TREATMENT STRATEGIES PAEDIATRICS

Volume 4 Issue 1

- Necrotising Enterocolitis
- Paediatric Cardiology
- Paediatric Infection
- Premature Infancy
- Preventative Cardiology
- Respiratory Illness

Highlights include:

Cat-scratch Disease
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Paediatric Tuberculosis: Treatment Strategies
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Treatment of Life-threatening Asthma in Children
Doreen Schutte and Joris Lemson

54th ANNUAL MEETING 2013

ESPID

Featuring reviews of
ESPID's 31st Annual Meeting, Milan
ESPR's 54th Annual Meeting, Porto

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

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

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

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

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

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Welcome...

I am delighted to welcome you to the latest edition of *Treatment Strategies - Paediatrics*. In our 2013 edition we bring you a range of informative articles, as well as reviews of the 31st Annual Meeting of the European Society for Paediatric Infectious Diseases (ESPID) and the 54th Annual Meeting of the European Society of Paediatric Research (ESPR). The theme of the 31st Annual Meeting of ESPID was 'Paediatric Infectious Diseases: Future Perspectives' and provided attendees with a full and exciting programme. The 54th Annual Meeting of ESPR's aim was to advance paediatric research in Europe, and featured a varied programme. We are excited to bring you reviews of both.

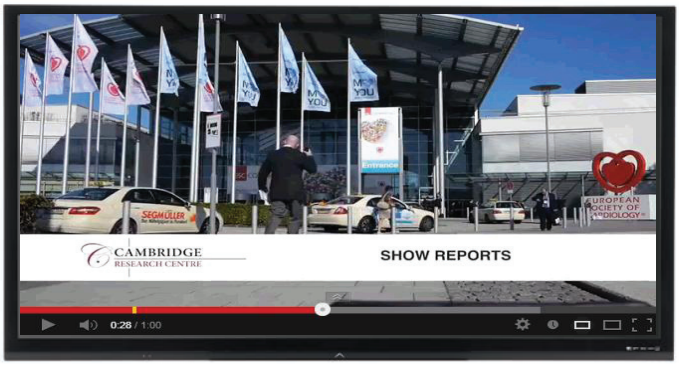
This edition also features a number of interesting papers on subjects such as paediatric respiratory illness, premature infancy and necrotising enterocolitis. With these papers we aim to bring you new insights into the latest treatment strategies for a number of different paediatric disorders. Furthermore, in this edition we are bringing you a further opportunity to read some of the most informative papers on paediatric issues which have recently been featured in the Treatment Strategies series.

We hope that you enjoy the content that we have presented to you in this edition, and please do share your thoughts with us on this edition. We are always looking for new ways to bring you our content and indeed, we have recently launched our growing range of interactive eBooks on iBooks, which is a great new way to read and download our content on your devices. We have also launched our Treatment Strategies TV channel, where you can find footage from all of the most important scientific conferences, as well as interviews, symposia proceedings, roundtable events and much more. Additionally, the team are also all active on Twitter and LinkedIn, and please do follow us or join our LinkedIn group to find out more about our upcoming releases.

We hope that you enjoy this edition of *Treatment Strategies - Paediatrics*, and we look forward to bringing you our 2014 edition of the publication, which will feature a review of the 5th Congress of the European Academy of Paediatric Societies (EAPS). which will be held in Barcelona, Spain.

Hannah Corby, Chief Sub-editor

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



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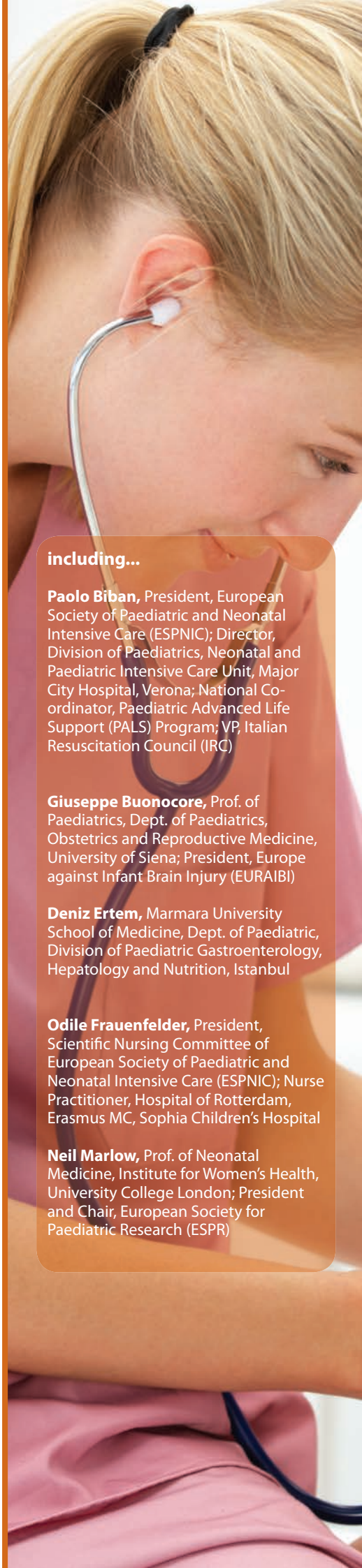

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Foreword

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We are in the midst of an exciting period in neonatal medicine, in which optimising nutrition of preterm infants is showing great promise for improving neurodevelopmental outcomes. This is critical, because studies in animals have universally shown that reduced nutrient supplies to the foetus produce smaller brains with fewer and shorter neurons that have fewer dendrites and synaptic connections and are associated with cognitive and behavioural impairments later in life.[1-3] Similarly, small for gestational age (SGA) human infants who had intrauterine growth restriction (IUGR) from nutrient deprivation have less than normal long-term neurodevelopmental outcomes, primarily to the extent that brain growth was restricted.[4, 5] Furthermore, this problem extends to human infants born preterm, who have also shown reduced brain size as early as term gestation and poorer cognitive and behavioural conditions later in life. Most importantly, however, such problems are ameliorated by enhanced nutrition.[6, 7] Many processes might contribute to reduced neuronal growth and development and overall brain growth in preterm infants. When and how they exert their impact is important to determine, particularly in light of studies[8-10] that have shown improved neurodevelopment in children and adolescents who were born preterm in direct proportion to their nutrient intake (both energy and protein) and head growth in their post-birth hospital period. The type of nutrition also is critical. Many studies have shown that more breast milk intake, primarily of mother's own milk, enhances neurodevelopmental outcomes in preterm infants,[11-13] and neurodevelopmental outcome is improved in direct relation to the duration of breast feeding after birth.[14]

Given such exciting promise of improved neurodevelopmental outcome from improved nutrition of preterm infants, new research is needed to advance these important observations now more than ever. First, new studies are needed to optimise intravenous (IV) amino acid mixtures, as those currently in use have barely been changed since their inception. For example, one study showed that appropriate rates of amino acid supply with TrophAmine® (B. Braun Medical Inc., Bethlehem, PA USA), a standardly used IV mixture in neonates, achieved considerably lower concentrations of lysine and threonine, both essential amino acids and thus limiting for protein synthesis, than found in normally growing human fetuses of the same gestational age.[15] Future studies of IV nutrition in preterm infants, therefore, need to determine the optimal mixture (quality) of amino acids. Other studies are needed to determine the appropriate mixtures and rates of infusion of IV nutrition that are best for infants who are physiologically unstable, including those with major illnesses (respiratory distress requiring ventilation and pressure/oxygen support, sepsis, necrotising enterocolitis, surgery for congenital malformations, and more), along with their attendant problems of hypoxia, acidosis, increased levels of catecholamines and cortisol, and poor renal function.[16-18] This is particularly important in light of a recent study showing markedly higher total amino acid concentrations and blood urea nitrogen levels in a group of preterm infants receiving appropriately high rates of infusion of an amino acid mixture designed for paediatric patients who later did not score as well on developmental tests.[19] Furthermore, while enhanced amino acid/protein intakes have improved protein balance, the optimal rates of administration need to be tested for how well they promote growth of the brain.[20] This could be particularly challenging, as one recent study showed normal brain volume and/or surface area at term among preterm infants,[21] while others have shown reduced brain growth,[22, 23] indicating that factors that promote or restrict brain development might be independent of overall body growth. Furthermore, most studies support the concept that improved nutrition could promote brain growth of preterm infants[24, 25] in concert with improved overall growth rates.[26] More exciting than just growth are new data from MRI studies, which demonstrate that the rate of microstructural maturation in preterm infants' brains correlates locally with cortical growth and predicts higher neurodevelopmental test scores at two years of age. Cortical microstructural development appears to be reduced in a dose-dependent fashion by longer exposure to the extrauterine environment (especially adverse

conditions such as the development of chronic lung disease) and preterm infants at term-corrected age possess less mature cortex than term-born infants.[27] Cortical growth and development may be particularly vulnerable in preterm infants who are under nourished, as the rate of cerebral cortical growth between 24 and 44 weeks post-menstrual age, the period of greatest postnatal growth restriction from under nutrition in the NICU, predicts global ability in later childhood, particularly complex cognitive functions.[28]

Other studies are needed to determine how to optimise the amount of protein in milk, including its source (human vs. bovine) and quality, to best promote brain growth and developmental outcomes.[29] Such studies also need to focus on approaches to enhance nutrition during the first days to week or two of life, as this period seems critical to establishing improved neurodevelopmental outcomes.[30-33] Other studies are still needed to determine those factors in milk, perhaps certain essential fatty acids,[34] which are notably deficient in the nutrition of preterm infants,[35] that might be as or more important than the amount and quality of protein in promoting brain growth and neurodevelopmental outcome. Not the least, future studies also must considered how under nutrition of the developing brain could lead to later life psychiatric conditions, an increasingly recognised possibility.[36]

The time is ripe to move beyond how much to feed a preterm infant just to get it to grow at normal *in utero* rates and to focus now on how to optimise nutrition of the preterm infant to meet the unique needs of brain growth and neurodevelopmental outcomes.

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ESPID Meeting 2013 Review

28 May - 1 June 2013 - Milan, Italy

31st ESPID Meeting - Paediatric Infectious Diseases: Future Prospectives

INSIDE...

The Meeting

The Exhibition

Sara Taheri, *Treatment Strategies*, was thrilled to attend the 31st Annual Meeting of ESPID, and in this review she brings you all of the breaking news, research and symposia proceedings from the show, as well as news of some of the most innovative products showcased at the meeting. The review is then followed by a poster synposes section, which brings you highlights of some of the most exciting posters that were presented at the event.

The 31st Annual Meeting of the European Society for Paediatric Infectious Diseases was held on 28 May - 01 June 2013 in Milan, Italy.

The Meeting was featured a full and exciting programme of keynote lectures, symposia, educational workshops and meet-the-expert sessions, which covered the entire field of paediatric infection-related diseases with presentations from many internationally renowned experts.

The central theme of ESPID 2013 was Paediatric Infectious Diseases: Future Prospectives, and the event provided clinical practitioners, researchers and industry professionals with access to the latest findings and analysis in the field of paediatric infectious diseases.

Delegates were given access to numerous interactive presentations of the results of applied research and the lessons learned in clinical and laboratory practice, which enabled an exchange of experiences among the various sub-specialties.

Over 3000 practitioners, researchers, and experts attended this event from all over the globe, making it the largest paediatric infectious disease meeting in the world.

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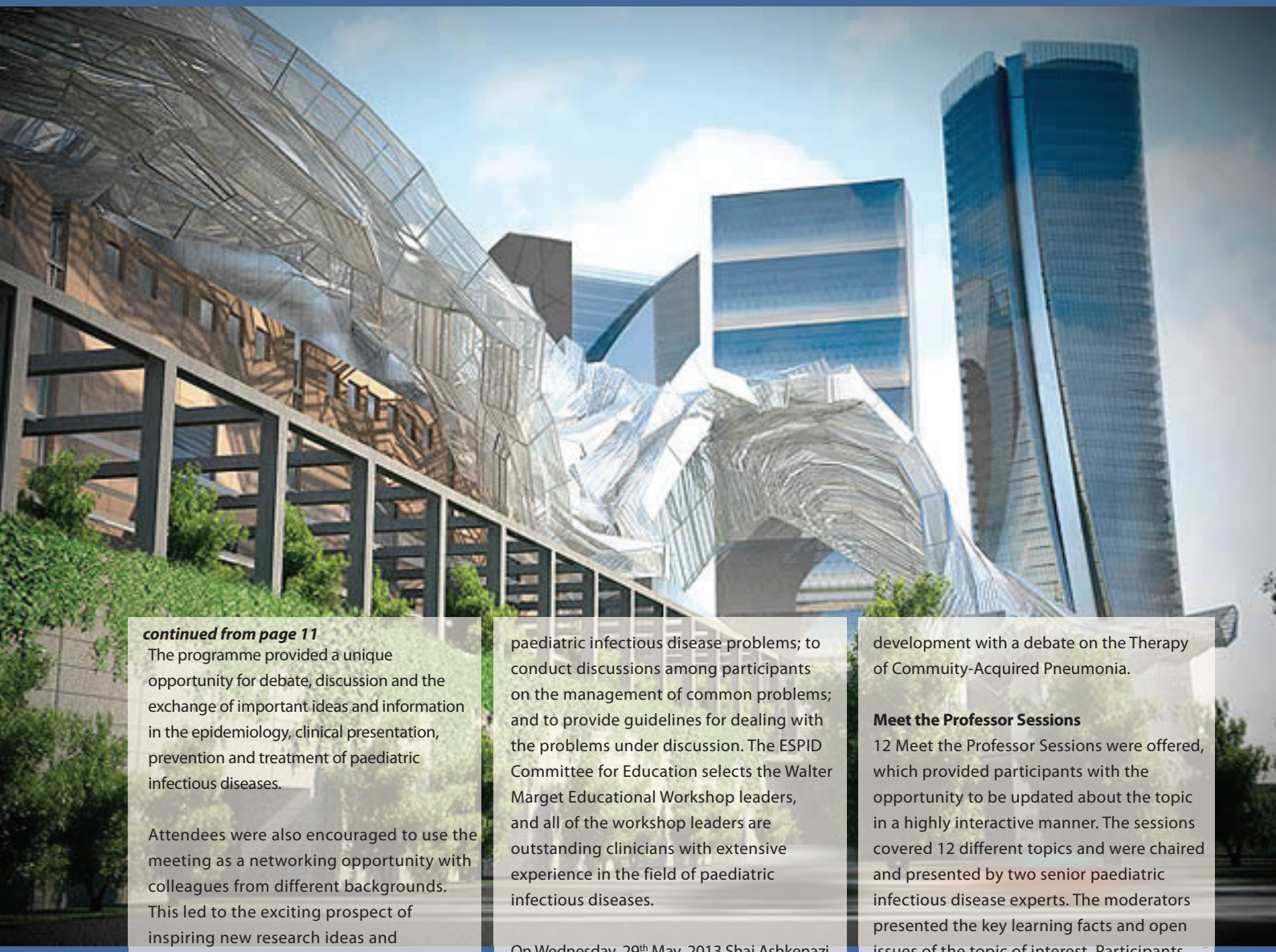
This Year's ESPID Meeting was held in Milan, Italy



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The programme provided a unique opportunity for debate, discussion and the exchange of important ideas and information in the epidemiology, clinical presentation, prevention and treatment of paediatric infectious diseases.

Attendees were also encouraged to use the meeting as a networking opportunity with colleagues from different backgrounds. This led to the exciting prospect of inspiring new research ideas and innovative ways of organising laboratory and clinical processes.

The programme provided a unique opportunity for debate, discussion and the exchange of important ideas and information in the epidemiology, clinical presentation, prevention and treatment of paediatric infectious diseases.

Walter Marget Educational Workshop

At each meeting, ESPID sponsors an educational workshop for selected trainees at the annual meeting. The workshop is clinically oriented and interaction between trainees and faculty is strongly encouraged.

The goals and objectives of the workshop are; to discuss, in depth, the management of common infectious diseases in children; to provide tools to cope with common problems in paediatric infectious diseases; to present updated knowledge on common paediatric infectious disease problems; to conduct discussions among participants on the management of common problems; and to provide guidelines for dealing with the problems under discussion. The ESPID Committee for Education selects the Walter Marget Educational Workshop leaders, and all of the workshop leaders are outstanding clinicians with extensive experience in the field of paediatric infectious diseases.

On Wednesday, 29th May, 2013 Shai Ashkenazi, Chair, ESPID Education Committee chaired the Walter Marget Educational Workshop with the theme of ; "Hard-to-Treat Paediatric Infection".

The ESPID 2013 programme included 6 oral session, where free paper communications are selected from the top abstracts. There were also 12 oral Poster Discussion sessions that were arranged on a variety of paediatric infectious disease related topics, and featured posters from submitted abstracts that will undoubtedly extend our knowledge of the latest scientific developments in these fields.

Plenary Sessions

The keynote plenary sessions at ESPID 2013 covered the following topics:

Viral Respiratory Infections Emerging respiratory viruses, When influenza should be prevented and treated, Viral infections, infectious wheezing and asthma development with a debate on the Therapy of Commuity-Acquired Pneumonia.

Meet the Professor Sessions

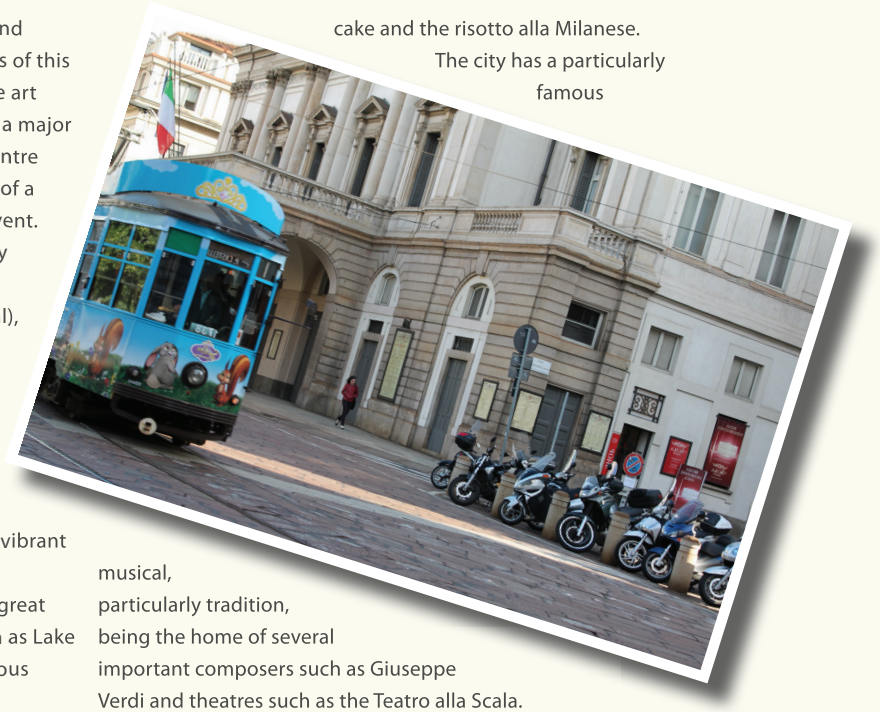
12 Meet the Professor Sessions were offered, which provided participants with the opportunity to be updated about the topic in a highly interactive manner. The sessions covered 12 different topics and were chaired and presented by two senior paediatric infectious disease experts. The moderators presented the key learning facts and open issues of the topic of interest. Participants were invited to actively prepare for the sessions.

Interactive Case Session

An Interactive Case Session was held on Friday, 31st May 2013 between 08:30-10:00. The objective of the session was to increase the knowledge on clinical aspects of diagnosis and therapy of paediatric infectious diseases. The session were chaired by two internationally recognised experts in the field, who prepared, presented and discussed case reports of children with common or unusual infectious diseases. A panel of paediatric infectious disease consultants challenged by moderators provided their insights on diagnosis and therapy. The audience were asked to actively participate in discussion with the experts and the panel members. An interactive electronic voting system was used to provide feedback to all participants.

Milan - Host of 31st Annual Meeting of ESPID

The 31st Annual Meeting of ESPID was held in Milan, and gave attendees the opportunity to take in the delights of this exceptional city. Milan is famous worldwide for its fine art and music, the diversity of its culture and its status as a major fashion and design capital. The Milano Convention Centre is located in the heart of the city, and the completion of a major renovation made it the perfect venue for the event. Although Milan is a sprawling metropolis, the majority of its attractions are also concentrated in the centre between Castello Sforzesco and the Duomo (cathedral), and just north of the Duomo, you will find not only the art galleries of the Brera, but also fashionable shopping avenues.



Milan is famous for being a world fashion and design capital, with a major influence in commerce, industry, music, sport, literature, art and media. It is a vibrant city, brimming with numerous events and an exciting nightlife. Milan is also a city of great beauty, with the great expanse of natural parks and magnificent lakes – such as Lake Como – surrounded by mountains that attract numerous hikers and skiers.

The city has an ancient cultural heritage and legacy. Indeed, it was the capital of the Western Roman Empire and boasts a unique, world-famous artistic heritage, of which the best known is Leonardo da Vinci's Last Supper. Milan is also home to numerous famous dishes, such as the Panettone Christmas cake and the risotto alla Milanese.

The city has a particularly famous musical, particularly tradition, being the home of several important composers such as Giuseppe Verdi and theatres such as the Teatro alla Scala.

Milan is also well-known for containing several important museums, universities, academies, palaces, churches and libraries such as the Academy of Brera and the Castello Sforzesco and two renowned football teams: A.C. Milan and F.C. Internazionale Milano.

The Bill Marshall Lecture: 215 Years of Vaccination: Job Done?

On Friday, 31st May 2013 at 15:30 The Bill Marshall Lecture: 215 years of vaccination: job done? Was presented by its awardee, Prof. Andrew Pollard.

Andrew Pollard, FRCPCH PhD, is Professor of Paediatric Infection and Immunity at the University of Oxford, Honorary Consultant Paediatrician, and Director of the Oxford Vaccine Group. He obtained his medical degree at St Bartholomew's Hospital Medical School, University of London in 1989, specialising in Paediatric Infectious Diseases in the UK and Vancouver, Canada. In 1999, he obtained his PhD degree at St Mary's Hospital, London, UK.

The research in his PhD thesis concerned studies on the immune-response of infections by to Neisseria meningitidis in children. He took up his current position at the University of Oxford, UK in 2001 and has since developed and directed a large research group, which currently contains 70 staff members. His current research activities include a wide range of topics such as clinical trials of new and improved vaccines for children, surveillance of invasive bacterial diseases in children in Nepal, studies of cellular and humoral immune responses to glycoconjugate and typhoid vaccines, and the development of a serogroup B meningococcal vaccine. He is using a controlled human infection model of typhoid to investigate disease pathogenesis and evaluate novel vaccines. Prof. Pollard has published well over 200 peer-reviewed papers, many in prestigious journals. Over the past decade, he has been the recipient of a large number of research grants and as part of his work he holds five patents. He has been a wonderful mentor and tutor for many PhD and medical students. In addition to being a excellent educator he is also a gifted speaker and presenter at national and international meetings.

Prof. Pollard has initiated the postgraduate course on Infection and Immunity in Children (IIC), which is one of the best courses in its field in the world.

Infant Vaccination with Serogroup C Neisseria Meningitides Conjugate Vaccines

At ESPID 2013 researchers presented their findings from research on the immunisation of infants against Neisseria meningitides. It was revealed that 1 month following a Haemophilus influenzae type b (Hib) serogroup C meningococcal (MenC) booster, MenC priming shows significantly improved generation of MenC-specific memory B cells over prior MenC-conjugate (CRM) priming.

The findings of this research where presented in "A Randomised Controlled Study to Evaluate Induction of Immune Memory Following Infant Vaccination With Serogroup C Neisseria meningitides Conjugate Vaccines" which was sponsored by GlaxoSmithKline Biologicals.

On 31st May Dr. A Khatami, Department of Paediatrics, Oxford Vaccine Group, University of Oxford, Oxford, United Kingdom presented the subset analysis of a randomised, controlled clinical trial. The results showed that there are no significant differences between single or double MenC CRM priming and no priming prior to the Hib-MenC-TT booster.

The researchers highlighted that during immunisation of infants against Neisseria meningitides, 1 month following a Haemophilus influenzae type b (Hib)-serogroup C meningococcal (MenC) booster, MenC priming shows significantly improved generation of MenC-specific memory B cells over prior MenC-conjugate (CRM) priming.

Furthermore, no significant differences between single or double MenC-CRM priming and no priming prior to the Hib-MenC-TT booster were found.

Dr. Khatami explained the hypothesis is that different vaccines and different dosing schedules may promote memory B cell induction at the expense of plasma cell production.

Similar or mixed priming and boosting of children with different MenC-conjugate vaccines appear to show differential immunogenicities and antibody responses.

Therefore this analysis was designed to determine MenC-specific memory B cell responses following different MenC-conjugate vaccine schedules in infants.

In this subset analysis 333 infants received priming with MenC-CRM as 1 dose at 3 months (n = 110) or 2 doses at 3 and 4 months (n = 103), or MenC-TT as 1 dose at 3 months (n = 76), or no MenC priming vaccine (n = 44; control).

All then received Hib-MenC-TT booster at 12 months. The children also all received the standard additional vaccine schedules.

At 1-month post priming (age 5 months), compared with the control group, there were significant MenC-specific memory B cell responses for all of the MenC-conjugate vaccine schedules (single-dose MenC-CRM, P = .04; double-dose MenC-CRM, P = .0006; single-dose MenC-TT, P = .001).

These responses increased with maintained significant by 12 months, at the pre-booster analysis (P< .0001; P = .03; P = .006), and were further enhanced with greater significance over the control 6 days after the Hib-MenC-TT booster (P< .0001 for all).

However, by 1 month after the Hib-MenC-TT booster (age 13 months), the control MenC-specific memory B cell response to the booster alone showed no difference from the single-dose and double-dose MenC-CRM priming plus Hib-MenC-TT booster.

At the same time, the single-dose MenC-TT priming plus Hib-MenC-TT booster response showed a trend to an increase over the control (P = .09), and was significantly greater than both single-dose (P = .001) and double-dose (P< .0001) MenC-CRM priming plus Hib-MenC-TT booster.

Dr. Khatami explained that at 1 month after the Hib-MenC-TT booster, there were no differences in children who received MenC-CRM priming compared with children who had received no priming doses at all.

Furthermore, at this time, MenC-TT priming with Hib-MenC-TT boosting showed greater generation of memory B cells than MenC-CRM priming with Hib-MenC-TT boosting.

Long-term Extension Study of Gardasil in Adolescents: Results Through Month 96

At the 31st Annual Meeting of ESPID, the study for Immune Responses Maintained Up to 96 Months in Adolescents Vaccinated With Quad HPV Vaccine was presented. Funding for this study was provided by Merck.

In pre-adolescents and adolescents the administration of a quadrivalent human papillomavirus (HPV) vaccine (Gardasil) shows anti-HPV 6, 11, 16, and 18 immune responses which persist over the long-term, according to data presented.

In addition, the rate of persistent infection is similar to that seen in vaccinated populations studied in phases 2 and 3 of the study. No breakthrough cases of disease have been observed, according to Ole-Erik Iversen, MD, Department of Clinical Science, University of Bergen, Bergen, Norway.

In the original study, 1,781 sexually inactive boys and girls were randomised to placebo (n = 597) or the quadrivalent HPV vaccine (n = 1,184). A single dose of the vaccine was given on day 1 and at months 2 and 6.

From the original trial, 1,179 patients from the vaccination group were enrolled in the extension study and followed to 96 months (52% female). At baseline at the time of the first dose, patients had a mean age of 11.9 years, and little seropositivity to HPV types 6, 11, 16, and 18 (0.7%, 0.1%, 0.7%, and 0.3%, respectively).

At 1 month post-dosing, vaccine-induced anti-HPV seropositive responses across 4 HPV types were seen for 99.8%, 99.8%, 99.7%, and 99.7%, respectively. These responses were seen to persist to 96 months for each of these HPV types, with 88.4%, 89.1%, 96.8%, and 64.1%, respectively, remaining seropositive.

At the 96-month evaluation, there were 2 cases of infections in girls (vaccine-type persistent infection, cervical intraepithelial neoplasia or external genital lesions) that were due to HPV-16-related persistent infection, for an annual rate of 0.3.

Similarly, there were 2 cases of persistent infection in boys (vaccine-type persistent infection or external genital lesions). 1 was HPV 6 related and one was due to HPV 16, for an annual rate of 0.4.

Quadrivalent Meningococcal Conjugate Vaccine Is Safe in Infants, Induces Robust Immune Responses

Novartis Pharma B.V. funded a study on Quadrivalent Meningococcal Conjugate Vaccine, and the results of the research on Immunogenicity and Safety of MenACWY-CRM, a Quadrivalent Meningococcal Conjugate Vaccine in Infants was presented at the 31st Annual Meeting of ESPID.

The researchers of this study stated that the MenACWY-CRM quadrivalent meningococcal conjugate vaccine (Menveo) is well-tolerated and induces robust immune responses when used in a 4-dose infant immunisation series. No evidence for clinically relevant interference with routine infant and toddler vaccines was shown.

Neisseria meningitidis is the causal agent of meningococcal disease, which represents a public health challenge as it results in significant morbidity and mortality worldwide. Additionally the highest disease burden is shown in infants.

Immunisation against meningococcal diseases can be achieved using the quadrivalent meningococcal conjugate vaccine against serogroups A, C, W-135 and Y: MenACWY-CRM. This vaccine is currently licensed in various countries; however there have been no reports on its immunogenicity and safety data in infants.

Dr. I Smolenov, Novartis Vaccines and Diagnostics and colleagues pooled data from three phase 3 trials where MenACWY-CRM was co-administered with other routine vaccines. In all of these trials, healthy infants aged 2 months were randomised to receive routine vaccines either alone or in combination with MenACWY-CRM. The quadrivalent vaccine was administered as a 4-dose series, at 2, 4, 6, and 12/16 months of age.

The normal range of routine vaccines were administered according to the immunisation series of each study country for infant and toddler primary and booster immunisations, including vaccines against diphtheria, tetanus, acellular pertussis, poliomyelitis, hepatitis B, Haemophilus influenzae type b, rotavirus, Streptococcus pneumoiae, measles, mumps, rubella, and hepatitis A.

MenACWY-CRM-promoted immunogenicity was assessed using the serum bactericidal assay with human complement titre (hSBA) ≥8 against serogroups A, C, W and Y. At 1 month post-vaccination, this was seen for 89% to 95%; 95% to 98%; 97% to 100%; and 96% to 100% for these 4 serogroups, respectively. Dr. Smolenov noted that some non-inferiority criteria for the meningococcal vaccine was also shown.

Across the groups within each study that received concomitant addition of MenACWY-CRM the reactogenicity and safety profiles were similar, compared with routine vaccinations alone.

When this was co-administered with routine infant and toddler vaccines no clinically relevant interference was evident.

In addition, the data showed no meaningful regional differences in reactogenicity and immunogenicity of MenACWY-CRM or these routine infant and toddler vaccines.

New Fully Liquid Hexavalent Vaccine Non-inferior to Current Hexavalent Vaccine: Presented at ESPID

On 30th May at ESPID 2013, researchers showed that a new fully liquid hexavalent vaccine (Hexaxim) shows similar immunogenicity for each antigen to the presently licensed hexavalent vaccine (Infanrix), when administered to infants as a 3-dose primary series at 2, 4, and 6 months.

The reconstituted hexavalent vaccine shows recognised combined immunogenicity towards diphtheria and tetanus toxoids and acellular pertussis (DTaP), inactivated poliomyelitis (IPV), recombinant hepatitis B (Hep B), and adsorbed conjugated Haemophilus influenzae type B (PRP-T).

Andrew Lane, PhD, Global Medical Affairs, Sanofi Pasteur, Lyon, France, said that this as a fully liquid vaccine, it behaves slightly differently. Researchers combined data from 4 recently completed randomised phase 3 clinical trials where it was possible to investigate directly the non-inferiority of this new vaccine versus the control vaccine. This analysis was based on the immune responses produced by each vaccine for each antigen after a 3-dose primary vaccination series in infants at age 2, 4, and 6 months.

Based on the per protocol analysis, a total of 1951/755 infants were immunised according to the new and control vaccines respectively, in the 4 study areas of Mexico (695/119), Thailand (189/190), Peru (132/130), and Colombia/ Costa Rica (935/316).

Where measured, each of the antigens of each of these 2 hexavalent vaccines induced similar strong immune responses. The seroprotection rates against the DT·IPV·Hep B·PRP-T components of both of the vaccines ranged from 94.6% to 100%, with seroconversion rates against the aP component from 89.6% to 98.4%.

According to all of the range of non-inferiority tests carried out across these data within the different study areas, these demonstrated non-inferiority of the new vaccine versus the control vaccine for both seroprotection and seroconversion.

In the safety analysis, occurrence of solicited injection site and systemic reactions, and unsolicited adverse events were similar in each of the vaccine groups. There were no vaccine-related serious adverse events within the 6-month follow-up for either vaccine group.

Overall, this new vaccine shows a good safety profile that is combined with high immunogenicity across the full hexavalency, while showing non-inferiority to the presently licensed control vaccine.

Dr. Lane explained that in terms of the public health perspective, this means that there are now 2 hexavalent vaccines available on the market. This provides the opportunity to increase vaccine coverage, with the potential to increase compliance to these complex paediatric vaccination schedules.

