TREATMENT STRATEGIES
RESPIRATORY

Volume 4 Issue 1

- Asthma
- Cystic Fibrosis
- Diagnostics
- Lung Cancer
- Obstructive Sleep Apnoea
- Paediatric Respiratory Diseases
- Pulmonary Fibrosis
- Pulmonary Hypertension
- Tuberculosis
- Ventilation

Papers include:

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TREATMENT STRATEGIES RESPIRATORY

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

Managing Director **Nigel Lloyd**
nigel@cambridgeresearchcentre.co.uk
Director **Yunus Bhatti**
yunus@cambridgeresearchcentre.co.uk
Publishing Director **Sara Taheri**
sara@cambridgeresearchcentre.co.uk
Chief Sub-editor **Hannah Corby**
hannah.corby@cambridgeresearchcentre.co.uk
Filming **Martin Janes**
video@cambridgeresearchcentre.co.uk
Credit Control Manager **Emma Jones**
emma@cambridgeresearchcentre.co.uk
Accounts **David Mansell**

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

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Welcome...

Hello and welcome to the latest edition of *Treatment Strategies – Respiratory*. We have a fantastic publication lined up for you, and we are particularly excited to bring you our review of the European Respiratory Society (ERS) Congress 2013, held in Barcelona this September. The European Respiratory Society is the leading professional respiratory organisation in Europe, and the Congress is one of the most important respiratory events held in the continent. Our review will bring you the latest news, research and products from the show, as well as special video content.

Indeed, video is a medium in which we have heavily invested, and this year saw the launch of our Treatment Strategies TV division. Please do visit our video pages and YouTube channel to view a wealth of new and exciting content, including CEO interviews, symposia recordings and much more.

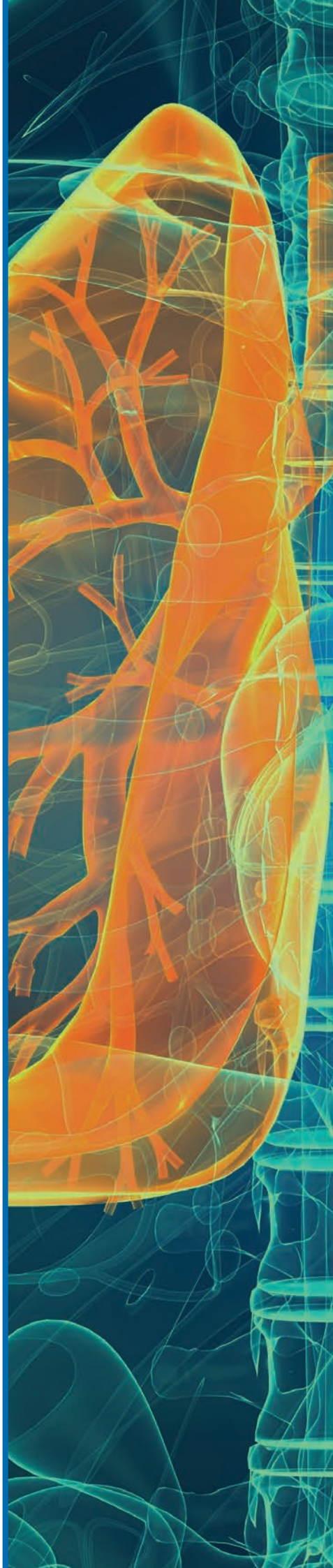
The publication also features a number of papers written by leading respiratory experts on a number of important issues within the field, including asthma, lung cancer, tuberculosis and ventilation. These papers have been carefully commissioned to give our readers an in-depth overview of some of latest developments and most important research in the field, and we hope that you find them both interesting and informative.

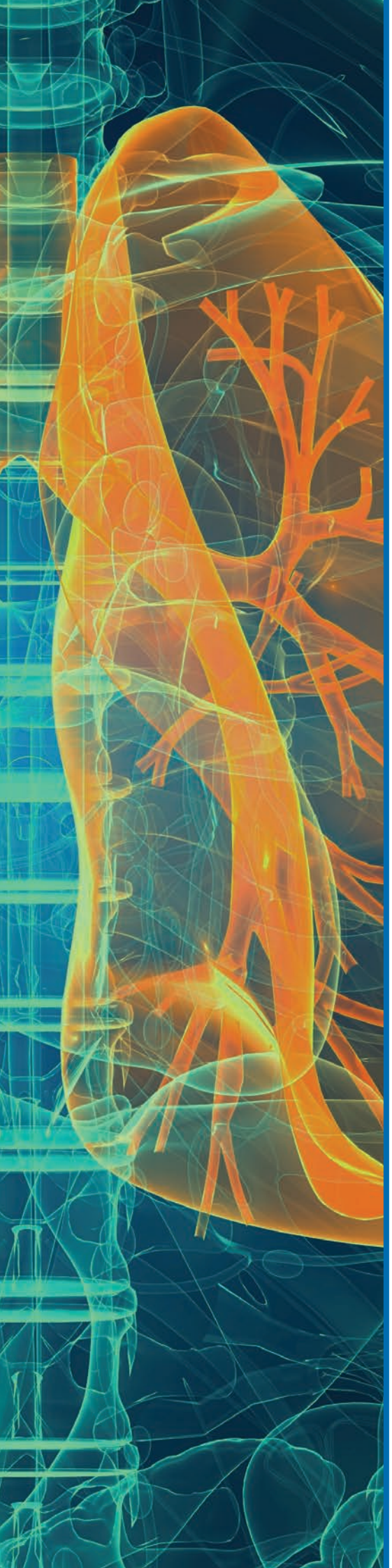
We hope that you enjoy this latest edition of *Treatment Strategies – Respiratory* and the changes that we have made to the publication. Please do let us know your thoughts, and you can find all of the team on both Twitter and LinkedIn. Remember, you can find all of the previous editions in the series for free on our website. We look forward to seeing you next year at the ERS Congress 2014 in Munich.

Nigel Lloyd, Managing Director

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

CONTENTS...





EDITORIAL ADVISORY PANEL

Foreword

Hannah Corby
Chief Sub-editor, *Treatment Strategies*, The Cambridge Research Centre

Welcome to the latest issue of *Treatment Strategies – Respiratory*. In this edition we are delighted to bring you an in-depth review of the European Respiratory Society (ERS) 2013, which features the breaking news, research highlights and the most innovative products that were showcased at the event.

This edition also features a number of papers which explore the latest treatment strategies within the respiratory field. Indeed, this is an important and dynamic area of medicine, in which new discoveries and developments are constantly being made. We hope that you enjoy the papers that have been selected.

Lung cancer is one of the most common and serious types of cancer, and so research in this area is ever developing in order to offer more effective treatment for patients. In this edition, Angelica Tiotiu and Yves Martinet discuss chemotherapy-induced anaemia in their article 'Management with Erythropoietic Agents of Chemotherapy-induced Anaemia in Patients with Lung Cancer.'

Asthma affects the daily lives of millions of people, and so is an important area of research. Ted Klok and Paul Brand investigate the need for comprehensive asthma care in achieving good adherence in children with asthma in their in-depth paper, while Bjorn Nordlund brings us a report about the links between health literacy and problematic severe childhood asthma. This issue also looks at other paediatric respiratory diseases in articles such as 'Viruses in Paediatric Pulmonology: A New Perspective' by Maria Teresa Romero Rubio, and 'The Child with Recurrent Pneumoniae: A Challenging Issue in Paediatrics' by Serena Moser and Giorgio Piacentini.

Cystic fibrosis was also identified as a thriving research area, and in Malcolm Brodlie, Chris Ward and Jim Lordan's article they evaluate a series of experimental models used to study cystic fibrosis lung disease, with an emphasis on primary airways epithial cell approaches. The long-term effects of tombramycin nebuliser solutions in patients with cystic fibrosis and chronic pseudomonas aeruginosa infection is discussed in Henryk Mazurek's report. Additionally, Colleen Denise Acosta, Sevim Ahmedov, Andrei Dadu, Martin van den Boom, Hans Henri Kluge, and Masoud Dara explore causal factors of drug resistance in tuberculosis in their paper, 'Causal Factors of Multidrug Resistant and Extensively Drug Resistant Tuberculosis: Regional and National Response in the WHO European Region.' We also touch on diagnostics in H. J. Smith's article, 'R-V Graph in Whole Body Plethysmography.'

This edition also includes a comprehensive events listing, which brings you details of the most important and most relevant shows within the respiratory field. We strive to bring you the most informative and up-to-date content, and we hope that you will enjoy the content within.

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ERS Congress 2013 Review

7 - 11 September, Barcelona

Annual Congress of the European Respiratory Society

INSIDE...

The Congress

The Exhibition

Sara Taheri, *Treatment Strategies*, is delighted to bring you our review of the ERS Congress 2013. Our largest review yet, it features all of the breaking news, awards, research, and symposia proceedings, as well as the most innovative products from the congress. This comprehensive review is followed with a series of posters that were showcased at the event, the findings of which will have a direct impact upon the future of respiratory medicine.

The European Respiratory Society (ERS) was founded in 1990 and has more than 10,000 members in 100 countries. The ERS Congress has experienced continued growth, making it one of the largest non-profit medical organisations in the world. Indeed, the ERS Congress is now the world's largest congress on respiratory health and disease. This year, ERS presented an outstanding scientific and educational programme addressing the needs of respiratory health specialists, healthcare professionals and general practitioners.

