for this, however might not reflect reality, and induce significant selection bias. As such, a large multicenter prospective observational study may be more informative and feasible.

Conclusions

The REPEM network study has tried to provide an up-to-date picture of morbidity associated with community-acquired paediatric sepsis

in Europe. Since early intervention has been proven extensively to improve outcome we focused on the first hours after first healthcare contact and the approach in the emergency department. A multicenter retrospective analysis of a large number of patients has demonstrated good outcome with low mortality under currently used management protocols. It's clear that the current definitions of sepsis and septic shock cover a spectre of disease severity and that as such different patients within a study population may be difficult to compare. This raises relevant questions on how to conduct further research. Large populations should be studied, which could be facilitated by a broad international paediatric emergency research network program.

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Treatment Strategies in RSV Infection

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Human Respiratory Syncitial Virus (hRSV) is the most common cause of lower respiratory tract infections (LRTI) in infant and young children worldwide and it is responsible for 64 million reported cases of infection and 160,000 deaths each year; but since 99% of these deaths occur in developing countries, hRSV associated mortality is likely to be underestimated.[1-2] RSV infection may be severe also in immunocompromised adult patients.[3,4] Acute infection may result in respiratory failure with varying degrees of severity, and there is evidence supporting a role for early RSV infection in the development of chronic respiratory disease, mainly recurrent wheezing and asthma.[5] Ribavirin, an antiviral molecule, and Palivizumab, a monoclonal neutralizing antibody, are the only approved drugs for treatment and prevention of RSV in high-risk patients. The aim of this article is to review the prevention and treatment strategies available to face RSV infection.

Natural Infection: Epidemiology Role of Inflammatory Response in Disease Pathogenesis

A few clues about how to treat RSV disease or how to develop effective prevention may come from the analysis of natural infection and host response to the virus. RSV is characterized by recurrent epidemics, repeated reinfection throughout life, and age-related incidence of severe disease.[6-8] Approximately two thirds (68%) of children experience their initial infection before their first birthday, and nearly all are infected at least once by 24 months of age. Primary infection usually results in the most severe disease and reinfections have normally lower symptoms. The study of an intensively monitored birth cohort elucidated that following infection, there is a reduced rate (60%–70%) of reinfection that is temporary (approximately of 6-month duration). A second point is the observation that the rate of infection is age dependent, with the lowest incidence in children <6 months of age, suggesting a protective role of maternal immunoglobulins. And a third observation is that the main factor independently associated with risk of LRTI and severe LRTI, following infection, is age, and the physiological changes associated with increasing age, such as larger airways or ontology of the immune system, rather than previous exposure, are associated with decreased risk.[4] The relative contribution of host versus viral factors to the pathogenesis of RSV disease remains controversial and incompletely understood.[9-11]

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Viral Factors

RSV is highly contagious but is not highly cytopathic or invasive. hRSV is the prototype of the Pneumovirus genus within the Pneumoviridae subfamily of the Paramyxoviridae.[12] It is an enveloped non-segmented negative-sense RNA virus which has two major surface glycoproteins (G and F) inserted into the viral membrane. Glycoprotein G is responsible for attachment of the virus to the target cell by interacting mainly with cell surface proteoglycans. The fusion (F) glycoprotein mediates fusion of the viral and cell membranes, facilitating virus entry. The F protein also promotes fusion of the infected cell membrane with that of adjacent cells to form large multi-nucleated syncytia, after which the virus is named. A multifunctional protein called nucleolin has been showed to be the necessary cellular receptor of RSV.[13] RSV targets both type I alveolar and non-basilar airway epithelial cells and different population of immune cells, including alveolar macrophages, affecting their antigen presenting capacity. The pathologic lesions caused by human RSV include bronchitis, bronchiolar epithelial necrosis, mucus secretion, bronchiolar occlusion, parenchyma inflammation and alveolar exudation.[14] The level of RSV replication correlates to the disease severity and several viral proteins, such as NS1 and NS2 proteins, play a role in modulating the host response to the infection by interfering with the IFN type I signaling and the phosphoinositide 3-kinase pathway, which results in reduced apoptosis and thus enhanced survival of the infected cells.[11,15]