Decreasing the Burden of Recurrent Respiratory Tract Infections in Children

On 29th May at 14.30 Prof. Vytautas Usonis and Prof.Stefan Zielen presented an innovation update, "Decreasing the Burden of Reccurrent Respiratory Tract Infections in Children," which was supported by OM Pharma.

Respiratory Tract Infections (RTIs) in children are common causes of morbidity and mortality worldwide. In industrialised countries, approximately 50% of consultations from children are the result of RTIs; these are often recurrent infections, occurring numerous times a year. RTIs represent an important health cost for governments and to society.

Risk factors for RTIs in childhood include attendance at day-care centres, overcrowding, contact with elder siblings, smoking at home and lack of breast feeding among others. The high incidence of respiratory infections in children, relative to older adolescents and adult populations, can be partially explained by the apparent limitations of their young immune systems. Defects or immaturity in immune responses are known to correlate with multiple RTIs.

RTIs are commonly treated with antibiotics, despite the fact that those might not be indicated and therefore having limited efficacy. Even more, the overuse and misuse of antibiotics keep perpetuating the major healthcare problem of antibiotic resistance in the world.

Priority should be given to preventative measures for avoiding complications and comorbidities related to RTIs. These strategies look to prevent the development of recurrent RTIs in children by reducing the risks of infection. Some of these measures include parent education, active immunisation and non-specific immunostimulation.

In this context, and because of the strong association between recurrent RTIs and inadequacies of the immune system, bacterial immunostimulants have been developed to non-specifically enhance the body's own defences against any invasive pathogens.

OM-85 is the most studied immunostimulant and has the longest post-marketing experience with regards to efficacy and safety. A recent study has shown that recurrent virus-induce wheezing in pre-school children can be safely and significantly reduced by administration of OM-85.[1] Another study published in 2013 highlights the benefit of OM-85 in the management of recurrent acute tonsillitus in children, showing a decrease in both the frequency of episodes in the short-term and the need for tonsillectomy on the long-term[2] follow-up.

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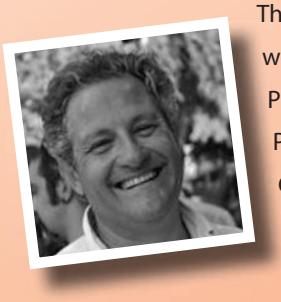
Rotavirus Vaccination - Why Europe is Moving Forward?

At the 31st Annual Meeting of ESPID, GlaxSmithKline ponsered a symposium on 'Rotavirus Vaccination - Why Europe is Moving Forward?'on Tuesday 28th May from 13.00 to 14.30. This symposium considered RVGE and RV vaccination in a European context, and provided an overview of current data on the effectiveness of oral, live attenttentuated RV vaccines, as well as summarising recent learnings which suggest that these vaccines could have a positive oublic health impact in Europe.



The Symposium started with a welcome and introduction by Prof. Carlo Giaquinto, Head of the Paediatrics AIDS and Paediatric Clinical Research Unit at the University of Padova, Italy.

This introduction was followed by a presentation entitled "Good Reasons to Introduce Rotavirus Vaccination in Europe, which was given by Prof. Catherine Weil-Olivier, Professor of Paediatrics, Paris VII University, France. In this presentation Prof. Weil-Olivier gave an overview of RVGE and why the RV vaccination should be introduced in Europe.

Dr. Marc Raes, Paediatrician and Paediatric Pulmonologist-allerologist, Jessa Hospital, Hassalt, Belgium followed with his presentation ' RotaBel Data: A European Example of Rotavirus Vaccine Effectiveness', in which he summarised the recent European experience with RV vaccination.

Next, Prof. Marco Safadi, Assistant Professor of Paediatrics, Santa Casea de Sao Paulo School of Medicine, Brazil gave a talk on 'Benefit-risk Assesment of Rotavirus Vaccination: The Decline of a Disease'. Here he considered the associated benefits and risks of vaccination, drawing on his own clinical experience.

Lastly, Prof. Adam Finn, Paediatrician, University of Bristol, UK and Head of Bristol's Children's Vaccine Centre gave his presentation on 'The UK Goes for Rotvirus Immunisation: Why and What Next?', in which he discussed why the UK has introduced RV vaccination and the implications for the UK and Europe. The session ended with a question and answer session, and concluding remarks from Prof. Carlo Giaquinto.

Childhood Vaccination Programme Implementation, Successes and Challenges: Taking a Step Forward

On Tuesday 28th May, Sanofi Pasteur MSD hosted a symposium entitled 'Childhood Vaccination Programme Implementation, Successes and Challenges: Taking a Step Forward', between 15.00-16.30 in Hall A. The symposium started with a introduction from Prof. Carlo Giaquinto, Professor of Paediatrics, Director of the Paediatric AIDS and Paediatric Clinical Research Unit, University of Padova, Italy. This was followed by the first presentation entitled 'Vaccination Programmes Work - "When Facts Speak, Gods Listen"', which was given by Prof. Federico Martinon Torres, Professor of Paediatrics, Hospital Clinico Universitario de Santiago de Compostela, Spain. The second presentation of the symposium was 'The Challenge of Implementing and Monitoring Vaccination Programmes - "Walking the Talk"', which was given by Prof. Markus Rose, Professor of Paediatric Pneumology Allergology and Infectiology, Goethe University, Frankfurt, Germany. Prof. Catherine Weil-Olivier followed with a presentation entitled 'What Lies Behind Trust and Acceptance of Vaccination Programmes - "Taking a Step Forward"'.

The symposium ended with a concluding summary and a question and answer session by Prof. Carlo Giaquinto.

Pertussis and Hepatitis B Childhood Immunisation Programmes in Europe

On Wednesday 29th May, Sanofi Pasteur and Sanofi Pasteur MSD hosted a joint symposium entitled Pertussis and Hepatitis B Childhood Immunisation Programmes in Europe', between 10.20-11.50 in Hall A.

The sympsium started with an introduction from Prof. Ulrich Heininger, Professor of Paediatrics, Head of Division of Paediatric Infectious Diseases and Vaccinology, University Children's Hospital in Basel, Switzerland. This was followed by the first presentation, 'Efficiacy, Effectiveness and Impact of Pertussis Vaccination in Children' by Prof. Johannes Liese, Professor of Paediatrics, Department of Paediatric Infectious Diseases and Immunology, University Children's Hospital Julius-Maximilians-University, Wurzburg, Germany.

Dr. Alberto Tozzi, Epidemiology Unit, Bambino Gesu Hospital, Rome, Italy then gave a presentation on 'Control of Pertussis: Where do we stand in 2013?'. This was followed by Prof. Pierre van Damme, Professor at the Faculty of Medicine and Health Sciences Centre for the Evaluation of Vaccination, Vaccine and Infectious Disease Institute, Antwerp, Belgium, 's presentation entitled 'Benefits of Hepatitis B Vaccination Programmes in Children'.

The last presentation of the symposium was entitled 'Impact of Hepititis B Childhoos Vaccination Programme: The Italia Experience', which was given by Prof. Alessandro Zanetti, Professor of Hygiene, Department of Biomedical Sciences for Health, University of Milan, Italy. Concluding remarks and a question and answer session were then given by Prof. Ulrich Heininger.

Tick-Borne Encephalitis May be a Tick-bite away – Are You Protected?

Prof. Dr. Michael Kunze from the institute for Social Medicine at the Medical University of Vienna and Chairman of ISW-TBE was at the Baxter booth for a meet-the-expert session

Tick-Borne Encephalitis

TBE (tick-borne encephalitis; FSME) is a viral disease of the central nervous system which is transmitted to man primarily by tick bites. "TBE is a serious case of acute central nervous system disease, which may result in death or long-term neurological sequelae in 35-58% of patients."[1] TBE is endemic to most European countries, The Russian Federation and possibly China. It is the most important arthropod-transmitted viral disease in Europe, and in some countries it represents a major public health problem. Large outbreaks of TBE, sometimes involving thousands of cases, continue to occur in endemic areas.[2]

Signs and Symptoms of TBE

The typical course of TBE is biphasic in at least two-thirds of patients.[6] During the two-phase progression, the so-called first phase of the illness occurs after an incubation period of 6 to 14 days; this is when the virus enters the bloodstream. Patients complain about general symptoms, such as temperature increase, headaches, weakness, and fatigue. These symptoms are often indicated as a common cold. After a frequently symptom-free interval between two and eight days, a sudden and significant increase in temperature marks the beginning of the second phase with typical additional symptoms like headache, neck stiffness, delirium, coordination problems and paralysis of the arms and legs.[7]

Protection Against TBE

Currently no causal treatment is known for TBE. Prevention by special clothing and tick repellents has proven not to be reliable enough.[3] However, TBE can be successfully prevented by active immunisation. The TBE vaccines produced by Baxter are inactivated whole virus vaccines containing a suspension of purified TBE virus, propagated in chick-embryo fibroblast cells of specific pathogen-free eggs, and subsequently subjected to inactivation. TBE vaccine has been approved in Austria since 1976 and has been widely used for many years in 25 European countries, Russia and Canada. Residents of and travelers to TBE endemic areas, who are at risk of tick bites, are advised to receive TBE vaccination.[8,9]

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3. Sünder U., Zu Vorkommen und Verbreitung von Borrelia burgdorferi in ausgewählten Naturherdgebieten Thüringens unter besonderer Berücksichtigung der Rolle des Hauptvektors Ixodes ricinus (L. 1758) (2003)
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Join Hands Against Meningitis - Prevent it Worldwide

The Confederation of Meningitis Organisations Inc. (CoMO) is an international member organisation which is working to reduce the incidence and impact of meningitis worldwide.

CoMO brings together patient groups, health professionals and organisations, meningitis survivors and families from more than 25 countries to help prevent meningitis through:

- Raising public awareness of meningitis through education
- Advocating for meningitis vaccines to be available to families around the world.
- Connecting and resourcing a strong global network of members who make sure their communities have access to meningitis information and support.

CoMO was founded in September 2004 at the World Conference of Meningitis Organisations, where delegates from across the world agreed to work together in the fight against meningitis. Today, CoMO represents 42 member organisations from 27 countries.

What We Do

Anyone can get meningitis: the disease kills or disables hundreds of thousands of people each year. Everyone has the right to prevention and treatment but awareness of the disease varies from country to country and not all immunisation programs include vaccines that prevent meningitis.

CoMO works with its members to address these issues through two core initiatives:

Global Advocacy

Meningitis is an important global health issue that should be on every government's agenda. By bringing our members together, CoMO speaks on behalf of a significant global community – one voice, one message. Together, we can't be ignored.

CoMO coordinates international advocacy campaigns to raise awareness of meningitis, lobby for policy change and fight for global prevention and treatment.

"At CoMO, we are committed to preventing meningitis worldwide, because we can and we should"

Bruce Langoulant
The Meningitis Centre (Perth, Australia)
President and Asia Pacific Regional Leader
The Confederation of Meningitis Organisations Inc. (CoMO)

mariPOC® for Rapid Respiratory Infection Testing

ArcDia were showcasing their range of products at ESPID 2014. mariPOC® is a new innovative test system for multianalyte point-of-care testing of respiratory tract infections. The system is a fully automated random-access immunoassay test systems.

Respiratory infections are the most common type of acute infection in children and adults. Pathogen-specific diagnosis is difficult due to overlapping clinical symptoms of various pathogens. Most infection cases are of viral origin, and they do not require antibiotic treatment. Identification of bacterial pathogens and influenza viruses would be important to enable pathogen-specific medication.

The mariPOC® multianalyte test system aims to provide an answer to diagnostic challenges. Pathogens commonly involved in both upper and lower respiratory tract infections can be rapidly detected with the mariPOC® test system. Timely diagnosis enables in-patient cohorting and accurate use of antivirals and antibiotics. The mariPOC® test system combines antigen detection with a novel diagnostic technology to deliver fast and objective results.

The sensitivity and specificity of the mariPOC® test is similar to laboratory methods and is superior to conventional rapid tests. The assay workflow is simple and has a short hands-on-time. The LIS-compatible mariPOC® is the first test system on the market which enables automated random-access testing of respiratory pathogens at point-of-care.

The mariPOC® is the first test system in the market for multianalyte POC testing. It is an automated random-access antigen detection test for nasopharyngeal swab samples and aspirates, and for throat swabs. Additionally, it is IVD-CE marked.

Why Choose mariPOC® for Respiratory Tract Infection Diagnostics?

- Accuracy similar to central laboratory antigen tests.
- Easy-to-use and has a short hands-on-time. The first result is available in 20 minutes.
- Automated results read-out.
- Replaces conventional rapid and laboratory antigen tests.
- Can be connected to laboratory information systems.

What Does the mariPOC® Point-of-care Diagnostics System Allow?

- Pathogen-specific diagnosis on time.
- Accurate use of virus-specific drugs and antimicrobials.
- In-patient cohorting.
- Efficient control of patient flow.
- Improved cost-effectiveness.

mariPOC Workflow

A swab is cut into the tube, to which the sample buffer and vortex are added. The bar-coded sample tube is then inserted into the analyser for an automated analysis. The results are available in 20 minutes for positive samples and are ready in 2 hours for low positive and negative samples.

Our rich heritage continued

SentrySuite®
Bodyplethysmography

1964 Bodytest – first commercially produced bodyplethysmograph by JAEGER®
1992 Autobox DL – first bodyplethysmograph with diffusion in one cabin by SensorMedics®
2012 MasterScreen Body – powered by SentrySuite

Past, present and future – you can continue to count on us!

carefusion.com

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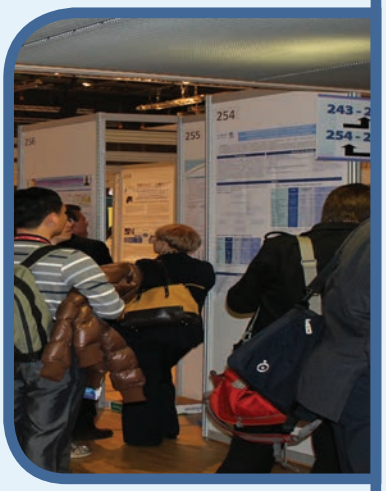
CareFusion

Poster Highlights from ESPID 2013

Bacterial Flora and Increasing Resistance to Antibiotics of Clinical Isolates from the Neonatal Unit in Poland



E. Kuchar,[1] A. Nisch-Osuch,[2] E. Stepnowska,[3] K. Życińska,[2] K. Wardyn,[2] and L. Szenborn[1]

1. Department of Pediatrics and Infectious Diseases, Wrocław Medical University; 2. Department, Warsaw Medical University, 3. St Family, Maternity Hospital, Warsaw

Poliomyelitis Risks in Adolescents and Adults in the 21st Century

Lucia Ferro Bricks,[1] and José Cássio de Moraes[2]

1. Sanofi Pasteur Brazil, the Vaccines Division of Sanofi; 2. Faculdade de Ciências Médicas Santa Casa

Cat-scratch Disease with Bone Involvement in Paediatric Cases

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Reference Values for Interleukin-6 and Interleukin-8 in Cord Blood of Healthy-term Neonates

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Relationship Between the Polymorphism of IL28B and RVR in HCV Infected Children Treated with Pegylated Interferon and Ribavirin

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Bacterial Flora and Increasing Resistance to Antibiotics of Clinical Isolates from the Neonatal Unit in Poland

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Introduction

Bacterial pathogens and their susceptibility patterns should be monitored in hospital settings. The aim of our study was to describe micro-flora and its susceptibility to antibiotics in newborns hospitalised in the Special Neonatal Care Unit (SNCU).

Material and Methods

A retrospective analysis of the results of cultures of clinical samples (blood, cerebrospinal fluid, urine, stool, eye, ear, naso-pharyngeal and skin swabs – see Table 1) taken from newborns hospitalised in one unit in Warsaw. The SNCU is a 9-bed 2nd level unit which cares for newborns born at the hospital and referred from 1st level units (for diagnostic and therapeutic procedures) and 3rd level units (for continuation of treatment and rehabilitation). In the period analysed, a total of 206 newborns were hospitalised in the SNCU. Most of these newborns were delivered at the hospital. The analysed period was 1st July-31st December 2010. A total of 832 samples were collected with 398 (43%) positive results. The species of isolated bacterial strains was identified using the VITEK 2 system (bioMérieux, France) by means of GN cards, following the guidelines issued by the producer. The results of susceptibility/resistance to antibiotics were interpreted in line with the European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria, which have been legally binding in Poland since 1 April 2011.

Results

The vast majority of the cultured microorganisms were Gram-negative bacteria (73.8%). The most common were Escherichia coli (28.6%) and Klebsiella pneumoniae (13.6%). Gram-positive bacteria were the main etiological agents of neonatal sepsis. The 37.7% of E. coli isolates were sensitive to amoxicillin/ampicillin and 98.2%-100% were sensitive to cefuroxym, ceftazidim, amikacin and netylmycin. The 100% of Kl. pneumoniae was sensitive to amikacin and netylmycin. Methicillin resistant Staphylococcus aureus (MRSA) strains were cultured in 2.7% of cases. There were single isolates of ESBL(+) Enterobacteriaceae (2 E. coli and 2 Kl. pneumoniae). They all came from rectal swabs and were classified as colonisation. No VRE, VISA nor KPC positive (Kl. pneumoniae carbapenemase producing) strains were isolated.

Source of Culture	Number of Samples	Number (and proportion) of positive results
Blood	222	9 (4%)
Cerebro-spinal fluid	8	2 (25%)
Urine	56	9 (16%)
External ear swabs	291	159 (55%)
Nasopharyngeal swabs	66	52 (79%)
Eye excretions	19	11 (58%)
Skin swabs	11	4 (36%)
Stool rectal swabs	165	115 (70%)

Table 1. Distribution of positive cultures according to the source of the culture in hospitalised neonates.

Discussion

The epidemiology of neonatal sepsis in developed and developing countries shows some differences. In the industrialised world, group B Streptococcus (GBS) caused neonatal sepsis predominantly, while E. coli was the second most common etiologic agent. Following GBS prophylaxis, a decreasing incidence of GBS and an increased rate of E. coli infections have been reported. Gram-negative bacteria were the most common commensal microorganisms in our hospital, while gram-positive bacteria were mainly cultured from the blood of neonates with sepsis (87.5%). E. coli were the most prevalent bacteria isolated from nasopharyngeal and external ear swabs as well as urine, present in 28.6% of positive samples, showing high resistance to amoxicillin and ampicillin (57.9%), and a low degree of resistance to cephalosporins and aminoglycosides. Only one strain (2.7%) of Staphylococcus aureus was methicillin resistant, but 7 strains (25%) of coagulase (-) Staphylococcus spp. were methicillin resistant. All strains of Staphylococci sp. were sensitive to vancomicin. We found 12 cases of Streptococcus agalactiae, and all of these were considered as colonising flora, not causative agents of infections. "Alarm" pathogens, including MRSA and ESBL (+) Enterobacteriaceae were cultured in only 5 neonates: 1 case of MRSA, 2 cases of E. coli ESBL (+), 2 cases of ESBL (+) Kl. pneumoniae. All of them were classified as gastrointestinal tract colonisation and cultured from rectal swabs.

Conclusion

Gram-negative bacteria continue to predominate as neonatal colonising microflora and important causative agents of neonatal infections. Increasing resistance to aminoglycosides, cephalosporins and commonly used ampicillin is a cause for concern, but the previously introduced infection control measures could have resulted in a low number of multi-resistant bacteria.

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Poster Synopsis

Poliomyelitis Risks in Adolescents and Adults in the 21st Century

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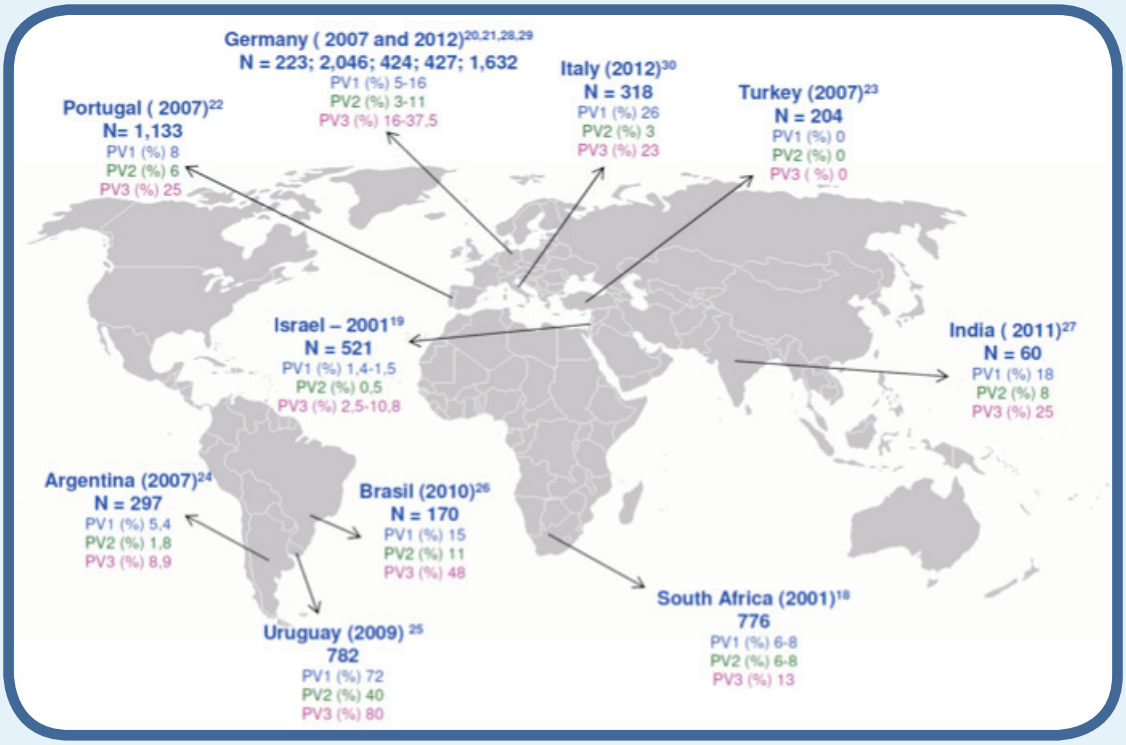
In 2012, only 223 cases of paralysis caused by wild type poliovirus were confirmed in the world. Since January 2011 no acute flaccid paralysis (AFP) due to wild type poliovirus has occurred in India. From January 1st until June 11th 2013, 55 wild polio cases were confirmed in the world, 41 in 3 endemic countries (Nigeria, Pakistan and Afghanistan), and 14 in non-endemic countries.[1]

In spite of the success of the Global Polio Eradication Initiative (GPEI), launched in 1988, poliomyelitis continues to be a global threat to non-immune people of all ages.[2,3] In the poorest regions of Asia and Africa, frequent conflicts and limited resources can put the success of this initiative at risk.[4]



The growth of international travelling may be associated with the importation of poliovirus into countries that had been free from poliomyelitis for extensive periods of time.[5,6] In addition, paralytic polio may be caused by Sabin strains (vaccine associated polio paralysis - VAPP) or vaccine-derived polioviruses (VDPV), including circulating VDPV (cVDPV), immunodeficiency-associated VDPV (iVDPV) and ambiguous VDPV (aVDPV). The true polio eradication demands zero incidence of poliovirus infection, and not only the eradication circulation of wild type poliovirus.[1] The great majority of individuals infected by wild type polioviruses or VDPV do not experience any symptom, and when one case of paralytic polio is identified, thousands of people have already been infected.[7]

National immunisation campaigns with OPV have been crucial for the reduction of polio AFP cases, but the effectiveness of OPV is variable, and children immunised with OPV can shred Sabin virus during months, even after prior vaccination.[8] Sabin virus can revert to neurovirulence, thus causing polio in immunised individuals and their contacts.[9]

Both wild type and VDPV viruses can cause paralysis in non-immune individuals of all age groups.[3] Few studies have evaluated the persistence of poliovirus-neutralising antibodies beyond childhood following primary immunisation. Polio vaccine recommendations are variable in different countries, considering the vaccine and boosters recommendations.[10]

In the absence of a natural booster, a reduction of neutralising antibodies occurs during the years after vaccination or natural infection.

We have reviewed the most recent publications that address polio risks in adolescents and adults, and national vaccination policies. Articles were retrieved from PUBMED and SCIELO databases from January 2000 to June 2013, and from the WHO, CDC, ECDC websites. PAHO countries were investigated for polio epidemiologic information and recommended vaccination

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schedules. The results of our survey have shown that poliomyelitis sequels and case fatality rates are higher in non-immune adolescents and adults as compared to children.[3, 11-14] Recent outbreaks of poliomyelitis due to wild type poliovirus and VDPV have confirmed such results in European countries,[11] in Africa[12,13] and China.[14] Sporadic cases of paralysis in adolescents and adults who traveled to endemic countries or had contact with children recently immunised with OPV or with immunodeficient individuals also demonstrated that the polio risk for adolescents and adults is low, but real.[6, 15-17]

Several studies were conducted in different countries, and showed that the proportion of individuals with potential poliomyelitis susceptibility increases with age, and in many countries, more than 20% of subjects > 15 years of age do not carry neutralising antibodies against one or more PV (Figure 1).[18-30]

Importations of wild type virus and exposure to VDPV can be a risk for non-immune individuals even in countries that have adopted the IPV full schedule.[16, 18] The risks are greater in people who travel to polio endemic areas, who are in contact with immunocompromised individuals or with children recently immunised with OPV.

Environmental surveillance for poliovirus has been conducted in many countries, and in 2013,[1] wild poliovirus[1] was identified in Egypt, where no wild polio case had been confirmed since 2004.[31] The genetic analysis demonstrated that these viruses were imported from Pakistan.[32]

This recent information should warn health authorities and open a discussion about the best strategies for polio prevention, not only for children but also for adolescents and adults in non-endemic countries, as recommended in some European countries.[10, 33, 34]

Considering that poliovirus can recombine with other enteroviruses, we believe that serosurveys to evaluate polio immunity status and environmental surveillance should be introduced in countries where polio is not endemic to help public decision-makers to establish the best vaccination strategies.

A few studies have demonstrated that a high proportion of OPV-primed subjects without antibodies against polio do develop booster response after challenge with OPV.[35] It is possible that previous vaccination and herd immunity can be insufficient to avoid poliomyelitis in non-immune people.

The complete version of this review will be published in Revista Pan Amazonica de Saúde in Portugues: http://revista.iec.pa.gov.br/

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Poster Synopsis

Cat-scratch Disease with Bone Involvement in Paediatric Cases

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Background

Bartonella henselae is a pleomorphic, aerobic, Gram-negative bacterium that causes cat-scratch disease (CSD).[1] Typical manifestations include regional lymphadenopathy localised to the draining site of a cat scratch or bite. Systemic manifestations have been described, including osteomyelitis.[1, 2]

Methods

During 2010 to 2012 four children were diagnosed with atypical CSD. Epidemiological, clinical and laboratory data are described.

Results

Four children between 2 – 15 years old were reported. Three of these children had contact with cats and one with dogs. All of them had an indolent (>2 weeks) semiology of local pain, three had fever and three had multiple adenopathies (cervical or axillary). One had splenomegaly, with hypoechogenic nodules on ultrasonography. No skin lesions were identified. MRI revealed osteomyelitis of the spinal column in two children, of the clavicle in one and of bilateral iliac and right sacroiliac arthritis in other. Clinical diagnosis was confirmed in all patients by seroconversion (four-fold increase), demonstrated by the appearance or increasing levels of IgM and IgG antibodies against B. henselae. In one patient, diagnosis was also confirmed by molecular detection of B. henselae in a bone biopsy with necrotising granulomas. They all received different antibiotic schemes: co-trimoxazole and gentamicin in one case; and rifampicin combined to ciprofloxacin or azitromycin or doxycicline in the other cases. Duration of treatment varied between 4 and 8 weeks. At follow-up, clinical remission was observed in all patients and radiologic improvement in three.

Discussion

B. henselae bone infection is rare but should be considered when bone pain and fever are present in patients with epidemiological context or nodal CSD. Lytic lesions are usually unifocal and have been observed in different sites, including vertebrae and clavicle.[3] MRI is suggestive of osteomyelitis showing increased T2-signal intensity.[3] Differential diagnosis should include malignancy, histiocytosis, tuberculosis and other bacterial osteomyelitis. In the presented cases diagnosis was suggested by the presence of prolonged fever, lymphadenopathy, splenic micro-abscesses in one case and contact with cats in three cases.

Serological or molecular methods were essential to confirm diagnosis.[1] The indirect fluorescent antibody assay is the most widely used, showing a variable sensibility (30 to 100%) and specificity (97%).[1, 2] In the first 10 days after disease onset serology may be negative, thus requiring a second serum sample after 2-3 weeks to confirm seroconversion. Also, IgG antibodies may persist for up to a year, being difficult to distinguish active from previous infection.[2] Assuming these facts, some authors advocate biopsy to rule out other pathogens or malignancy.[4] However, only one of our cases was submitted to biopsy. Indeed, in the presence of a typical initial presentation, positive serology and a favourable evolution, biopsy can probably be deferred.[5] When a biopsy is available, it is possible to use immunohistochemistry to detect the bacilli by Warthin-Starry stain reaction, however, molecular detection by PCR and sequencing are the only method besides culture that can confirm Bartonella species,[5] as shown in one case.

The indications for the type and duration of antibiotic treatment are controversial.[6] In typical CSD spontaneous evolution to cure is the rule, in a few weeks or months without specific treatment.[1] For B. henselae osteomyelitis, various antibiotic regimens have been used with high cure rates.[1, 7] Margileth *et al*. showed that rifampicin, ciprofloxacin, gentamicin and co-trimoxazole were effective for typical presentations.[8] Azithromycin and clarithromycin can also be recommended.[9] Doxycycline plus rifampicin have been used with success in retinitis and encephalitis and could be an alternative in patients with other systemic disease.[7] For children below 8 years of age in whom tooth discolouration is a concern, azithromycin or ciprofloxacin may substitute doxycycline. In our cases we decided to combine two of these antibiotics, favouring the association with rifampicin,[7] with good results.

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Reference Values for Interleukin-6 and Interleukin-8 in Cord Blood of Healthy-term Neonates

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Introduction

Clinical signs of early-onset neonatal sepsis (EONS) are non-specific. Measuring the concentration of C-reactive protein in neonatal blood and blood cultures, which is the diagnostic procedure for the detection of EONS, has severe restrictions. Therefore, there is a need for new markers that have a more optimal diagnostic profile and are able to rapidly detect EONS. Such markers can be helpful in reducing the use of antibiotics and avoiding hospital admissions. Interleukin-6 (IL-6) and -8 (IL-8) have been proposed as promising candidates. However, reference values for these interleukins are incompletely known. The aim of the present study was to determine IL-6 and IL-8 values in cord blood of healthy-term neonates that apply to both vaginal delivery and elective caesarean section (ECS). Moreover, interleukin levels in a subgroup of newborns born via vaginal delivery combined with epidural analgesia or vacuum extraction were measured to study potential influences of these perinatal stress factors on IL-6 and IL-8 levels. Cord blood was chosen, as it is the earliest haematologic sample taken from the neonate and, therefore, can guide the clinicians to carry out effective therapeutic strategies at a very early stage. IL-6 and IL-8 values were determined using an automated assay well-suited for clinical applications.

Subjects and Methods

From April 2012 to August 2012, healthy-term neonates born via vaginal delivery or by elective caesarean section at the Spaarne Hospital, Hoofddorp, The Netherlands, were enrolled into Project NESCIO, a study of reference values for neonatal interleukins. Exclusion criteria were gestational age <37 weeks, clinical signs of infection within 72 hours after birth, syndromal abnormalities, foetal tachycardia, suspicion of ABO haemolytic disease of the newborn or rhesus isoimmunisation, prolonged rupture of membranes, maternal fever or maternal tachycardia during labour, meconium in the amniotic fluid, maternal leukocytosis, cervical cerclage or conization with rupture of membranes, and perinatal and maternal infections. Immediately after birth, cord blood (with a maximum of 7 mL) was collected in regular serum tubes. IL-6 and IL-8 were measured by an automated solid-phase chemiluminescent immunometric assay (Immulite® 1000; Siemens, Munich, Germany).

Results

139 cord blood samples were collected, of which 25 were excluded because they met any of the predefined exclusion criteria. Characteristics of all mother-child pairs were comparable, except for a shorter gestational age for infants delivered by ECS. For both IL-6 and IL-8, the limit of detection for the automated assay used was 2 pg/mL; values below the limit of detection are noted as <2 pg/mL. For vaginal delivery, the median concentration of IL-6 was 3.3 pg/mL with a range of <2 to 9.5 pg/mL; the mean value for IL-8 was 8.4 pg/mL with a range of 2.8 to 17.0 pg/mL. For ECS, the median concentration of IL-6 was <2 pg/mL with a range of <2 to 12.8 pg/mL, which appeared to differ significantly from the vaginal delivery group (p=0.001). The mean value for IL-8 was 7.4 pg/mL with a range of 3.0 to 16.9 pg/mL, and showed no significant difference with the vaginal delivery group. For subgroup analysis, neonates delivered vaginally combined with epidural analgesia or vacuum extraction were included. Although these groups were small, a preliminary attempt was made to analyse the interleukin levels of these groups. Except for the median concentration for IL-6 in neonates delivered vaginally combined with vacuum extraction (5.3 pg/mL), no significant differences between these sub-groups and vaginal delivery were found.