The focus for this years congress was the advocacy for lung health in Europe and beyond, as well as a broad range of other activities aiming to alleviate suffering from respiratory diseases. Bringing experts together from across Europe, the congress aimed to identify crucial gaps in lung health research and find innovative ways in which to bridge them. In particular, it looked to explore the areas of lung biology and the ageing lung and personalised medicine and risk factors.

The ERS are always looking at ways of making the congress more attractive to younger members, and ERS President, Francesco Blasi, gave a special welcome to these individuals, highlighting the new Junior Members Committee and its dedicated website. He highlighted the fantastic opportunites to interact with colleagues and specialists, and the congress' staus as an important arena for new proposals. He also emphasised how important younger members are for the future of the society.

Other highlights mentioned in the welcome included the recipient of the ERS 2013 Educational Award, Prof. Nicolino Ambrosino and the recipient of the

Fira Barcelona was the host to this year's exciting ERS Congress.

Jean-Claude Yernault lecture, Prof. Patrick Levy. There were also welcome speeches from the congress chairs including the Congress Co-chair Judith Garcia Aymerich and Congress Chair Joaquim Gea.

Overall, the ERS covers a wide range of disciplines, all of which are important to maintaining the success of the congress. Several highlights were in place with colour tracks and assembly topics to guide attendees through the sessions. These sessions were shortlisted and tagged in order to ensure that participants could quickly and easily create their personal programme throughout the duration of the event.

The educational programme incorporated topics and formats designed to appeal to professionals from all fields of respiratory medicine: 20 Postgraduate Courses, world-renowned teachers and exponents at the 13 Meet the Expert Seminars, 6 Early Morning Seminars focused on the practical application of knowledge, and 9 hands-on Educational Skills Workshops.

The society continues to achieve numerous successes in public policy, voicing needs in key areas of respiratory medicine as well as in public health, research, environment and tobacco control. It adopts a variety of approaches and strategies to influence the EU legislative processes through widely disseminating ERS policy positions, engaging with EU policy makers, leading policy awareness campaigns and inviting supportive members of the European Parliament to host high-level ERS events.

Last year, the society's focus was the Horizon 2020 programme, which will be the main European research and innovation tool during 2014–2020. Together with other societies the ERS has actively encouraged the funding for health research under the programme. As a member of the Alliance for BioMedical Research in Europe (BioMed Alliance), ERS has been working towards improving the entire structure of coordinating European Health Research. They believe that by facilitating the interpretation of research findings in the fragmented research landscape where duplication often occurs, this will result in health and economic benefits. Together with the Biomed Alliance, the ERS has proposed establishing a strategic advisory body, which would comprise experts with first-hand experience in the health research field. This body could help strengthen and empower the existing EC advisory bodies' structure in order to adopt a more strategic approach to research and innovation, as well as develop a long-term vision and provide proactive advice, in close cooperation with the EU Commission.

Additionally, the ERS is also participating in the new 'Economics of Chronic Diseases' EU project, which will examine the best methods for assessing the cost-effectiveness of preventing, screening and treating chronic diseases, including COPD. The project will increase the knowledge base for reducing early death from COPD and which interventions are most cost-effective over time.

The ERS is also dedicated to tobacco control and with the Tobacco Control Committee (TCC) they develop solid partnerships with cancer and heart organisations, who together have assisted in producing a strict code of conduct for relations with the tobacco industry.

The TCC's main activities this year include setting up a research-based website for policy makers on the health effects of smoking in Europe, 'SmokeHaz' and promoting for the strongest possible EU Tobacco Products Directive. As one of the founding members of the Smoke Free Partnership (SFP), the ERS has been at the forefront of the campaign to achieve comprehensive smoke-free laws across Europe.

Barcelona

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

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

Barcelona is also one of the world's leading centres for world-class meetings such as the ERS, as well as for tourism, economics and sports. Its influence in science, commerce, education, entertainment, media, fashion and the arts all contribute to its current status as one of the world's major global cities.

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

Young Fellows and Scientists Sessions

This year at the congress, specially prepared sessions were available for young fellows and scientists which provided them with key information and encouraged networking opportunities

The Fellows' Get-Together was held on Saturday 7th September, and was organised and chaired by Robert Bals (ERS Research Director) and Co-chaired by Laurent Nicod (ERS Programme Committee Chair).

This gathered ERS Fellows who were awarded an ERS Fellowship between 1997 and 2013, as well as the experts who were involved in the reviewing procedure of the applications. Fellows shared experiences with those interested in applying for an ERS Fellowship, which provided invaluable information on funding opportunities in 'How to build a career' and European Commission Fellowship funding opportunities.

Indeed, the congress provided a valuable networking platform for young individuals wanting to interact with experienced ERS Officers or those that want to share their experiences with other young fellows. A special focus was placed upon the topics 'How to write a good successful grant application' by Rory R. Morty, an ERS Evaluation Committee Representative, and 'The future of respiratory medicine and young fellows' by Prof. Stephen Holgate, the ERS Scientific Committee Chair.

These sessions provided a valuable networking platform and enabled Fellows to present the results of their work. Prospective Fellows were also encouraged to join the get-together and find out what they could achieve by applying for an ERS Fellowship.

The ERS Young Scientist's Networking Evening took place on Tuesday 10th September. This event provided the opportunity to meet and interact with leaders in respiratory medicine and the ERS leadership. Prof. Stephen Holgate, ERS Scientific Chair, gave a presentation on 'Making the best of opportunities to create a career in respiratory research'.

The results of the ERS Best Abstract Awards for Young Investigator Competition 2013 were also announced at this event.

Importantly, educational opportunities were provided throughout the Congress, in sessions including Meet the Expert Seminars, Morning Seminars and Educational Workshops in the educational programme.

There was also the opportunity to take the European examinations in adult and paediatric respiratory medicine (HERMES examinations).

The Postgraduate Courses were held on Saturday 7th September and included:

- How to build an experimental animal lung lab.
- Assessing the health status and quality of life in asthma and COPD patients.

The Educational Skills Workshop was held on Sunday 8th September and covered sessions on Endoscopic lung volume reduction and endosonography.

On Sunday 8th September the 'Meet the Expert Seminars' including the Nuts and bolts of cardio- pulmonary exercise testing (CPET): theory, guidelines and practice were held, while the session 'What can we learn from large scale COPD studies?' was held on Monday 9th September. The management of severe sepsis in respiratory tract infections was held on Tuesday 10th September.

The scientific programme ran from Sunday 8th September to Wednesday 11th September. This was a highly comprehensive programme which addressed the latest advances in clinical diagnosis and treatment of lung disease.

Awards and Grants Presentation

ERS Assembly Lifetime Achievement Awards

The ERS Scientific Committee honoured Prof. Elisabeth Brambilla, Prof. Marc Estenne and Prof. Francine Kauffmann with the 2013 Assembly Lifetime Achievement Awards

Prof. Elisabeth Brambilla was awarded a Lifetime achievement award during the Cell and Molecular Biology Assembly, on Monday 9th September. She has made major contributions to the ERS and their members in her positions as Group Chair, Assembly Secretary and Assembly Head of the Cell and Molecular Biology Assembly. In particular, she supported both basic and clinical research and was very successful in bringing basic scientists and clinicians together to benefit patients suffering from lung diseases. Her research is focused on lung pathology and lung cancer, and she has significantly moved this area forward, both within the ERS and in other societies.

Prof. Marc Estenne was honoured with a Lifetime achievement award during the Thoracic Surgery and Transplantation Assembly Meeting, which took place on Sunday 8th September. He served both as Secretary (1994-1996) and Chairman (1996-2000) of the ERS Scientific Group on Transplantation. Prof. Estenne was a true pioneer in advertising lung transplantation among chest physicians and convincing them this was no longer an experimental treatment. He organised plenary sessions devoted to transplantation during the ERS Annual Congress. Under his guidance the Lung Transplant Group developed into a highly effective and friendly interactive forum where anyone seeking advice about the challenging medicine that transplantation was at that time got connected. As one of the most important lung transplant pioneers, Prof. Marc Estenne significantly contributed to the success and advancement of lung transplantation within Europe.

During the Occupation and Epidemiology Assembly Meeting held on Monday 9th September, Prof. Francine Kauffmann was awarded with his lifetime achievement award. Prof. Francine Kaufmann is currently Director of Research at INSERM (Institut National de la Santé et de la Recherche Médicale), in Villejuif, France. Internationally renowned as a respiratory epidemiologist with a continuous involvement in both environmental and genetic factors, she chaired the long-range planning committee of the Prof. Marc Estenne served both as Secretary (1994-1996), Occupation and Epidemiology Assembly and Chairman (1996-2000) of the ERS Scientific Group on successful research seminars on 'Post Genome Epidemiology'.

Congress Chairs' Award

This year, the Congress Chairs honoured the achievements of Prof. Josep Roca, Director of the Lung Function Unit at the Hospital Clinic, Barcelona. Josep Roca is Prof. of Medicine at the University of Barcelona, Coordinator of a Master in Respiratory Medicine, and Coordinator of BioHealth Computing Erasmus Mundus in Barcelona. He is leading the deployment of the ICT program on chronic patient management at the Hospital Clinic.

Prof. Roca is currently leading a multidisciplinary team working on research and development projects addressing different aspects of chronic diseases. He is the coordinator of the NEXES project, aiming to validate and promote adoption of innovative services for chronic patients supported by information and communication technologies. Prof. Roca is also the scientific coordinator of SYNERGY, and member of the VPH NoE Advisory Board. He is currently leading two consortia on research and development projects addressing different aspects of chronic diseases, including NEXES and Biobridge.