Host Factors

More severe LRT RSV infections correlated to premature birth, chronic lung disease of prematurity, congenital heart disease (CHD), and T-cell immunodeficiency. Incomplete development or damage to the airway, and/or airway hyperreactivity of premature infants contribute to RSV-induced morbidity.[15-16] Immunodeficiency, immunosuppression or old age may lead to prolonged viral replication and more severe illness.[3-4] Other risk factors are male gender, low birth weight, multiple births and low titer of RSV-specific maternal antibodies. Moreover, recent evidence suggests that cord blood vitamin D deficiency in healthy neonates is associated with increased risk. Several genetic polymorphisms, including genes involved in the innate defense, surfactant protein genes, host cell receptor genes, neutrophil response genes, Th1/Th2 response genes and gene effectors of adaptive immunity, have been reported. Several chemokines and cytokines including IL-8/CXCL8, IP-10/CXCL10, MCP-1/CCL2, MIP-1a/CCL3, MIP-1b/CCL4, RANTES/CCL5, IL-6, TNF-a, IL-1ab, and IFN-a/b are produced by epithelial cells and macrophages in response to RSV infection, and found in enhanced amounts in respiratory secretions of children hospitalized for RSV infection.[17] Upregulation of IL-8 is correlated to the severity of RSV disease, and leads to recruitment of neutrophils, which constitute the majority of infiltrating cells (at least 84%). While the RSV-specific T cell response plays a major role in viral clearance and the clinical outcome of infection, an exaggerated cytotoxic T-lymphocyte responses and an imbalanced T-helper cell (Th)2/Th1 responses, have been proposed as a pathogenesis mechanism for more severe disease and for long term bronchial obstructive disease and asthma.[15,18]

In the clinical setting the disease presents with different levels of lung involvement, which initially resemble very much a severe y prolonged asthma attack. It is mainly an airway disease, but with the increased inflammatory response it can eventually become a severe adult respiratory distress syndrome (ARDS).

Strategies to Face the hRSV Infection

Direct or indirect contact with the nasopharyngeal secretions or droplets (sneezing, coughing and kissing), fomites, and food from infected patients can potentially transmit hRSV. Basic hygienic measures reduce RSV morbidity and are considered mandatory preventive actions.

Inmunoglobulins

Based on the observation that maternal antibodies at least partially protect against RSV infection, polyclonal antibodies from healthy human individuals resistant to RSV were successfully used in preventing RSV infection in high risk infants. More recent randomized controlled studies on pooled and purified RSV immunoglobulins (RSVIG) showed that RSVIG is effective in preventing hospitalizations and admission to the intensive care unit, but not in preventing mechanical ventilation.[19] The numbers needed to prevent one hospitalization and one ICU admission are 17 and 50 respectively.[19] However, the evidence on RSVIG as a treatment for RSV severe infections is limited.[20]

Vaccines

In the mid-1960s, only few years after the virus was identified, a formalin-inactivated hRSV preparation (FI-hRSV) was used in a field trial, as an initial attempt to vaccinate against the virus. Unfortunately, after natural infection with hRSV, children that were immunized with this formulation showed an exacerbated pulmonary disease and suffered more severe symptoms than unvaccinated children.1 Data explaining the vaccine failure suggested that immunization with formalin-inactivated hRSV promoted an allergic-like response in the lungs. After the above-mentioned FI-hRSV vaccine failed, several new strategies were attempted, including DNA vaccines (DNA fragment coding part or whole protein of RSV inserted into an appropriate expression plasmid vector under a constitutive promoter control), subunit vaccines, nanovaccines, (a special way to deliver DNA vaccine through a small particle made of a polymer that has mucoadhesive property and biodegradability, which balances the purpose of longer retention and controlled release of carrier molecules encapsulated).[21] However, to date no efficient and affordable RSV vaccines are available for public health.