Conclusions

Based on these results, the following reference values are proposed in cord blood of healthy term neonates: <10.2 pg/mL (97.5th percentile total group) for IL-6.and <14.1 pg/mL (mean+2SD) for IL-8. Epidural analgesia *per se* did not appear to significantly influence IL-6 and IL-8 levels, whereas vacuum extraction was associated with a small increase in IL-6 level.

Daan Barug graduated from VUmc School of Medical Sciences, Amsterdam, in 2013. A clinical study on interleukin values in cord blood at the Spaarne Hospital, Hoofddorp, formed part of her Master's programme. After graduation, she participated in a study on long-term effects of biologicals in juvenile arthritis at the Wilhelmina Children's Hospital, Utrecht. Recently, she has joined the Internal Medicine Department at the Tergooi Hospital, Hilversum, as a Practising Physician.

Poster Synopsis

Relationship Between the Polymorphism of IL28B and RVR in HCV Infected Children Treated with Pegylated Interferon and Ribavirin

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Hepatitis C infection (HCV) in children is mostly mild or asymptomatic, but with time it can lead to liver cirrhosis and hepatocellular carcinoma. Mother-to-child transmission has become the main route of transmission in the paediatric population.[1,2] Standard therapy for chronically infected patients consists of pegylated interferon plus ribavirin (PEG-INF+RIBA). The efficacy of this treatment depends upon viral and host factors and varies from 40-60% in so called "difficult-to-treat" genotypes 1 and 4 and up to 80-90% in genotypes 2 and 3.[3] Standard treatment has many side-effects such as anaemia, neutropenia, leucopenia or weight loss which may bring about a modification or discontinuation of the therapy. Identification of the determinants of response to therapy is a high priority. Rapid virologic response (RVR) is defined as an undetectable serum HCV RNA level at week 4 of treatment. RVR is used to predict 24-48 weeks therapy effectiveness. It has a positive predictive value for sustained viral response (SVR) of up to 90% in patients with genotype 1 HCV infection.[4] Polymorphism of IL28B (rs12979860) is thought to be a pre-treatment predictor of virologic response, particularly in adults infected with genotype 1 HCV.[5,6] Favourable CC genotype was found to be the strongest predictor of SVR, independent of serum HCV RNA, fibrosis stage or ethnicity.[5,6] Patients with poor-response IL28B alleles: TT are considered as difficult to cure patients.[7] The importance of that genetic factor in children remains unknown.

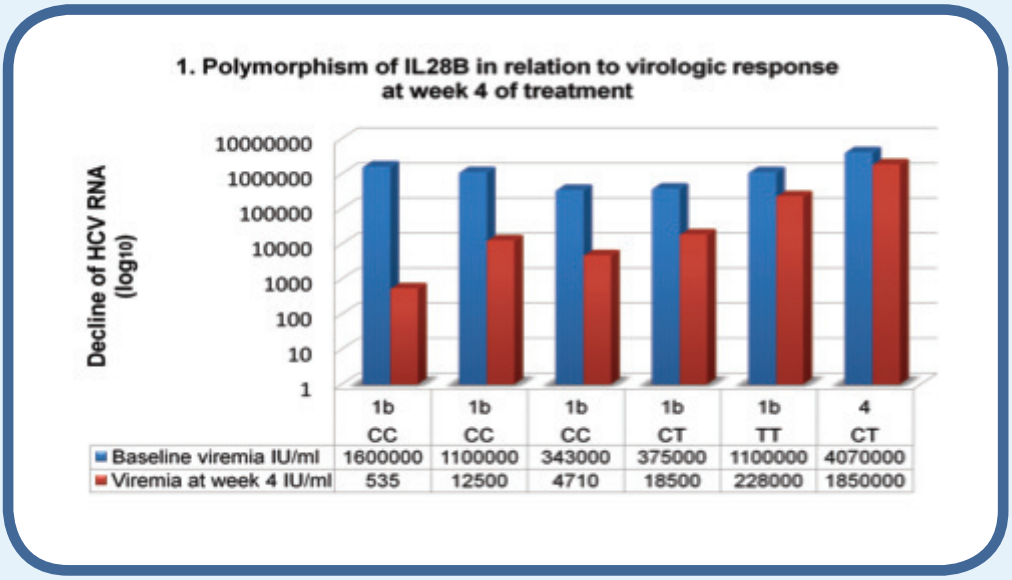

Figure 1. Polymorphism of IL28B in relatio to virologic response at week 4 of treatment.

The aim of the study was to prospectively evaluate the relationship between single nucleotide polymorphism (SNP) of the IL28B (rs12979860) and RVR in HCV infected children treated with pegylated interferon and ribavirin.

Patients and Methods

The study included 6 children (6,1-9.5 years): 4 girls, 2 boys, vertically infected with HCV. All of them acquired difficult-to-treat genotypes of HCV. 5 patients were infected with 1b HCV (among them following SNPs of IL28B were observed: 3- CC, 1- CT, 1- TT) and 1 with 4 HCV (IL28B: CT).

All children underwent liver biopsy (LB), in 4 non-invasive FibroTest (FT) was performed. The baseline viral load (VL) and ALT activity was evaluated after 4 weeks of treatment. Therapy is being continued in all children.

Results

High baseline VL (>600000IU/ml) was present in 4/6 children, among them IL28B was as follows: CC-2, CT-1, TT-1. Low baseline VL (<600000IU/ml) was observed in 2/6 children, among them SNPs of IL28B: CC-1, CT-1. RVR was not attained in any case. Decline of VL at 4 weeks was in all patients: <2log10 in 5 cases (IL28B: CC-2, CT-2, TT-1), >2log10 in one

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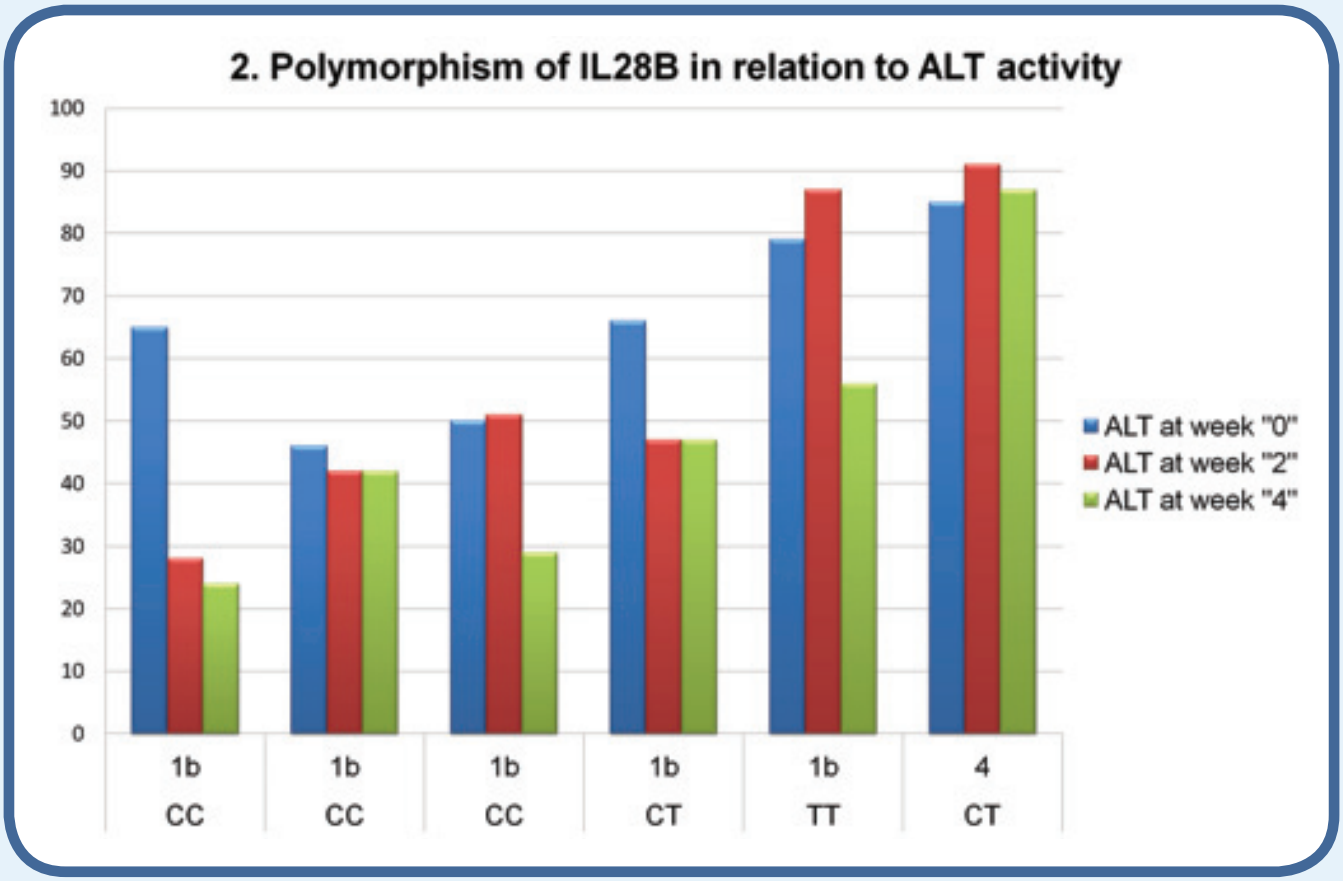

Figure 2. Polymorphism of IL28B in relation to ALT activity.

child (IL28B-CC) (Figure 1). Baseline ALT was elevated in all, ranging from 46-85 UI/l (mean: 65). At week 4 reduction of ALT was observed in 5/6 patients, among them normalisation of ALT was present in 2 (IL28B-CC) (Figure 2).

Girl with IL28B:TT, infected with HCV1b, had highest fibrosis score: LB(F2), FT(F1-F2), high baseline VL, at week 4 she declined VL<1log10 and did not normalised ALT.

Conclusion

RVR was not attained in any children, although 50% of the patients have favourable CC genotype. Faster decline of HCV RNA was observed in carriers of CC variants. The course of infection and response to therapy at week 4 were worse in girl with IL28B:TT, which corresponds with the data from publications. Further studies are necessary to explain the clinical significance of the association of host characteristics with viral kinetics.

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Decreasing the Burden of Recurrent Respiratory Tract Infections in Children

Introduction

Respiratory tract infections (RTIs) involve both the upper and the lower respiratory tracts and occur often in children. Their recurrence constitutes a demanding challenge, particularly in the case of paediatric RTIs. They are one of the most common reasons for physician visits, antibiotic prescriptions and hospitalisation, and are associated with significant morbidity and mortality. The immaturity and inexperience of the immune system in children, along with exposure to social and environmental risk factors such as day care attendance, family size, air pollution and parental smoking contribute to the increased prevalence of recurrent RTIs in children.

Burden of Recurrent Respiratory Tract Infections in Children

Stefan Zielen,

(Johann Wolfgang Goethe University, Germany)

Childhood infectious diseases represent a substantial healthcare cost in terms of expenditure and hospital time. Hospitalisation is most likely in the first year of life, and peaks during the winter months. Childhood RTIs contribute to more than one half of these hospitalisations and thus represent an important financial burden to society[1] (Figure 1).

The risk factors that contribute to increased frequency of RTIs in children include: the immaturity and inexperience of the developing infant immune system and lack of breastfeeding which would normally provide immune protection, an increased exposure to pathogens in the early years of life, especially if the child is at day care attendance, school or in a large family, and finally, exposure to environmental factors such as parental smoking or air pollution (Table 1).

RTIs are major contributors to healthcare costs because each episode of RTI makes another episode more likely, and each recurrent RTI in children leads to a greater risk of complications and development of chronic symptoms. Indirectly, the costs incurred by the complications arising from the morbidities of recurrent RTIs include: missed day care or school, parental absenteeism from work, costs for medical care and a contribution to increased antibiotic resistance.

Respiratory viral infections also contribute to the inception of asthma, which is a major public health problem with a huge social and economic burden. Indeed, airway inflammation from recurrent RTIs in early life may lead to complications including otitis media, mastoiditis, sinusitis, pneumonia and sepsis, each with deleterious long-term effects on respiratory function, and the potential for the induction of persistent asthma.[2]

The link between incidence of viral infections and development of asthma has long been recognised. It was observed as far back as 1929, when a report in the *Lancet* noted that 80% of asthma patients had suffered from respiratory infection just before asthma started.[3] More recently, Johnson *et al*. showed that viruses are associated with 80-85% of asthma exacerbations in school age children in the community.[4]

A history of wheeze associated with respiratory viral infections early in life is one of the major risk factors for the later development of asthma. The currently accepted therapies for the treatment of wheezing associated with recurrent RTIs in children include beta agonists as relief for acute episodes and montelukast/corticosteroids in the longer term to reduce the

Decreasing the Burden of Recurrent Respiratory Tract Infections in Children
Innovation Update Session at the 31st Annual Meeting of the European Society of Paediatric Infectious Diseases (ESPID), Milan, Italy, 29th May 2013

Burden of Recurrent Respiratory Tract Infections in Children
Professor Stefan Zielen, Professor of Paediatrics, Chair of Paediatric Allergy, Pneumology and Cystic Fibrosis at the Johann Wolfgang Goethe University, Frankfurt, Germany

OM-85 and Recurrent RTIs in Children
Professor Vytautas Usonis, Head of Vilnius University Clinic of Paediatrics and Deputy Director of Vilnius University Children's Hospital, Lithuania

• **Increased exposure to respiratory pathogens** (family, day-care ...)
• **Immaturity of immune defence** (including lack of breast-feeding)
• **No immunological memory yet**
• **Environmental factors** (smoking, pollution)

Table 1. Risk factors of respiratory tract infections in children.

frequency and/or severity of episodes. However, these therapies are not equally effective in all children.

Preventative strategies are urgently needed in children with RTI-induced wheezing attacks. One strategy is to interrupt or reduce the spread of respiratory viruses. Meticulous hand hygiene, with frequent hand washing and avoiding touching one's nose and eyes, is an effective measure to reduce the risk of viral respiratory infections. Another approach is to boost the immune function of susceptible children. This requires the education of parents to follow simple advice including a healthy lifestyle with regular exercise, a balanced diet, vitamin supplementation, adequate sleep, routine vaccination (influenza) and avoiding environmental tobacco smoke, stress and unnecessary antibiotics. The use of probiotics may also confer some preventative effect, although further confirmation is needed as the results are inconsistent[5] (Figure 2).

There is evidence that some monoclonal antibodies can help to prevent viral infection by stimulating the immune system. For example, palivizumab, a humanised monoclonal antibody, is effective against the respiratory syncytial virus and may reduce recurrent wheezing episodes in children.

OM-85 is an oral immunoenhancer derived from common bacterial pathogens of the respiratory tract. Results from clinical studies on the use of OM-85 to prevent RTIs in children are encouraging. OM-85 works by enhancing the infant's immature immune system.

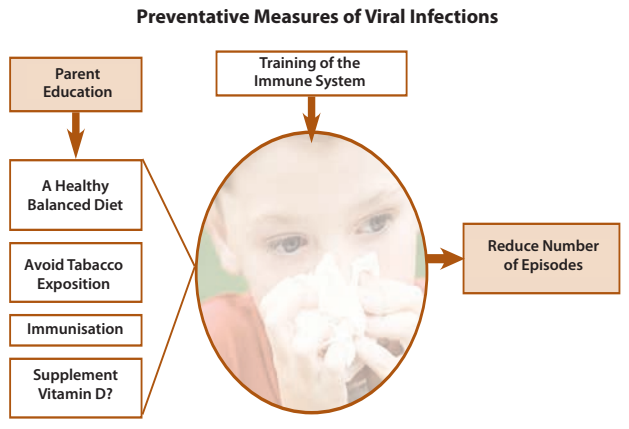

Figure 2. Preventive measures of viral infections.

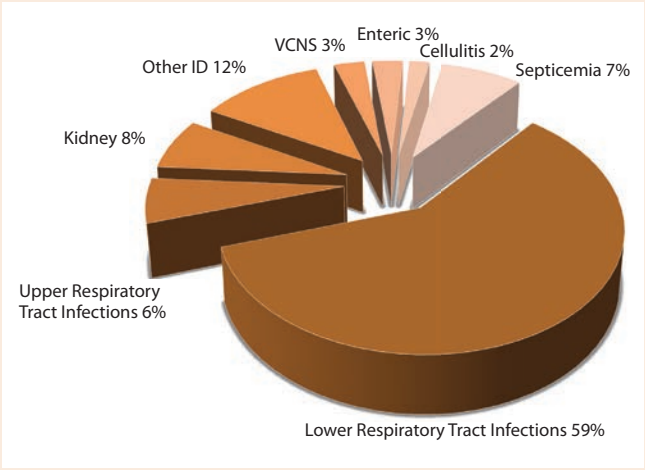

Figure 1. Hospitalisations according to diagnostic group. Adapted from Yorita *et al. Pediatrics* (2008) 121: 244-252.

Infants start life with an essentially anti-inflammatory Th2 profile that slowly reverts to a Th1 pattern. Research suggests that one of the immunoprotective effects of OM-85 are mediated by stimulation of the Th1 cellular response.[6] Although direct evidence of the mechanisms involved are lacking in human studies, recent data from rodents shows that baseline regulatory T lymphocyte activity in the airways can be boosted by microbe-derived stimulation of the gut[7] (Figure 3).

More recently Razi *et al*. have shown that OM-85 used in high risk children with virus induced wheezing can prevent wheezing episodes significantly.[8]

The simple strategy of good hand hygiene is the best measure for the prevention of a primary viral infection, supported by other preventative strategies including influenza vaccinations, a healthy diet and possibly vitamin D supplementation. In addition to these measures, there is evidence that OM-85 is a useful therapy to reduce recurrent infections and viral-induced wheeze in children.

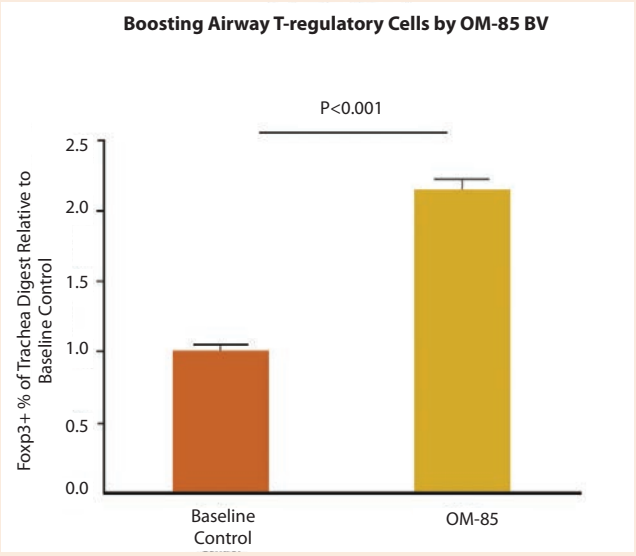

Figure 3. Boosting airway T-regulatory cells by OM-85 BV. Adapted from D H Strickland *et al. Mucosal Immunology* 2011.

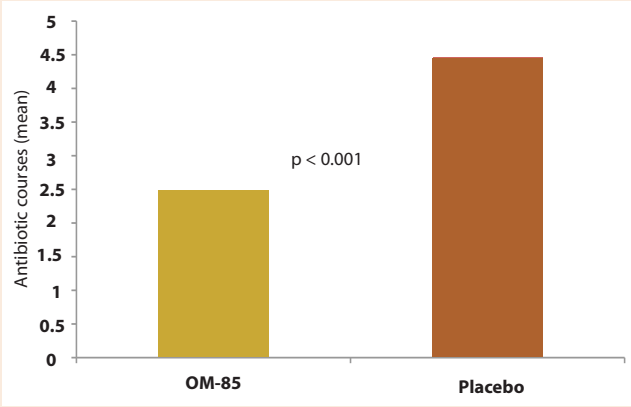

Figure 4. Number of antibiotic courses required during the study in both groups. From Gutiérrez-Tarango *et al*. *Chest* 2011;119:1742-1748.

OM-85 and Recurrent RTIs in Children

Vytautas Usonis,

(Vilnius University Clinic of Paediatrics and Vilnius University Children's Hospital, Lithuania)

OM-85 is a standardised immunoenhancer extracted from 21 bacterial strains common pathogens of the respiratory tract: *Haemophilus influenzae*, *Diplococcus pneumoniae*, *Klebsiella pneumoniae and ozaenae*, *Staphylococcus aureus*, *Streptococcus pyogenes and viridans*, and *Neisseria catarrhalis*.[9]

The registered indication of OM-85 is the prevention of recurrent infections of the airways in adults and children aged 6 or 12 months of age and older. It is available for children as a 3.5 mg dose in capsules or sachets, or as 11 mg/ml drops. The dosage is one capsule or sachet or 10 drops per day for 10 consecutive days per month for 3 consecutive months.

An overview of the positive clinical evidence supporting the efficacy of OM-85 in children has been provided by many double-blind, placebo controlled clinical studies.

In an early study, Schaad *et al*. carried out a randomised double-blind, placebo-controlled, multicentre trial with OM-85 in infection prone children aged 36 to 96 months.[10] They found that OM-85 treatment significantly reduced the rate of upper RTIs; 16% reduction in the active treatment group versus placebo. Furthermore, safety and tolerance of OM-85 were reported as good and comparable to placebo.

A study by Gutiérrez-Tarango *et al*. in 2001 showed that OM-85 reduced the burden of acute RTIs in children.[11] In this study, OM-85 demonstrated a preventative effect on acute RTIs in susceptible children for 12 months and also reduced antibiotic requirements and the number of days of suffering acute RTIs (Figure 4).

These findings were confirmed by a meta-analysis by Schaad in 2010, in which 8 randomised double-blind, placebo controlled

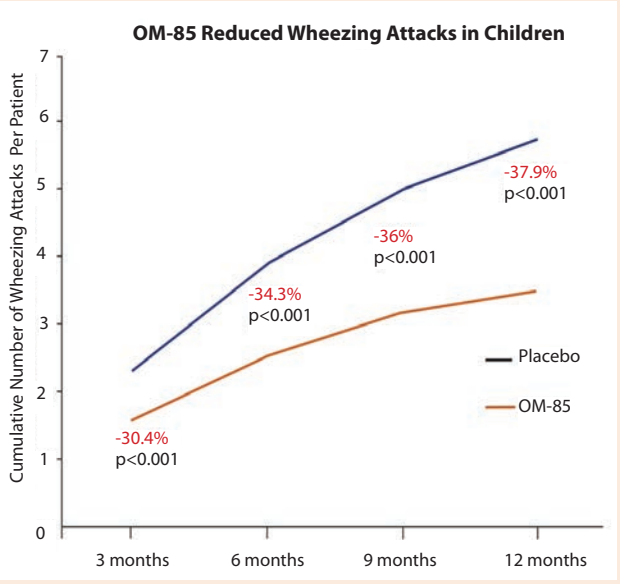

Figure 5. Reduced wheezing attacks in children after OM-85. The cumulative difference in wheezing attacks between the 2 groups was 2.18 wheezing attacks per patient in 12 months; there was a 37.9% reduction in the group given OM-85 compared with the group given placebo (P < 0.001). Adapted from Razi *et al. J Allergy Clin Immunol* 2010;126:763-9.

clinical trials were analysed.[12] Patients treated with OM-85 had significantly and consistently fewer cases of recurrent RTIs. The data also suggested a greater effect in patients at increased risk of recurrent RTIs.

Of particular interest, a randomised, double-blind, placebo-controlled, parallel-group study by Razi *et al*. showed that when OM-85 was given to children aged between 1 and 6 years with recurrent wheezing, there was a 40% reduction in the rate of wheezing over the subsequent 12 months compared to placebo (p<0.001)[7] (Figure 5).

In addition, the duration of each wheezing attack was 2 days shorter in the OM-85 group versus placebo (p=0.001). OM-85 also reduced the total number of RTIs in these wheezing children at 12 months by 2.5 episodes.

OM-85 may prevent recurrent acute tonsillitis in children. A 2013 study by Bitar *et al*. found that a considerable proportion of children (75.6%) receiving OM-85 for recurrent acute tonsillitis had a decrease in the frequency of episodes in the short term.[13] Among these responders, 51.2% of the children showed a total response and 24.4% had a partial response. In this study, total and partial responses were defined as >50% and ≤50% decreases in the frequency of acute tonsillitis episodes after 3 months of therapy respectively. Importantly, none of the patients showing total response required tonsillectomy on long-term follow up. (Figure 6).

With regards to safety, OM-85 has 30-years of post-marketing experience. It has been used in around 60 million patients (adults and children) worldwide, with a very low incidence of adverse event cases

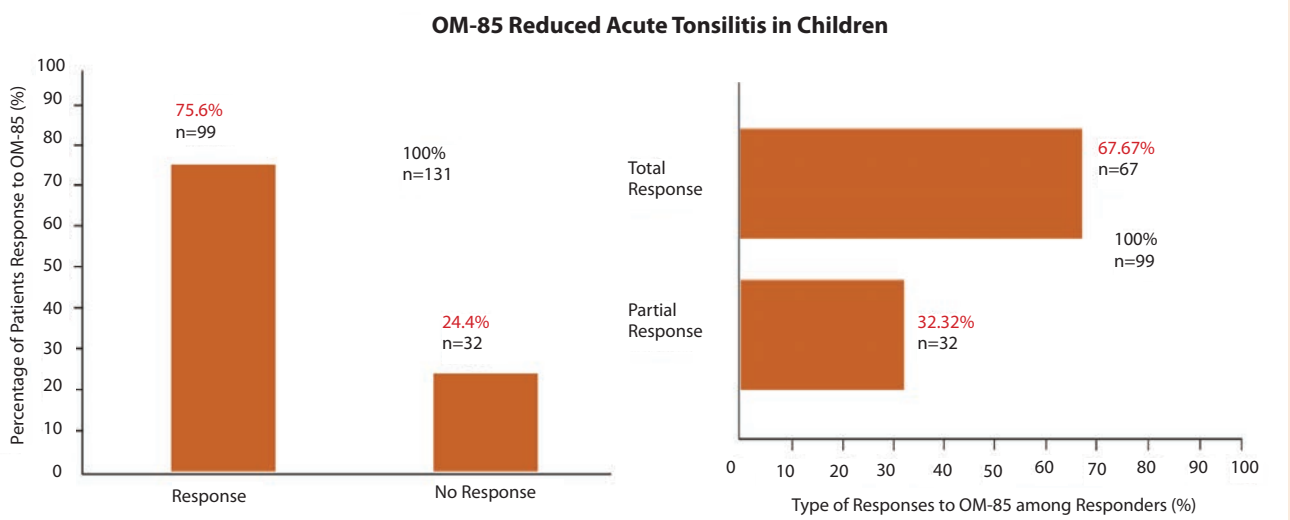

Figure 6. Reduction of acute tonsillitis in children after OM-85 treatment. A considerable proportion of children treated with OM-85 for recurrent acute tonsillitis show a decrease in the frequency of episodes in the short term, and very few patients required tonsillectomy on long-term follow-up. Adapted from Bitar *et al. Int J Pediatr Otorhinolaryngol* 2013;77(5):670-3.

reported (3 cases per 100,000 patients treated). OM-85 is considered a well-tolerated drug with identified adverse events, which are mainly non-serious and transitory.[8] Finally, there is no known risk of autoimmunity when using OM-85. The possible role of OM-85 in triggering autoimmunity in children with IgA deficiency (IgAD) was studied by Karaca *et al.* in 2011.[14] In this study, 63 children with sporadic IgAD and recurrent febrile infections were given prophylactic treatment with OM-85 or placebo and the development of clinical autoimmunity or autoantibodies was evaluated. The study revealed no significant difference between the two study groups.

Zaniolo *et al.*[15] demonstrated the potential economic benefits of a prophylactic strategy using OM-85 for the prevention of upper RTI recurrences in children. Their analysis, which included drug efficacy data from controlled, randomised trials and Italian economic data, calculated a saving of €107.42 per patient, and €231.26 for society, per half year.

Conclusion

RTIs in children may be triggered by a range of microorganisms and represent a major healthcare problem with substantial healthcare costs. The detrimental effects of recurrent RTIs in early life are linked to the induction of asthma, a chronic lung disease with a global economic burden. Preventative strategies include the use of hygiene measures to reduce the spread of infection, an improvement of immune function, and immunostimulation. OM-85 is a bacterial immunoenhancer that non-specifically increases the immune response and enhances innate defence mechanisms, therefore having a potential effect against bacterial and viral respiratory infections. The efficacy and safety of OM-85 have been demonstrated in several clinical trials with encouraging evidence regarding relief from symptoms, duration of illness, a decrease in antibiotic consumption, and number of infections. The use of OM-85 as a preventative strategy for RTIs in children offers potential economic savings for health services and society.

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ESPR 2013 Annual Meeting

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54th ESPR Annual Meeting - European Society for Paediatric Research

Yunus Bhatti, *Treatment Strategies*, presents an overview of the 54th Annual Meeting of the European Society for Paediatric Research. He looks back over the show, as well as some of the most interesting products that were showcased at the event. These products will have a direct impact upon the field of paediatric research.

This year the 54th Annual Meeting of the European Society for Paediatric Research (ESPR), took place in the historic city of Porto, Portugal between 11-14 October 2013. Previous ESPR meetings have been held in Hamburg (2009) and Newcastle (2011), and the EAPS meetings held in Copenhagen (2010) and Istanbul (2012) were great successes, which 2013's meeting built upon.

The Aims of ESPR 2013

- To advance paediatric research in Europe, help exchange of information, and spread ideas on new developments in paediatric research.
- To serve the European Society of Neonatology members and European neonatology with a focus on training and accreditation.

The programme for ESPR 2013 consisted of a mixture of research interaction, training and continuing professional development. The congress started with pre-congress courses for neonatal trainees and established clinician scientists. The courses for neonatal trainees were on "Nutrition" and "Stabilisation of the pre-term infant in the delivery room". During the congress there was a track for neonatal continuing professional development in partnership with the Union of European Neonatal and Perinatal Societies (UENPS): topics were brain and development, nutrition, epidemiology, and circulation.

The scientific programme contained State of the Art plenary lectures alongside specialty tracks featuring international experts as keynote speakers, combined with free oral presentations. Poster presentations also received special attention. The meeting dedicated ample time for poster discussion sessions, so that all posters that were accepted for presentation could be properly discussed. Young investigator award sessions and post-doc awards, the Bengt Robertson Award for pulmonary research and Robertson Lecture were once again the highlights of the conference.

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

Free papers on basic and clinical research were invited and encouraged on all aspects of paediatric research. Presentation of project work to improve clinical quality and training of neonatologists were also welcomed, with the key criteria for acceptance for presentation being that others can learn from the results.

ESPR 2013 was successful in providing an opportunity for participants to interact and discuss all of the meeting's content in a friendly and enjoyable atmosphere.

This year, Porto played host to ESPR 2013. Porto is especially known for its wonderful Port wine, and is one of the most important cities of

This year's ESPID Meeting was held in Milan, Italy

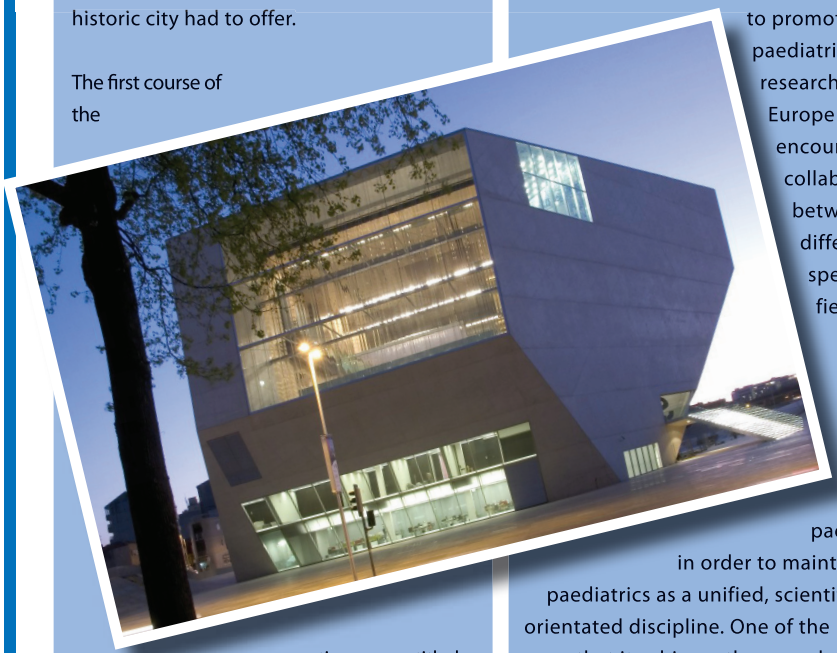
INSIDE...

Europe in the area of modern architecture. The congress site was at the centre of the city by the river the Douro, which offers beautiful views over the river and bridges. The social programme took full advantage


Ursula Felderhoff-Müser

of the fantastic sites and attractions this historic city had to offer.

The first course of the



meeting was entitled 'Stabilisation of the preterm infant after birth', which featured many presentations including 'What do we know about respiratory and circulatory transition after birth?' and 'What do we know about clinical impact of delayed cord clamping?', as well as several workshops. The second course focused upon Nutrition and Gastroenterology, and featured presentations such as 'Early nurtition, growth and later outcome.' The third course focused upon


Heike Rabe

Epidemiology, and looked at issues such as 'Hospital or population based studies: What about selection bias?' amongst many others.