Within the ERS, Josep Roca was President of the European Respiratory Society during the period 2000–2002, Chairman of the Pulmonary Circulation, Gas Exchange and Exercise Group, and the Congress Chair of the ERS 20th Annual Congress in 2010.

Presidential Award

The Presidential Award 2013 recognised the work and achievements of Julio Ramirez, currently Chief of the Division of Infectious Diseases in Louisville, US. Julio Ramirez is the Chief of the Division of Infectious Diseases, Prof. of Medicine, and Director of the Infectious Diseases Fellowship Training Program at the University of Louisville School of Medicine in Louisville, Kentucky. He is also a Fellow in the American College of Physicians.

Dr. Ramirez's research interests include: clinical research in the field of pneumonia, and basic research in the field of diagnosis and pathogenesis of infections due to atypical pathogens.
With more than 100 publications in these areas in journals such as Annals of Internal Medicine, Archives of Internal Medicine, Clinical Infectious Diseases, and Chest. He is also a reviewer for several journals including the *New England Journal of Medicine* and *Annals of Internal Medicine*.

Dr. Ramirez served as a member of the American Thoracic Society Committee for the development of national guidelines for management of community-acquired pneumonia and was also a member of the Food and Drug Administration advisory committee for anti-infective drugs. His activities within the ATS led him to collaborate with the ERS and the ERJ and expand his influence in Europe.

'Quit Smoking with Barça' Recognised for Boosting Smoking Cessation in Europe

At the opening ceremony of the ERS Congress, The European Lung Foundation (ELF) and The European Respiratory Society (ERS) proudly presented the prestigious annual public health award to the 'Quit Smoking with Barça' campaign.

The ELF and ERS recognised this campaign specifically for its contribution to improving European lung health, and for being the first initiative of its kind between a major public institution and a world leading sports club.

'Quit Smoking with Barça' was launched in December 2012, to build on the success of the EC's "Ex-smokers are Unstoppable" campaign. The programme is built around the FCB iCoach, an evidence-based, digital quit smoking tool to help you quit smoking for good. The programme invites smokers to complete a short questionnaire that determines the type of coaching that they will need in order to quit. Based on their responses, the individual receives personalised tips, information and motivation directly from FC Barcelona players, coaches and staff. By harnessing the support of FC Barcelona's millions of fans, this unprecedented partnership set out to help many more of Europe's 140 million smokers to become unstoppable ex-smokers for life. Barça pride themselves on being more than a club, and they demonstrate this by encouraging their fans to be as passionate about their health as they are about their heroes on the pitch.

The campaign has drawn praise from the scientific and medical community for promoting the life-long benefits of quitting smoking.

Monica Fletcher, ELF Chair explained that it was a unanimous decision to honour the campaign with this year's ELF award, "What impressed us most about this campaign was its unique approach to reach people who have not previously been successful at quitting smoking, or hadn't even tried to quit. The campaign has helped these people quit for good, making a significant impact in our shared quest to highlight the importance of good lung health."

Paola Testori Coggi, Director-General for Health and Consumers, European Commission said that a major catalyst for the European Commission and Barça working together is their shared commitment to protecting people's health. "We are honoured to be here alongside FC Barcelona to receive this award for the 'Quit Smoking with Barça' campaign. I am pleased that the positive impact we've made through this partnership has been recognised by the wider health community."

After only 3 months, more than 70,000 smokers across Europe had already been reached by the campaign and that number continues to rise. So far, nearly 400,000 smokers across Europe have sought to quit using the programme; with a 37 percent self-reported quit rate.

"We are delighted to have been able to collaborate with the European Commission on such an important public health issue. We are proud to stand alongside the EC, especially here in our city of Barcelona, to collect this ELF award. It shows that thankfully our message is being noticed and that our combined efforts are making a positive difference. At Barça we firmly believe in our motto 'more than a club' and we promote values of respect, health and social commitment. The 'Quit Smoking with Barça' programme allows us to live that motto" said Dr. Jordi Monés, head of FC Barcelona's medical area.

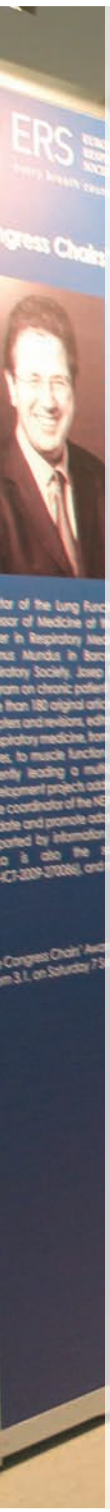
ELF and ERS are proud to be associated with the campaign and to be working together in Barcelona during this congress to support and promote the message of lung health and smoking cessation.

ELF Chair, Monica Fletcher, said: 'As healthcare professionals we are really inspired by the "Quit Smoking with Barça" campaign and the incredible steps they've taken in de-normalising smoking across Europe. I am proud to present the campaign with the 2013 ELF Award and would like to extend my thanks and congratulations to all who have made this campaign a success.'

Please find more information on the initiative and the tool at:

www.quitsmokingwithbarca.eu

COPD Biomarker Qualification Consortium Announces New Biomarker



The COPD Biomarkers Qualification Consortium (CBQC) has announced that it has submitted a Qualification Package to the Food and Drug Administration (FDA) for plasma fibrinogen as a new drug development tool. The Qualification Package is the result of progressive discussions between the FDA's Qualification Review Team and the CBQC.

The CBQC brings together government agencies, academic institutions and pharmaceutical companies that will share research data on COPD biomarkers—indicators of disease progression/severity. The goal is to assemble data under the auspices of the Consortium that will permit official recognition of biomarkers that can improve disease monitoring and expedite new therapies for the world's fourth leading cause of death.

"The heterogeneous nature of COPD complicates development of new treatments, with COPD patients responding differently. Fibrinogen has been submitted to the FDA as a tool that will help address this problem."

"To the best of CBQC's knowledge, fibrinogen is the first clinical biomarker achieving this milestone in the U.S.," says Dr. Ruth Tal-Singer, CBQC Co-chair, Vice President, Clinical Discovery, Respiratory Area Therapy Unit at GlaxoSmithKline.

"This breakthrough highlights the power of working together across multiple companies, academic centres and government organisations to achieve our common objective of improving the way we study novel medicines. The CBQC looks forward to the results of FDA review while planning for a fall 2013 submission to the European Medicines Agency."

To support the Fibrinogen package, CBQC compiled a unique database of subjects from five individual studies, allowing integrated analyses to support two proposed uses as a prognostic biomarker to enrich clinical trial populations with Chronic Obstructive Pulmonary Disease (COPD) subjects at increased risk for all-cause mortality or COPD exacerbations.

Fibrinogen, a protein that can be measured in the blood, is a promising biomarker – a tool used for early detection of a disease – that identifies a group representing 25 to 30 percent of all COPD patients.

Dr. Stephen Rennard, CBQC Co-chair and Larson Professor of Medicine, University of Nebraska, states, "The heterogeneous nature of COPD complicates development of new treatments, with COPD patients responding differently. Fibrinogen has been submitted to the FDA as a tool that will help address this problem."

John W. Walsh, President and Co-founder, COPD Foundation, adds, "The Consortium is providing a unique and productive opportunity to bring new drug development tools to the research community, with the ultimate goal of providing new treatments to patients who urgently need them."

For more information Visit
www.copdfoundation.org

The 2013 Yernault Lecture

The Jean-Claude Yernault Lecture honours active members of ERS who have made an outstanding contribution to education in respiratory medicine or the allied professions.

Jean-Claude Yernault was Chair of the first ERS Annual Congress in Brussels in 1991, ERS President 1991–1992 and the first Chief Editor of the European Respiratory Journal (1988–1989). He was instrumental in the creation of the European School of Respiratory Medicine (ERS School) in 1992, which he chaired from 1992 to 1998.

The Yernault Lecture honours active members of ERS who have made an outstanding contribution to education in respiratory medicine or the allied professions.

On Sunday 8th September, Patrick Lévy, Prof. of Physiology at Grenoble University Hospital, France spoke on 'Obstructive sleep apnoea as a model of systemic disease' for the 2013 Yernault Lecture. In his lecture summary, Prof. Lévy discussed how sleep apnoea generally results from pharyngeal collapse and leads to the so-called obstructive sleep apnoea syndrome (OSAS). OSAS is associated with excessive daytime sleepiness and chronic fatigue and with cardiovascular and metabolic consequences. Acute haemodynamic changes during obstructive apnoea are mainly due to sympathetic activation. These results from changes in blood oxygen and carbon dioxide content, as well as sleep fragmentation and intra-thoracic pressure changes. Chronic consequences are linked to the sustained increase in sympathetic activity as well as endothelial dysfunction and vascular remodelling. These vascular changes seem to be a consequence of the oxidative stress and systemic inflammation associated with OSAS. Metabolic impairment also plays a role.

There is evidence of multi-organ impairment, which has been related to the severity of hypoxia. Thus OSAS increases the risk of hypertension, coronary heart disease, arrhythmias, sudden death and cardiovascular mortality, and represents a model of systemic disease. Finally, continuous positive airway pressure (CPAP) has been the first-line treatment for the last 30 years, and partly prevents the excess cardiovascular morbidity and mortality. It also suggests adding other treatment modalities to deal with the global consequences of sleep apnoea.