Passive Immunization and Treatment with Palivizumab

Currently the only approved compound for RSV prophylaxis is passive immunization with humanized F protein monoclonal antibody, palivizumab. In a recent meta-analysis, the authors concluded that palivizumab prophylaxis, given at 15 mg/kg every 30 days during RSV epidemic season is effective in reducing the frequency of hospitalizations due RSV infection, i.e. in reducing the incidence of serious LRT RSV disease in children with chronic lung disease of prematurity, congenital heart disease or those born extremely preterm.[22] Based of these results, pediatricians in charge of children with immunodeficiency, chronic lung disease other than bronco-pulmonary dysplasia, cystic fibrosis, neuromuscular disease or congenital anomalies, are favorable to extend the indication of RSV passive immunization with palivizumab to other high risk groups.[23-27] Evidence on the efficacy and safety of palivizumab prophylaxis in each subgroup of patients, together with the data about its cost effectiveness in specific population and setting, could be useful for reconsidering current recommendations on when to provide RSV immunoprophylaxis.[28-30] Moreover, at least two longitudinal study could demonstrate the long-term effects of RSV prophylaxis on a child's morbidity and mortality by reducing wheezing days during the firsts year of life, even after the end of treatment.[29,31] However, cohort studies are needed to determine the long-term effects of immunoprophylaxis on asthma. Also, randomized studies are needed to establish the safety

and efficacy of palivizumab in children with cystic fibrosis. In a recent metaanalysis only one randomized controlled trial comparing five monthly doses of palivizumab to placebo in infants up to two years old with cystic fibrosis was found.[32] While the overall incidence of adverse events was similar in both groups, it was not possible to draw firm conclusions on the safety and tolerability of RSV prophylaxis with palivizumab in infants with cystic fibrosis.

Results from economic evaluations of palivizumab prophylaxis are inconsistent, implying that economic findings must be interpreted with caution.[33-35] The incremental cost-effectiveness ratio (ICER) values varied considerably across studies, from highly cost-effective to not cost-effective. The availability of low-cost palivizumab would reduce its inequitable distribution, so that RSV prophylaxis would be available to the poorest countries where children are at greatest risk.

Although the American Academy of Pediatrics (AAP) states that passive antibody administration is not effective in treatment of RSV disease and palivizumab is not approved or recommended in acute infection, containment of RSV outbreak in high-risk children, as well as treatment of RSV infected haemopoietic stem cell transplant recipients have been achieved with the early use of intravenous palivizumab.[36] More studies are needed in order to propose palivizumab as treatment of RSV infection in a clinical setting.

Passive Immunization and Treatment with Motavizumab

Motavizumab is a second-generation monoclonal antibody with improved binding affinity to RSV F protein. It showed noninferiority to palivizumab in several studies, including in children with hemodynamically significant CHD or premature infants and, unlike palivizumab, motavizumab may reduce RSV viral load in the upper respiratory tract, as well as in the lower respiratory tract, but it seems to have a threefold increase in hypersensitivity reactions. 29,37-38. For these reasons, motavizumab has not yet received a clear indication in the clinical setting, neither in prevention nor in treatment of RSV infection.

Antiviral drugs: Ribavirin and New Molecules

The only licensed antiviral treatment available today against RSV is ribavirin, a guanosine analogue generally administered as a small particle aerosol to immunocompromised patients with LRT disease due to RSV.[18] This drug has also been utilized orally with a recommend starting dose of 20 mg/kg/day, which may be increased up to 60 mg/kg/day and continued until virological clearance was achieved, as assessed by either PCR or direct immunofluorescence on respiratory secretions.[39-40] Ribavirin intravenously, again mainly in immunocompromised patients, it has been used when the inhaled or oral form of administration were not possible and in the most severely affected patients.[42] The usefulness of ribavirin against RSV is not only due to its anti-viral activity but also to its capability to modulate the immune system.