The European Society for Paediatric Research (ESPR) aims to promote paediatric research in Europe and encourage collaborations between different specialised fields of paediatrics in order to maintain paediatrics as a unified, scientifically orientated discipline. One of the ways that it achieves these goals is by organising its annual congress and co-organising other events. These prestigious paediatric meetings attract thousands of experts in all fields of paediatrics, providing them with networking opportunities and exposure to the latest available research, treatments and patient care.

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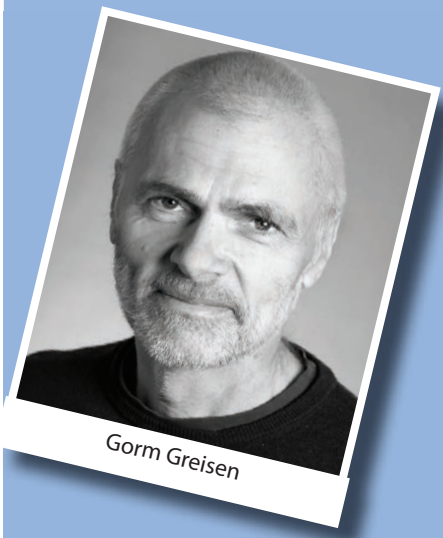
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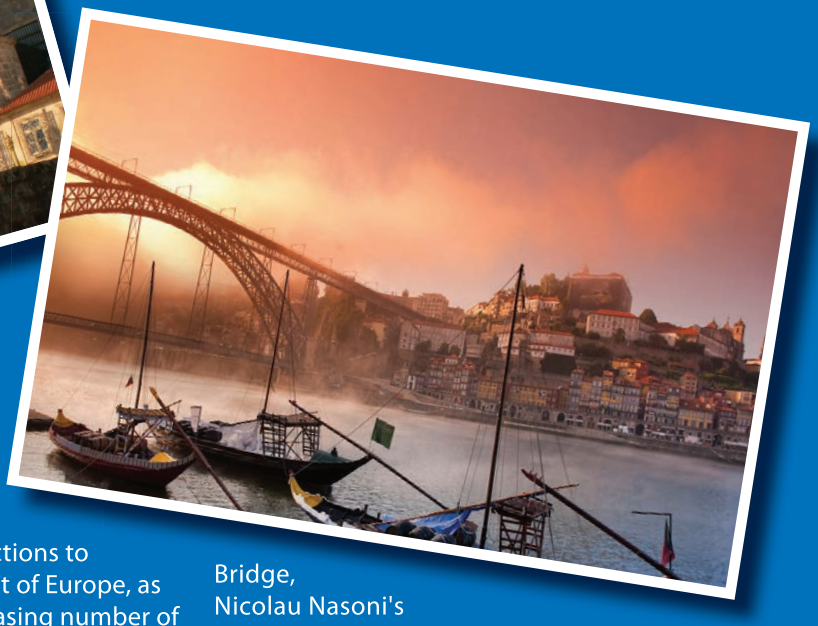
54th ESPR - The Meeting Place - Porto



Monuments by leading world architects from the past and the present, fantastic baroque carvings and world-famous sweet wine mean that Porto is well-known around the world. Porto is Portugal's second largest metropolis, and one of Europe's most charismatic cities.

Porto is also one of the last undiscovered European metropolises, but this looks set to change.

Direct flights from New York and connections to and from the rest of Europe, as well as an increasing number of low-cost airlines show that the city is fast developing.

Porto is an ancient port which is steeped in history and tradition. It is a highly atmospheric place which is known for its monuments by renowned architects (Gustave Eiffel's Dona Maria Bridge, Nicolau Nasoni's Clerigos Tower, Rem Koolhaas' Casa da Musica, or Siza Vieira's Serralves Museum).
This is the city that originated and named Port Wine, and gave birth to one of world history's legendary figures, Prince Henry the Navigator.

The congress gave attendees the chance to not only attend a fantastic show, but also to experience this fantastic city.

SLE Launches New Transport Incubators in the UK

In recent months, SLE has brought a sophisticated range of infant transport systems to UK customers. As a complete solutions provider, SLE offer one-stop-shopping and bespoke design of systems for air transfers, road transfers and internal transfers.

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Each customer has a different list of equipment that they need to take with them during infant transport, and so every system is customised to incorporate all the equipment safely and securely.

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SLE

New Jaundice Meter for the Tiniest of Patients

Dräger, an international leader in the fields of medical and safety technology, was showcasing its products which aim to protect, support and save lives at ESPR 2013. One of the most exciting products was the Dräger Jaundice meter JM-105.

With the Dräger Jaundice meter JM-105, caregivers can non-invasively measure bilirubin levels in newborns as young as 24 weeks gestational age. Screening with the medical device can reduce painful blood draws, which have possible long-term consequences in young patients. JM-105 can store up to 100 measurement results and transmit them via a docking station to the clinic's patient data management system.

Different factors determine whether infants develop jaundice and this is true for both preterm and full term infants. More than half of healthy newborn infants have bilirubin levels that are too high after birth.[1] In order to diagnose jaundice, nurses often draw blood from the heel for total serum bilirubin (TSB) testing. While this is a routine procedure, the blood draws may leave trace effects, particularly in neonates, and the repeated pain experiences in this early stage of development may have a negative impact during childhood.[2] A study of early preemies from the 24th week proves that multiple pain stimuli can affect the maturation of neuronal structures.[3] According to the scientists, this may affect the brain development of babies.[4] With the help of transcutaneous bilirubin screening (TcB), however, jaundice can be determined reliably[5] and painlessly. Studies have shown that non-invasive measurement results correlate with bilirubin levels collected by venipuncture.[6] Study results have also shown that TcB measurements were comparable with TSB values for premature babies from the 24th week gestational age.[7] "Until now, jaundice screening as early as the 24th week gestational age was not yet approved for use in many countries. The JM-105 contributes to reducing painful examinations for these tiny patients, thereby supporting their development," said Inken Schroeter, Product Manager at Dräger.

Simplified Measuring without Consumables

The Jaundice Meter JM-105 allows nurses to non-invasively measure a value that correlates with the total serum bilirubin level. The device configuration setting can be adjusted so it is possible to take a single measurement or up to five measurements for an average value. This means that the meter can identify newborns at an increased risk for hyperbilirubinemia with high accuracy. All device functions can be controlled using a colour touch screen. The measurement is taken by gently pressing the sensor on the baby's forehead or sternum. The sensor is easily cleaned with rubbing alcohol before every screening process. Since the measuring unit is reusable, nurses need no further disposable products, therefore reducing additional costs.

The JM-105 stores up to 100 readings in its patient history. A nurse can identify abnormal values by attaching a flag symbol to a patient's measurement. Thus, the clinical team can later locate the patient more quickly for further assessment.

Managing Without Paper

Entering or transferring measured values by hand is a thing of the past with the JM-105. All readings and data stored in the device can be transferred electronically by placing the device in the docking station and using a USB connection to a laptop or PC to the clinic's PDMS (Patient Data Management System). The JM-105 enables data transfer via the interface standard HL 7 (Health Level 7).

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New Treatment Strategies for Stage 2 Necrotising Enterocolitis: Lactobacillus Paracasei F-19 and Preventive Peritoneal Drainage

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Introduction

After the birth and development of Neonatal Intensive Care, necrotising enterocolitis (NEC) has become the most common perinatal gastrointestinal emergency. The incidence of NEC among patients in Intensive Care Units ranges between 1 and 8%, with a mortality rate between 20 and 40%.[1]

Many factors have been suggested to be predictive of NEC but the pathogenesis is still controversial.[2-4] The most commonly identified histological finding is a coagulative necrosis. This suggests the key role of ischemia in its pathogenesis, with the consequent onset of inflammatory processes and bacteria proliferation.[2]

Clinical diagnosis is based on specific signs (i.e. respiratory distress, instability of body temperature, lethargy and hypoglycaemia etc.) as well as on signs correlated with the gastro-intestinal system, such as abdominal distension, rectal bleeding, gastric stagnation or low food tolerance, oedema and abdominal rash. Instrumental diagnosis is performed with direct abdominal X-rays which may show intestinal distension following ileum palsy, pneumatosis intestinalis or gas in the portal venous system and, finally, pneumoperitoneum as a sign of intestinal perforation.

The preferred treatment remains to be standardised: in the initial stage the treatment is exclusively medical and is based on suspension of nutrition in favour of total parenteral nutrition, with administration of large-spectrum antibiotics. In the following stages, and particularly if there is evidence of intestinal perforation, surgical treatment is advisable.

Although there can be many different investigational approaches to study NEC prevention (use of probiotics, early nutrition vs. late nutrition, etc.), at present there are no investigational guidelines on the role of surgery to prevent the onset of intestinal perforation and the use of probiotics on advanced stage.[3-7]

In the treatment of NEC, Bell's Stage 2 is to be considered the key stage in the necrotic development of this condition. For this reason when NEC reaches this stage, clinicians should use all possible resources to prevent intestinal perforation.

This study is focused on two new treatment options for stage 2 and reports our results on the early placement of an abdominal percutaneous drain in presence of portal vein gas or pneumatosis intestinalis (data not published) and the use of a specific priobiotics (data not yet published). These approaches may prove useful in preventing intestinal perforation, since they reduce the abdominal pressure in infants (peritoneal drain) and reduce bacterial translocation (probiotics).

Scientific Rationale

Abdominal distension and bowel dilatation is a common finding in patients with NEC. The diameter of the bowel of babies is relatively small and according to Poiseuille's equation, the pressure in a tube is inversely proportional to its radius to the power of four. Therefore, the pressure required to dilate the bowel of premature babies must be very high. Since E. coli translocation is commonly found in patients with distal intestinal obstruction and the most common sites for NEC

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are the distal ileum and colon which are densely populated by bacteria, it is possible that NEC results from bacterial infection in bowels under high pressure. Abdominal pressure increases with bowel dilatation; the abdomen is a close space, and for this reason the enlarged bowel is compressed to the abdominal wall, with subsequent ischemia with perforation.[8]

NEC is characterised by the lack of intestinal mucosal integrity leading to acute clinical evidence of feeding intolerance, blood in the stools, and *pneumatosis intestinalis*.[9]

For all of these reasons, these two treatment options are useful for: the insertion of peritoneal drains could avoid bowel ischemia offering more compliance of the abdominal wall and probiotics, maintaining mucosal barrier integrity, triggering general intestinal immune defenses, regulating appropriate bacterial colonisation, modulating intestinal inflammation, and may be the first step to prevent the pathogenesis of NEC and bacterial traslocation.

Lactobacillus paracasei subsp. paracasei F19 - Why?

It has been demonstrated that *Lactobacillus paracasei subsp. paracasei F19* plays an important role in many diseases such as irritable bowel syndrome (IBS)[10] and others,[11-14] as it has genetic stability and it is able to suppress human t cell proliferation.[15] Human feeding trials demonstrated that LF19 was well-tolerated by young children, adults and the elderly with no side-effects being observed. Furthermore, results of the trials demonstrated that LF19 (or very closely related strains) is part of the indigenous microbiota in some subjects in the Nordic countries.[16, 17]

Materials and Methods

Starting from September 2007 we performed two clinical studies, one between September 2007 and September 2011 (prospective study for preventive peritoneal drainage) and one (prospective randomised trial approved by the Ethics Committee of the University of Verona using lactobacillus paracasei F-19) between December 2008 and December 2011.

Informed consent was obtained by parents before treatment. Each study design was divided into two phases:

Phase 1: Comparability of samples (enclosures: Bell's classification and modified classification); surgeons and neonatologists enrolled patients only following Bell's classification. It was therefore necessary to spend some time in which to familiarise with the classification.

Phase 2: Treatment with abdominal percutaneous drainage and a second group with probiotics.

For stage 2 patients the preferred treatment was the placement of abdominal drains (classifications enclosed: Bell's Stage 2a-b) (Table 1).

Selection of Patients

Inclusion criteria were created: Patients in Bell's Stage 2, Weight at birth < 1,500 g, gestational age <32 weeks; radiological evidence of Stage 2 NEC.

Exclusion criteria were the following: grade III and IV intraventricular haemorrhage (to avoid any correlations with compromised intestinal blood flow), Stage I NEC (not considered real NEC), babies with other malformations, multiple episodes of NEC; treatment in Neonatal Intensive Care Units with no involvement of paediatric surgeons.

Efficacy of early treatment (absence of subsequent intestinal perforation) was the primary endpoint in both studies. Secondary endpoints of the trial were: clinical data; duration of hospitalisation (hospital stay); mortality and morbidity (short-term); duration of parenteral nutrition (days); time to full enteral feeding (days); long-term intestinal complications.

Clinical Monitoring of Patients

Clinical Charts were used to monitor the clinical status of patients upon enrolment in the study, and then at days 1, 2, 7 and 21. Neutrophils, coagulation indices and C-reactive protein were also measured. Blood culture was performed once every week and when clinically indicated.

Procedure

Peritoneal Drain

All procedures were performed in the right iliac fossa under local anesthesia; type of fluid in the tube drain were recorded;

Probiotics

The product was administered by the nurses in the Departments taking part in the trial after standard preparation, via either nasogastric tube (with syringe) or oral administration (syringe).

Dosage Scheme

6 x 109 CFU/day for 21 days L-F19 (*Lactobacillus paracasei subsp. paracasei F19*); each bottle contained: 10 ml, 6 mld LACTOBACILLUS PARACASEI SUBSP. PARACASEI F19 + 600 mg GLUCOLIGOSACCHARIDES. Final dosage: ½ Bottle (5 ml) with Lactobacillus – with a 5 ml syringe. The product was administered orally in 5 hours, 1 ml/ hour; if a nasogastric tube was used, the nurse was advised to put first 2 ml into the tube and then 1 ml.

Data Analysis

Data were processed using the S.P.S.S. statistical programme. Chi-square test, Fisher test and T-student test for coupled data;.A p value < 0.05 was considered as statistically significant.

Results

During the study period, 245 infants with Stage II NEC were observed

Modified Bell Staging	Classification	Systemic Signs	Abdominal Signs	Radiological Signs
I A	Suspected NEC	• Temperature instability • Apnoea • Bradycardia • Lethargy	• Aspirates • Mild abdominal distension • Positive faecal occult blood	• Normal • Mild intestinal dilatation • Mild ileus
I B	Suspected NEC	As above	• Fresh blood PR	As above
II A	Proven NEC - mildly ill	As above	As above, plus • Absent bowel sounds • +/- abdominal tenderness	• Intestinal dilatation • Ileus • Pneumatosis intestinalis
II B	Proven NEC - moderately ill	As above, plus • mild metabolic acidosis • mild thrombocytopenia	As above, plus • absent bowel sounds • definite tenderness • +/- abdominal cellulitis • RLQ mass	As above, plus • Portal vein gas • +/- ascites
III A	Advanced NEC - severely ill, bowel intact	As above, plus • Hypotension • Bradycardia • Severe apnoea	As above, plus • Signs of generalised peritonitis • Marked tenderness • Marked distension	As above, plus • Definite ascites
III B	Advanced NEC - severely ill, bowel perforated	As above	As above	As above, plus • Pneumoperitoneum

Table 1: Modified Bell's classification.

and admitted to Neonatal Intensive Care Units. At the end of the study the results showed that:

• 24 patients were treated with preventive peritoneal drain; 3 of these patients (12.5%) underwent surgery for advanced NEC (intestinal perforation).
• 32 patients were treated with probiotics: 6 of these patients (18.75%) underwent surgery for advanced NEC (intestinal perforation).

The use of these two treatments was associated with lower progression to Stage 3 in both group respect to controls in each study ($p<0.05$).

Study Population and Data Monitoring

In both studies all advanced NEC patients were delivered before the 30th gestational week; 80% required intubation after birth for respiratory distress respect to the non-advanced NEC ($P<0.05$).

In both studies the type of gastric residuals (blood) was strictly correlated with the development of advanced NEC. It was not possible to establish significant statistical differences between the two groups as for start of feeding, type of feeding and need for nasogastric tube ($p>0.05$).

Patients with suspected or advanced NEC showed longer time of meconium evacuation if compared to the others (mean 5 vs. 2 days, $p<0.05$). We found that both study groups had lower mortality rate and shorter hospital stay compared to controls ($p<0.05$).

In both groups mortality was associated with lower gestational age and lower Apgar score at 1 minute; mean gestational age was 26th ± 4 days and mean Apgar score was 3±1.

No collateral effects were observed during the study period; none of our patients presented sepsis due to *Lactobacillus paracasei subsp. paracasei F19*. No patient required preventive exclusion from the study.

It was interesting that patients with advanced NEC (intestinal perforation) in both groups had perforation at day 7±2 after beginning of treatment respect to controls that showed perforation at 3±2 days after enrolment ($p<0.05$).

Discussion

The incidence of NEC in premature infants with birth weight < 1,500 g has increased in recent years mainly in relationship to an increased survival rate related to better post-natal support treatment and more efficient Neonatal Intensive Care Units (N.I.C.U.).

There is lack of consensus on the management of NEC and the need for ongoing clinical research to identify the most appropriate methods to manage this challenging group of patients. It has been shown that the later patients pass meconium, the higher the risk of developing NEC is, due to an increased intraluminal pressure in the bowel causing both bacterial translocation and ischemia of the bowel walls following excessive dilatation.[18-22]

Following this consideration, it is therefore useful and necessary to stimulate the evacuation of meconium starting from the early hours after birth and to decrease the abdominal pressure.[18]

As reported above, our studies were based on the necessity to decrease abdominal pressure and to improve the bowel compliance.

Portal venous gas is considered an absolute indication for laparotomy by only 8% of surgeons, despite evidence that it is a marker for significant disease (with a mortality of up to 71% in some series). First described by Marshall in 1975, peritoneal drainage has now become a useful tool in the armamentarium of the paediatric surgeon, but surgeons' expectations seem to vary considerably. The survey highlighted that the role of peritoneal drainage in perforated NEC is becoming well-recognised, as 53% of surgeons would consider pneumoperitoneum as an absolute indication for its use.[23, 24]

Subspecies of *Lactobacillus* were the commonly used probiotic organisms in trials reported in the literature. The intestinal microbial flora of pre-term neonates differs from that of normal-term neonates. Neonates with a very low birth weight usually become infected by microbial flora mainly from the N.I.C.U. rather than from their mother.[25, 26]

Even if the preventive role of probiotics in the prevention of NEC is well known, the most important clinical key points to consider are which patients will develop a Stage 3 NEC and what clinicians can do to prevent it.

The preliminary findings of our studies demonstrate the efficacy of both treatment if used in selected patients in Stage 2, reduction in the perforation rate, reduction in the overall mortality rate and hospital stay. Also, early enteral feeding suggests that probiotics have a beneficial role also in these specific groups of patients.

Data collected in our study support the idea that risk factors for advanced NEC are gestational age but without any correlation with birth weight, and low 1-minute Apgar score (but not 5-minute Apgar score). Also, failed evacuation of meconium in the first hours of life is supposedly the main cause of higher bacterial translocation with consequent sepsis and clinical development of NEC.[17-22]

Conclusions

Study results support the use of the probiotic *Lactobacillus paracasei subsp. paracasei F19* and preventive peritoneal drain in the prevention of advanced NEC. The incidence of perforation in the PPD group is very low especially on the mortality and morbidity rates. The low incidence rate of Stage 3, shorter hospital stay, earlier oral feeding and lower morbidity seem to justify the use of these treatment.

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Remote Diagnosis and Management of Paediatric Heart Murmurs at John Radcliffe Hospital, Department of Paediatric Cardiology

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Background

I was encouraged to investigate the possibilities of tele-auscultation because, from a study performed by Mayo clinic and data reported in the *Journal of Telemedicine and Telecare* back in 2004, I knew that telemedicine-directed auscultation of patients is just as successful as an "in-person" assessment for the detection of cardiac arrhythmias.[2]

Though the yield of echocardiograms is virtually zero,[3, 4] and there is little doubt that with a careful clinical examination and good auscultation innocent murmurs can be correctly identified, there are growing requests to perform echocardiograms on patients who present with an innocent murmur.

In 2012, cardiology services at John Radcliffe took referrals for 1020[5] such patients. The patients were examined by the cardiologist, who provided a confirmation of an innocent murmur by means of auscultation. There is an expectation from GP's and patients that a consultation will include an echocardiogram. It is explained to parents that there is a possibity that incidental findings may arise, which will have no bearing on the management of the child but could significantly impact on them later in life, simply due to the knowledge of a pre-existing condition. In spite of this, it is rare for an echocardiogram to be declined.

Proposal

The basic question that I asked is whether we would ultimately be able to reassure referring paediatricians, general practitioners and parents about an innocent murmur and, in doing so, avoid a full consultation and echocardiogram. I also wanted to establish if we could offer a reporting service, similar to that provided for echos, in which our referring sites will send us their auscultatory files for assessment. I wanted to determine whether a diagnosis can be arrived at remotely, and if this information can be conveyed back in a timely manner.

Objectives

The objectives of this investigation were:

- To immediately reassure general practitioners and parents of a non-pathological finding.
- To decrease the anxiety currently experienced by parents and patients.
- To avoid secondary care referral, where there is an average waiting time of 90 days.[5]
- To greatly improve the service provided to the patients who need an intervention from the cardiology services.
- Significantly impact on the cost associated with providing a confirmed diagnosis.

Reasoning

The cost of the current service is met by the referring practitioner, but the additional burden to the secondary care environment has taken on a greater significance with the ever growing local and national drives to deliver patient care in a more appropriate manner. In the UK, QIPP – Quality, Innovation, Productivity and Prevention Challenge[6] – has placed a requirement upon the NHS to improve the quality of care it delivers, whilst at the same time making up to £20billion of efficiency savings by 2014-15. This is to be reinvested in frontline care.

Our proposed service meets these objectives head on, and once our

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Figure 1. 3M™ Littmann® TeleSteth™ Server System.

providers are equipped, several additional opportunities to change care pathways are available:

- Delivering primary care in the community.
- Reducing patient movement in secondary care.
- Delivering cost benefits for primary and secondary care.

In parallel, I believe that auscultation sounds captured from patients presenting with a pathological condition can be assessed for the purposes of triage and monitoring post-intervention.

Most importantly perhaps, we can deliver additional patient and service benefits once the technology is in place, for example in the monitoring of low-grade systolic murmurs discovered in otherwise healthy middle-aged men, and for whom there is an increased risk of AVR but no increase in risk of CVD death.[7]

The Technology

The technology required to provide such a service had been thoroughly assessed throughout 2012 from within the hospital, however this was focused upon real-time sessions connecting two locations. Experience with our tele-echocardiography facilities made it clear to us that a robust service would require the use of a "store and forward" model to be implemented successfully and without insurmountable service requirements from the consultancy standpoint.

The 3M™ Littmann® portfolio was principally able to meet our needs but, due to the ever-shifting regulations surrounding the security and hosting of patient data, the final "server-based" solution for tele-auscultation, TeleSteth™, only finally became available to us in June 2013. The 3200 model comes with Heart and Lung Visualisation Software 3M™ StethAssist™, which allows auscultations to be recorded and played back whilst being displayed as a phonocardiogram, and has the ability to switch between bell, diaphragm and extended range modes, even after the file is saved. Essentially, stethoscopes are connected to a personal computer via a Bluetooth[8, 9] wireless link.

The hosted server solution TeleSteth™ simply provides a secure mechanism for these files to be referred to a consultant with the minimum amount of effort, and then for a return of the files with the added consultancy information and report. Importantly, whilst we wanted to focus on a "store and forward" solution, the ability to perform a real-time streaming session is preserved within the 3M™-hosted TeleSteth™ solution.

Proof of Concept

During 2012, we had satisfied ourselves that the sound captured by the stethoscope chest piece at the patient site can be heard equivalently at both the patient and consulting sites through the stethoscope's binaural headset, using "real-time streaming". I wanted to confirm that the server-based solution did not in any way alter the files from a sound perspective, and that we could assess the auscultation sounds in isolation, and arrive at the right diagnosis with a "store and forward" solution. Our pilot study set out therefore to answer the following questions:

- Are the auscultation sounds transferred through TeleSteth™ solution identical to the originals?
- Can referring GPs and paediatricians easily produce recordings?
- Are the sounds of sufficient quality to facilitate accurate diagnosis?
- Can the sounds be assessed remotely, and used to produce a robust diagnosis?
- What is the cost of the existing service to primary and secondary care?
- What is the cost of the newly proposed service to primary and secondary care?

Design

A group of local GPs were engaged to commence use of the 3M™ Littmann® 3200 Digital Electronic Stethoscope and the associated StethAssist™ software. Sound profiles were captured by recording auscultations made from patients who were found to present with a murmur. From the offset, I found a great enthusiasm and desire to engage in this exercise. This provided a rare opportunity to capture a deep knowledge of the complete and detailed roadmap from the first meeting of the GP and patient, through to the concluding discharge and communication. Twenty second recordings were captured from each of the following standard auscultation positions.

- Aortic
- Pulmonary
- Tricuspid
- Mitral (Apex)
- Left Infraclavicular
- Left 3rd/4th Parasternal

The StethAssist™ software allows entry of free-text data which is

user, time and date-stamped on entry. Each patient assessed also had the following information captured:

- Indication
- Symptoms
- Pulse (Radial and femoral)
- BP

The length of each appointment was logged by the practice IT systems, and this was compared to pre-existing data to ascertain the additional requirements and cost implications for the GP. Additionally, the individual component activities which occur in the GP practice were mapped and costs calculated, and the costs incurred in the secondary care service were derived from existing tariffs (Figure 2, 3). The sound recordings were transferred through the TeleSteth™ server according to standard operating instructions and, in parallel, were transferred between the collecting PC and the consultant's PC using physical media. Sounds were compared to check for any perceivable difference in quality. The assessment of each recording was logged so that a record of the time spent on each assessment was produced.

Results

Children presenting to their GP's with innocent systolic murmurs, and who will be referred to a cardiologist, as normal, for confirmation, were assessed using the TeleSteth™ hosted server solution. All but two of the referrals contained a complete sound profile as prescribed in the procedure. (These referrals had a

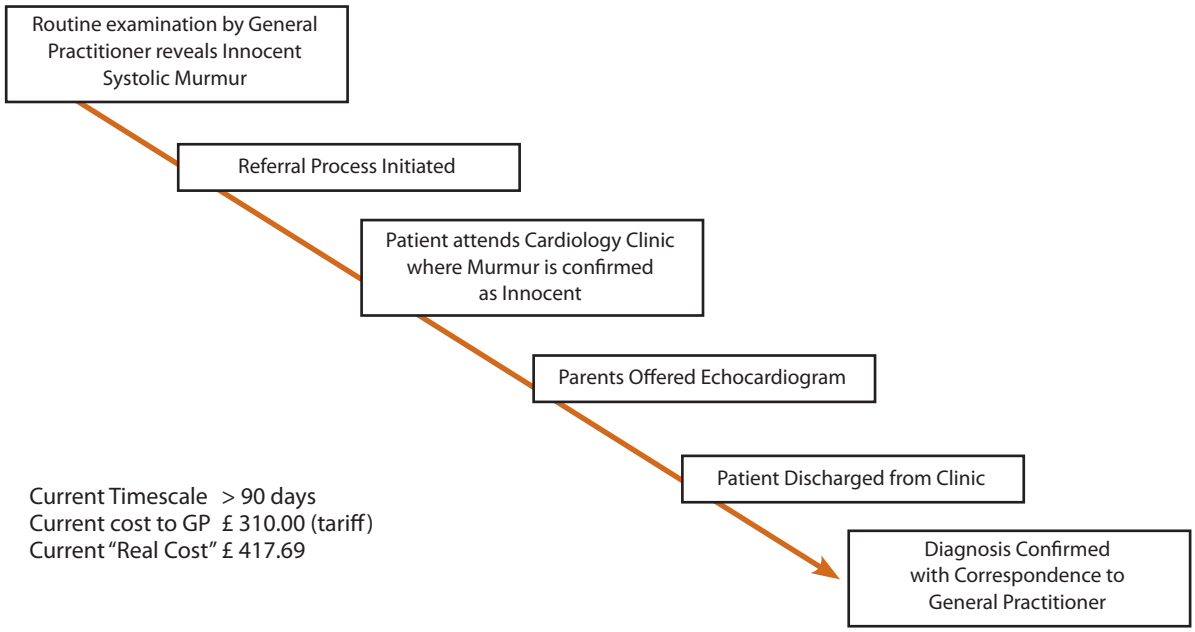

Figure 2. Existing Patient Journey

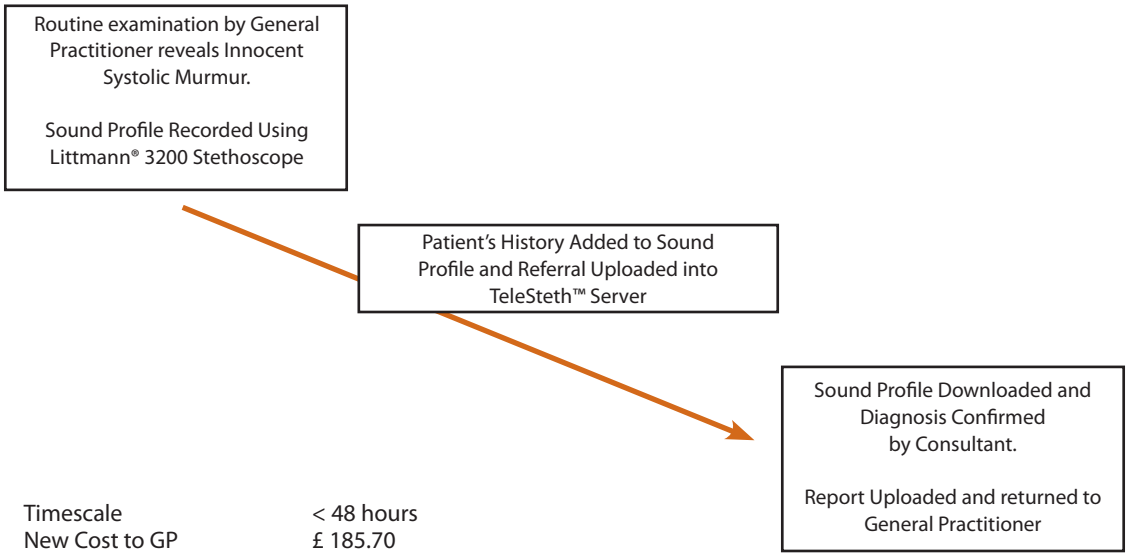

Figure 3. New Proposed Patient Journey.

General Practice:	
Physician	£ 234.60 per hour
Administration	£ 27.00 per hour
Tariffs:	
Referral to Cardiologist	£ 230.00
Simple Echocardiography	£ 80.00
Cost of current patient pathway to manage innocent systolic murmurs in children:	
Physician	£ 89.93
Administration	£ 17.76
Tariffs	£ 310.00
Total	£ 417.69
Cost of new patient pathway to manage innocent systolic murmurs in children:	
Physician	£ 105.57
Administration	£ 8.64
TeleSteth Referrals	£ 25.00 (assumes 20 patients per annum)
New Tariff	£ 46.49 (derived as component of current tariff)
Total	£ 185.70
Secondary Care:	
Cardiologist	£ 460.00 per hour
Current Tariffs	
Consultation	£ 230.00 (30 minutes)
Simple Echocardiogram	£ 80.00

Table 1. Health Economics data collected during the trial.

reduced number of recordings, due to difficulties gaining cooperation from the young patient). In all cases, I felt able to confirm the diagnosis of the GP by assessing the sound files. It remains our belief that with appropriate use of tele-auscultation, we could discharge a patient without the need for a face to face appointment in a clinic.

Conclusions

Recordings of auscultations delivered through the TeleSteth™ server solution appear to be identical to those heard live and digital copies maintained on the local PC.

The introduction of a reporting service for innocent systolic murmurs would allow us to reassure referring paediatricians, general practitioners and parents about a large proportion of children with an innocent murmur, and in so doing, avoid a full consultation and echocardiogram. This is particularly appropriate when the characteristic still's murmur is encountered in pre-school assessments.

We can remotely arrive at a diagnosis and convey this information back in a timely manner, reducing the discharge of the patient from in excess of 90 days, to 48 hours or less. We can reduce the direct cost to the general practitioner from £417.69 per patient, to a maximum of £185.70 per patient (Table 1). We can also introduce a triage process for all new murmurs leveraging the TeleSteth™ server and significantly improve the current process of referral.

A full clinical study will now be pursued in order to demonstrate the statistical sensitivity and specificity of the service, and establish the extent to which the service can be used to introduce benefit. This will be run as a retrospective comparison using the patients who have been enrolled into the pilot phase and further subsequent patients, until a suitable size cohort has been achieved.

This paper is also available in *Treatment Strategies - Cardiology* Volume 5 Issue 1: Adwani, S., 'Remote Diagnosis and Management of Paediatric Heart Murmurs at John Radcliffe Hospital, Department of Paediatric Cardiology', *Treatment Strategies - Cardiology*, 5 (2013 October) 77-80. Available at www.cambridgeresearchcentre.co.uk.

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9. The USB dongle device complies with Part 15 of the FCC Rules. Operation is subject to the following two conditions: 1. This device may not cause harmful interference; 2. This device must accept any interference received, including interference that may cause undesired operation.

Cat-scratch Disease

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Introduction

Cat-scratch disease (CSD) is an infection caused by Bartonella henselae, a gram-negative bacillus associated in the majority of cases with cat exposure, specifically kittens, who are more likely to be bacteremic than older cats.[1] It usually affects inmunocompetent children and adolescents < 21 years old.[2] Cases have a seasonal distribution with a peak in fall and early winter.