The European Lung White Book

The second edition of the European Lung White Book was launched at the 2013 congress following the first issue, which was published over ten years ago. The original White Book provided the first comprehensive picture of lung health in Europe.

This new edition contains 41 completely revised chapters, drawing on the latest data from the World Health Organization and European Centre for Disease Prevention and Control and input from national societies and ERS members to present a rigorous examination of lung health and disease in Europe as it stands and an informed analysis of future trends.

The major risk factors for respiratory disease, from genetics and antenatal exposures through to tobacco smoking and occupational health are also included in this edition. Laying out the development of the various fields of respiratory medicine, it reveals the variations in training and staffing levels across the continent and presents the results of a wide-ranging survey of patient support organisations and their activities.

The White Book is also an advocacy tool for health professionals, policymakers, patient advocates and the media, and so it concludes with a series of policy recommendations to ensure a brighter, better future for respiratory health.

The White Book is also available online and the website features the full content of the book, with downloadable data files for all the key maps and charts, as well as extra epidemiological data.

Results from the REALISE™ Survey

Data show asthma exacerbation rates remain high, even among patients meeting criteria for current clinical control

New data from the Mundipharma International sponsored REcognise Asthma and LInk to Symptoms and Experiences (REALISE™) survey was presented during the ERS Congress, and the results showed that an alarming 45% of all respondents reported experiencing acute asthma exacerbations requiring oral steroid use in the past 12 months. This was evident even amongst those meeting the GINA criteria for current clinical control.[1, 2] Asthma exacerbations are associated with significant societal costs and a negative impact on the day-to-day lives of patients.[3, 4] The latest insights signal a need to address the problem through greater understanding of patient experiences of asthma to help achieve better disease control.

"REALISE highlights that the way patients describe the impact of their condition is inconsistent with their actual experience of symptoms, lifestyle limitations and exacerbations. This is seen across healthcare systems in Europe. I think a new model for engaging with our patients is required. An approach which seeks to understand patient attitudes and experiences in a way that works for them, for example, through the use of online resources, could make a difference in addressing this disconnect and ultimately improve the way asthma is managed"

The survey, which was developed in partnership with asthma experts, is a large pan-European survey of asthma patients which aimed to assess patient attitudes and behaviours towards asthma. The survey was conducted in 8,000 people with asthma aged 18-50 across 11 European countries between July and October 2012.[1] More than a third (35%) of respondents who met the GINA criteria for current clinical control (20% of survey population) had experienced symptoms on one or two days in the previous week[1] and 7% had been treated in hospital emergency departments in the last year due to the severity of their symptoms.[2]

Almost one-in-eight (12%) respondents reported that they had been hospitalised and had to stay overnight because of their asthma once or more in the past year,[1] which can result in substantial costs to healthcare systems.[5] In Germany, for example, the average cost of a hospital stay between two and seven days is estimated to be €1,402.25*.[6] Further results from the REALISE™ survey suggested that more than a third of people with asthma (36%) have had at least one day off work or education due to their condition in the past year.[1] Using average annual salaries for the EU[5] countries (France, Germany, Italy, Spain, United Kingdom), each missed day of work is estimated to cost an average of €146 per person due to loss of productivity.[7] The survey also highlighted the limitations that asthma can place on peoples' lives, with one third of respondents (33%) saying asthma stops them living their life to the full.[1] These findings suggest that there remains a need to accurately assess asthma symptoms and experiences in everyday clinical practice to reduce the burden of disease for the estimated 30 million people in Western Europe who have asthma.[4]

REALISE™ survey experts have suggested that gaining a greater understanding of patient needs, attitudes and experiences of asthma may help to improve levels of asthma control. The findings of this survey suggest that factors affecting patients' mindset towards asthma and its management, such as confidence in managing asthma, knowledge about treatments, and concordance with healthcare professional advice, may affect how well patients respond to disease management. Although 24% of REALISE™ respondents were treated in hospital emergency departments in the 12 months prior to the survey, this figure ranged from 8% to 45% based on the patient's mindset.[1] Understanding the variation in asthma patient experiences and mindsets could support the development of personalised asthma action plans with the aim of improving disease control, in line with clinical best practice.[8, 9]

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The BRONCH Mentor

Simbionix, one of the world's leaders in medical training and simulation, showcased the BRONCH Mentor and the U/S Mentor.

The BRONCH Mentor provides enhanced bronchoscopy training to the full Extent of the actual procedure for users. An innovative new addition to the Simbionix line of medical simulators, this shares a platform with the well-established GI-Mentor.

The BRONCH Mentor provides a comprehensive solution for the flexible bronchoscopy training needs of pulmonary and critical care physicians, anesthesiologists and interventional pulmonologists. This combines basic skill tasks and complete clinical procedures to provide an optimal learning environment for motor, cognitive and coordinative skills acquisition and also diagnostic and therapeutic clinical experience. It offers the most comprehensive environment while supporting gradual and controlled complexity and simultaneity.

Full clinical procedures of diagnostic or therapeutic nature are simulated comprehensively, offering a variety of virtual patients exhibiting real-life patient environment and behaviour.

The U/S Mentor offers Comprehensive self-training hands-on solution for ultrasonography skill tasks, bedside echocardiography and eFAST hands-on training.

A high-end medical simulator for the training of ultrasound-related examinations and interventions, this offers multidisciplinary, realistic hands-on training for the ever-growing utilisation of ultrasound in medicine especially at point of care (POC) setting. It provides residents, fellows, and practicing physicians an opportunity to acquire and improve their sonography-related skills on a variety of virtual patients.

For more information visit www.simbionix.com

Interventional Pulmonology - EVIS EXERA III Video-Bronchoscopes

Olympus' portfolio for interventional pulmonology includes the stunning EVIS EXERA III video-bronchoscopes, endoscopic ultrasound and EndoTherapy devices for LC staging, ablation, foreign body removal, emphysema and air leak treatment. Systems integration and hygiene solutions complete the line-up.

Olympus product experts and application specialists were demonstrating exciting hands-on bronchoscopic procedures on anatomical models using Olympus's large variety of EndoTherapy instruments for diagnostic and therapeutic interventions. Advancements in bronchoscopy with the latest video platform EVIS EXERA III with major advances in visualisation, manoeuvrability and versatility were revealed.

On Monday, 9th September Olympus also organised an evening Mini Symposium entitled "Bronchial valve treatment: from patient selection to follow-up".

A. Valipour(Vienna, Austria), and R. Eberhardt (Heidelberg, Germany) chaired the evening symposia which started off with 'Introduction to bronchial valve treatment' by A. Valipour and lead into the first session 'Patient selection - who is the right candidate for bronchial valve treatment'.

R. Eberhardt gave the 'Patient examples - challenge yourself to see if your guess is correct' session, which was followed by a session entitled 'Patient follow-up and complications - what to consider after the valve treatment'.

The symposia was concluded with an in-depth discussion session.

Home Healthcare Services for Chronic Disease Patients

Air Liquide Medical Systems showcased their complete range of devices for respiratory assistance in the patient's home and at the hospital at the congress.

A leader in home healthcare, Air Liquide provide home healthcare services in compliance with medical prescription for patients suffering from chronic diseases such as COPD, sleep apnoea and diabetes.

The rise of chronic diseases poses a major public health challenge and in the respiratory field Chronic obstructive Pulmonary disease (COPD) and sleep apnoea in particular are on the rise.

With over 30 years of experience of working in home healthcare, Air Liquide Healthcare has the necessary experience and expertise to guarantee high quality treatment for these patients. Its qualified medical teams are made up of pharmacists, nurses, nutritionists and technical advisors, who all have in depth knowledge of both the various diseases and their treatments.

Medical experts from Air Liquide develop, evaluate and integrate new technologies such as medical devices and telemonitoring to create support programmes and enhance patients' compliance to treatment and quality of life.

Their patients are provided with a continuum of care, from hospital to home with medical products, specialty ingredients, and services that support patients in the management of disease increasingly efficient. With personalised follow-ups they help to improve the therapeutic efficacy of treatments, train the patient and the patient's family and act as a link between the various healthcare professionals involved throughout treatment.

Multidisciplinary teams support patients and provide the required equipment prescribed by the doctor for treatment requirements such as medical respiratory assistance, infusion, or nutritional assistance equipment at home.

Currently, over one million patients worldwide, along with the healthcare professionals treating them, are putting their trust in Air Liquide Healthcare.

For more information visit www.airliquide.com

EPK-i5000: State-of-the-art Endoscopy

PENTAX Medical, experts in high-definition endoscopy, had representatives on hand to showcase the innovative product range from PENTAX Medical, in particular the EPK-i5000 video processor.

The PENTAX Medical EPK-i5000 video processor is designed for practitioners who require routine function in their day-to-day clinical work.

One of the latest developments in high definition endoscopic imaging, the EPK-i5000 combines high illumination, HD+ resolution and PENTAX's advanced i-scan image processing technology. The EPK-i5000 ensures excellent endoscopic imaging and outstanding precision when assessing surface structures. This supports faster, more accurate diagnoses for routine applications through to challenging examinations.

The EPK-i5000 features 3 pre-set buttons, assigned to the recommended profiles of Surface Enhancement (SE) and Tone Enhancement (TE). Simply at the touch of a button, users benefit from clearly defined i-scan settings designed to support the endoscopic pathway of detection, demarcation and characterisation.