There are many other compounds that can inhibit RSV replication in pre-clinical studies and a well-known compound RSV604 showed promising results against RSV.[43] The derivatives of antibiotic geldanamycin, 17AAG and 17DMAG, have now attracted researchers attention due to their antiviral properties. These compounds are heat shock protein (HSP90) inhibitors and thus helpful against RSV, as RSV is dependent on HSP90 for its replication.[22] Promising new antiviral agents under development by multiple pharmaceutical and biotechnology companies include small molecule fusion inhibitors, as BMS-433771, VP-14637, JNJ-2408068, TMC353121 and BTA9881, attachment inhibitors as the dendrimer SB105-A10 or RFI 641, and inhibitors of RNA synthesis such as POM1, none of them yet prepared for clinical setting.[44-45]

In addition, the emergence of nanotechnology has opened new avenues for RSV treatment because the reactivity and anti-microbial activity of metals can be modulated by reducing their size to nanoscale. Fusion inhibitor peptide functionalized gold nanoparticles and carboxylated gold nanoparticles 13nm of size have been used against RSV, showing 83% and 88% inhibition of RSV, respectively. A similar approach was employed by recombinant RSV F protein functionalized on gold nanorods.[22,46]

Among novel antiviral agents being developed against RSV, the most innovative approach is the use of siRNAs (small inhibitory RNAs) with specific anti-RSV activity.[47] ALN-RSV01 was the first of these siRNA agents being developed for clinical use. Initial studies conducted in healthy volunteers who were experimentally infected with RSV demonstrated a good safety profile as well as anti-viral activity. Further studies with ALN-RSV01 conducted in lung transplant recipients with acute RSV infection showed that it was safe and well tolerated, and that it was associated with a statistically significant improvement in symptoms and decrease in the incidence of new or progressive bronchiolitis obliterans compared to placebo. Following the initial success of single intranasal siRNA against RSV, two new strategies are currently under clinical evaluation: (1) second-generation siRNAs, used against the paramyxoviral RNA polymerase large subunit, (2) siRNA cocktail with a novel transfection reagent, which can be highly effective against multiple viral strains and subtypes.

GS-5806 is a novel oral small molecule that inhibits RSV entry at low nanomolar concentrations by blocking viral-envelope fusion with the host-cell membrane. The results of a double blind placebo-controlled challenge study conducted among healthy adults inoculated intranasally with approximately 4 log10 plaque-forming units of RSV Memphis-37b demonstrated that GS-5806 has antiviral activity for the treatment of an established RSV infection.[48] It does not have a prophylactic or mixed

effect. The antiviral activity was exposure-dependent, being a minimum plasma concentration required during 4-5 days after treatment initiation for great anti-viral effects. Although this study shows that GS-5806 reduced both viral load and severity of RSV disease, without clinical relevant side effects, further studies aimed to access the effectiveness in cases of natural infection, both in pediatric and immunocompromised population, are needed. GS-5806 effects on the emergence of resistant viral strains should also be investigated before making therapeutic indication in the clinical setting.

Anti-inflammatory and Immunomodulators

It should be considered that once an individual experiences the symptoms of RSV infection, the inflammatory response is no longer directly linked to virus replication. Then, the use of replication inhibitors to control lung damage is not useful. Immunoregulatory therapies could be more effective to control the negative sequelae of severe RSV disease. In a recent article, Kitazawa and Villena carefully review the modulatory effect of Lactobacillus rhamnosus CRL1505 on respiratory immunoresponse and they propose that both viable and heat-killed immunobiotics could be an interesting alternative as mucosal adjuvants (both by nasal application or given orally through intestinal mucosa) to improve respiratory defenses and protect against viral infections.[49] On the other hand, the role of macrolides in RSV infection is still controversial. As severe RSV infection is associated with the excessive production of Th2 cytokines, a treatment that restores the Th1/Th2 cytokine balance to the relative type 1 predominance may ameliorate short and long-term effects of RSV disease. Macrolides may normalize the Th1/Th2 lymphocyte balance and in a double-blind, randomized, placebo-controlled trial in RSV bronchiolitis, daily treatment with clarithromycin for 3 weeks was associated with a statistically significant reduction in the length of hospital stay, the duration of need for supplemental oxygen, the need for β2-agonist treatment, and readmission to the hospital within 6 months after discharge.[50-51] Furthermore, there were significant decreases in plasma IL-4, IL-8, and exotoxin levels after 3 weeks of treatment with clarithromycin. In contrast to favorable effects of macrolides on RSV infection reported in number of papers, Kneyber et al., showed that the use of azithromycin did not reduce the duration of hospitalization in mild-to-moderate RSV LRTD.[52]