The most common manifestation of human disease is unilateral lymphadenitis with a benign course. However, it can affect visceral organ, neurologic and ocular involvement.[3] These manifestations result from either local infection (such as lymphadenopathy) or from bloodborne disseminated infection (such as visceral organ involvement).

The diagnosis should be suspected from the typical clinical manifestations and laboratory tests are required to confirm the clinical impression. There is not a universal therapy, therefore treatment should be chosen individually.

Clinical Manifestations

CSD is generally a benign, self-limited illness of regional lymphadenopathy. The "typical CSD" usually involves lymphadenitis of the nodes draining the site of a primary inoculation (85-90%), but up to 10% of patients will exhibit more unusual manifestations which affect the spleen, liver, eye or central nervous system.[4]

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Cutaneous Manifestations

CSD typically begins with a cutaneous lesion at the site of inoculation, the primary inoculation lesion. This lesion usually develops 3-10 days after the inoculation and generally evolves through vesicular, erythematous and popular phases. In less than 5%, the inoculation site occurs in eyes or mucous membranes.[5]

Other skin lesions of CSD are uncommon, occurring in less than 5% of patients infected. These include erythema nodosum, erythema multiforme, urticarial eruptions or leukocytoclastic vasculitis.[6, 7] Bacillary angiomatosis can occur in immunocompromised hosts, such as patients with AIDS or organ transplant recipients,[8] affecting various organ systems such as the spleen, liver, bone narrows or lungs, but skin lesions are more frequent, occurring in up to 90% of cases.[6] Lesions are reddish-brown papules that are difficult to differentiate from pyogenic granuloma or Kaposi's sarcoma.

Lymphadenopathy

Regional lymphadenopathy is the most common clinical manifestation. It develops 1-2 weeks after inoculation and their location depends on the site of this inoculation. The most frequent locations are the upper extremities, epitrochlear, cervical and submandibular areas. The nodal distribution reflects the fact that feline contact most often occurs with the hands. These lesions are usually ipsilateral and solitary (85%).[9] They appear less commonly in several anatomic sites or as a generalised lymphadenopathy.[10] The nodes are almost always swollen, tender, often have erythema of the overlying skin and may eventually suppurate (10-15%),[11] thereby requiring drainage. They can persist for up to 4 months, but some reports describe cases with persistence of nodes for 1-3 years.[5]

Hepatosplenic Manifestations

After lymphadenopathy, visceral organ involvement is one of the more common manifestations of CSD in children.[12, 13] These cases can be associated with peripheral adenopathy (< 60%)[14] and they are

often accompanying constitutional symptoms such as persistent fever of unknown origin, weight loss or abdominal pain. More than half of patients have hepatomegaly, splenomegaly, or hepatosplenomegaly on physical examination, with a tender liver palpation.

Erythrocyte sedimentation rate and other acute phase-reactant proteins are increased, but activity of liver enzymes is typically normal, even in the presence of severe and multiple hepatic lesions.[7]

Hepatosplenic involvement in CSD is characterised by multinodular lesions throughout the liver and spleen. Although radiologic features are not specific, these lesions seem hypoechoic on ultrasound, and there are typically multiple low-density lesions on computed tomographic scan that can mimic metastatic tumour.[15, 16] Biopses are now rarely perfomed, but the histologic examination show necrotising granuloma.[17]

Visceral lesions usually recover within 6 months, sometimes with residual calcifications.[7]

Ocular Manifestations

Parinaud's oculoglandular syndrome is the most common ocular presentation of *B. henselae* infection, affecting from 2-8% of patients with CSD.[18] It consists of fever, regional lymphadenopathy, which involves submandibular or cervical nodes, and follicular conjunctivitis characterised by unilateral eye redness, serous discharge and foreign body sensation. Route of infection is thought to be direct conjunctival inoculation.

More rarer manifestation is neuroretinitis, which main symptom is the abrupt unilateral loss of visual acuity, although cases with bilateral affectation have been described. The finding of disc swelling associated to macular star exudates is considered to be a predictable sign of this ocular manifestation of CSD.[19]

Neurological Manifestations

Neurological manifestations are rare, occurring in up to 2% of infected patients.[6] Acute encephalopathy is the most common presentation. These patients usually develop combative behaviour, disorientation, headache and confusion, which can progress to lethargy and coma. Seizures are present in 46-80%, with some presenting with status epilepticus.[20] Less common findings are transverse myelitis,[21] cerebral arteritis,[22] aphasia,[23] basal ganglia involvement,[24] cerebellar ataxia[18] or meningomyeloradiculopathy.[25] Onset of symptoms occurs from 2 days to 3 months after lymphadenopahy, when present.[7] Most of cases, these manifestations are self-limiting, but some will have residual neurological defects.

Orthopaedic Manifestations

Bone involvement in cat scratch disease is rare. Lesions are often osteolytic and occur as an osteomyelitis in the context of disseminated visceral manifestations of CSD, suggesting hematogenous spread, but in a few cases with regional limited extension, lymphatic route is proposed.[26] In most patients, osteolytic disease is isolated to one bone[6] and it is described that predominant affected sites are the vertebral column and pelvic girdle.[27] In the majority of patients with osteomyelitis resulting from *B. henselae* infection generally have an excellent prognosis.

Other, often musculoskeletal, manifestations are myalgia, arthritis or arthalgia, and according to a published study in 2005,[28] the knee, ankle, wrist, hand and elbow joints are the most frequently affected. Female sex, age > 20 years old and erythema nodosum were characteristics significantly associated with arthropathy (arthritis or arthalgia) in patients with CSD.

Other Manifestations

Some reports have documented other atypical manifestations of CSD, including pneumonia,[29] pleural thickening,[30] endocarditis,[31] glomerulonephritis[32] or hypercalcaemia.[33]

An increasing number of cases has been reported in the literature of *B. henselae* infection mimicking different malignancies.

Diagnosis

The diagnosis of CSD must be suspected based on a child's history of exposure to a cat or kitten and a physical examination, but laboratory tests are required to confirm clinical suspicion.

Common laboratory findings are often non-specific, such as normal or mildly elevated white blood cell counts, or increase of acute phase-reactant proteins in disseminated disease.

Isolation of *B. henselae* in culture is difficult and requires a 2-6 weeks incubation with specific laboratory conditions for optimal growth.

Intradermal skin test, one of the early laboratory aid in detection of *B. henselae*, is no longer used and is not approved by the Food and Drug Administration.[34]

Histopathologic examination of affected lymph nodes has no specific finding and depends upon the stage of the disease. The bacillus is difficult to see with conventional staining methods, but a positive Warthin-Starry silver stain can suggest a diagnosis of CSD if observed with compatible clinical manifestations.

Polymerasa chain reaction can detect different Bartonella species with high specificity, but sensitivity is lower than with serology.

Currently, diagnosis is mainly serological through two methods, the indirect fluorescence assay (IFA) and enzyme inmunoabsorbent assay (EIA). The IFA is the most usually used serologic method, but it has some shortcomings, including medium sensitivity, cross-reactivity at

the species level between *B. henselae* and *B. quintana*, and the fact that 4-6% of general population has positive Bartonella serology.[35] In general, IFA IgG titers < 1:64 suggest the patient does not have a current Bartonella infection. Titers between 1:64 and 1:256 represent possible Bartonella infection and it is recommended repeat testing in 10-14 days. Titers > 1:256 strongly suggests active or recent disease.[11] Positive IgM EIA indicates acute disease, with duration of detection < 3 months. Despite this, serology remains the most practical diagnostic method in the detection of *B. henselae* infection.

Treatment

Typical CSD

Treatment of CSD depends on the disease presentation and immune status of the patient. Most of cases occurring in immunocompetent hosts with typical CSD have gradual resolution of symptoms even without using antibiotic therapy. Because of this natural history in uncomplicated CSD and the risk of side-effects from antibiotics, some experts do not recommend antimicrobial therapy for immunocompetent patients with mild to moderate *B. henselae* disease.[36-38] They only propose its use in case of unresolved lymphadenopathy or when de lymphadenopathy is associated with significant morbidity. Other authors[39] recommend to treat all patients with typical CSD. The proposed regimens are:

- Azithromycin: 10 mg/kg (max. 500 mg) on day one, followed by 5 mg/kg (max. 250 mg) for four days.
- Clarithromycin: 15-20 mg/kg (max. 500 mg) per day in two doses, during 7-10 days.
- Rifampicin: 10 mg/kg (max. 600 mg) every 12 hours, during 7-10 days.
- Trimethroprim-sulfamethoxazole: Trimethroprim 8 mg/kg per day, sulfamethoxazole 40 mg/kg per day, in two divided doses, during 7-10 days.

Hepatosplenic CSD

It is recommended[39] instaured longer antibiotic therapy in forms of hepatoesplenic CSD, with a regimen including Rifampicin, for 10-14 days, in combination with either:

- Gentamicin: loading dose 2 mg/kg then 1.5 mg/kg every 8 hours.
- Azithromycin.

Endocarditis

Because of the high mortality rate of *B. henselae* endocarditis, this condition should be treated aggressively. The frequent antibiotic regimen is an aminoglycoside combined with doxycycline or ceftriaxone.[6]

Encephalopathy

There are no controlled trials of antimicrobial therapy in *B. henselae* encephalopathy, but some reports recommend a combination of doxycycline and rifampicin for 10-14 days. In children < 8 years old, doxycycline should be substituted for azithromycin or trimethroprim-sulfamethoxazole.

Neuroretinitis

For neuroretinitis,[6] doxycycline, because of its excellent intraocular penetration, and rifampin, are the preferred drugs. But in case of children < 8 years of age, erythromycin may be substituted for doxycycline. However, because CSD neuroretinitis is a self-limited disease with good prognosis for complete vision recovery, conservative management also has been advocated.[40]

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Paediatric Tuberculosis: Treatment Strategies

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Introduction

The most recent World Health Organization (WHO) report estimates 8.8 million incident cases of tuberculosis (TB) globally in 2010: 1.1 million deaths among HIV-negative subjects and an additional 0.35 million deaths among HIV-positive subjects.[1] About 1 million TB cases involve children (75% of them occurring in 22 high-burden countries), with a global estimate of 130,000 deaths per year, making TB among the top 10 causes of death in childhood.[2]

Despite these worrying data, control of TB in children has often been neglected because children are ineffective transmitters of the bacillus and frequently escape the attention of TB control programmes. However, much of the morbidity and mortality of TB occurs in childhood, and the acquisition of TB infection during childhood contributes to the future reservoir of cases.[3]

The emerging global epidemic of paediatric TB is becoming even more worrisome due to the fact that multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB also affect children.[4] There were an estimated 440,000 cases globally of MDR-TB during 2009.[5] Given the fact that childhood TB represents at least 10 to 20% of the total cases in areas with poor epidemic control, this translates into a minimum global estimate of about 40,000 paediatric cases of MDR-TB per year.[6]

Due to the new TB epidemic the world is faced with, it's of paramount importance for even primary care physicians to have at least a basic knowledge of the currently available medications for the management of TB in children, their indications, dosages, pharmacokinetic properties and their potential adverse effects.

This article discusses the available first- and second-line anti-TB drugs in respect to paediatric usage and, briefly, the potential interaction between TB drugs and the antiretroviral medications; nevertheless, the management of TB-HIV co-infected children is of special difficulty due to the peculiar immunologic background and the extensive drug-drug interaction, and so requires a broad discussion. Therefore it will only be shortly addressed in this issue. Finally, clinical and radiological findings, diagnosis and other clinical aspects of paediatric TB is outside of the purpose of this manuscript.

Basic Principles of Therapy

1. When approaching the treatment of a child with active TB, there is a single but fundamental aspect to consider: the environment where *Mycobacterium tuberculosis* (Mtb) is "working".

It is hypothesised that, within any TB lesion, there are several populations of mycobacteria that differ in metabolic activity and susceptibility to anti-TB agents,[7] which we can divide into two categories:[8]

→ The actively metabolising bacilli (large amount), found in the alkaline surface of pulmonary cavities, with ready access to oxygen.
→ The intermittently active or dormant bacilli (low number), found deeper within the walls in caseation tissue and within macrophage.

Killing the mass of rapidly metabolising organisms is relatively easy and we can call this phase the bactericidal/intensive phase.

The major problem in TB chemotherapy is to kill dormant and intermittently active organisms, and this is of particular importance as a failure to do so may lead to relapse. Therefore we will need long treatment courses aimed to completely sterilise the lesions (sterilising/continuation phase).[8] As a consequence, we will need to use two groups of drugs on these different bacilli populations: bactericidal and sterilising drugs.

Bactericidal activity refers to the agent's ability to rapidly kill the actively metabolising organisms present in the sputum of patients with pulmonary tuberculosis. Isoniazid (INH) is the most bactericidal agent and is also important for preventing resistance to companion drugs, making INH a key drug in the management of TB.[8]

Sterilising activity describes an agent's ability to prevent relapse by killing all remaining viable bacilli in the patient's lesions. The first-line

Drugs	Daily dose (mg/kg/day)	Maximum dose (mg/day)	Three times weekly dose (mg/kg/day)	Maximum dose (mg)	CNS penetrance	Toxicities
Isoniazid	10 (10-15)	300	10 (8-12)	600	100%	Hepatitis, peripheral neuropathy, nausea, renal impairment
Pyrazinamide	35 (30-40)	2000	35 (30-40)	2000	100%	Gout, rash
Rifampin	15 (10-20)	600	15	600	10-20%	Hepatitis, nausea, renal impairment
Ethambutol	20 (15-25)	2500	30 (25-35)	1200	Minimal	Optic neuritis, although at the standard dose of 20 mg/kg the incidence is less than 3%
Streptomycin	15 (12-18)	1000	20	1000	Minimal	Ototoxicity, nephrotoxicity; resistance relatively common worldwide

Table 1. Recommended doses of first-line anti-TB drugs for adults and children.[3, 10]

agents ranked in order of sterilising activity in 6-month regimens are: rifampin (RMP; high), pyrazinamide (PZA; high), INH (intermediate), streptomycin (SM; low) and ethambutol (EMB; low).[8]

2. Any child suspected of having TB disease should be started on combination therapy.[3]
3. INH and RMP kill the fast growing bacilli, PZA acts against intracellular organisms in acidic medium while extracellular slow growing bacilli are best killed by RMP. Thus every case of TB must be treated with at least these three drugs.[8]
4. Mtb when exposed to certain concentration of most currently used anti-TB drugs *in vitro* shows an inhibition of growth for 1 to several days. This suggests that the drugs can be effective even when used on an intermittent basis, as a continuous high serum level of these drugs is not needed. This forms the basis of intermittent therapy. However, intermittent therapy is not safe when self-administered because of possible errors in taking medications.[8]
5. All active TB cases should have medication administered via directly observed therapy (DOT) - a public health worker supervises medication administration. DOT has been shown to increase medication compliance and decrease the emergence of resistant isolates.[3]
6. Deciding which medications to prescribe for a child suspected of having TB disease or infection depends on several factors: disease classification (exposure versus latent TB infection (LTBI) versus disease), anatomic location of disease, HIV-status, route of administration, drug adverse effect profiles and potential drug-drug interactions, and data on isolate susceptibility, when available.[3]

Drugs

There are, at present, five 'first-line' anti-TB agents: INH, RMP, PZA, EMB and SM, that have now been in use for 30 years. Recognised 'second-line' agents include ethionamide (ETH) or prothionamide, kanamycin (KM) or amikacin (AM), terizidone/cycloserine, capreomycin, viomycin and para-aminosalicylic acid. Fluoroquinolones have also attained a prominent position in regimens for the treatment of drug-resistant TB, and there are clinical studies underway that may lead to their inclusion in 'first-line' regimens.[8]

INH

INH remains the cornerstone of anti-TB regimens due to its high bactericidal activity, excellent pharmacokinetics and relatively low toxicity.[8] INH is rapidly absorbed and has excellent penetration into most body compartments, including the central nervous system.[8]

Risk of INH-related hepatitis in infants, children, and adolescents is minimal, therefore routine monitoring of serum liver enzymes is not necessary unless the child has risk factors for hepatotoxicity. Peripheral neuropathy occurs in less than 0.2% of people taking INH at conventional doses, and is more likely in the presence of other conditions associated with neuropathy such as diabetes, HIV, renal failure, and alcoholism. Although still debated, pyridoxine (vitamin B6) supplementation may be administered at a dose of 1-3 mg/kg in children with such conditions or in those who are not eating a good diet or are not getting enough nutrients.

The American Academy of Pediatrics and WHO recommend an INH dose of 10–15 mg/kg (max 300 mg/die),[9, 10] since it has been shown that only with these dosages INH will reach, in all children, the 2-hour serum concentrations of 2–3 mg/ml that guarantees the highest bactericidal activity.

RMP

RMP is an essential component of modern short-course regimens, and RMP resistance is a major disaster for both patients and control programmes, since resistance to RMP means that patients must receive potentially more toxic agents, and take treatment for at least 12 months and probably 18 months or longer.[8]

RMP has a moderate bactericidal activity. RMP, although highly protein bound, penetrates most compartments, with the exception of the central nervous system, where it reaches about 20% of serum concentrations.[11]

The new World Health Organization dosage recommendation in children is 15 mg/kg (range 10–20 mg/kg, max 600 mg/day).[10]

Drugs	Mechanism	Daily dose (mg/kg/day)	Maximum dose (mg/day)	CNS penetrance	Toxicities	Monitoring parameters
Ethionamide or prothionamide	Bactericidal	15-20	1000	100%	Vomiting, gastrointestinal upset, hypersensitivity reactions, hypothyroidism, peripheralneuropathy, optic neuritis	Consider baseline ALT and TSH
Fluoroquinolones					Arthropathy, Arthritis, CNS stimulation	
Ofloxacin Levofloxacin Moxifloxacin Gatifloxacin Ciprofloxacin	Bactericidal Bactericidal Bactericidal Bactericidal Bactericidal	15-20 7.5-10 7.5-10 7.5-10 20-30	800 1000 - - 1500	16-20% 10%		
Aminoglycosides					Ototoxicity, hepatotoxicity	Baseline and monthly creatinine, drug concentrations (for amikacin), and hearing screen
Kanamycin Amikacin Capreomycin	Bactericidal Bactericidal Bactericidal	15-30 15-22.5 15-30	1000 1000 1000	Low Low Minimal		
Para-aminosalicylic acid	Bacteriostatic	150	12000	10-50%	Vomiting, gastrointestinal upset, hypersensitivity reactions, hypothyroidism	Baseline ALT, TSH; check monthly if used >3 months
Cycloserine or terizidone	Bacteriostatic	10-20	1000	100%	Psychiatric, neurological, rash	Monthly neuropsychiatric evaluation; serum concentrations available

Table 2. Second-line anti-TB drugs for treatment of MDR-TB in children.[3, 20]

PZA

PZA has good pharmacokinetics and penetrates most tissues, including cerebrospinal fluid.[11] It is generally held that PZA resistance is uncommon,[12] but recent data suggest that the prevalence of resistance to PZA is higher than thought,[13] particularly in those already resistant to INH and RMP. The new recommended dose of PZA in both adults and children is 35 mg/kg (range 30–40 mg/kg, max 2000 mg/day).[10]

EMB

The main function of EMB, at the recommended dose, is to prevent resistance to companion drugs or to broadening of the resistance spectrum when mono-resistance exists.

The main limit of EMB is its association with optic neuritis. The frequency with which optic neuritis develops is dose related, but it can occur at any clinically effective dose. The dose of EMB currently recommended by the WHO is 20 mg/kg (range 15–25 mg/kg).[10] Published evidence suggests that children are exposed to significantly lower serum concentrations of EMB than adults given equivalent doses;[14] perhaps, for this reason, the incidence of optic neuritis in children is so low that EMB in a currently recommended doses can be safely prescribed for children. A corollary is that if EMB should be used for the management of drug resistance in a child, it would be appropriate to use the higher dose range of 25 mg/kg, although this might increase the risk of optic toxicity.[8]

SM

SM has the highest bactericidal activity *in vitro* of any anti-TB agent.[15] SM contributes little to sterilisation, and, as with EMB, its function is to prevent resistance to companion drugs. SM must be given by injection, with the potential for HIV and hepatitis virus transmission in poorer countries. In addition, SM can cause otovestibular toxicity and nephrotoxicity.[8]

ETH

ETH has a final pathway of action similar to that of INH.[8] ETH penetrates well in cerebrospinal fluid. However, its use is limited by an obnoxious

Classification	Initial treatment	Duration of treatment	Notes
TB exposure, >4 years old and immunocompetent	None	-	Repeat TST and/or IGRA 2 to 3 months after contact with source case is broken; if second TST/IGRA result is positive, see section on TB infection
TB exposure, <4 years old or immunocompromised	INH	3 months	Repeat TST and/or IGRA 2 to 3 months after contact with source case is broken; if second TST/IGRA result is positive, see section on TB infection
TB exposure, infant	INH	At least 2 to 3 months	Because TST/IGRAs are less reliable in infants compared with older children, the TST/IGRA results of other children in the family should be considered when making decisions about terminating chemoprophylaxis; expert opinion should be sought
TB infection	INH Rifampin	6 months 4 months	Biweekly therapy should be administered only via DOT
TB CASES	**Regimens**		
	Intensive phase	**Continuation phase**	
New smear-positive pulmonary Tuberculosis (PTB)	HRZE (2 mo)	HR (4 mo)	
New smear-negative severe forms of PTB *	HRZE (2 mo)	HR (4 mo)	* extensive parenchymal involvement
New severe forms* of extra-pulmonary TB	HRZE (2 mo) 2 mo HRZE(or S) HRZE (6 mo)***	HR (4 mo) HR (7-10 mo)** none	* Other than single limph node site or unilateral pleural effusion For TB meningitis: **American Academy of Pediatrics (2006) – American Thoracic Society (2003); ** British Thoracic Society (1998) *** Donald *et al*. (1998);
Smear-positive relapse, treatment failure or treatment after default	SHRZE (2mo) + HRZE (1 mo)	HRE (5 mo)	
Cases who are smear negative but considered to have relapse, treatment failure or defaulted	SHRZE (2mo) + HRZE (1 mo)	HRE (5 mo)	
Less severe forms of pulmonary TB*	HRZ (2 mo)	HR (4 mo)	* Primary Pulmonary complex
Less severe forms of extra-pulmonary TB*	HRZ (2 mo)	HR (4 mo)	* limph node site or unilateral pleural effusion

Table 3. Anti-TB regimens.[3, 24] INH-H: Isoniazide, R: rifampin, Z: pyrazinamide, E: ethambutol, S: streptomycin.

taste and gastrointestinal irritation. In children, this can often be overcome by gradually introducing the drug. ETH is used for MDR tuberculosis and remains active when INH resistance is caused by KatG gene mutation; when INH resistance is mediated by a mutation in the inhA gene, ETH will be ineffective.[8] ETH is given in a dose of 15–20 mg/kg.

Fluoroquinolones

These agents have a well-known activity against Mtb. Initially, ciprofloxacin and ofloxacin were used sporadically in the treatment of multidrug-resistant (MDR) tuberculosis.[16] A number of newer fluoroquinolones have shown potential sterilising capabilities and bactericidal activity close to that of INH[17, 18] and low relapse rates following their use for the treatment of pulmonary TB.[19]

CM

CM is a macrocyclic peptide antibiotic that must be given by intramuscular injection and has side-effects similar to the aminoglycosides. It is not recommended for children but might still be used in case of MDR-TB at a dose of 20 mg/kg.[8]

KM-AM

KM and AM are aminoglycosides with similar structure, pattern of resistance and relatively low efficacy.[8] There is no cross-resistance with SM, and they can be used in the presence of resistance to SM. AM is considered to be less ototoxic than KM and might be preferred in children at a daily dose of 15–22.5 mg/kg body weight.[20]

Para-aminosalicylic Acid

Para-aminosalicylic acid is a weak agent and, although one of the oldest anti-TB agents, remains useful in patients with an extended spectrum of resistance. The lack of paediatric formulations is a drawback, particularly in younger children, due to the high number of

Side effect	INH	RMP	PZA	SM	EMB	ZDV	3TC	ABC	RTV	LPV/r	NVP	EFZ
Hepatitis		X	X								X	X
Agranulocytosis	X					X	X					
Nausea		X				X	X	X	X	X		
Vomiting		X								X		
Abdominal pain		X								X		
CYP-3A4 inducer		X							X	X	X	X
Lethargy	X					X	X	X		X		
Skin rash	X	X	X	X	X						X	X
Renal impairment	X	X	X	X								
Ototoxicity				X								
Peripheral neuritis	X	X		X			X					
Drug-induced lupus	X	X		X								

Table 4. INH isoniazide; RMP rifampin; PZA yirazinamide; SM streptomycin; EMB ethambutol; ZDV zidovudine; 3TC lamivudine; ABC abacavir; RTV ritonavir; LPV/r lopinavir/r; NVP nevirapine; EFZ efavirenz. Adapted by WHO: Treatment of tuberculosis: guidelines – 4th ed. WHO/HTM/TB/2009.420 e Rowe JS *et al*. Pediatr Infect Dis J 2009;28:147-148.

tablets or sachets of granules mixed with orange juice or yoghurt that need to be taken. The usually recommended dose is 150 mg/kg in two or three divided doses.[8]

Terizidone/Cycloserine

Terizidone/cycloserine, although only moderately active, is useful in second-line regimens to prevent resistance in companion drugs. It has side-effects on the central nervous system, including depression, although these have rarely been seen in paediatric experience. The maximum daily dose is 15–20 mg/kg.[8]

Steroids

Definite indications for concomitant steroid therapy include TBM and pericarditis. Steroids are routinely not indicated in lymphadenitis and pleural effusion. Their use may also be considered in the case of mediastinal compression syndrome, pleurisy with severe distress and miliary disease with alveolo-capillary block. Predinsone 2-4 mg/kg/d or its equivalent is used for 2-4 weeks and then tapered over next 2 weeks.[21]

Table 1 and 2 summarise dosages, side-effects and main pharmacodynamic characteristics of first and second-line anti-TB drugs.

Treatment Regimens

Active TB

The standard initial regimen should be the four most commonly used agents in the treatment of TB disease: INH, RMP, PZA and ETH. INH, RMP and ETH are administered for 6 months and PZA is stopped after the first 2 months. If the source case's isolate is known to be susceptible to the other three drugs, ETH need not be given (See Table 3).[3]

LTBI

The mainstay of therapy for LTBI is INH administered for a 6-month course. An alternative for patients intolerant of INH is rifampin, which is administered for 6 months. Therapy for LTBI can be daily and self-administered or intermittent (biweekly or thrice-weekly) and supervised through directly observed therapy (DOT).[3]

HIV/TB Co-infection

Due to the peculiar immunologic background and to the extensive drug-drug interaction, it's always necessary to involve an expert in the management of HIV/TB co-infection. Table 4 and 5 summarise anti-HIV and TB drugs interactions and main therapeutic regimens for HIV-TB co-infection, respectively.

Drug resistant TB

The optimal regimen and number of drugs needed for the successful treatment of DR-TB is unclear because of the lack of controlled trials comparing different regimens.[22, 23] Most guidelines are based on expert opinions or uncontrolled case series from single institutions.[22] The design of such regimens are particularly complicated for childhood DR-TB due to the lack of sufficient experience and dosing information in children.[24] An extensive discussion on this topic is outside of the aim of this manuscript. To address this issue, readers can refer to Al-Dabbagh M *et al*.[24]

Nevertheless, the basic principles for treatment of childhood DR-TB should be known and can be summarised as follows (adapted from reference 24):

→ Always involve an expert in the management of childhood DR-TB.
→ Use at least 4 drugs certain to be effective.
→ Using daily treatment and DOT is essential.
→ Never add a single drug to a failing regimen.
→ Treat the child according to the drug susceptibility pattern (including treatment history) of the source case's MTB strain or prevailing strains in the region/country, if an isolate from the child is not available for susceptibility testing.
→ Counsel the child's caregiver at every visit about the importance of

Clinical context	Recommended anti-TB regimen	Timing of ART following initiation of TB treatment (RFM containing regimen)	Recommended ART regimen
HIV-TB co-infection	6-month rifampin based regimen* OR 9-month (pulmunary TB) to 12-month (extrapulmunary TB) regimen	Start ART soon after TB treatment between 2 and 8 weeks following start of TB treatment	Children <3 years: Triple NRTI first-line regimen (WHO) (d4T or AZT+3TC+ABC) or Standard first-line regimen of 2NRTI + NVP or 2 NRTI+Lopinavir/ boosted ritonavir or ritonavir only Children ≥3 years: Standard first-line regimen (2 NRTIs + EFV) (for many this will be the first choice) or Triple NRTI first-line regimen(d4T or AZT)+3TC+ ABC)
TB diagnosis while on first line regimen (2 NRTIs + NNRTI)			Continue on 2 NRTIs + NNRTI; if on NVP, substitute with EFV if the child is ≥3 years; if <3 years, increase NVP on maximum dose or substitute NNRTI to triple NRTI first-line regimen
TB diagnosis while on PI regimen (2 NRTIs + boosted PI)			Continue same regimen, consider adding RTV to achieve full therapeutic dose (increase RTV until same dose as LPV in mg, in a ratio of 1:1)
*if the clinical, radiological and microbiological response is poor, prolonging the treatment duration to 9-12 months should be considered. ABC. Abacavir; NRTIs. Nucleoside reverse transcriptase inhibitors; NNRTIS. Non-nucleoside reverse transcriptase inhibitors; EFV. Efavirenz; NVP.nevirapine			

Table 5. Adapted from World Health Organization. Antiretroviral therapy of HIV infection in Infants and Children in Resource-limited Settings: Towards Universal Access. Recommendations for a Public Health Approach 2006. Geneva: World Health Organization, 2006.1-163.

compliance and completion of treatment.

→ Clinical, radiological, bacteriological and pharmacological follow-up is essential.

→ Treatment duration should be 12 to 18 months from first negative culture, if available.

Follow-up

In childhood TB, culture of Mtb is possible in only a minority of cases deserving treatment and acid-fast bacilli are visualised in even fewer cases. Consequently, treatment response will often be judged on clinical criteria such as symptom improvement, weight gain or improvement or regression of radiological findings. The radiological features of chest disease may, however, respond slowly, despite symptom improvement and weight gain. Nevertheless, when a culture of Mtb is obtained, the attainment of culture negativity should be confirmed.[8]

Follow-up cultures should also be requested, even if initially negative, should there be any doubt about a child's progress. It is clear that many children still have radiological abnormalities on completion of treatment, and several years may pass before the final resolution of the abnormalities. Failure to respond radiologically is particularly likely in the mediastinal nodes but does not require treatment prolongation. For these reasons, it is not suggested to repeat chest X-ray at the end of the intensive phase, if the clinical improvement is on expected lines.[8]

Routine monitoring of liver transaminases in patients on therapy is not recommended though hepatitis is the commonest serious drug toxicity seen. As the anti-TB drugs are hepatic enzyme inducers, asymptomatic biochemical derangement without an increase in bilirubin level may be tolerated until the enzymes remain up to 5 times the normal range. However, if a patient develops jaundice or other signs of liver dysfunction during therapy, it is prudent to stop therapy immediately irrespective of enzyme levels.[21] The drugs should be withheld until the serum bilirubin becomes normal and the enzymes also start touching the normal range. Drug re-introduction is better to be done in a place where the liver function can be monitored. The drugs should be re-introduced in sequential order starting with RMP, followed by INH and then PZA. It can be prudent to add the first drug and reassess for its impact on liver enzymes. If the enzymes remain within the acceptable range, then only the subsequent drugs are added in the given sequence every 5-7 days and so on.

Drugs causing severe intolerance on re-introduction should be avoided and substituted with other drugs. If the period without drugs is likely to be prolonged, and the patient is sick and requires treatment, at least two other drugs should be given. Nevertheless, it's clear that all patients who require alteration from the standard regimen should be referred to experienced pediatricians.[21]

Conclusions

Today, there is a clear appreciation of the whole scientific community of the serious nature of the ongoing TB epidemic in developing countries, with its possible worldwide impact due to the increase in international travels and immigration from high TB–burden countries and the poor socioeconomic and living conditions of migrants in the arrival destination.[2]

In 2000, the Global Alliance for TB Drug Development was established to accelerate the development of new anti-TB agents and ensure their availability and affordability in high TB burden countries.[25]

There are now several new drugs with very promising characteristics in various stages of development.[26, 27] Nevertheless, before these drugs can be used in routine regimens, a considerable amount of work still has to be done. Thus, despite some optimism, it is the responsibility of all physicians to use existing regimens and drugs with due care in order to improve single patient and communities' outcomes and to prevent the development of drug resistance.

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Further Reading

Please see the abstracts below for further reading on paediatric respiratory diseases. These articles plus others are available in previous editions of *Treatment Strategies - Pediatrics*. Please see our website for more articles on paediatric respiratory diseases and a range of other topics within paediatrics.

Bronchial Carcinoid Tumours in the Paediatric Population

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Bronchial Carcinoid (BC) tumour is the most frequent primary lung cancer in the paediatric population, but it remains a rare entity. Bronchoscopy plays an important role in diagnosis, symptoms relief and proper operation planning. Surgery is the treatment of choice, and parenchyma saving procedures (sleeve or bronchoplasty) should be employed whenever possible, associated with lymph-node dissection. A correct early diagnosis and a careful surgical management of paediatric BC ensure an excellent survival and a good quality of life. Relapses can occur also many years after radical dissection, therefore a careful and prolonged follow-up is recommended.