When the new video processor is used in combination with PENTAX's 90i series endoscopes, the HD+ images provide the highest endoscopic image resolution available. This delivers enhanced visibility of vessel architecture, miniscule structures, identification of margins or lesions and improved pit pattern classifications.

Bringing together an endoscopy offering that makes operation of i-scan quick and comfortable.

www.pentaxmedical.com

Electrical Auricle Stimulation for Sleep Apnoea

With the goal of treating all types of sleep apnoea, NasoPhlex BV's non-invasive treatments are based on minor electrical stimulation evoking a reflex. Results show improvements of up to 95% in treating central, mixed and obstructive apnoea. These products not only prevent apnoea's, but are non-invasive and comfortable to use.

To prevent short cessations of breathing, which develop into apnoeas, the Electrical Auricle Stimulation (EAS) provides a small electrical stimulus to a carefully selected point on the auricle of the ear. This is based on evoking upper airway reflexes by addressing electrical stimulations to the auricle of the ear. The patient's breathing is continuously monitored and, when there is a cessation of breathing for a certain minimum time, the patient receives a short, weak electrical stimulus. If this stimulus does not cause breathing to resume, a further short, weak stimulus is addressed. This process is repeated until the patient resumes breathing. By doing this, most apnoeas are prevented. In order not to arouse the patient, the intensity of the electrical stimulus is continuously adjusted based on several parameters that are monitored in real time. Polysomnography shows EAS does not induce arousal.

By monitoring the patients' airflow and other parameters, the moment and intensity of each stimulus is determined. Typically EAS provides stimulations that last exactly one second. When breathing has not resumed one second after the last stimulus, an additional one-second stimulus is given.

Nasophlex conducts experiments on a nightly basis in their sleep laboratory. All of the patients that are invited in the sleep laboratory must first undergo a full PSG without any treatment. These nights are referred to as baseline of reference nights.

EAS works for obstructive, mixed and central sleep apnoea. This is explained by the fact that EAS indirectly stimulates the respiratory centre, thus evoking an upper airway reflex. This reflex can restart breathing in mixed and central sleep apnoea. The reflex also induces upper airway muscle patency, which helps to minimise obstructions in patients with OSAS.

For more information
www.nasophlex.com

Pulmonx Unveiled New Interventional Pulmonology Products

Pulmonx, an emerging leader in interventional pulmonology, has unveiled two new products. The 4.0-J EDC and the Zephyr® EBV are both designed to enhance deliverability in patients with difficult anatomy that will result in the effective treatment of a larger number of eligible patients.

The 4.0-J EDC is a specifically designed, J-shaped Endobronchial Delivery Catheter which aims to maintain maximum bronchoscope articulation while inserted in its working channel.

This feature facilitates the treatment of hard-to-reach segments that were more difficult to access with the current version of the 4.0 EDC. The new 4.0-J EDC is compatible with the standard Zephyr® 4.0 Endobronchial Valve (EBV) as well as the recently introduced Zephyr® 4.0 LP EBV, designed for short bronchial segments or sub-segments.

The second, the Zephyr® EBV is a minimally invasive device intended to treat patients with emphysema. These patients suffer from hyperinflation, an increase in volume of the diseased portions of their lungs, which then compresses the healthier areas. The Zephyr® EBV therapy involves bronchoscopic placement of one-way valves designed to reduce the hyperinflation in the diseased portion of the lungs, thereby improving the ability of the healthier portions of the lungs to function.

The Zephyr® EBV received the CE Mark in 2003. Since becoming commercially available in Europe and select countries worldwide the company estimates that it has been used to treat over 6300 patients, over 40 percent of whom have been treated in the last 12 months.

In addition, Pulmonx also showcased the next version of the Chartis Pulmonary Assessment System. This provides pulmonologists with lobe-specific information about a patient's lung enabling physicians to plan valve treatments to account for anatomical variations in the lungs of individual patients which impact the effectiveness of the valves. The addition of the Pulmonx Chartis assessment now ensures that a very high percent of treated patients will experience benefit from EBV treatment.

The latest Chartis includes a new Ventilator Mode that offers users the added capability to conduct Collateral Ventilation (CV) assessments with the patient under mechanical ventilation in addition to spontaneous respiration within the Standard Mode, which preserves the features that current users rely on. The option to choose between the Standard mode of assessment and the Ventilator mode of assessment is available on multiple screens to make the physician experience seamless and easy. The updated Chartis also features an enhanced graphical user interface, which includes a German language option, better screen-to-screen navigation and assessment of CV within the segments of each lobe.

These new products will be rolled out in Europe and selected markets throughout the world over the coming months.

Inhaled Medicine for Respiratory Diseases

Verona Pharma plc, the drug development company focused on first-in-class medicines to treat respiratory diseases, presented the results from successfully completed RPL554 clinical trials at the congress.

Verona Pharma is developing first-in-class drugs to treat respiratory disease, such as COPD, asthma and chronic, severe cough. The company has three drug programmes, two of which are in Phase II. The lead programme, RPL554, is an innovative dual phosphodiesterase (PDE) 3 and 4 inhibitor with both bronchodilator and anti-inflammatory properties. This is being developed as a novel treatment for chronic obstructive airways disease such as COPD and asthma with bronchodilator and anti-inflammatory effects. Both effects are essential to improve symptoms in patients with COPD or asthma. RPL554 is currently in phase II for both diseases.

At the congress an oral presentation, discussing the anti-inflammatory effects of RPL554 from the clinical study completed earlier this year, formed part of the session entitled "Hot topics in airway disease: New horizons in treatment". A poster describing safety and bronchodilator effects from a phase I/II clinical study of the drug in patients with mild allergic asthma and rhinitis was also presented.

Both the oral presentation and the poster support Verona Pharma's view that RPL554 could become an important, novel and complementary inhaled medicine for the treatment of respiratory diseases such as asthma and COPD, either as monotherapy, or as an addition to existing therapies. The company is initially progressing further development of the drug, in nebulised form, as a treatment for severe COPD, a significant unmet medical need.

Portable Device to Measure Airway Inflammation

Aerocrine launched NIOX VERO® at the congress, a new, fully portable hand-held point-of-care device for the measurement of airway inflammation, such as asthma.

NIOX VERO® is a new and upgraded version of the gold standard for measurement of Fractional exhaled Nitric Oxide (FeNO), a validated and clinically proven method for assessing allergic airway inflammation such as asthma. NIOX VERO® provides accurate, reproducible and rapid measurement results. The NIOX VERO® has an onboard rechargeable battery, upgraded software, wireless technology, patient journaling and has a useful life of 15,000 tests or 5 years compared to its predecessors (NIOX MINO®) 3,000 tests or 3 years.

The CE-marked device used to measure airway inflammation - an underlying cause of inflammatory airway diseases – helps physicians to improve patient outcomes and reduce healthcare expenditures. The product will initially be introduced in selected market segments in Q4 2013 Sweden, United Kingdom and Germany with the objective of conducting a real-life handling test of this device in the daily practice of a limited number of sites. Further introduction in the remaining European countries is expected during spring 2014. Among the benefits of NIOX VERO, physicians will have more objective insights into treatment efficacy and can better predict a patients' response to therapy and the risk of an asthma relapse. Moreover, physicians will be able to identify patient non-compliance with medications, and can adjust the dose of medication based on individual patients' needs. By using NIOX VERO® doctors can measure the underlying inflammation that causes asthma within a few minutes directly in their offices.

Asthma is a chronic disease affecting millions, including many children. Aerocrine's NIOX products are created to help physicians identify patients that will respond to the optimal therapy. Patients are different, requiring different treatments and dosages. Therefore, airway inflammatory disease management and control can be significantly improved through 'personalised' monitoring of the airway inflammation rather than just following symptoms and assessing lung function.

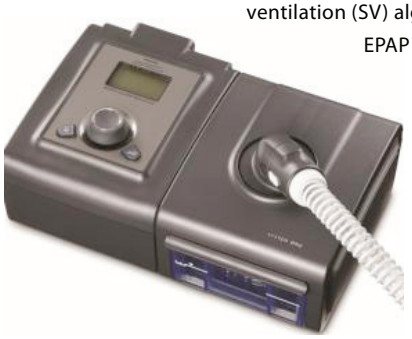
Innovations for Better Sleep and Breathing

Philips Respironics, part of Royal Philips, showcased patient-centred innovations for the future treatment of healthcare for patients with chronic respiratory diseases. Dedicated to improving the lives of individuals suffering from sleep and respiratory issues, Philips Respironics demonstrated integrated programs and science-based solutions at ERS.

Philips Respironics presented a holistic suite of solutions for sleep-disordered breathing and chronic respiratory conditions and solutions for patients with ineffective cough.

"Philips is committed to making a difference in the management of sleep and respiratory diseases," said Yann Goïot, Market Group Leader for Europe, Middle East, and Africa. "Our goal is to help clinicans establish healthier patients, healthier practices and, in turn, healthier businesses."

The BiPAP autoSV Advanced System One for complex sleep-disordered breathing patients was also be on display at ERS, featuring clinically-validated technology such as servo-ventilation (SV) algorithm, unique auto-EPAP and automatic backup rate functionalities.



BiPAP autoSV Advanced

New patient benefits of the BiPAP autoSV include a heated tube humidifier, which provides extra comfort for patients sleeping in a cold environment, those with pre-existing nasal conditions, or those using sinus drying medications.

"Thanks to servo-ventilation, we managed to stabilise ventilation, resolving central and obstructive apnoea, night hypoxemia and improving hemodynamics in a patient with congestive heart failure," said Dr. M. Brunori of Policlinico Umberto and University of Rome.