Montelukast was also highlighted in a successful clinical trial aimed at prevention of post-RSV reactive airway disease.[53] Infants hospitalized with RSV bronchiolitis were randomized to treatment and non-treatment groups, the treatment group receiving montelukast tablets (and the non-treatment, matching placebo) within 7 days of RSV symptoms emerging. The study group reached the conclusion that montelukast treatment effectively reduced negative lung inflammatory sequelae subsequent to RSV bronchiolitis. Other anti-leukotrienes are under laboratory investigation.

The studies aimed to investigate the role of anti-oxidant, cytokines and cytokines signaling blockage in RSV infection both in the acute phase as well as in the long-term effects are still in the pre-clinical setting.[50]

The immunomodulatory effect of steroids is still a subject of controversy. High-dose early initiated inhaled corticosteroids during respiratory syncytial virus bronchiolitis partially and transiently prevented subsequent recurrent wheeze but did not improve the long-term respiratory outcome, at the age of six.[54] A randomized prospective study in infants hospitalized with acute RSV infection showed no effect of systemic prednisolone treatment either in the acute state of RSV infection, nor in the follow-up 1 month and 1 year after admission to hospital.[55] On the other hand, in RSV bronchiolitis patients with atopic manifestation such as eczema or family history of asthma in a first-degree relative, oral dexamethasone administered with salbutamol significantly reduced the duration until clinical readiness for discharge.[56] However, these results were not confirmed by another trial.[57] Large reviews performed over the years concerning the use of both systemic and inhalation steroids for bronchiolitis have shown no consistent effects in decreasing incidence and duration of hospitalization or in improving short– and long-term prognosis. This is probably due to the fact that bronchiolitis is characterized by a profound neutrophilic airway inflammation.[58] For all these reasons several guidelines including the 2014 AAP Clinical Practice Guideline about the Diagnosis, Management, and Prevention of bronchiolitis strongly recommend that clinicians should not administer systemic corticosteroids to infants with bronchiolitis.[59]

Supportive Therapies

Lacking a specific etiological treatment, therapies for RSV infection include supportive and pharmacological measures to control respiratory and systemic symptoms. The supportive therapies include adequate feeding and hydration, that can be achieved by nasogastric tube or intravenously when oral intake is not sufficient or safe.[58-59]

Nebulized hypertonic saline solution has been proven to decrease of airway edema, improve ciliary clearance of mucus and decrease respiratory secretion viscosity in RSV bronchiolitis, it is well tolerated without adverse effects, and it is therefore recommended.[58-59] Other nebulized drugs, such as Beta2-agonists, epinephrine, steroids, or the association of any of them should not be recommended routinely because they do not decrease the length of hospitalization or the mortality related to RSV infection. Although the last guideline from the AAP does not recommend routine treatment with nebulized Beta2-agonists or epinephrine, these medical have proven to be effective in same children to avoid hospitalization when applied in the emergency room and it seems worthy a trial.

Humidified oxygen may be administered by means of nasal prongs or mask to achieve oxyhemoglobin saturation consistently above 90%. Oxygen supplementation should be discontinued when hemoglobin saturation is about 93%, in presence of a stable improvement of

symptoms, and if the child has resumed intake of fluids and feeds. The use of high flow heated and humidified oxygen up to 2 L/kg/min (maximum of 10 L/min), may rapidly improve oxygen saturation in infants suffering from RSV bronchiolitis. In the most severe cases of respiratory distress bilevel no invasive ventilation or conventional mechanical ventilation may be required to decrease the work of breathing and achieve a correct tissue oxygenation. When the respiratory system completely fails, then an extracorporeal membrane oxygenation support should be considered.