Frequent Respiratory Infections among Young Children — Is there Anything to Worry about?

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Recurrent respiratory infections raise concern when there are too many infections a year, have bolstered the course, extend to, be accompanied by additional symptoms or no improvement is expected. Children with recurrent infections belong to four categories: healthy children (usually up to 60%), children with atopy, children with other chronic illnesses and children with immunodeficiency.

The average number of infections per year ranges from 4 to 8, but may be 10 to 12. According to the history, physical examination and basic laboratory tests can qualify for a child to the appropriate group. It determines further treatment. Healthy children do not require detailed study and handling is based on respect for hygiene, proper immunisation and immunostimulated treatment. Children with allergies and other diseases (such as gastroesophageal reflux disease) should be treated in accordance with the standards. A small number of patients with immune deficiency require detailed research and treatment under the supervision of the immunologist.

The Need for Comprehensive, Patient-centred Asthma Care to Achieve Good Adherence in Most Children with Asthma

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Introduction

The keystone of current asthma management is the regular use of inhaled corticosteroids (ICS), the effectiveness of which has been shown in large trials.[1] Despite the effectiveness and widespread use of ICS, many asthmatic children continue to suffer from uncontrolled asthma.[2] Because poor adherence to ICS is the rule rather than the exception, with rates of adherence among patients with asthma ranging from 30% to 70%,[3, 4] this is thought to be a major cause of the limited effectiveness of ICS in achieving asthma control in most children. Improving adherence to ICS in children with asthma is probably the most effective method through which healthcare providers can reduce the burden of uncontrolled asthma.

We recently finished a research project on determinants of adherence to ICS in 2-12 year old children with asthma from primary and secondary care. Some of the results of this project have already been published.[5-9] One of the most remarkable findings was a very high median adherence over a 3-month follow-up period of 92%, in a population of 2-6 year old children receiving comprehensive, guideline-based asthma care at our hospital-based paediatric asthma clinic. In this study, medication beliefs were important determinants of adherence to ICS, even at this high median adherence rate.[6] The project also showed striking differences in the illness perceptions and medication beliefs between parents from primary care and secondary care. Compared to parents from primary care, parents from secondary care had illness perceptions more concordant to the medical model of asthma and they expressed higher perceived necessity of ICS.[5] Furthermore, major differences in the organisation and content of asthma care between primary and secondary care were observed. Whilst children in primary care received education and instruction only once, and were seen for follow-up only when things were not going well, children and parents in secondary care received repeated and comprehensive self-management education, and were seen regularly for scheduled follow-up.[5]

Our research project has shown that good adherence can be achieved in most children with asthma. The results strongly suggest that modifying parental medication beliefs into adherence-promoting constructive beliefs is a key determinant of such good adherence, and that these perceptions can be modified and adherence improved when parents and children receive patient-centred asthma care. These findings may have major clinical implications (Figure 1).[10] In this paper, therefore, we discuss the theoretical background of this mechanism and the evidence provided by other studies.

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Illness Perceptions and Medication Beliefs Determine Adherence

Recent research on self-management and adherence in various chronic conditions lends support to a theoretical model which has become known as the 'Common Sense Model' (Figure 1).[11] In this model, the central tenet pertains to people making sense of physical sensations, and the steps they take as a result of this process of sense-making.[12] A patient with asthma who perceives the asthma to have an episodic nature will not perceive the necessity to take preventive medication on a daily basis. This 'no

symptoms, no asthma' behaviour has shown to lead to the inadequate control of asthma.[13, 14] This example shows how patients create their own personal representation of their illness, called illness perceptions, and how such personal perceptions determine adherence.[12]

An extended self-management theory that includes treatment beliefs as well as illness perceptions has been put forward in particular by Horne *et al.*, whose research showed strong correlations between treatment beliefs and adherence (Figure 2).[15, 16] In adult patients with asthma, self-reported non-adherence was associated with doubts

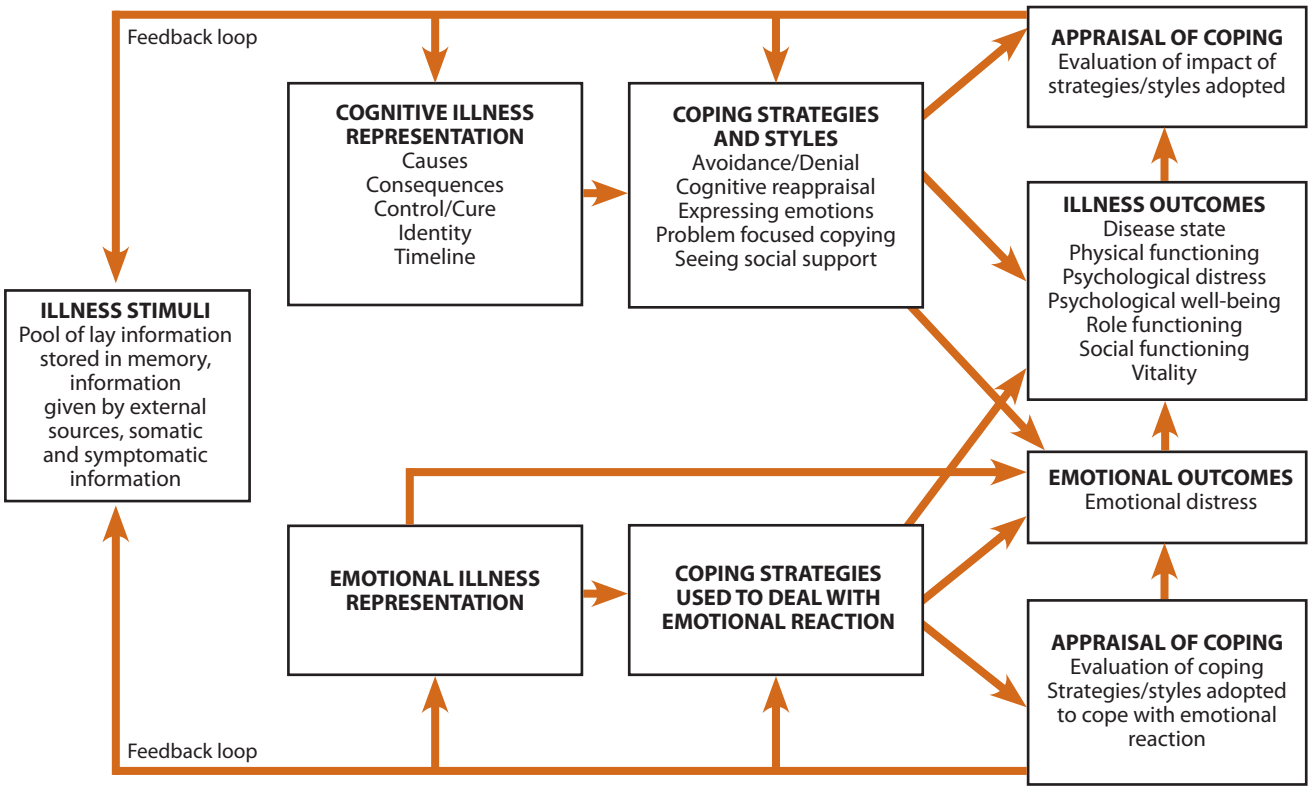

Figure 1. The Common Sense Model, (adapted by Orbell & Hagger).[10]

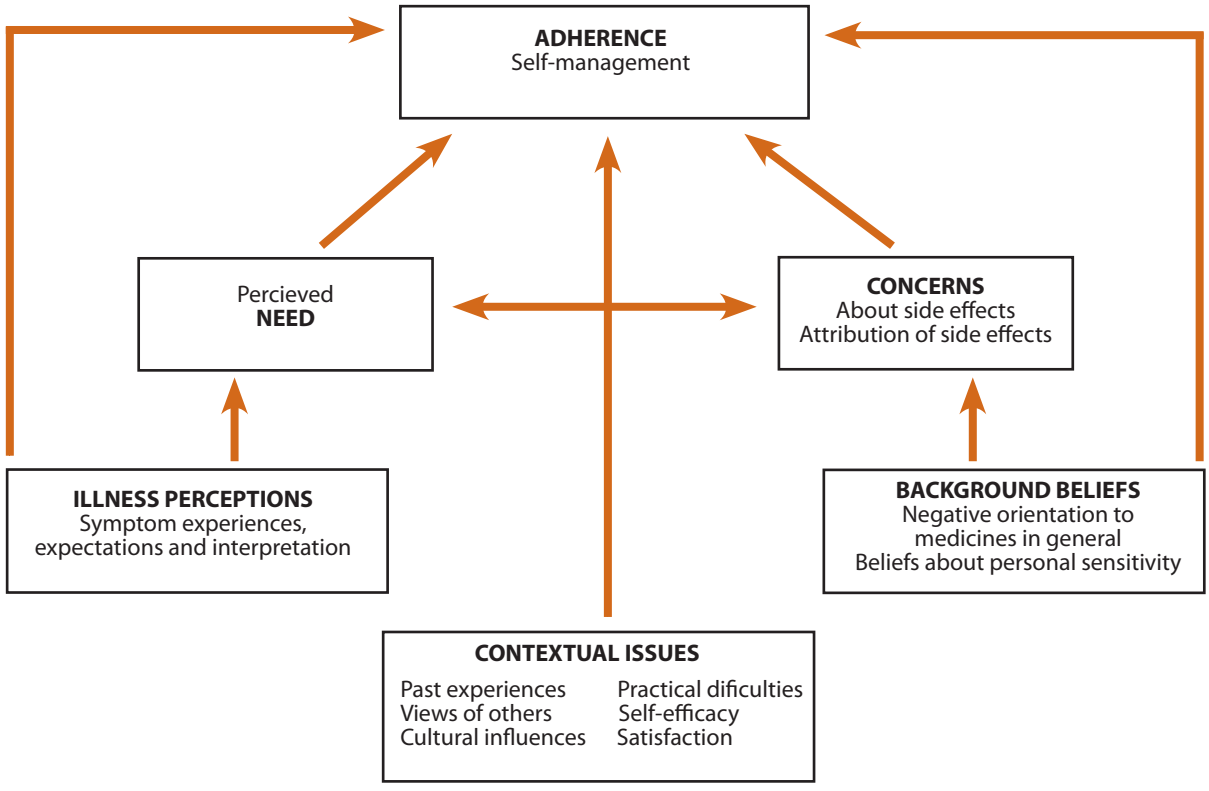

Figure 2. A theoretical model of the relationship of illness perceptions, medication beliefs and adherence as presented by Horne.[15]

First author, year, country	Nr. patients, age	Assessment of parental medication beliefs	Assessment of adherence/ underuse of controller medication	Results
Conn[50] 2007 USA	622 children 2-16 yrs	BMQ*	Parental self-report	Mean adherence scores increased as the necessity-concern differential increased.
Koster[51] 2011 the Netherlands	170 children 8 yrs	BMQ*	Parental self-report	Parents with strong need beliefs towards their child's medication use showed higher therapy adherence rates.
Koster[52] 2011 the Netherlands	527 children 4-12 yrs	BMQ*	Parental self-report	Parental necessity beliefs about medication were associated with higher adherence.
McQuaid[53] 2012 USA and Puerto Rico	277 children 7-16 yrs	BMQ*	Electronically measurement and counter teller	Parental belief regarding medication necessity was associated with adherence.
Riekert[54] 2003 USA	318 children 5-12 yrs	5-item questionnaire¶	Parental self-report	More overall positive attitudes toward asthma management associated with concordance to prescribed medicines.
Smith[55] 2008 USA	754 children 2-13 yrs	5-item questionnaire¶	Parental self-report	High score on medication concerns summary measure associated with underuse of controller medication.
Van Dellen[56] 2008 the Netherlands	232 children 7-17 yrs	2 questions‡	Pharmacy records and parental self-report	Significant association between the positive subjective view to ICS of the parents and poor adherence.
Vasbinder[57] 2012 the Netherlands	90 children 1-1 yrs	BMQ*	Electronically measurement	Medication beliefs showed a borderline association with adherence in the univariate analysis.
Yoos[14] 2007 USA	228 children 5-12 yrs	AIRS#	Parental self-report	Parents whose attitudes to medication was more concordant with the professional model of asthma had children who were more likely to be on an adequate medication regimen.

Table 1. Quantitative studies on the relationship between parental medication beliefs and adherence to controller medication in children with asthma. *: Beliefs about Medicines Questionnaire; ¶: Higher scores reflect a more positive attitude toward preventive care, increased confidence to manage asthma attacks, and fewer concerns about side effects; ‡: It keeps the asthma of my child under control, it reduces the risk of having an asthma attack; #: The Asthma Illness Representation Scale.

about the necessity for preventer medication to maintain health and with concerns about the potential adverse effects of this medication.[17]

Horne *et al.*'s observation that treatment beliefs were substantially and independently related to adherence is consistent with findings in a range of chronic illness samples.[16] In agreement with these findings, a number of qualitative studies suggested that parental perceptions about illness and medication are major determinants of the use of controller medicines in their children.[18, 19] An overview of (mostly very recent) quantitative studies supporting this is provided in Table 1. Therefore, it can be concluded that illness perceptions and medication beliefs have been found to determine self-management behaviour and outcomes (Figure 2).[11]

Illness perceptions and medications beliefs are hardly, if at all, determined by the professional medical model of asthma. They are strongly influenced by cultural, social and psychological factors.[11] They are shaped, for example, by early experiences with illness-related episodes (e.g. flu, minor trauma), in which children learn how to respond to pain and discomfort from their parents. In addition, public images of how to respond to various complaints and illnesses are learned by watching television, and nowadays more importantly, by surfing the internet.[11] Every practicing physician is confronted with patients coming up with their perception about the cause of their symptoms, the need for medical investigations and the treatment of the symptoms as patients have been reading on the internet, illustrating its great influence on illness perceptions and treatment beliefs. However, for optimal self-management, these patients' and parents' perceptions and beliefs should be modified to be concordant with our professional medical model of the disease that the patient is suffering from. Therefore, an important question has to be answered: how can healthcare professionals modify such personal illness perceptions and medication beliefs?

Modifying Illness Perceptions and Medication Beliefs

It is important to examine the evidence on the effectiveness of interventions in the context of the central tenet of the common sense model. If illness perceptions determine outcome, then changing illness perceptions should lead to changes (i.e., improvements) in self-management and, therefore, in outcome. When medication beliefs determine adherence, changing counterproductive beliefs into constructive and useful medication beliefs should improve adherence.

A number of intervention studies support this hypothesis. For example, Jansen *et al*. described an intervention programme which focused on changing both misperceptions and negative perceptions of illness and treatment. This programme increased the patients' self-efficacy and stimulated social support, and showed encouraging results on short-term outcome in patients with end-stage renal disease.[20] Comparable promising results of interventions targeted on changing illness perceptions have been reported for patients with cardiac disease, diabetes and chronic low back pain.[21-23] Very few studies, however, have examined interventions focused on modifying medication beliefs to improve adherence. To our knowledge, only Petrie *et al*. studied such an intervention by sending participants tailored text messages based on their illness perceptions and medication beliefs. In the intervention group, the perceived necessity of preventer medication increased, and this was associated with higher self-reported adherence to ICS compared to the control group.[24]

Taken together, these observations support the findings of our research project that exploring parental illness perceptions and medication beliefs, and providing tailored self-management education based on this, may help to modify medication necessity beliefs. This is a likely explanation of the strong association between guideline-based, comprehensive asthma care and high adherence in our study. On the other hand, it also suggests that such a discussion of patients' and parents' perspectives is missing in many consultation rooms.

The Reality of the Consulting Room

We observed limited self-management education and no regular follow-up for most patients in primary asthma care, both in the narratives provided by parents and by the GPs themselves.[5, 7] Previous studies in primary care settings in several countries, including but not limited to the Netherlands, have shown comparable deviation from guideline-based asthma care.[14, 25, 26] Moreover, this finding is not unique for asthma, but has also been reported for other chronic illnesses. Recent surveys indicate that many physicians fail to provide self-management education on a regular basis, although there is now consistent evidence supporting the effectiveness of such education in patients with chronic illness.[10, 27-29] The lack of attention to adherence in follow-up consultations in daily practice is even more striking,[30, 31] to such an extent that it has been called a 'conspiracy of silence'. Our observations suggest that this conspiracy of silence also includes insufficient attention to discussing illness perceptions and medication beliefs. This is in agreement with several studies showing a lack of exploration of the patient's perspective in many medical consultations.[31-36] The reality of patients self-managing their illness, as determined by their illness perceptions and medication beliefs, is therefore not acknowledged in most consultation rooms. The change needed to improve this acknowledgement can be defined as a change to more patient-centred communication.

Patient-centred Communication: Time to Change

The paucity of randomised controlled trials studying the effect of patient-centred interventions fuels an on-going discussion between believers and sceptics about the effectiveness of patient-centred care. This paucity of evidence from trials, however, is likely to remain for the following two reasons. First, patient-centred care is a complex multifaceted intervention. Clinical trials, mainly designed and suited to study straightforward drug interventions, are difficult to perform for such complex interventions, and their interpretation is fraught with difficulties.[37] Second, documenting effects of patient-centred care on illness outcomes in chronic diseases requires long-term follow-up, which increases the complexity and cost of trials, and reduces the willingness and possibilities of researchers to embark on them. Criticasters of patient-centred care can therefore rely on an on-going 'absence of evidence' to support their rejection of the concept. Because of the substantial indirect evidence supporting the adoption of patient-centred care, this attitude appears to be short-sighted, however. Meanwhile, the disparity between the level of evidence showing the effectiveness of patient-centred care and the worldwide urgent call for patient-centred care is striking. The call for patient-centred care is driven by patient associations, which have developed a strong lobby on governmental institutes and quality-of-care institutes to encourage doctors to adopt patient-centred care.[38, 39] This lobby reflects the almost universal patients' preferences to collaborate with their doctors.[40, 41] The call for patient-centred care is also driven by an ethical and humanistic perspective as patient-centred care is increasingly being viewed as the paradigm of "good quality" care.[42]

Although these humanistic and ethical arguments may already provide sufficient reason to implement patient-centred care, there also is accumulating evidence for a range of chronic conditions showing the benefits of patient-centred communication and care. A large systematic review reported a consistent relationship of patient-centred communication to good adherence.[43] In the next section we will discuss barriers to the widespread adoption of patient-centred care.

Barriers to Patient-centred Care

Organisational issues and time constraints are frequently mentioned as a reason to avoid patient-centred communication such as discussing patients' perspectives and adherence to treatment.[31, 44] Research has shown that patient-centred consultations do indeed take slightly longer than traditional doctor-centred consultations.[45] A major barrier to providing patient-centred care and to discussing illness perceptions, medication beliefs, and adherence, is the absence of training of such communication skills in current graduate and postgraduate medical education. Most medical students are now being sufficiently trained in basic communication skills, including eliciting the patient's perspective and preferences.[46] However, when these students enter clinical practice, they experience that many of their role models show different professional communication behaviour altogether. Instead of eliciting the patient's perspective and agenda, most senior consultants perform their consultations in a doctor-centred fashion, and they do so with great confidence and efficiency.[47] This lack of training in and role-

modelling of patient-centred care may help to explain the ignorance and denial of the patients' perspective.

In a recent European study among GPs, large variations were noted between physicians, not only on their perspectives on asthma and its management, but also on how the doctor-patient relationship can be used optimally to treat the condition effectively.[48] In the focus group interview with the GPs in our study, we recorded several beliefs about ICS which were not concordant with the current state of the evidence, and these physician's beliefs determined their prescription behaviour.[7] In another Dutch study, GPs reported the belief that they could not modify patients' attitudes to the use of medication as an important reason to refrain from discussing adherence.[31]

Such individual perspectives are major determinants of behaviour, comparable to the central tenet of the Common Sense Model: the role of patients' perspectives about illness and medication in determining self-management behaviour. Therefore, understanding physicians' perspectives about the management of chronic diseases (particularly childhood asthma) may provide an explanation for the reason why these physicians prescribe long-term medication without providing the necessary self-management education and regular follow-up. Furthermore, such perspectives may hamper implementation of patient-centred communication: providing patient-centred care requires a paradigm shift from the traditional medical care most physicians have been trained in.[49]

Taken together, patients' preferences for collaborative care, the solid theoretical framework of the Common Sense Model supporting patient-centred care, the humanistic and ethical perspective that patient-centred care is the desirable paradigm for good quality healthcare, and the accumulating evidence showing the benefits of such care justify the call for a paradigm shift in healthcare towards a widespread adoption of patient-centred care.

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Health Literacy and Severe Childhood Asthma

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Overview

Asthma is a global disease requiring treatment and healthcare to prevent serious health effects. Although most children respond well to their given treatment, some remain symptomatic despite high levels of anti-inflammatory treatment. This failure in treatment response may be associated with underlying disease severity and with extended aggravating factors that can be identified in patients' history. For children's health and for the quality of healthcare including costs, effectiveness, efficiency and safety, the evaluation of aggravating factors is of the utmost important. In adult studies, poor health literacy is reported as an independent predictor of impaired asthma control. To date an increasing number of paediatric studies have elucidated the effects of limited health literacy on poor health outcomes in children with asthma, especially with severe asthma. The current evidence which suggests targeting limited health literacy in children with severe asthma presents major challenges for paediatric healthcare. This review will outline interventions suitable for targeting limited health literacy in paediatric healthcare of severe asthma.

Current evidence from studies of children with asthma suggests that poor health literacy is a very costly barrier for optimal asthma control. The link between health literacy and poor asthma outcomes in children is not completely understood. To approach limited health literacy in children and parents with education, in both clinical, home and school settings has proved to be important.

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Background

Asthma causes major health problems in children. Children with severe asthma have a disproportionate consumption of healthcare and impaired health-related quality of life,[1,2] despite high-dose treatment with inhaled corticosteroids. In a population based birth cohort, severe asthma was prevalent in 4.5% among 10 year olds with asthma.[3] The severe asthma nomenclature established by World Health Organization (WHO) emphasises subgrouping and identification of patients with aggravating factors, e.g. environmental exposures and comorbid conditions in patient's history.[4] The nomenclature recommends subgrouping "difficult to treat" asthma on the basis of identifiable aggravating factors. In a cohort of schoolchildren with severe asthma, 39% were "difficult to treat" based on environmental exposures at patients home (furred animals, mould and tobacco smoke) and untreated rhinitis and gastroesophageal reflux.[5] In assessment with nurse-led home visits, Bracken *et al*. found multiple causes for poor asthma control in 79% of severe asthma patients.[6] The major factors were mainly the same, including environmental exposures within the home (e.g. allergen exposure, tobacco smoke), psychosocial issues and adherence. Adverse factors in children's history need to be resolved before applying novel or advanced therapies.[7,8]

Health literacy is commonly defined as "the degree to which individuals can obtain, process and understand basic health information and services in order to make appropriate health decisions".[9] Parental failure to understand or follow health information may be associated with child's poor adherence, untreated and unrecognised comorbidities, not avoiding trigger factors and poor recognition of signs of asthma worsening.[10] These aspects are included in the definition of limited health literacy.[11] Although there are major gaps in the current knowledge of what brings low health literacy, there is an association to general literacy skills and socio-economy.[12] Low health literacy is more common in certain groups in society, such as members of ethnic minorities, immigrants, low income groups and those with limited education.[13] The aim of this article was to encompass health literacy in

children with asthma through evidence based literature, and discuss the evidence in relation to healthcare quality of children with severe asthma.

Health Literacy and Asthma

A literature search in MEDLINE® using the key words "health literacy in children with asthma" was conducted in March 2013, and there were 30 articles consisting of descriptive studies (n = 11) and clinical interventions (n = 11). Analysed information was also extracted from review articles (n = 6), whereas 2 publications concerning diagnosis other than asthma were excluded.

The reason for the association between low health literacy and adverse health outcomes in children's asthma is unclear. In a retrospective study, DeWalt *et al*. found that the likelihood for a child missing school days and requiring an emergency visit or hospitalisation because of asthma was higher among families with low parental literacy.[14] The authors controlled for asthma-related knowledge but this did not remove the negative association for literacy, suggesting that literacy may exert its effects on health outcomes in ways that are not only knowledge mediated. For example, low literacy may also relate to self-management behaviours like inhalation technique. It is well known that poor adherence to therapy is an obstacle for optimal asthma control,[15] and that parents easily overestimate children's use of medication.[16] Yin *et al*. analysed parental knowledge of dosing child's medication. 23% of the caregivers reported that the primary dosing tool used at home was a non-standardised tool like a kitchen teaspoon or tablespoon and 67% were unaware that weight was the basis for medication dosing.[17] In addition, observations were associated with poor parental health literacy.

In Sweden, children in families with social adversity were seen to have an increased risk for exacerbations and for hospital admissions because of asthma.[18] It is also relevant to consider that poor health literacy has larger health effects on children with more severe asthma disease than on children with, for example, mild asthma. Importantly, limited health literacy emphasises the challenges in targeting both child and parents with tailored education,[14] and with information to healthcare professionals in order to optimise their communication and education skills.

Shone *et al*. conducted home interviews to examine associations between parent health literacy and measures related to child asthma,[19] and found that low literacy was associated with greater parent worry, parent perception of a greater asthma burden, and lower parent-reported quality of life. The clinical implication is to enhance parent understanding about child asthma.

Interventions

Healthcare for children with severe asthma and limited health literacy is very costly.[20] The resources to help patient's with limited health literacy are poorly identified. The main areas of evidence address home visits and education to reduce costs for asthma care through decreased emergency visits and hospitalisations, and improved asthma self-care.

Home Visits

A randomised home-based family intervention evaluated the efficacy of targeting asthma management and stressors in low-income children with asthma.[21] Outcomes of emergency visits and hospitalisations were improved after a one year intervention. A similar and promising home-based study with improved asthma control in children with atopic asthma was made by Morgan *et al*., who conducted an intervention with a reduction of environmental exposures and family education.[22] Taken together, an individual approach with home visits addressing medical and psychosocial needs is probably beneficial for patients with severe asthma.

Education

Improving patient's awareness and understanding of asthma are core components for successful asthma care. Health education has proven to be effective for disease management in patients with low health literacy.[23] Incorporating both the child and their family in education has demonstrated promising effects in several studies,[24-26] especially in children with more severe asthma.[27] In addition, Wood *et al*. showed cost-effective asthma education by specifically addressing health literacy levels and care, which reduced the cost for asthma care (emergency visits and hospitalisation).[28] The authors underlined the importance in prioritising nurse-led asthma education on physician visits, particularly for parents/caregivers with limited health literacy with use of Action Plans, tailored education material that pays attention to literacy levels and patient abilities.

Patient self-management of asthma is critical for successful asthma care. A six-month intervention which targeted children with severe asthma and examined the effect of general literacy programme on improved asthma self-care showed improved outcomes in both hospitalisation and emergency visits.[29] Furthermore, education programmes in classrooms of public schools have raised awareness and understanding of asthma, not just in those with the condition.[30] Indeed, schoolchildren with severe asthma disease could benefit from a collaboration between school and healthcare professionals, since severe asthma is associated with increased number of lost school days due to symptoms and exacerbations,[31] e.g. to increase teachers awareness of how asthma affects children's capacity in school work and to revise the possible impact of environmental exposures.

Educational interventions for children with severe asthma could improve asthma-related outcomes but the programmes require resources. Information technology may help to reduce barriers to access health information. Vargas *et al*. found that touch screens with incorporated video clips were superior to paper-and pencil questionnaires in the collection of information about children's asthma.[32] Computer technology composed with flexible and

accessible health information can provide educational support for patients with asthma.[33] Despite this, there could be disparities around accessibility, both in terms of computer ownership and technology literacy, and so it is essential that education packages in computer interventions are evidence-based and validated.

In conclusion, there is evidence showing that poor health literacy is a costly barrier associated with impaired asthma control in children. However, the reason between health literacy and asthma control are not to fully understood. Tailored education programmes and home-based interventions have shown promising effects.

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The Child with Recurrent Pneumoniae: A Challenging Issue in Paediatrics

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Introduction

Recurrent pneumonia is most commonly defined as the occurrence of at least two episodes within the same year or at least three episodes during a lifetime, with radiographic clearing of densities between occurrences.[1] On the other hand, pneumonia is considered to be persistent when symptoms or X-ray abnormalities last more than 1-3 months.[1] Pneumonia is quite a common condition in children. MacIntyre *et al*. have estimated that 7% of the paediatric population has a lifetime diagnosis of this lower respiratory tract infection.[2] The incidence of recurrent and persistent pneumonia is not well known. However a Canadian study observed that 8% of 2952 children hospitalised for pneumonia had recurrences.[3] Owayed *et al*. have also pointed out that most children with recurrent pneumonia had an underlying predisposing illness.[3]

Predisposing Factors

Many factors were found to predispose to the development of these recurrent infections. The main classification criterion is represented by the localisation of recurrences, that is whether episodes always occur in the same region or in different regions of the lung.[4]

The three most common underlying causes of site-specific recurrent pneumonia are local intraluminal obstructions, extraluminal compression or structural abnormalities.[5] The most frequent cause of intraluminal obstruction in children is foreign body inhalation, which should always be suspected in case of unexplained persistent cough and refractory parenchymal infiltrates, recurrent pneumonia in the same region, atelectasis or bronchiectasis.[6] Children under the age of 3 are at a higher risk of foreign bodies inhalation and there is a history of choking symptoms in only 40% of cases.[6] An unrecognised foreign body aspiration should be taken in mind in case of a child with wheezing, cough, dyspnoea and haemoptysis.[6]

Other causes of intraluminal obstruction, such as bronchial tumours, are less common in children.[7] Bronchial obstruction leads to an impairment in mucociliary clearance with accumulation of secretions and promotion of pulmonary infections. The main clinical conditions causing extraluminal compressions are lymphadenopathy, parenchymal tumours and congenital vascular anomalies, such as vascular rings and slings. Enlarged lymph nodes, especially parabronchial, subcarinal and perihilar nodes, may cause compression and narrowing of lung airways, resulting in reduced mucociliary clearance and increased risk of pneumonia because of the accumulation of infected secretions.

TBC plays an important role as a cause of lymphadenopathy in children but it can manifest with only non-specific symptoms such as cough, weight loss, fever and sweats.[8]

Other conditions determining the enlargement of lymph nodes are malignancies, such as mediastinal tumours and lymphomas, sarcoidosis, histoplasmosis and coccidiomycosis.

The main airway structural abnormalities; a further group of causes leading to recurrent pneumonia in a specific region of the lung, are pulmonary sequestration, congenital cystic adenomatoid malformations (CCAM), bronchomalacia, bronchial stenosis or atresia, localised bronchiectasis, tracheobronchus and bronchogenic cysts.

Pulmonary sequestration is a non-functioning mass of abnormal lung tissue that characteristically has no connection with the tracheobronchial tree and that receives its arterial blood supply from systemic circulation.[9] Depending on its location, pulmonary sequestration can be classified into intralobar or extralobar. Intralobar is the most common, and accounts for about 75% of sequestrations. It is characterised by an intra-pleural localisation of a pulmonary lobe, especially the left posterobasal region, and by a venous drainage into pulmonary veins.[10] Extralobar is localised outside the normal lung, it has its own visceral pleura and it usually drains into systemic veins.[11] Congenital cystic adenomatoid malformations (CCAM), classified into 5 types, represent approximately 25% of congenital cystic lung lesions, and their diagnosis can be suspected prenatally by ultrasonography.

Most cases are diagnosed within two years of life, rarely in later years, and they frequently present with recurrent or persistent pulmonary infections.[12] CCAMs deserve particular attention by the clinician since they may be associated with the early development of malignancies.[13, 14]

Structural abnormalities often require a surgical approach aimed at removing the underlying causes of recurrent pneumonia. The right middle lobe syndrome is a particular type of site-specific recurrent pneumonia and it is characterised by atelectasis, recurrent pneumonia or bronchiectasis, typically localised in the right middle lobe that is more susceptible to obstruction because of narrow diameter, pliable walls and the acute angle of its bronchus.[15] Although many conditions can result in this syndrome, the most common is asthmatic bronchial inflammation.