To offer better management for chronic respiratory diseases, Philips introduced a series of solutions with enhanced features, including CoughAssist E70, Trilogy ventilator series with mouthpiece ventilation (MPV), and SimplyGo portable oxygen concentrator (POC).

CoughAssist E70 clears secretions from the lungs by gradually applying positive air pressure (insufflation) to the airway and then rapidly shifting to negative air pressure (exsufflation). This in-exsufflation shift in pressure creates a high expiratory flow that simulates a deep, natural cough. The CoughAssist E70 incorporates several innovations and features like Cough-Trak, oscillations, and flow waveforms that improve comfort and aid in the efficacy of the therapy.

CoughAssist E70

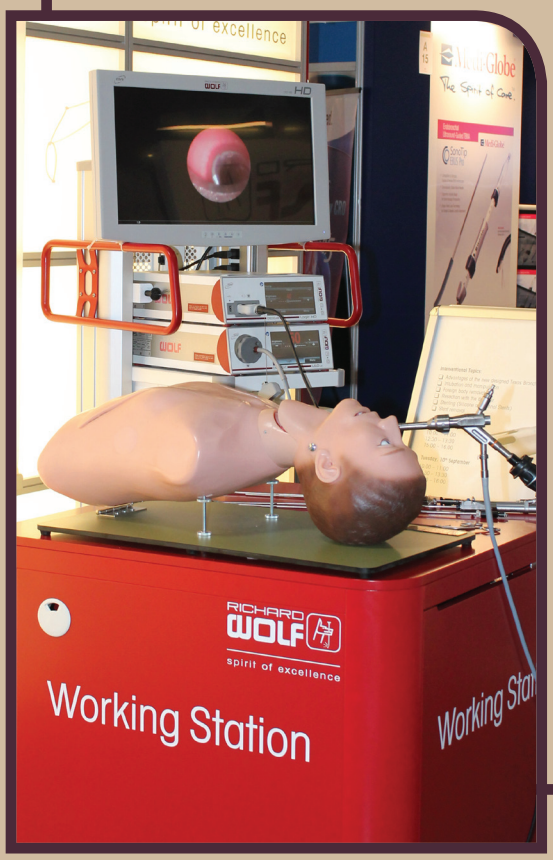
The Trilogy ventilators are designed for use at home, hospital and alternative care sites, providing invasive and non-invasive ventilatory support for adult and paediatric patients. The mouthpiece ventilation (MVP) support system enables on-demand ventilation without the need for an exhalation device. "MPV technology is the beginning of a paradigm shift in how ventilatory support will be provided, non-invasively rather than invasively," said Dr. John R. Bach.

Additionally, the light-weight SimplyGo portable oxygen concentrator (POC) delivers simplified care by providing continuous flow and pulse dose oxygen therapy to fit most oxygen patients' needs in the treatment of COPD.

SimplyGo

The Next Generation of Rigid Bronchoscopes

One of the leading manufacturers and a full-range supplier in endoscopic products, Richard Wolf, showcased their Optical Fully Integrated Rigid Bronchoscope at the congress. Endoscopes can be used in arthroscopy, surgery, gynaecology, laparoscopy, ENT, thoracoscopy, urology and visualisation.



Richard Wolf supports a broad range of endoscopic surgical specialties while also providing support to specialised niche markets. Leading surgeons all over the world work with Richard Wolf to develop endoscopic innovations, as well as assist in the improvement of existing products. As a result, Richard Wolf has pioneered many endoscopic products and procedures.

The TEXAS Optical Fully Integrated Rigid Bronchoscope was designed in close co-operation with Dr. Garrett Walsh, Professor of Surgery, Department of Thoracic and Cardiovascular Surgery, University of Texas MD Anderson Cancer Center, Houston, Texas. This bronchoscope was designed for both diagnostic and therapeutic bronchoscopy applications, such as biopsy, tumour resection, foreign body removal, stent placement and removal. The integrated telescope adds another layer of protection, with separate channels for optic and instruments.

The endoscope is integrated directly in the bronchoscope tube and always offers an optimum view whilst intubation is made significantly easier as the view is always available.

The integrated irrigation channel means that the distal lens of the endoscope can be irrigated during an operation if it becomes cloudy due to secretions or blood.

For more information visit: www.richard-wolf.com

AeriSeal System Therapy

The AeriSeal System provides a minimally invasive lung volume reduction solution for patients with advanced upper-lobe predominant (ULP) or homogeneous emphysema, without the attendant risks of lung volume reduction surgery (LVRS).

LVRS has recently become an accepted therapy for patients with advanced emphysema. This involves the removal of diseased portions of the lung in order to enable the remaining, healthier portions to function better. This invasive surgical procedure, although effective for many patients, is complicated and is accompanied by substantial morbidity and mortality risk.

In the AeriSeal System therapy, a physician uses a bronchoscope to direct treatment to the most damaged areas of the patient's lungs. The treatment delivers a proprietary Foam Sealant designed to seal and collapse the treatment area, thereby reducing lung volume. Reduction in lung volume creates more space for adjacent healthier parts of the lungs to function more effectively, thereby improving breathing function and quality of life in patients with advanced emphysema.

www.aerist.com

Positive Phase II Clinical Data for AF-219

In a Late-breaking Oral Presentation New Findings from a Study on AF-219 Showed Reduced Daytime Cough Frequency by 75% in Patients with Treatment-Refractory Chronic Cough

AF-219 also being Studied in Phase 2 Trials in Patients with Osteoarthritis Pain and with Interstitial Cystitis/Bladder Pain Syndrome

Afferent Pharmaceuticals has announced positive clinical efficacy results from the Phase 2 study of the company's first-in-class oral P2X3 antagonist, AF-219, in patients with treatment-refractory chronic cough.

A clinical-stage biopharmaceutical company, Afferent is leading the development of first-in-class, proprietary, small molecule compounds that target P2X3 receptors for the treatment of chronic pain, respiratory and urological conditions. In a randomised, double-blind, placebo-controlled, crossover Phase 2 clinical study, AF-219, dosed orally twice daily, was demonstrated to markedly reduce daytime cough frequency by an unprecedented 75% at week 2 of treatment (as measured using an ambulatory sound monitoring system) in patients with treatment-refractory chronic cough ($p < 0.001$). The study results were featured in a late-breaking oral presentation titled, "Inhibition of ATP-gated P2X3 channels by AF-219: An effective anti-tussive mechanism in chronic cough" (Abstract No. 1965).

"The Phase 2 results provide what we believe is the first demonstration of a statistically significant improvement in objective ambulatory cough frequency following pharmacological intervention".

According to the study findings, daytime cough frequency reduction was accompanied by concordant, statistically significant improvements compared to placebo across a range of secondary endpoints – cough severity, urge to cough, global rating of change, and responses to the Cough Quality of Life Questionnaire (CQLQ) – at week 2 of treatment. Further, there were no safety concerns identified in the study.

"The Phase 2 results provide what we believe is the first demonstration of a statistically significant improvement in objective ambulatory cough frequency following pharmacological intervention," commented Jacky Smith, Ph.D., clinical trial principal investigator and Reader and Honorary Consultant in Respiratory Medicine, University Hospital Manchester NHS Foundation Trust.

"No new licensed treatments for cough have appeared in more than 50 years. There is a compelling need for new options given the ineffectiveness of many current treatments and the potential for cognitive side effects with certain therapies, such as codeine-containing cough medicines. I look forward to the further progress of this important programme in chronic cough."

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Anthony P. Ford, Ph.D., Afferent's Chief Scientific Officer, commented, "We are very excited with the findings for AF-219 in chronic cough, which greatly exceed our initial expectations. Further, as far as we are aware, this is the first clinical proof-of-concept study to be completed implicating P2X3 receptor mechanisms in any clinical disease. Based on these and other mechanistic insights, we believe P2X3 receptors may be involved more generally in a number of disorders involving neuronal hypersensitivity."

Bruce G. McCarthy, M.D., Chief Executive Officer of Afferent Pharmaceuticals, stated, "The cough study results are important validation for our focus on and approach to P2X3 antagonism. Afferent's lead candidate has been tested in 164 individuals to date, and based on the overall progress of our clinical programs, we anticipate reporting additional POC data in patients with osteoarthritis pain and with interstitial cystitis/bladder pain syndrome by mid-2014. We also are initiating a challenge study in asthma patients later this year."

A New Therapy for Obstructive Sleep Apnoea

Inspire Medical Systems Inc., showcased their nerve stimulation systems at the show. This device is most effective for a subset of patients who have a certain type of soft-palate collapse and are not significantly obese. It is designed to significantly reduce the burden of obstructive sleep apnoea by delivering mild stimulation to the upper airway during sleep.

A small, fully implantable system this utilises electronic stimulation therapy to reduce obstructive sleep apnoea (OSA).

Inspire's implantable Upper Airway Stimulation (UAS) Therapy is a promising treatment for moderate to severe OSA in patients who do not respond to or can not tolerate continuous positive airway pressure (CPAP) therapy.

Inspire therapy is designed to deliver physiologically-timed, mild stimulation to the main nerve of the tongue on each breathing cycle during sleep in order to restore tone to key airway muscles and prevent airway collapse. The stimulation is sufficient enough to evoke a response from the nerve but mild enough not to disturb sleep.