Beside the respiratory support, when RSV affects an immunocompromised patient multiorganic failure may occur and other supportive therapy, such as extracorporeal renal replacement or cardiac and hemodynamic support might be indicated.

Conclusion

Currently, an effective RVS vaccine is not available in the clinical setting, and, when indicated, prophylaxis of RSV infection with palivizumab is the most important prevention strategy, together with basic hygienic measures. Besides ribavirin, the only antiviral accepted for treating RSV infection, several drugs with different antiviral activities are under investigation. Immunomodulatory treatments may open new insight into both short and long term outcomes of RSV disease.

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Upcoming Congresses and Meetings

Children's Environmental Health Network Research Conference 2015

4th - 6th February, 2015

Austin, USA

The Children's Environmental Health Network (CEHN) is a national multi-disciplinary organisation whose mission is to protect the developing child from environmental health hazards and promote a healthier environment. Engage in an event that explores how the interaction between food and environmental factors affect children's health: - Micro-level factors such as nutrient-mediated microbiome effects - Macro-level influences such as contaminants rising from modern food production practices.

www.cehn.org/2015_research_conference

BORN Ontario Conference 2015

6th - 7th February, 2015

Ottawa, Canada

How are you improving maternal-child health in your corner of the world? Be inspired by your colleagues! BORN is hosting a two-day conference to bring health care providers, policy makers, health administrators, educators, quality and risk management leaders, and researchers together to share experiences, enhance knowledge, foster partnerships, and promote research. What can you expect from the conference? Gain new insight into gathering, analyzing, and using maternal-child data for a variety of purposes: improving outcomes, supporting program planning, and informing policy making. Hear about innovations, emerging trends and best-practices in maternal-child health. Learn how data, coupled with advances in information technology, can improve your ability to monitor services and outcomes and integrate evidence into decision-making. Gain new perspective: cross-pollinate your ideas with others during interdisciplinary discussions.

http://bornontarioconference.ca/

33rd Annual Meeting of the European Society for Paediatric Infectious Diseases

12th -16th May, 2015

Leipzig, Germany

ESPID 2015's scientific programme will consist of a range of sessions and learning opportunities, given by the top experts on Paediatric Infectious Diseases. Come discover the latest developments in our fast-changing world in Liepzig.

www.espid2015.kenes.com

ESPR 2015 — 52nd Annual Meeting & 38th Post Graduate Course

2nd - 6th June, 2015

Graz, Austria

The meeting is the largest European meeting of paediatric radiologists aiming to present innovative techniques for all who have to deal with imaging and treating children. Topics being covered include: paediatrics, radiology, imaging, and so on.

http://www.espr2015.org

ESPNIC 2015 - 26th Annual Meeting of the European Society of Paediatric and Neonatal Intensive Care

10th - 13th June, 2015

Vilnius, Lithuania

ESPNIC 2015 is an influential forum for colleagues from around the world to discuss a wide variety of specialties.

Topics will include: Paediatric Intensive Care, Neonatal intensive care, PICU , NICU, intensive care, Respiratory Failure, aemodynamics & Congenital, Heart Disease, Ethics, Infection, Systemic Inflammation and Sepsis, Neuro Critical Care, Metabolism, Endocrinology and Nutrition, Pharmacology, Paediatric and Neonatal Intensive Care Nursing.

www.kenes.com/espnic

European Academy of Paediatrics, congress and Mastercourse 2015

17th - 20th September, 2015

Oslo, Norway

European Academy of Paediatrics exists to promote the health of children and young people in Europe. It aims to improve standards in training, service and research and to represent the professional interests of paediatricians in the EU. EAP is the paediatric section of European Union of Medical Specialists and therefore has influence in the political arena to advocate for children and young people as well as for the profession. The congress will provide the most updated, state-of-the-art information on the latest developments in research and clinical practice in the main areas of Paediatrics. It also gives the opportunity to debate on controversial issues and to contribute, with your own voice, to the progress of the practice of paediatrics. The Congress will cover many important topics over 3 days and in parallel to this academic event.

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