The main predisposing factors to non-site-specific recurrent pneumonia are immune disorders, asthma, aspiration syndrome secondary to oropharyngeal muscular incoordination or cough impairment, cystic fibrosis, primary ciliary dyskinesia (PCD) and other disorders of the mucociliary clearance mechanisms.[5]

Aspiration syndrome seems to be a significant cause of recurrent pneumonia, which may be the only manifestation. Indeed silent aspiration is very common in children and is often associated with neurologic impairment, developmental delay, and enteral feeding.[16, 17] Aspiration mostly occurs in right middle lobe because of its anatomical predisposition. Several etiologic factors, such as swallowing dysfunction, oropharyngeal lesions or esophageal disease, can determine an aspiration syndrome. Swallowing dysfunction is primarily associated with abnormal cough and gag reflex, impaired state of consciousness and inappropriate clearance of secretions.[18] Congenital esophageal atresia and tracheoesophageal fistula are congenital anomalies that often result in symptomatic aspiration, recurrent pneumonia and impaired pulmonary function.[19] The association of gastroesophageal reflux with aspiration is difficult to prove.[5] Asthmatic children are more likely to develop recurrent pneumonia, for example because they are more prone to develop middle lobe syndrome. Besides, airway hyperreactivity and obstruction caused by excessive mucus production may predispose asthmatic children to infections.[20] Finally, bronchiectasis, abnormally dilated bronchial segments that are inflamed and chronically infected by bacteria, should be taken into account not only as a predisposing factor to recurrent/persistent pneumonia but also as a major complication of this disease. They can be classified morphologically as cylindric, cystic or saccular and etiologically as congenital or acquired. The most common etiologic factors are cystic fibrosis, immunodeficiency and aspiration. Treatment of the underlying causes of bronchiectasis is important to prevent its further progression.[21]

Diagnostic Investigations

Children with recurrent or persistent pneumonia should be carefully screened to evaluate predisposing factors. The first approach to the child with recurrent pneumonia should be based on careful history taking since neonatal period, and the investigation of unexplained deaths or chronic respiratory diseases in the family. The presence of not only previous respiratory symptoms but also growth retardation, frequent or severe systemic infections, nocturnal symptoms or other diseases should be investigated. The second step in the diagnostic process includes a systematic physical examination. Fever, weight loss, retarded growth and other systemic symptoms may indicate tuberculosis, systemic diseases such as leukaemia or systemic infections. The latter are common in immunodeficiency disorders such as Wiskott-Aldrich syndrome, especially when eczema is present. Nasal polyps in children may be suspected to induce cystic fibrosis, while recurrent sinusitis, frequent otitis and situs inversus associated with recurrent pneumonia suggest primary ciliary dyskinesia. Dysmorphic features should make us search for chromosomal syndromes or immunodeficiencies instead. A physical examination of the pulmonary system can provide useful information for the differential diagnosis of lung diseases predisposing to recurrent pneumonia. The presence of cyanosis or clubbing at the extremities means that there is a condition of poor blood oxygenation, such as it happens in chronic respiratory diseases.

First-line laboratory investigations, such as white cell count, total neutrophil count, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) have an important role in the diagnostic process of pneumonia.[22] Evaluation of immunoglobulin and complement factors levels are also recommended as first-line laboratory investigations. High levels of major immunoglobulin classes due to persistent inflammation may mask significant defects in specific antibody production.[23] Therefore if antibody deficiency is suspected, baseline specific antibody levels should be measured. Specific antibodies responses should be tested versus both universal antigens, such as tetanus toxoid, and targeted ones, such as capsular polysaccharides of Streptococcus pneumoniae and Haemophilus influenzae type b. When baseline antibody levels are low, a re-measurement is warranted after three weeks from immunisation with specific antigens.

If antibody screening is normal but there is clinical suspicion or family history of immunodeficiency or serious infections in the history of a child, second-line immunological investigations are recommended. They include T-cell and B-cell typisation, complement system evaluation and phagocyte assessment. Laboratory investigations such as specific IgE levels (RAST) in asthma and aspergillus precipitins in allergic bronchopulmonary aspergillosis are useful in the diagnostic process. If tuberculosis is suspected, tuberculin skin test or Quantiferon are recommended. Instrumental examinations that can be used are imaging studies and invasive diagnostic procedures.

Chest X-ray is an essential criterion to define recurrent/persistent pneumonia, but it is not very sensitive for the diagnosis of early

bronchiectasis. That's why CT/HRCT is needed to investigate focal abnormalities and to diagnose bronchiectasis. Children with suspected aspiration or gastrointestinal anomalies require a barium study, while those with suspected gastroesophageal reflux need a 24h esophageal pH monitoring to be performed. Evaluation of the swallowing mechanism by videofluoroscopy or endoscopy is advisable in children with a history of coughing during feeding. If chronic aspiration is suspected, radionuclide salivogram with ^{99m}Tc-sulfur colloid needs to be performed.[5]

Since asthmatic children are more likely to develop recurrent pneumonia, pulmonary function testing, skin prick test and provocation testing may suggest a bronchial hyperreactivity or an underlying asthmatic condition.[20]

All children with bronchiectasis should be investigated to exclude cystic fibrosis unless an alternative cause can be identified. Two measurements of sweat chloride and CFTR mutation analysis are recommended to diagnose cystic fibrosis.

Primary ciliary dyskinesia should always be considered in children with history of neonatal respiratory distress and continuous rhinitis since neonatal age, situs inversus or bronchiectasis without other specific cause. In children with suspected ciliary defects a screening test with saccharin or nasal nitric oxide (NO) measurement should be performed.[24] For diagnostic confirmation, ciliary ultrastructure and function such as ciliary beat frequency are needed.

In a child with the suspect of foreign body inhalation or bronchial anatomical abnormalities, a bronchoscopy investigation should always be performed. It can be also associated with bronchoalveolar lavage when a pathogen characterisation or cytology of the lower respiratory tract are required.

Therapeutic Management

The recognition of predisposing factors in children with recurrent pneumonia is important for adequate prevention and specific treatment. According to Li *et al*., the identification of a cause led to a change in specific management in 56% of the cases.[21] A specific therapy should be prescribed to all underlying causes, such as gastroesophageal reflux and asthma, requiring medical treatment, or pulmonary sequestration and structural abnormalities, which often need a surgical approach. Middle lobe syndrome unresponsive to medical treatment should even undergo surgical resection of middle lobe to prevent severe complications.[15]

In some cases of immunodeficiency, replacement therapy with intravenous gammaglobulin (IVIG) significantly reduces the incidence of pneumonia, as well as mortality and morbidity.[5]

In children with bronchiectasis and cystic fibrosis or other disorders of mucociliary clearance mechanisms, airway clearance with respiratory physiotherapy, physical exercise or mucolytic and hyperosmolar therapies is very important for both the therapeutic management and the prevention of further progression of the disease.

Hypertonic saline nebulisation enhances tracheobronchial clearance inducing a liquid flux into the airways and thus preventing mucus accumulation.[25]

Children with bronchiectasis and recurrent or persistent pneumonia often require inhalatory drugs, such as bronchodilators, anti-inflammatory drugs, and antibiotics during exacerbations. Therapies should be administered for about 14 days. Indeed bronchiectasis in children appears to be more likely to improve or resolve with long-term appropriate antibiotic and physiotherapic treatment. Improvement in bronchiectasis appearance was observed in about one third of children treated with medical therapy alone.[26] Antibiotic choice is often empirical, unless an organism has been isolated by cough swab, sputum or bronchoalveolar lavage.

Conclusions

Children with recurrent pneumonia require a careful assessment to detect underlying predisposing factors and a specific management in order to promote early treatment and prevention. Recurrent pneumonia classification depending on the occurrence in a specific or in different lung regions, is essential in the differential diagnosis of the underlying causes. Careful history, physical examination, laboratory and imaging tests may provide a diagnosis in most cases. The most common complication of recurrent pneumonia in children is bronchiectasis, which should therefore always be investigated. An appropriate treatment is necessary to resolve underlying conditions and prevent further pneumonia episodes.

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Viruses in Paediatric Pulmology: A New Perspective

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Background

The recent development of new techniques of microbiological diagnosis through molecular biology has allowed the identification of new viruses involved in respiratory diseases in children, such as metapneumovirus (hMPV), bocavirus (HBoV), and new coronavirus (SARS-CoV, CoV-NL63 and CoV -HKU1). On the one hand, their involvement has been demonstrated in acute processes (bronchiolitis, bronchitis, pneumonia) in which, until now, only respiratory syncytial virus (RSV), influenza or rinovirus were considered as major causes. On the other hand, there is evidence of a relationship between viral infection and the subsequent development of chronic respiratory diseases, such as asthma. Recent data also highlights the potential role of viral reactivation in maintaining chronic respiratory conditions, such as cytomegalovirus (CMV).

Emerging Viruses in Acute Respiratory Diseases

Respiratory infections are one of the biggest causes of morbidity and mortality in paediatrics. The World Health Organization ranks respiratory-tract infection as the second leading cause of death in children aged <5 years. However, previous difficulties in identifying viruses as etiological agents of the infection, led to many processes being mistakenly considered as bacterial. This situation has led to a misuse of antibiotic treatment, prolonged hospitalisation and increased bacterial resistance.

In the past few years, the diagnosis of viral infections was based on immunofluorescence techniques, cell culture and serology. This situation has recently changed with the increasing development of direct identification techniques using molecular biology and polymerase chain reaction (PCR). This has allowed the identification of new etiologic agents, and has changed the classical vision of these acute processes.

These viruses, metapneumovirus (hMPV), bocavirus (HBoV), and new coronavirus (SARS-CoV, CoV-NL63 and CoV-HKU1) are often called "emerging viruses", but have probably been circulating in the human population for decades.

Human Metapneumovirus (hMPV)

Human metapneumovirus (hMPV) was first described in 2001 by Dutch researchers, using molecular biology techniques in respiratory secretions from children with lower respiratory-tract disease, in which the detection of the well-known viruses had been negative.[1] It has also demonstrated its presence in frozen respiratory samples from 1958, what suggests that hMPV has been present among humans for decades. Based on limited sequence data, this virus appeared to be closely related to the avian pneumovirus, a member of the *Metapneumovirus* genus, and was called human metapneumovirus (hMPV).

This RNA virus belongs to the *Paramyxoviridae* family and shares structural and clinical features with respiratory syncytial virus (RSV). hMPV has a worldwide distribution and has been identified on every continent. In temperate climates, hMPV circulates predominately in the late winter and spring, and the peak of activity at any given location often coincides with or follows the peak of RSV activity. In the last 10 years after its description, several scientific communications have proliferated referring to its prevalence and pathogenicity.

One of the largest series published about hMPV features is from the Spanish group, with a 5-year prospective study of this virus in a population of children hospitalised due to respiratory infections.[2-4] Their findings showed that it is a major etiologic agent of lower respiratory tract infections (LRTI), after RSV, rhinovirus, adenovirus and bocavirus, and is more frequent than influenza and parainfluenza, especially in infants and young children.[4] Subsequent studies have shown similar results, with a minor percentage of variations between series.[5-6] Furthermore, evidence from many studies has demonstrated that hMPV is responsible for a substantial proportion of lower LRTI in infants and young children.

Metapneumovirus is also the second leading cause of bronchiolitis in early childhood, only surpassed by the RSV, and their clinical

manifestations are indistinguishable. Features of hMPV infection included tachypnea, fever, cough, hypoxia, and changes on chest radiographs such as infiltrates, hyperinflation, and peribronchial cuffing. Other clinical manifestations were asthma exacerbations, otitis media, flulike illness and community-acquired pneumonia.[7]

Because of their similar seasonal distribution, co-infection between hMPV and RSV is common, and has been extensively documented.[7] However, there are conflicting data about its pathogenic effect. Some studies conclude that co-infection between VRS-hMPV carries a core outcome of the process, with an increased risk of hospitalisation, admission to the paediatric care unit, oxygen and even mechanical ventilation.[8] In contrast, other results suggest that co-infection with hMPV does not imply a worse outcome of the positive RSV bronchiolitis.[2, 3, 9, 10] Most likely, one of the causes of these differences remains in the risk factors present in the patients, such as prematurity or other underlying respiratory disease.

Human Bocavirus (HBoV)

Human bocavirus (HBoV) was first detected in 2005 by a group of Swedish researchers.[11] It is a DNA virus most closely related to the minute virus of canines (MVC) and the Bovine Parvovirus (BPV), which have been classified in the genus *Bocavirus* within the *Parvoviridae* family. HBoV infection has been detected worldwide and its seasonal distribution shows a peak in winter and spring.

Since initial observations, several series have reported that it has a great prevalence: HBov is found in 1.5-19% of children with respiratory diseases.[7] The differences in the results of these studies could be explained by the different methodologies and periods of the year in which samples are collected. All reports agree upon its high frequency in paediatric patients, especially in children aged < 3 years. Nowadays, it is considered as the second or third most frequently detected virus in children hospitalised for respiratory infections, after RSV and rinovirus.[7] The incidence in older children and adults is much less common.

HBoV infections showed a variety of clinical symptoms, including lower respiratory tract infections with high fever, cough, bronchitis, bronchiolitis, rhinitis, otitis media, laryngotracheitis, pneumonia and asthma exacerbations.

Bocavirus does not only have respiratory symptoms, but extrapulmonary features have also been reported, including skin rashes, gastrointestinal symptoms such as diarrhoea and lymphocytic meningitis.[7, 13]

One of the characteristics of HBoV is the high frequency of detection with other respiratory viruses. The percentage of co-infections is variable, between 50 and 90% of cases, and is more frequently mixed with infections such as RSV, rhinovirus and adenovirus. It has also been described with *Streptococcus spp* and *Mycoplasma pneumoniae*.[7] This phenomenon has questioned its role as a pathogen, being considered by some authors as a mere spectator of the infection.[7] Serological studies have shown that the mere presence of HBoV-DNA does not ensure an acute primary infection,[14] and indeed the DNA of the virus has been detected with high frequency in healthy asymptomatic children.[15]

Despite these data, other recent studies have shown that HBoV detection is very common in hospitalised children with LRTI, and their detection is significantly lower in healthy children.[16, 17] One explanation of these differences could be that the virus shedding period is so long that it can be detected months after the acute infection.[18, 19] That is the reason that some authors prefer to call it "co-detection" instead of "co-infection".

Although there is increasing evidence that HBoV is pathogenic for the human respiratory tract, nowadays there is no evidence to support Koch's assertions, and further investigations are needed to prove its pathogenic role.[20]

New Coronarivus

After the identification of SARS-CoV in China in 2002, new coronavirus have been discovered: CoV-NL63 (in 2004)[21] and CoV-HKUI (in 2005).[22] Both viruses circulate more frequently in winter and predominantly affect infants and young children.

Their clinical presentation is similar to other respiratory viruses, with upper and lower respiratory tract symptoms: croup, asthma exacerbations, bronchitis, bronchiolitis and pneumonia which, in some cases, is indistinguishable from RSV. Co-infection/co-detection with other respiratory viruses is also very common.[7] The possible relationship of CoV-NL63 with Kawasaki disease could not be demonstrated,[23] although there are still many questions to be answered.

In 2012 a novel coronavirus was identified. Human coronavirus (HCoV-EMC)[24] is associated with severe respiratory disease, although its clinical spectrum is not completely defined.

Viruses in Chronic Respiratory Diseases

Virus and Asthma

The relationship between RSV-bronchiolitis and the subsequent development of recurrent wheezing during childhood has been debated for decades, with multiple scientific evidence supporting this association.[25] Since hMPV is currently considered the second leading cause of bronchiolitis, the next question to answer is if this infection is also related to the subsequent development of recurrent wheezing or asthma.

Although there are few published data, it has been reported in animal models that hMPV infection induces lung inflammation and bronchial hyperreactivity in mice.[27, 28] Reviewing the literature, only one report studies the respiratory outcome of children hospitalised due to hMPV-bronchiolitis five years after their admission.[26] The conclusion is

that hMPV in infancy is an important risk factor for asthma at age 5, at least as strong as the observed with RSV infection. Further studies are necessary to support these data.

Rhinovirus infection has also been considered as one of the major risk factors of developing recurrent wheezing during childhood, even stronger than RSV infection (OR= 10 vs OR=3).[29, 30]

The rest of the emerging viruses are subject to the same questions. However, the high frequency of co-detections makes it difficult to demonstrate the association between one specific virus and subsequent weezing in infancy.

Viruses in Chronic Respiratory Diseases with No Acute Exacerbation

In the context of an acute respiratory infection, it is common to consider the virus detected in respiratory secretions as an etiological agent of the process.

However, the increasing development of molecular biology techniques has demonstrated that viruses are not only present in respiratory samples from respiratory exacerbations. These viruses have also been detected in the lower respiratory tract (bronchoalveolar lavage fluid obtained by bronchoscopy) of children with chronic or recurrent respiratory diseases whom underwent a bronchoscopy in a stable phase, without an exacerbation at the time of performance that could justify their presence.[31]

The purpose of the question is to elucidate the meaning of this viral presence, to clarify if it might have any involvement in the pathogenesis, development and prognosis of these chronic respiratory processes, as poorly controlled asthma, bronchiectasis, recurrent pneumonia and other diseases with torpid outcome.

On the one hand, we must remember the high frequency of co-infections and co-detections between different viruses, without having been able to so far exactly establish the pathogenic meaning of some of them.[7] Furthermore, the excretion periods of the viruses are sometimes very long,[18, 19] what could justify their presence.

However, in recent years there have been several studies published which focused on the reactivation of cytomegalovirus (CMV) in chronic inflammatory processes, which raises the question of whether this phenomenon might also occur with other respiratory viruses. CMV has traditionally been considered as a major cause of opportunistic infection in the immunosupressed patient, with a worse respiratory outcome. Nevertheless, recent data suggest that CMV may be a relevant cause of morbidity in non-immunosupressed patients with chronic inflamatory diseases, in whom active CMV infection is frequently detected in either the inflamed tissues or in the blood compartment.[32-35] Most of these studies refer to adult patients with severe acute diseases requiring admission to the intensive care unit.

According to the paediatric population, a study has recently been published which evaluates the presence of active CMV infection in children with chronic respiratory disease in a stable phase with no exarcerbation.[36] The presence of viral DNA was detected in respiratory samples (bronchoalveolar lavage obtained by fiberoptic bronchoscopy) and plasma through molecular biology techniques (PCR). At the same time, the CMV serostatus was studied (IgG-IgM) for each patient. Surprisingly, more than 50% of seropositive patients had CMV-DNA present in the respiratory tract, plasma, or both, indicating a local or systemic reactivation of the virus. This leads to the conclusion that active CMV infection is common in non-immunosuppressed children with chronic respiratory disease.

It has been suggested that pro-inflammatory cytokines from the underlying disease could promote CMV reactivation and replication. Similarly, persistent replication of virus in the lower respiratory tract induces inflammation that could lead to the local reactivation of the virus. In addition, CMV itself has immunosuppressive capacity that may potentiate the replication of other respiratory viruses, leading towards a vicious circle difficult to break.[34, 35]

These data should be checked with prospective studies to elucidate the clinical translation of this viral reactivation and the effects of CMV replication in lower respiratory tract in children.

Conclusions

The development of new diagnostic techniques using molecular biology has changed the microbiological map of viral respiratory infections in children. Although the clinical spectrum of some of these agents is still unclear, it involves new clinical and therapeutic challenges. The progressive understanding of these new infectious agents will allow better management of infection, access to vaccines and rational use of antibiotics.

This paper is also available in *Treatment Strategies - Respiratory* Volume 4 Issue 1: Romero Rubio M. T., Sendra, R. L., and Montaner, A. E., 'Viruses in Paediatric Pulmonology: A New Perspective', *Treatment Strategies - Respiratory*, 5 (2013 October) 75-78. Available at www.cambridgeresearchcentre.co.uk.

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Further Reading

Please see the abstracts below for further reading on paediatric respiratory diseases. These articles plus others are available in previous editions of *Treatment Strategies - Paediatrics*. Please see our website for more articles on paediatric respiratory diseases and a range of other topics within paediatrics.

Forecasting Models Of Pediatric Viral Respiratory Illness – Can We Predict The Future?

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In the United States, viral respiratory infections are a leading cause of illness and hospitalisation in young children. The United States Department of Health and Human Services estimates that in 2009 over 300,000 children were hospitalised as a result of infectious respiratory illnesses. Bronchiolitis related to respiratory syncytial virus (RSV) is the leading cause of hospitalisation in infants under the age of one year with an estimated 120,000 admissions and greater than 200 deaths per year.

Caring for infants and children with viral respiratory infections like RSV imposes a substantial resource burden in both the outpatient and inpatient settings. Children with risk factors such as chronic lung disease, congenital heart disease and neuromuscular impairment, are at increased risk of morbidity and mortality from viral respiratory infection. Population-based studies have demonstrated that up to 11% of hospitalised children with laboratory-confirmed influenza required treatment in the intensive care unit with 3% requiring mechanical ventilation.

This paper takes an in-depth look at time series modelling, and demonstrates both its positives and limitations using examples.

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

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

Non-invasive Respiratory Support (NRS) is an alternative respiratory treatment without the need for endotracheal and tracheostomy tubes. NRS could be delivered as non-invasive Continuous Positive Airway Pressure (nCPAP) or non-invasive Positive Pressure Ventilation (nPPV) via an interface (nasal/facial mask or helmet).

The aim of this paper is to update a recently published review by Chidini *et al*. (*Treatment Strategies - Paediatrics*, Volume 1 Issue 1, Page 45-49) on NRS in children with ARF by adding articles available in the literature since July, 2010 to November, 2011. The authors searched Medline, EmBase, and the Cochrane database, using the keywords "non-invasive" or "non-invasive (mechanical) ventilation", or "non-invasive respiratory support" for all reports of children with ARF. Papers on neonates were excluded.

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Treatment of Life-threatening Asthma in Children

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Introduction

Asthma is a chronic inflammation of the airways, with reversible airflow obstruction and enhanced bronchial reactivity. The symptoms are episodes of wheezing, breathlessness, chest tightness, coughing and excess sputum production.[1] It is one of the most common diseases in children worldwide, with a prevalence varying from 3.4% in Africa to 29.2% in Oceania. In Western Europe the prevalence is 9.7% in children from 6-7 years old, and 15.8% in children from 13-14 years old.[2] From these children respectively 12.6% and 15.2% have severe asthma, which is defined as at least 4 attacks in the past year, or sleep disturbance from wheezing 1 night per week, or wheezing severe enough to affect speech.[2] Approximately 50% of asthma exacerbations are triggered by respiratory infections. Other causes include allergen exposure (like dust mites, molds, animal dander), irritant inhalation (like tobacco smoke, air pollutants) and exercise.[3, 4] Exacerbations may have a progressive or abrupt beginning and always include a decrease in expiratory airflow, related to both airway inflammation and airway smooth muscle constriction, which may occasionally be severe enough to lead to life-threatening airway obstruction even in the absence of mucous plugging. Inflammation in asthma consists of airway oedema, cellular infiltration by eosinophils, activated CD4+ T lymphocytes and mast cells and intraluminal mucous plugs. In addition, during severe asthmatic exacerbations, dynamic hyperinflation affects airflow even more.[3, 4] Asthmatic exacerbations can be mild and resolve spontaneously or with home medication, but can also be severe and unreponsive to treatment, leading to death. Fewer than 10% of patients have exacerbations severe enough to be life-threatening, whereas around 2–20% of patients are admitted to the ICU and 4% of patients are intubated and mechanically ventilated.[3, 5]

This review aims to provide an overview of the treatment modalities of severe asthma.

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Conventional Asthma Treatment

The therapeutic aim of an acute severe asthma episode is to restore oxygenation and CO_2 removal by reducing bronchoconstriction, decreasing inflammation, and dissolving mucus plugs. The primary treatment of bronchoconstriction is nebulised short acting β2-agonists, like salbutamol. Anticholinergic drugs, like ipratropium bromide, decrease the secretion of mucus and give an additional effect when used in combination with a β2-agonist. The inflammation is treated with oral corticosteroids, like prednisone. Oxygen is given to improve hypoxemia, caused by a ventilation-perfusion mismatch. When inhalation therapy is not effective, intravenous β2-agonist and corticosteroids can be used. Intravenous magnesium sulphate has proven to be beneficial too, because of its smooth muscle relaxing properties. When the attack is triggered by an allergic reaction, epinephrine can be given intramuscular.[6, 7]

Intensive Care Treatment

Some children will not respond to the therapy mentioned above. These children with imminent ventilator muscle fatigue and progressive respiratory failure must be transferred to the paediatric intensive care unit. They may require mechanical ventilation and invasive monitoring of blood pressure and blood gasses.[8]

Although potentially lifesaving, the use of mechanical ventilation during an asthma exacerbation is associated with an increased risk of death from asthma. It has a risk of worsening bronchospasm and hyperinflation, barotrauma, and cardiovascular depression.[9, 10] Before starting intubation, proper sedation is in order. Sedation is indicated to improve comfort, safety and patient-ventilator synchrony, while at the same time decreasing oxygen consumption and carbon dioxide production. The most commonly used medication in adults is propofol.[3] It can be administered rapidly to a deep sedation level and has rapid reversal after discontinuation. Patients with life-threatening asthma sometimes only need mechanical ventilation for a short period, which makes propofol an elegant choice. In addition, it has some bronchodilatory properties.[3] In children it is used much less because of a possible fatal side-effect that is described in several case

series called the propofol-related infusion syndrome, with symptoms like metabolic acidosis, cardiac arrhythmias, renal failure, and rhabdomyolysis.[11-14] Other sedative agents like midazolam or sevoflurane are used, but time to awakening after discontinuation is longer and also difficult to predict.[3] Ketamine is often used in combination with another sedative agent, because it will maintain arterial pressure and it is thought to relieve bronchospasms. However a Cochrane Database Review showed that ketamine has no beneficial effect on children with severe acute asthma compared to a placebo.[15]

Rocuronium is the first choice for fast muscle relaxation. The addition of an opioid (morphine, fentanyl, sufentanyl or remifentanil) is often desirable in order to provide sedation, analgesia and respiratory drive suppression.[3] Mechanical ventilation supports gas exchange and lowers the workload of the respiratory muscles until other therapeutic interventions improve the clinical status of the patient. Initial ventilator management is aimed to prevent excessive lung inflation and ventilator-induced lung injury due to air trapping. This requires a slow respirator frequency, a prolonged expiratory time and permissive hypercapnia.[9, 10] In ventilated asthmatic patients the pharmacological therapy to improve the clinical status of the patient remains bronchodilation with intravenous short acting β2-agonists and corticosteroids. There are other experimental therapies attempted to obtain a faster improvement of the patient and enhance the successful outcome of patients.

Experimental Treatments

Sodium Bicarbonate

The most common acid-base disturbance in patients with life-threatening asthma is initially respiratory alkalosis, followed by metabolic acidosis. There are several causes of metabolic acidosis in asthma, including increased production of lactic acid by respiratory muscles due to exhaustive work of breathing, tissue hypoxia due to ventilation-perfusion mismatch and reduced cardiac output, decreased lactate clearance due to hypoperfusion of the liver, and increased renal bicarbonate loss due to compensation for the preceding period of respiratory alkalosis. Acidosis has a vicious negative effect on patients with asthma because it may decrease the effectiveness of β2-agonists and may produce ineffective rapid, shallow ventilation.[16] Several reports describe the use of IV sodium bicarbonate to treat the acidosis, and thereby indirectly increasing the effect of β2-agonists.[16-19] In these studies a significant decrease of pCO_2 with a significant increase of pH, and a prompt improvement of the clinical condition of the patient is observed.[16-19] Despite these reports, the use of sodium bicarbonate in the treatment of life-threatening asthma is not standardised in protocols, and is thereby not used in many centres. This could partly be due to the theoretical risk of a $PaCO_2$ rise after sodium bicarbonate administration because of inadequate gas exchange and hypoventilation, but this isn't observed in these studies.[16] Although, it should be recognised that increasing the effect of β2-agonists may cause hyperlactatemia and lactic acidosis, a reduction in β2-adrenergic therapy may be appropriate.[20]

Nebulised Epinephrine

Nebulised racemic epinephrine is used to treat upper airway inflammation such as croup[21] and lower airway inflammation in bronchiolitis.[22] A case report describes the successful use of nebulised racemic epinephrine in a patient with severe acute asthma refractory to standard therapy with salbutamol, ipratropium bromide, corticosteroids and magnesium sulfate. They observed a clinical improvement within 5 minutes.[23] A meta-analysis of randomised controlled trials comparing nebulised epinephrine (racemic or regular) to nebulised salbutamol in the initial treatment for acute asthma documented no statistical difference in improvement of pulmonary function.[24] Airway oedema and increased mucous production are other pathophysiologic factors besides bronchospams. It is possible that some patients with severe acute asthma may have relatively more airway oedema contributing to their respiratory distress than bronchospams. They may respond better to nebulised epinephrine than to nebulised salbutamol, or they may respond to nebulised epinephrine despite a failure to respond to aggressive β2-agonist therapy.

Aminophylline

The effects of aminophylline in asthma include bronchodilation and improved diaphragmatic contraction, for this reason it was the drugs of choice for many years.[25, 26] A disadvantage of aminophylline is the narrow therapeutic range and the toxic effects that occur when above this level, like hypokalaemia, insomnia, tachycardia, cardiac arrhythmias, convulsions and sudden death.[25, 26] A Cochrane Database Review in 2009 found that in children with severe acute asthma, who were not responding to maximal inhaled therapy and systemic corticoids, the addition of intravenous aminophylline improved lung function within six to eight hours of treatment with an improvement in symptoms up to eight hours after therapy. However, the addition of aminophylline was not associated with a significant reduction in the number of nebulised bronchodilator treatments and length of hospital stay.[25] More recently another systematic review found that there is insufficient evidence to support the routine use of aminophylline in the management of acute asthma when adequate inhaled β2-agonist treatment is provided. The authors observed no statistically significant differences in lung function between aminophylline and placebo at any time period studied, and the use of aminophylline caused more side-effects, like vomiting, palpitations and arrhythmias.[26]

DNA-se

One of the problems in asthma is mucus plugging and atelectasis. There have been a few reports that describe a positive effect of recombinant human DNAse to dissolve mucus plugs in children with severe asthma, improving the clinical condition of these patients.[27, 28] rhDNAse is an agent that reduces viscoelasticity of sputum in patients with cystic fibrosis. A recent study in adults tested the hypothesis that rhDNAse has a therapeutic role in acute asthma, and did not see a

clinical improvement compared to placebo. This suggests that there is no role for rhDNAse in the treatment of acute severe asthma.[29]

Volatile Anaesthetics

For several years inhalation of volatile anaesthetics, like halothane, sevoflurane, desflurane and isoflurane, have been used as last resort for the treatment of life-threatening asthma in children.[30, 31] These agents provide beneficial physiological effects including dilation of airway smooth musculature and reversal of bronchospasm, but the exact mechanism of its effect is not clear.[7] Proposed mechanisms include lowering of vagal tone, direct relaxation of smooth muscle tissue, inhibition of the release of bronchoconstrictive mediators, and synergy with catecholamines.[32] There is a clinical improvement within 1 hour after starting with a volatile anaesthetic, without severe side-effects.[33] Therefore it seems a promising therapy, however a major drawback for this therapy is that most PICU's don't have the equipment and knowledge needed for save delivery of volatile anaesthetics.

Heliox

The use of helium–oxygen mixtures (heliox) as a therapy for asthma is first described in 1935. Heliox is less dense than air, thereby improving expiratory flow and decreasing work of breathing. Because of this property it should also improve the delivery of aerosolised β2-agonists to the distal airways.[34-37] There have been small studies that describe this positive effect of heliox therapy in both children and adults with status asthmaticus. A Cochrane review didn't support the therapeutic use of heliox-driven albuterol in patients with status asthmaticus, but they noted that patients with a moderate-to-severe asthma exacerbation were perhaps more likely to benefit from albuterol delivered with heliox.[38] A recent study has tested this hypothesis in patients with a moderate-to-severe asthma exacerbation. They observed that heliox-powered nebulised albuterol therapy for children admitted to the hospital with moderate-to-severe status asthmaticus does not shorten hospital length of stay or hasten rates of clinical improvement when compared with air/oxygen-powered nebulised albuterol.[34] This suggests that the use of heliox treatment in the therapy for asthma is limited.

Extra Corporeal Life Support (ECLS)

Some patients will not improve, even though they receive the most aggressive therapy, including mechanical ventilation with controlled permissive hypercapnia, and general anaesthesia. They are unable to maintain adequate gas exchange, which leads to oxygenation failure, and with that multi-organ failure. Some case reports describe the use of ECLS as last resort in these patients.[39-41] ECLS supports adequate gas exchange until pulmonary function improves. All patients on ECLS recovered. These results suggest that ECLS has a place in the treatment of patients with life-threatening asthma, but only as last resort.[39-41]

Conclusion

Only a small portion of children admitted to the hospital because of an acute asthma attack require intensive care treatment. Aggressive therapy and optimal mechanical ventilatory management will be effective in the vast majority of patients. However some children require last resort treatment modalities to survive.

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Challenges in the Current Management of Patent Ductus Arteriosus in Extremely Low Birth Weight Preterm Babies

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Introduction

Ductus arteriosus (DA) is a blood vessel connecting the pulmonary artery to the proximal descending aorta. During foetal life, patency of DA is essential for the foetus to survive, as most of the pulmonary arterial blood is shunted through the pulmonary artery through the DA into the aorta. In term infants, functional closure of DA is usually within 24 hours of birth, and is followed by anatomical closure.[1] In preterm babies the presence of patent ductus arteriosus (PDA) is inversely proportional to the gestational age. The median time to spontaneous closure is considerably longer in extremely low birth weight (ELBW ≤1000grams) babies.[2]

Haemodynamically significant PDA can result in systemic hypoperfusion and pulmonary hyperperfusion. Therefore, the presence of a haemodynamically significant PDA potentially increases the risk of necrotising enterocolitis (NEC), intraventricular haemorrhage (IVH), congestive heart failure, pulmonary haemorrhage and chronic lung disease (CLD). However, these associated morbidities have not been shown to be directly caused by the presence of the PDA. These factors therefore influence the ideal timing to treat a haemodynamically significant PDA in ELBW babies, which remains controversial.

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Diagnosis

A small PDA is usually not associated with any significant symptoms or signs. However a haemodynamically significant PDA will result in a classical continuous murmur heard loudest in the left 2nd intercostal space, radiating to the back with peripheral bounding pulses. The apical impulse in ELBW babies can be prominent and may be heaving in the presence of a heamodynamically significant PDA. If a haemodynamically significant PDA persists, it may result in worsening respiratory status secondary to heart failure.