Patient's control when the Inspire therapy is turned on and off using a handheld controller. The pulse generator processes information from the sensor and determines the most beneficial time in the breathing cycle to deliver the stimulation. The single lead pressure sensor provides real-time breathing cycle data throughout the night.

In contrast to other surgical procedures which treat sleep apnoea, Inspire therapy does not require removing or altering a patient's facial or airway anatomy.

"The device's battery is expected to last between eight and 10 years", says Randy Ban, Senior Vice President, External Operations.

www.inspiresleep.com

EndoSheath Technology

Vision-Sciences were presenting their EndoSheath® Technology, which provides advanced flexible video and fiber optic endoscopy. The EndoSheath® Bronchoscopy provides practitioners with a bronchoscope that allows for rapid equipment turnaround, enhanced infection control, less capital and service costs.

EndoSheath® Bronchoscopy is a new alternative to conventional bronchoscopy procedures. Pulmonologists and Bronchoscopists can get sterile, high performance endoscopic imaging and functionality.

The EndoSheath® Technology provides a durable, protective barrier, as well as a disposable working channel that is the only flexible video bronchoscope that never comes in contact with the patient. All patient materials and instrumentation from biopsy tissue samples to BAL fluid removal, travel through the channel in the disposable sheath and never come in contact with the reusable bronchoscope.

This digital video bronchoscopy system is ultra portable and its compact size makes it perfect for bedside procedures or tight quarters such as the busy ICU with different channel sizes, uniquely provides the freedom for the practitioner to 'customise' the bronchoscope to fit the procedure.

The Next Generation of Lung Function Imaging and Assessment Technology

PneumaCare demonstrated their unique non-invasive lung function imaging devices, which allow for observing active real-time regional respiratory function via chest wall movements. This provide respiratory information in post-operative assessments, intensive care and patient management.

These are revolutionary advancement in respiratory assessment and clinicians are able use PneumaCare's lung function imaging devices to rapidly identify pulmonary-related issues across a broader patient population, earlier in the patient-care life cycle.

The PneumaScan™ and Thora-3DI™ use PneumaCare's proprietary SLP technology to capture functional images of the lungs by analysing chest wall movement, and translate this data into pulmonary function outputs. This is all done without any physical contact with the patient or the need to subject them to radiological or resonance treatments.

PneumaCare's Thora-3DI™ allows surgeons and doctors to understand the patient's pulmonary function and to view that effort in regional segments, all by measuring chest wall movement. The non-contact measurement process and portable nature of the Thora-3DI™ means that the clinician can perform assessments as soon as the patient is able to take a deep breath, without needing to transfer them to a lung function lab. Images can be taken with the patient still in their bed. From this early first assessment, the patient's recovery process can be monitored on a regular basis, leading to an efficient recovery through the hospital care system and a swifter return home.

What sets the Thora-3DI™ apart from traditional pulmonary measurements is its ability to show traditional lung function data in a 3D format. Using the PneumaView™ 3D viewer software, the clinician can rotate the recorded image of patient's chest wall movements. In addition, the pulmonary contribution from the defined regions of the chest can be displayed for analysis. The clinician now has the option to review the left and right side contributions or the upper chest and lower abdominal function as they relate to the recorded respirations. All of this advanced information is obtained in a real-time measurement that can be performed almost anywhere in the hospital setting.

Novotec Medical Galileo Training

Treatment Strategies were shown Novotec Medical's new Galileo Training products.

Galileo is a brand of vibration training

platforms that can be used as exercise equipment as well as part of therapy. It consists of a vibration platform, which vibrates sinusoidal side alternating like a seesaw.

While one leg is lifted the other drops, a side alternating motion mimicking the human gait in order to utilise nearly physiological motion patterns close to the side alternating human gait. The side alternation causes the hip to tilt, thereby activating the contra lateral muscles of the back.

Depending on the device size it oscillates with amplitude of up to 6 mm and a frequency of 5 Hz to 30 Hz (5 to 30 repetitions per second). Due to its high amplitudes and vibration frequencies above 12 Hz it is able to utilise stretch reflexes.

This side alternating motion results in low acceleration acting on the centre of gravity of the upper body and the head and is used in a wide range of applications such as fitness, professional sports, prevention as well as in medical and therapeutic use.

The Parameters which can be altered in vibration training including amplitude, frequency, Position & Posture and Repetitions.

A higher amplitude results in a more intense training, with higher elongation of ligaments and muscles as well as in a higher elongation speed. Hence the amplitude influences the maximum stretching as well as the maximum motion velocity. The amplitude can be varied by the foot position, and the further apart the feet are positioned the larger the amplitude. If the amplitude cannot be increased, additional weights can be used to increase the training. Number of repetitions per second,and the frequency can be chosen to select the training objective.

Depending on the position and posture different muscle groups are tensed. Stretch reflexes are triggered in any tensed muscle, which is additionally stretched fast enough by vibrations.

Repetitions and the number of training days per week are an important factor to increase efficiency.

Covidien and Vida Diagnostic Expand Minimally Invasive Treatment of Lung Disease

Covidien, a leading provider of healthcare products, announced an agreement with VIDA Diagnostics, a pioneer in quantitative pulmonary imaging analysis software to distribute VIDA's Apollo® pulmonary imaging software services.

"We are committed to improving patient outcomes. The combination of our technologies results in a powerful, minimally invasive, more informative imaging solution for areas of the lung not accessible by traditional bronchoscopy and for patients who cannot tolerate more invasive procedures," said Michael Minette, Vice President, Interventional Lung Solutions, Covidien.

"This collaboration brings together two companies dedicated to the early detection, evaluation and treatment of pulmonary disease." This agreement enables Covidien to offer a unique combination of market-leading technologies from VIDA and Covidien's i-Logic™ lung navigation system. i-Logic provides pulmonary physicians and other clinicians with enhanced detail for the minimally invasive diagnosis and treatment planning of lung cancer, chronic obstructive pulmonary disease (COPD), asthma and other lung diseases.

The i-Logic system uses advanced Electromagnetic Navigation Bronchoscopy® technology to extend beyond the capabilities of the bronchoscope to distant regions of the lungs not accessible through traditional bronchoscopy. The i-Logic system enables physicians to locate previously inaccessible small lung lesions for diagnostic testing and enhancing treatment options. The Apollo platform provides more precise analyses of imaging data for more objective insights on patient diagnoses and treatment options.

"Together, VIDA and Covidien, leaders in their specialised fields, provide a more unified, comprehensive approach to managing patients with lung disease."

"The integration of quantitative pulmonary image analysis with innovative devices and therapies is an emerging requirement to obtain effective outcomes in patients with lung disease," said Scott Ferguson, M.D., Associate Professor and Director of Interventional Pulmonology in the Division of Allergy, Pulmonary and Critical Care Medicine, University of Wisconsin School of Medicine and Public Health; who has worked as a consultant to Covidien. "Together, VIDA and Covidien, leaders in their specialised fields, provide a more unified, comprehensive approach to managing patients with lung disease."

"Our partnership with Covidien is an opportunity to transform the management of patients with lung disease to an objective, evidence-based approach leading to more precise diagnoses and targeted therapies," said Susan A. Wood, Ph.D., President and CEO of VIDA Diagnostics. "We are thrilled to be collaborating with the leaders in minimally invasive techniques to bring new diagnostic and therapeutic planning opportunities for patients with lung disease."

Decasan has antimicrobial and antifungal effects, and concentrates on the cytoplasmic membrane (CPM) of a microbial cell and links with the membrane's phosphatide lipid groups, disrupting the penetrability of the microorganism's CPM. Decamethoxin has a pronounced bactericidal effect on staphylococci, streptococci, diphtheria and blue pus bacilli, and capsuliferous bacteria; a fungicidal effect on yeast, yeast-like fungi, agents of epidormophytosis, trichophytia, microsporia and erythrasma, certain mold fungi (aspergilli, penicilli); an antitenial effect on trichomonads and giardia lamblia; and an antiviral effect on viruses.

Solutions for Infusion

The drug is highly active against antibiotic-resistant microorganisms. Creation of decamethoxin-resistant forms during prolonged therapy is slow and does not exceed the effective concentrations of the drug. Bacteriostatic (fungistatic) concentrations are similar to its bactericidal (fungicidal), virusocidal and antitenial concentrations. The sensitivity of antibiotic-resistant microorganisms to antibiotics is increased during the drug therapy.

Absorption of the drug by mucous membranes, undamaged skin and wound surface is virtually absent.

The Provocholine Challenge

Licensed to Methapharm in 1996, Provocholine (methacholine chloride) originally received FDA approval in 1986. It is indicated for the diagnosis of bronchial airway hyper reactivity in patients who do not have clinically apparent asthma, especially in those with unclear or non-specific symptoms. A parasympathomimetic (cholinergic) bronchoconstrictor, Provocholine is administered in solution only through inhalation for diagnostic purposes.

It is a ß-methyl homolog of the neurotransmitter acetylcholine, which occurs naturally in the body. Showing longer duration and is more selectivity, Provocholine is metabolised more slowly than acetylcholine by cholinesterase.

Bronchoconstriction occurs when the vagus nerve is stimulated and acetylcholine is released from the nerve endings. Asthma patients are markedly more sensitive to methacholine-induced bronchoconstriction than healthy subjects. This difference in response is the pharmacologic basis for the Provocholine inhalation diagnostic challenge.

Provocholine is a direct challenge test that acts directly on airway receptors and with a high negative predictive value produces few false-negatives.