Currently, the majority of the neonatal units in the United Kingdom (UK) use echocardiogram to assess the PDA. The echocardiograms are predominantly performed by either neonatologists or paediatricians with echocardiography skills to assess the significance of the PDA and decide on the subsequent management.[3-5]

The ductal diameter is measured in the parasternal short axis view on echocardiogram. Evans *et al*., in their study identified PDA diameter of more than 2 mm as being significant.[6] It is also essential to ensure that the flow across the PDA is left-to-right and the character of the ductal Doppler flow pattern. A wide-open, unrestricted pulsatileduct results in volume overloading of the left heart and causes left atrial dilatation. A left atrial to aortic root ratio of ≥ 1.5 is said to be significant.[7] These collective echocardiographic findings about the PDA help us in deciding if it is haemodynamically significant and whether we should treat the PDA in an ELBW baby.

Management Options

Treatment options include conservative management, pharmacological management with cyclo-oxygenase (COX) inhibitor or surgical ligation of the PDA. The benefit of fluid restriction in the management of PDA in ELBW babies is uncertain but is commonly practiced in neonatal units. Prolonged use of fluid restriction would impact on the nutritional needs of these vulnerable ELBW babies.

Pharmacological management involves using a COX inhibitor, either

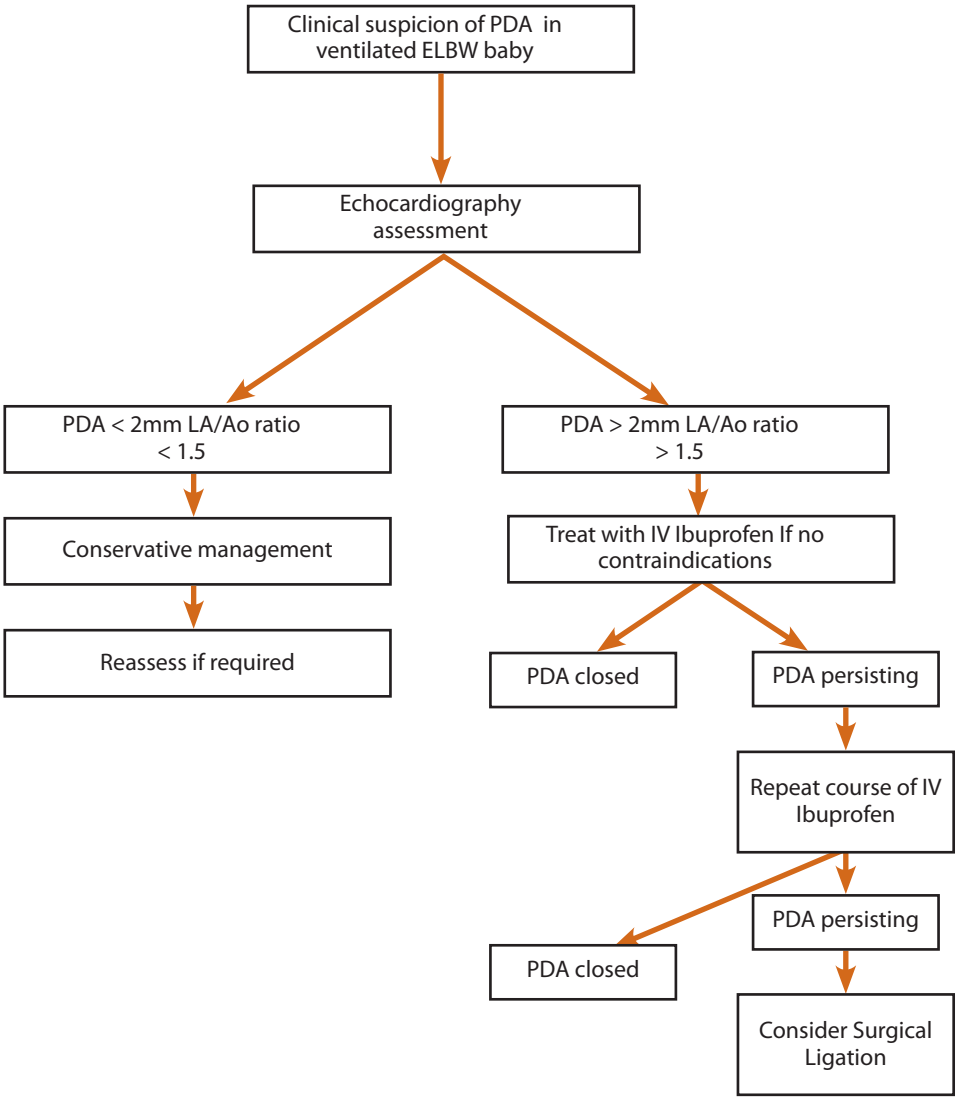

Figure 1. Algorithm for the management of PDA in ventilated ELBW babies.

indomethacin or ibuprofen. They are both administered intravenously (IV). Indomethacin and ibuprofen have equal efficacy in the closure of PDA in preterm babies.[8] Prophylactic indomethacin was shown to reduce the incidence of pulmonary haemorrhage and severe intraventricular haemorrhage but not death or disability in the long-term.[1,3] Meta-analysis of studies[9-12] comparing both COX inhibitors demonstrated short-term benefits of closure of PDAs and a reduced need for surgical ligation. However it did not show any significant reduction in NEC, and CLD at 36 weeks corrected gestational age or neurological outcome at 18 months. Based on this evidence, neonatal units across UK were using either indomethacin or ibuprofen to manage PDA in preterm babies ranging from prophylactic to symptomatic treatment.

Indomethacin is no longer available in the UK and the only available licensed COX inhibitor at the moment is IV ibuprofen. Because of this there has been a gradual move towards using ibuprofen. However, IV ibuprofen is contraindicated for prophylactic use because of increased risk of pulmonary hypertensive crisis in the trials conducted.[14] We currently practice early targeted treatment for the management of PDA in ELBW babies in our neonatal unit as shown in Figure 1.

Surgical ligation of the PDA involves a thoracotomy and has its associated complications such as pneumothorax, chylothorax, laryngeal nerve palsy, hypotension and cerebral injury.[15-17] Therefore it should only be considered after failed pharmacological management of a haemodynamically significant PDA in a ventilator dependent ELBW baby.

Controversies

Despite over 50 trials spanning 4 decades, there are still controversies in the management of PDA in preterm babies.[18] These are mainly around the long-term benefits of pharmacologically closing a PDA in preterm babies. There is a school of thought that the PDA is a consequence of being born prematurely, and that managing the underlying condition would facilitate its closure physiologically in time.

When we analyse the trials in detail, we find that the majority of the

trials that studied the use of prophylactic indomethacin were conducted before 2000 except for the TIPP trial. There were also heterogeneous dosing regimens used in these trials (except for the TIPP trial). All trials included babies older than 28 weeks of gestation. In the TIPP trial[13] ELBW were randomly assigned to receiving Indomethacin or placebo soon after birth (the presence of PDA was not assessed). They concluded that in ELBW infants, prophylactic indomethacin reduced the frequency of patent ductus arteriosus, need for surgical ligation and severe periventricular and intraventricular haemorrhage but it did not improve the rate of survival without neurosensory impairment at 18 months. Despite the lack of long-term benefits, several units in the UK were using indomethacin prophylactically in the past. Prophylactic management of PDA was discontinued because of the issues around the availability of indomethacin in UK.

The other studies also have their limitations. The studies that investigated the prophylactic use of ibuprofen included babies over 28 weeks of gestation as well[19-23] (except for 2 studies).[24, 25] The studies which looked at ibuprofen and indomethacin for the treatment of symptomatic PDA did not have adequate power and the babies were also older than 28 weeks of gestational age.[26-40] For early targeted treatment there were only a few studies with small number of babies in the groups. Despite one study showing a very high rate of CLD (92%) in the control arm, early targeted treatment with ibuprofen did not reduce CLD rate in this group of babies.[41]

Kluckow *et al*.[15] prospectively studied 126 babies born before 30 weeks with serial echocardiography. They noticed that the majority of the babies with PDA diameter of 1.6 mm at the age of 5 hours needed treatment for PDA later on in the life. They suggest using the above criteria for early targeted treatment. Given the current availability of only IV Ibuprofen, most units in the UK treat haemodynamically significant PDA following an echocardiographic assessment.

Conclusion

Recently, there are growing controversies as to whether we need to aggressively close the PDA in preterm babies with a COX inhibitor. The available evidence to date does not show any long-term benefits of pharmacologically closing a PDA in preterm babies. This causes significant dilemma in the management of these vulnerable ELBW babies in neonatal units across the country.

If we consider the pathophysiology of a haemodynamically significant PDA in an ELBW ventilated baby, weighing the risk benefits of the current option available, it might be worth considering pharmacological management with IV ibuprofen. If the haemodynamically significant PDA still fails to close after a course(s) of COX inhibitor and the baby is still symptomatic with static or increasing ventilatory requirements, surgical ligation should be considered in this group of babies.

In light of the controversy on pharmacological closure of PDA in preterm babies, we need a large multi-centre randomised controlled trial looking at the short-term and long-term benefits of early targeted pharmacological management of PDA with IV ibuprofen in ELBW babies. Furthermore, safety profile of oral ibuprofen should be confirmed by further large studies as an alternative to the IV preparation.

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Childhood Obesity; Top Priority in Preventive Cardiology?

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Introduction

Childhood obesity is evolving into a pandemic that jeopardises the health of middle-aged and even young adults. Associated co-morbidities are numerous and range from cardiovascular diseases (CVD) and diabetes to sleep apnoea, asthma and emotional disturbances caused by stigmatisation. Fortunately, timely intervention leading to normal weight in adult life restores cardiovascular risk to a level that is no different from those who have never been obese.[1]

The advent of non-invasive techniques that allow assessment of peripheral endothelial function has changed our understanding of the sequential steps that underlie the pathophysiology of CVD related to childhood obesity.

The endothelial cell layer, long underappreciated as a simple inert barrier, plays a crucial role in maintaining vascular tone, thereby regulating blood flow in relation to demand. The process of Vascular Smooth Muscle Cell (VSMC) relaxation is governed by nitric oxide (NO) (Figure 1). In response to increased shear stress or as a result of insulin signalling, increased phosphorylation of endothelial Nitric Oxide Synthase (eNOS) will increase NO formation. NO activates guanylyl cyclase, which induces VSMC relaxation, through increased production of cyclic Guanosine MonoPhosphate (cGMP).

Healthy endothelium, however, also guarantees atheroprotection through the control of platelet aggregation, of VSMC proliferation, and of adhesion and diapedesis of leukocytes. However, the maintenance of normal endothelial function requires a balance between vasodilating (NO-related) mechanisms and vasoconstrictive factors, which mainly result from damage imposed on endothelial cells. The latter for instance include classical risk factors, which are associated with obesity.

During the past decade it has become clear that endothelial dysfunction, which is the earliest demonstrable step in the process of atherosclerosis,[2] could serve as a major target and even a surrogate endpoint of interventional studies which aim to reverse the detrimental effects of long-standing obesity in children.

Factors Responsible for Obesity-related Endothelial Dysfunction

Hypertension is highly prevalent in obese children[3] and is associated with multiple factors that adversely affect endothelial function, including an overactive renin-angiotensin aldosterone and sympathetic nervous system, leading to impaired eNOS activity, peripheral vasoconstriction and increased oxidative stress.

The PEP Family Heart Study,[4] conducted in 3038 adolescents (12 to 18 years) has demonstrated that central obesity promotes hyperlipidemia, with elevated triglycerides, LDL-cholesterol, non-HDL cholesterol, triglyceride/HDL-cholesterol ratio and low HDL-cholesterol. Physical activity and physical fitness are increasingly recognised as independent determinants of longevity. Physical inactivity in obese children is manifest and a relation between physical activity/fitness and endothelial dysfunction has been demonstrated.[5]

Adipocytes are no longer considered a simple storage for free fatty acids. It is now generally accepted that adipose tissue is an endocrine organ, responsible for the release of a whole series of so-called adipokines (adipocyte-derived cytokines).[6] In addition, hypertrophic adipose tissue releases pro-inflammatory cytokines such as Tumour Necrosis Factor alpha (TNF-α), leading to enhanced expression of Intercellular Adhesion

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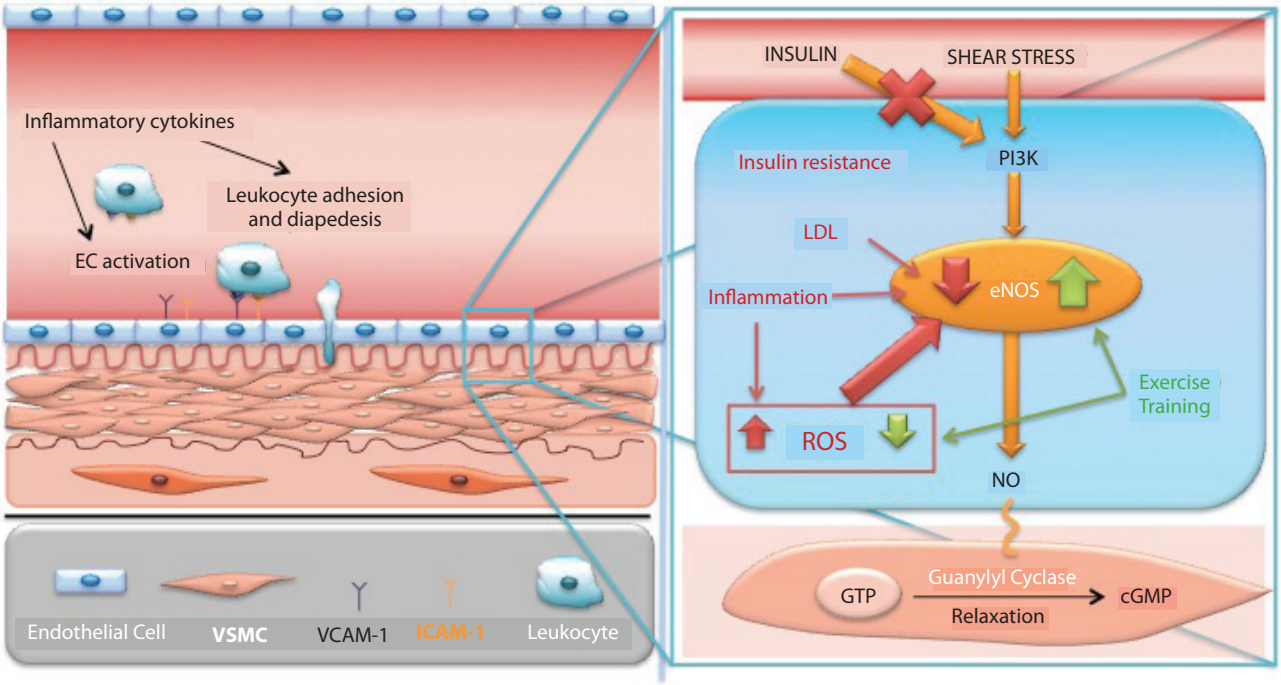

Figure 1. Left side: upon activation by inflammatory cytokines endothelial cells express adhesion molecules (i.e.; VCAM-1 and ICAM-1), which allow leukocytes to adhere, transmigrate and initiate a cascade of inflammatory reactions. Right side: schematic overview of nitric oxide (NO) production and relaxation of Vascular Smooth Muscle Cells (VSMC). In response to increased shear stress or as a result of insulin signaling, the phosphoinositol 3 kinase (PI3K)/akt pathway is activated leading to phosphorylation of endothelial Nitric Oxide Synthase (eNOS). eNOS converts L-arginine to L-citrulline and NO. NO activates guanylyl cyclase, which induces smooth muscle relaxation, through increased production of cyclic Guanosine MonoPhosphate (cGMP). Superoxide reduces NO bioavailability by reacting with NO to form peroxynitrite (ONOO-), which has strong oxidant properties.

Endothelial dysfunction in obese children is characterised by insulin resistance impairing insulin mediated NO production and subsequent vasodilation. Furthermore LDL and inflammatory cytokines are inhibitors of eNOS activation. Localised chronic inflammation leads to increased reactive oxygen species (ROS) generation, which also contributes to reduced bioavailability of NO and vasoconstriction. Finally, exercise training up regulates both eNOS protein expression and eNOS phosphorylation, and increases anti-oxidative mechanisms.

EC, Endothelial Cell; VSMC, Vascular Smooth Muscle Cell; VCAM-1, Vascular Cell Adhesion Molecule 1; ICAM-1, InterCellular Adhesion Molecule 1. PI3K, PhosphatidylInositol 3-Kinase; LDL, Low Density Lipoprotein Cholesterol; ROS, Reactive Oxygen Species; eNOS, endothelial Nitric Oxide Synthase; GTP, Guanosine TriPhosphate; cGMP, cyclic Guanylyl MonoPhosphate.

Molecule-1 (ICAM-1), InterLeukin (IL)-6, and Macrophage Chemo attractant Protein-1 (MCP-1). As a consequence, leucocytes adhere to the endothelium and diapedesis of monocytes from the circulation to adipose tissue is stimulated. As such, the stage for a chronic low grade inflammatory status is set, leading to enhanced oxidative stress and the subsequent inhibition of the vasodilating effects of NO, impaired generation of NO and eNOS uncoupling. Firstly, the production and secretion of adiponectin, a cytokine with anti-inflammatory, insulin-sensitising and anti-atherogenic properties, is reduced. Lower adiponectin levels affect endothelial function by reducing NO bioavailability and through its effect on circulating angiogenic cells.[7] Secondly, leptin is mainly secreted by white adipose tissue. It suppresses appetite, increases energy expenditure and has pro-angiogenic effects, including enhanced eNOS phosphorylation and the stimulation of endothelial cell proliferation. However, the benefits of increased leptin levels in obese individuals are mitigated by a selective leptin resistance for both central (appetite) and peripheral (pro-angiogenic) effects.[8]

Insulin resistance, and especially type II diabetes, are feared complications of childhood obesity. Since insulin is a potent vasodilator, the co-occurrence of endothelial dysfunction with insulin resistance comes as no surprise. In addition, insulin resistance is associated with increased levels of endothelin-I, a potent vasoconstrictor, and the upregulation of adhesion molecules. Diabetes mellitus leads to increased levels of reactive oxidant species (ROS) and Advanced Glycation End products (AGE), which further compromise NO bioavailability.

Finally obesity is an independent risk factor for sleep apnoea. Both in children and adults, sleep apnoea predisposes to the development of endothelial dysfunction,[9] through mechanisms that include hypertension and altered autonomic cardiovascular control.

Established and Novel Techniques to Assess Endothelial Dysfunction

Assessment of flow-mediated dilation (FMD) at the level of a large conduit artery, usually the brachial artery, is still the gold standard for evaluation of peripheral endothelial function, also in children.[10] It implies the use of high-resolution ultrasound to measure the internal diameter of the artery, from lumen-intima interface on the near and far vascular wall.[11] Thereafter, the brachial artery is occluded during 5 minutes using an inflated sphygmomanometer. After release, increased flow causes endothelial-dependent dilation through raised shear stress.[12] An

impaired proportional response (i.e., related to baseline diameter) is the signature of NO-dependent impaired endothelial dysfunction. Despite its universal application, the use of FMD is hampered by inter- and intra-observer variety and requires high levels of experience. Moreover, correct assessment of endothelial function demands strict technical and environmental standardisation, as well as patient adherence to diet and abstinence from smoking.

More recently, peripheral arterial tonometry (PAT) has been put forward as an alternative technique, which is semi-automated and less subject to interpretation. It involves probes that are placed on the index finger of both hands and by which pressure differences secondary to dilating arterioles in the fingers are measured. Similar to FMD, the brachial artery is occluded during 5 minutes. Following release of the cuff, the Reactive Hyperemia Index (RHI) is calculated after 90 to 150 seconds during the hyperemia phase and defined as the mean Pulse Wave Amplitude (PWA) divided by the pre-occlusion period. The ratio is corrected for the ratio measured at the contralateral hand and multiplied by a correction factor. Despite its clinical and outcome correlates, RHI is a measure of microvascular endothelial function and therefore, contrary to FMD, it does not solely depend on NO.[13] Other factors such as the vasodilator prostacyclin (PGI2), as well as Endothelium-Derived Hyperpolarising Factor (EDHF) and sympathetic tone play a significant role.

How Should we Approach Childhood Obesity and the Associated Endothelial Dysfunction?

The obvious goal of the management of childhood obesity is to achieve weight loss. In order to ensure a sustained adaptation of lifestyle, a multi-disciplinary approach is essential. Besides significant diet changes, the introduction of physical activity is an essential component of such a strategy. Mental coaching, psychological evaluation and family counselling are increasingly evaluated for their additive value in order to achieve long-term success.

Weight Loss

Weight loss ameliorates CV risk factors, such as hypertension, lipid abnormalities and glucose metabolism, all of which are known to be associated with endothelial dysfunction. It is difficult to tease out the absolute net effect of weight loss in terms of improved endothelial function, since the available literature mainly deals with multi-disciplinary approaches. In a small single-centre study, Kaufman *et al*. demonstrated that a 5 to 8% decrease in total body mass obtained with diet alone led to a significant decrease in weight, body fat percentage and BMI, with a trend towards improvement of endothelial function.[14] Comparing combined diet and 6 weeks of exercise training to diet alone in 82 overweight children, 9 to 12 years of age, Woo *et al*. saw improved endothelial function in both groups, albeit significantly more pronounced in the diet plus exercise group.[15]

Exercise Training

Based on a large study involving 6000 children between 11 and 19 years, De Bourdeaudhuij *et al*. concluded that overweight children are significantly less active than their healthy counterparts. Significant differences were also noted for vigorous and moderate physical activity.[16]

Exercise training is a potent adjunct treatment modality when it comes to improving endothelial function in obese children. As little as eight weeks of exercise training consisting of three 1-hour sessions of circuit training each week led to a significant improvement in endothelial function, even without weight loss in a randomised cross-over study involving 19 obese adolescents.[17] Two other studies confirmed the effect of exercise alone on endothelial function. Meyer *et al*. investigated the effects of 1 hour of training, 3 times a week during 6 months and noted a significant improvement of endothelial function and a reduction in IMT in young (14.7 ± 2.2 years) obese children.[18] Tjønna *et al*. demonstrated that 3 months aerobic interval training outweighed a multidisciplinary treatment programme of 1 year in terms of improved endothelial function and reduction in CV risk factors.[19]

Besides the modulatory effect of regular physical activity on CV risk factors, exercise directly impacts endothelial function by increasing endothelial shear stress. In adult patients undergoing coronary artery bypass surgery (CABG), exercise training prior to CABG led to upregulation of eNOS mRNA and higher eNOS protein and phosphorylation in arterial segments.[20] ROS generation was significantly lower in the training compared with the control group. On a functional level, exercise training resulted in improved acetylcholine-mediated vasodilatation of the arterial segments obtained from the left internal mammary artery.

Pharmacological Treatment

The available literature on pharmacological treatment of obese children with respect to the effect on endothelial function is limited. Since the withdrawal of both rimonabant and sibutramine, due the increased risk of psychiatric adverse events[21] and increased CV risk[22] respectively, orlistat, a reversible blocker of lipase, is the only drug still available to aid weight loss in Europe. Based on a recent meta-analysis of data obtained in children, it appears that a drug-related weight loss of 5 kg and 5 cm reduction in waist circumference after at least 6 months of therapy, did not improve lipid abnormalities nor insulin levels.[23] In an open-label trial conducted in adults and consisting of a calorie-restricted diet and 120 mg of orlistat, there was no demonstrable effect on FMD.[24]

Metformin is approved in many countries to treat insulin resistance in obese children. Despite its benefit in adults with metabolic syndrome, adding metformin to a structured lifestyle intervention did not reverse insulin resistance in obese children.[25]

Psychological Approach

Obesity in children is associated with both psychological and social problems. Psychosocial distress and eating disorders are more prevalent[26]

and are associated with a generally worse quality of life, further aggravating obesity. Therefore many treatment programs successfully included cognitive behavioural therapy, leading to a longer lasting effect in terms of weight maintenance. The main goal of such programs is to educate children about energy balance, so they learn to understand how obesity develops. To achieve lifestyle modifications children are taught self-regulation skills and actively participate to set up a tailor fit personal plan.[27]

Parents are involved in helping their child obtain a new lifestyle, including changes in food preparation and organising exercise, since including the parents is not only effective in treatment,[28] but also in prevention of childhood obesity.[29] The current evidence for preventive programmes is strong and recommended by the European Society of Cardiology in their recent guidelines on cardiovascular disease prevention,[30] to start in early childhood and to continue throughout adulthood and senescence.

Although the association of anger and hostility and coronary artery disease related morbidity and mortality is proven in adults,[31] it remains to be determined whether these psychological traits, which are highly prevalent in obese children, impose an additional cardiovascular risk. Interestingly, Osika *et al*. were able to demonstrate in 248 healthy children, that scores for anger, depression and anxiety are inversely correlated to endothelial function as assessed with Endo-PAT.[32]

Conclusion

The prevalence of childhood obesity is rapidly increasing and exposes these children to a significant cardiovascular risk. Research has mainly focused on vascular alterations in adults who have been obese for several decades, yet obese children represent the other end of the spectrum with respect to the pathogenesis of atherosclerosis. Endothelial dysfunction has been demonstrated to be the first, reversible step towards atherosclerosis and more translational and clinical research is necessary to fully understand this *primum movens*.

Finally, intensifying the collaboration between researchers and clinicians is essential to both understand and efficiently tackle childhood obesity associated cardiovascular disease.

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Upcoming Congresses and Meetings

13th National Autism Today: Winter Meeting

21 - 22 November 2013

Manchester, UK

The 13th National Autism Today: Winter Meeting will bring together leading experts from healthcare and education to discuss the central issues and practical management of autism and Asperger's syndrome. The meeting will look at many aspects of these disorders and their treatment, including the value of early screening methods, the use of assistive technologies, and potential co-morbidities amongst other topics. The meeting aims to facilitate the exchange of ideas between leading professionals in the field.

5th Annual Excellence in Paediatrics Conference

04 - 07 December 2013

Doha, Qatar

EiP has always prided itself in tackling the global needs of children, and indeed, the conference's delegates come from over 90 different countries. 2013's event aims to mark a turning point for paediatric education, and will feature more than 90 top academics and international key opinion leaders as well as presenting interactive case studies and hosting a number of workshops and Parents' Talks, in which media representatives will also participate. Both cutting edge and practical information will be at the forefront of this interactive conference, which will be comprised off symposia, plenary sessions, courses, workshops and ask-the-expert sessions amongst others.

World Congress on Controversies in Pediatrics (CoPedia)

24 – 27 April 2014

Prague, Czech Republic

CoPedia is a concept congress which is devoted to clinical controversies, debates and consensus in paediatrics. An academic gathering for physicians and scientists, the congress is based on debates and discussing controversial issues in a critical manner, with an emphaisis on clinical solutions. Ample time is given for speaker and participant interaction, and the congress is a leading forum for opinion leaders, clinicians and key companies within the industry. Copedia will feature sessions including lectures, workshops, poster and oral sessions, as well as many debate sessions.

7th World Congress on Pediatric Intensive and Critical Care (PICC)

04 – 07 May 2014

Istanbul, Turkey

PICC 2014 has built upon the success of previous meetings, and has incorporated comments that it has received from attendees to organise an innovative, collaborative programme which looks towards the future of paediatric intensive and critical care. Sessions will feature the latest interactive technologies, which will give delegates the opportunity to share experiences and increase their knowledge. The congress has a focus towards multidisciplinary care, and aims to be a creative and original congress in which attendees are stimulated and a real impact is made on the care of critically ill and injured children.

32nd Annual Meeting for the European Society of Paediatric Infectious Diseases (ESPID)

06 – 10 May 2014

Dublin, Ireland

Over 3,000 clinicians, researchers, residents and students will come together to enjoy the 32nd Annual Meeting of ESPID. Attendees will be treated to an unparrelleled educational forum where they will have the opportunity to learn about the newest developments, innovative techniques and advanced practices in the field of paediatric infectious diseases. The programme will include interactive case sessions, educational workshops, networking sessions and meet the professor sessions amongst others, which will be presented by international experts. ESPID 2014 looks set to be a fantastic event that is not to be missed.

European Society for Paediatric Urology 25th Anniversary Congress

07 - 10 May 2014

Innsbruck, Austria

The European Society for Paediatric Urology is a non-profit society which aims to promote paediatric urology, appropriate practice and education as well as encourage the exchange of ideas between practitioners involved in the treatment of genitourinary disorders in children. Held in the beautiful location of Innsbruck, Austria, this event is one of the biggest in the field of paediatric urology. The programme will feature a number of different sessions including symposia, poster and oral sessions, and will give delegates a well rounded understanding of this area of paediatrics.

Society for Pediatric Radiology (SPR) Annual Meeting and Postgraduate Course

13 - 17 May 2014

Washington D. C., USA

The Society for Pediatric Radiology is dedicated to fostering excellence in paediatric healthcare through diagnostic imaging and image-guided care in the treatment of neonates, infants, children and adolescents. The annual meeting is a powerful tool in achieving this aim, as it

features a number of symposia led by world-renowned experts in the field of diagnostic imaging, as well as plenary lectures, poster and oral sessions, workshops and much more.

European Society of Pediatric Otorhinolaryngology (ESPO) Conference 2014

31 May - 03 June 2014

Dublin, Ireland

The European Society of Pediatric Otorhinolaryngology aims to promote the quality of care of children with otorhinolaryngologic disorders within Europe. Indeed, paediatric otorhinolaryngology is quite different from that found in adults, and so each meeting pays close attention to all aspects wihin this field. The theme of ESPO's 2014 conference is 'Decision Making in Pediatric Otorhinolaryngology', and will feature sessions focussing on areas such as the airway, head and neck, otology and rhinology. As well as plenary lectures and symposia, the event will also feature workshops, round tables, free papers, albatross cases and a large exhibition hall.

12th Congress of the European Academy of Paediatric Dentistry

05 - 08 June 2014

Sopot, Poland

The 12th Congress of the EAPD will address research and clinical topics related to oral health promotion, the management of dental caries, tooth regeneration and challenges in treating children with autism spectrum disorders. The event encourages scientific discussion and debate, as well as the exchange of experience, as the society believes that this has an immense benefit for patients. The event will feature a mix of symposia, plenary sessions, and poster and oral sessions that will both inform and inspire those attending.

47th Annual Meeting of the European Society of Paediatric Gastroenterology, Heptology and Nutrition (ESPGHAN)

09 - 12 June 2014

Jeusalam, Israel

The 47th Annual Meeting of ESPGHAN is being jointly held by ESPGHAN and the Israeli Society for Paediatric Gastroenterology, Hepatology and Nutrition, and will include recent advances and state of the art lectures covering genetic, immunological, microbioogical and clinical developments in the field of gastrointestinal disorders, liver diseases and nutritian. The meeting is a fantastic place to network with colleagues and discuss and share clinical and research interests with others.

British Association of Paediatric Surgeons (BAPS) 61st Annual Meeting with IPEG 22nd Annual Meeting

22 July 2014

Edinburgh, UK

This year, the British Association of Paediatric Surgeons Annual Meeting is jointly held with the International Pediatric Endosurgery Group's 22nd Annual Meeting. Both organisations are interested in improving the standards of paediatric surgery, and the meeting will feature a number of keynote lectures, plenary sessions, meet-the-expert sessions and poster presentations focussing on current and future issues in paediatric surgery.

15th Congress of the international Society for Peritoneal Dialysis (ISPD)

07 – 10 September 2014

Madrid, Spain

The 15th Congress of ISPD will be a fantastic opportunity for specialists to congregate in one place from all over the world. The field of peritoneal dialysis is a growing field, which is increasingly contributing to cutting edge research in nephrology. The congress will be an excellent opportunity to realise the changes in the field and to envision new perspectives for basic and clinical research. The translational programme will bring together international experts and will focus upon innovations in diagnosis, advances in clinical practice, novel therapeutic approaches, and new insights into cellular and animal models. In addition, specific educational sessions, covering a basic knowledge will be available to encourage the participation of ISPD junior members.

The 5th Congress of the European Society of Paediatric Societies

17 - 21 October 2014

Barcelona, Spain

The 5th Congress of the European Academy of Paediatric Societies brings together Europe's foremost paediatric societies, European Academy of Paediatrics (EAP), European Society for Paediatric Research (ESPR) and European Society of Paediatric and Neonatal Intensive Care (ESPNIC), to give paediatric professionals unparalleled access to the best scientific research programmes. The congress will give a comprehensive insight into the most important areas within paediatrics, in particular the promotion and advancement of quality paediatric care and training worldwide, through a combination of plenary lectures, symposia, and parrellel sessions, as well as offering pre-congress courses. Submitted abstracts also play an important role in the congress, as they give rise to robust debates and furture collaborations, and shape the future of the paediatrics field. World-class experts will be speaking throughout the event, which prides itself on featuring something for everyone.

42nd Meeting of the British Society for Paediatric Endocrinology and Diabetes

12 - 14 November 2014

Winchester, UK

The British Society for Paediatric Endocrinology and Diabetes (BSPED) aims to improve the care of young people with endocrine disorders and diabetes mellitus by bringing together professionals from a range of disciplines including tertiary paediatric endocrinologists and diabetologists, general paediatricians and researchers amongst others. The society promotes research and training by encouraging collaboration and open dialogue, with abundant opportunities for the dissemination of results of research. The meeting of the BSPED will feature a range of sessions including symposia events, poster sessions, oral communication sessions, and plenary lectures, as well as many social events and opportunities to network with other healthcare professionals.

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