The primary indication for a Provocholine challenge test (methacholine chloride powder for inhalation) is the diagnosis of bronchial airway hyper reactivity in subjects who do not have clinically apparent asthma.

Methacholine challenge testing is considered when asthma is a serious possibility and traditional methods, have not been successful in establishing or eliminating the diagnosis.

Treatment Strategies spoke with Samuel Constant from Epithelix and Bill Wilkinson from Inova Labs Inc. to learn more about the products that they were showcasing at the event

3D Human Airway Epithelia MucilAir

Epithelix presented their latest advances in the field of *in vitro* evaluation of the efficacy and safety of drug canditates for asthma, cystic fibrosis, flu, COPD, etc., which included the robust 3D Human Airway Epithelia MucilAir.

MucilAir is a standardised Air-liquid Interface *in vitro* cell model of the human airway epithelium free of limitations such as failure of reproducing the *in vivo* physiological characteristics and a limited shelf-life. MucilAir tissues can be kept in culture for more than 12 months, allowing long-term and or repeat toxicity and efficacy studies *in vitro*.

Epithelia from several pathologies can be reconstructed whilst maintaining the fully differentiated characteristics of the native tissues for more than one year, morphologically and functionally.

Due to its unique long shelf-life, MucilAir can be used for studying human respiratory diseases, and for testing the long-term or chronic effects of drugs on the respiratory tract.

Using cells from diseased donors, different versions of MucilAir can be made for conditions such as asthmatic, allergic, and COPD. MucilAir has applications in drug development due to its fully differentiated nature. It can be used for studying various respiratory diseases including viral infections in the likes of the influenza virus and respiratory viruses such as syncytial virus and Human Rhinovirus.

LifeChoice Activox Portable Oxygen Concentrator

Inova Labs Inc., the creators of the LifeChoice portable oxygen concentrator, showcased the LifeChoice Activox, a new portable oxygen concentrator which is the latest product from Inova Labs.

Weighing merely 4.83 lbs, this new device is a lightweight portable oxygen concentrator with sleep mode technology. It operates on a larger internal battery which can provide up to seven hours of use and can be increased to over ten hours with the additional battery pack, giving an unprecedented amount of mobility, which is unseen in other portable concentrators of its size.

The Activox delivers pulse doses equivalent to 1, 2 and 3 lpm, and is equipped with SLEEP MODE technology, which allows the unit to automatically adjust patient therapy based on oxygen requirements during activity and sleep.

The Activox also features PULSE-WAVE Technology, which delivers oxygen continuously during inspiration.

As one of the newest concentrators on the market, the LifeChoice Activox has a lot to offer. The custom carrying case has a special pouch for the external battery and it comes with a 4-way strap system. This allows patients to carry the concentrator over their shoulder, like a backpack, like a briefcase, and around their waist, and has even been FAA approved for airline travel.

The Activox sleep mode technology allows patients to sleep while using the device and it even has a mute button. The mute button has been incorporated so that patients have the ability to mute the audible alarms.

The Inova LifeChoice is virtually maintenance free, and with its compact size it is perfect for maintaining the quality of life that patients are looking for.

Author Interviews

Sara Taheri interviewed three of the authors featured in this edition, Dr. Maria Teresa Romero Rubio, Dr. Masoud Dara and Dr. Angelica Tiotiu, at the ERS congress. Each author gave us a brief summary of their papers. See these interviews in their entirety on our YouTube channel.

Dr. Maria Teresa Romero Rubio

Dr. Maria Teresa Romero Rubio spoke about what attending the ERS meant to her and gave a summary of her article entitled 'Viruses in Paediatric Pulmology: A New Perspective', which can be found on page 75.

Dr. Masoud Dara

Dr. Masoud Dara discussed his article 'Causal Factors of Multidrug Resistant and Extensively Drug Resistant Tuberculosis: Regional and National Response in the WHO European Region' in more detail. Read this article in full on page 87.

Dr. Angelica Tiotiu

Dr. Angelica Tiotiu talked to Treatment Strategies about attending the congress and summarised her article entitled 'Management with Erythropoietic Agents of Chemotherapy-induced Anaemia in Patients with Lung Cancer.' Find this article on page 67.

wwww.youtube.com/user/CambridgeResearch

Satellite Symposia Highlights

Treating Bronchiectasis in Respiratory Patients

On Tuesday 10th September Bayer HealthCare conducted an oral presentation session on treating bronchiectasis in respiratory patients. This was an oral presentation of the abstract entitled 'Influence of severity of outcome in a phase II trial of ciprofloxacin DPI in patients with non-cystic fibrosis bronchiectasis' aimed to explore the study results in different severity populations.

Bayer HealthCare is currently investigating the effects of an innovative drug device combination for non-cystic fibrosis bronchiectasis (NCFB). Ciprofloxacin dry powder for inhalation (DPI) is the development name of this drug device combining ciprofloxacin DPI 32.5mg with the Novartis T-326 inhaler, a small and convenient breath-actuated delivery device.

In a Phase II study NCFB treatment with ciprofloxacin DPI led to reduction of bacterial load in the lung.[1] The hypothesis is that as chronic intermittent treatment, ciprofloxacin DPI will increase the time to the next exacerbation and reduce the overall number of exacerbations per year.

1. Wilson, R *et al.*, 'Ciprofloxacin dry powder for inhalation in non-cystic fibrosis bronchiectasis; a phase II randomised study,' Eur Respir J, 41, 1107-1115, 2013.

Developments in Asthma Combination Therapy

MundiPharma International Ltd. sponsored an evening symposium on Sunday 8th September. In this evening symposium Mundipharma explored the formula for optimising the effectiveness of inhaled corticosteroid long-acting beta 2 agonist (ICS/LABA) combination therapies in clinical practice.

ICS/LABA combination therapies are highly efficacious treatments for asthma in clinical trials, but levels of control in the real world remain low. This is a problem faced by many clinicians in practice, solutions to tackle this are being investigated.

A distinguished faculty of experts took part in this symposium including David Price, J. Christian Virchow, Leif Bjermer, Nicholas Roche, and Thys van der Molen. Together this eminent group of professors reviewed the efficacy of ICS/LABA combination therapies, including that of flutiform (fluticasone propionate and formoterol fumarate) the single-aerosol combination of fluticasone propionate and formoterol fumarate for the maintenance treatment of asthma. The faculty explored the variables influencing the real world effectiveness of these therapies. In particular they discussed the utility of phenotypes and endotypes in diagnosing asthma, and took a detailed look at whoosh attributes. ICS/LABA combination therapy are important to both physicians and patients.

Finally, using data from the Mundipharma sponsored REALISE™ survey, the largest and most recent study of asthma in Europe, the faculty will look into the attitudes of different patient types towards asthma and its management.

Looking Beyond FEV: New Mechanisms and Clinical Outcomes with NAC at High Doses in COPD

Zambon sponsored a symposium entitled 'Looking beyond FEV: new mechanisms and clinical outcomes with NAC at high doses in COPD'. In this they addressed the question: does high-dose N-acetylcysteine (NAC) provide additional clinical benefits in the long-term management of COPD?

Ulrich Costabel and Luca Richeldi chaired this evening symposium on Tuesday 10th September.

Jurgen Behr spoke on 'Oxidative stress in chronic lung diseases: focus on NAC'. This was followed by a presentation on 'Risk reduction of COPD exacerbations: relevant results from PANTHEON study', by Jin-Ping Zheng. Hoi Nam Tse (China) then discussed the effects of NAC at high doses on small airways: the HIACE study. Wilfried De Backer (Belgium) gave the final presentation of the evening. This was 'Functional respiratory imaging: a new tool to assess the effect of NAC treatment on airways geometry and oxidative stress.'

These leading experts debated over the key areas in the evolving evidence base for high-dose NAC in COPD: from innovations in imaging and functional assessment studies to the latest randomised-controlled trials in patients with stable COPD.

The Group is strongly working on the treatment of chronic respiratory diseases such as COPD and focusing on strengthening the respiratory area with the treatment of severe disease such as chronic obstructive pulmonary disease (COPD) and cystic fibrosis (CF), with the recent acquisition Profile Pharma and Philips.

Poor Asthma Control, Device Handling and Phenotype

On Monday, 9th September Teva sponsored an evening symposium on 'Poor Asthma Control, Device Handling and phenotype'. Poor adherence and poor inhaler technique are continuing barriers to successful asthma management.

Roberto Rodriguez-Roisin chaired the Teva Respiratory symposium, which featured several leading experts including Christian Virchow, Cynthia Rand, Richard Dekhuijzen, and Michael Wechsler. This prominent group explored and discussed the impact of poor adherence and poor inhaler technique on asthma outcomes, as well as the etiology of asthma and the role of IL-5 in severe asthma.

The session started with a 'Welcome and introduction" from the chair, Roberto Rodriguez-Roisin, which followed by Christian Virchow's talk 'Poor advice technique affects outcome'. Cynthia Rand followed these with a talk on 'How important is inhaler adherence to outcomes?' and Richard Dekhuijzen discussed the 'The various types of uncontrolled asthma'. Finally, Michael Wechsler talked about 'Severe asthma: role of IL-5'. The symposium was rounded up with a Q&A sessions.

Influence of Obesity and Nasal Polyps on Severe Asthma

Federica Novelli[1,2]

1. Clinical Medicine (LIM20), FMUSP; 2. Nove de Julho University (UNINOV)

Asthma is often associated with comorbidities (e.g. upper airway disease, obesity, gastro-oesophageal reflux disease, psychological disturbances, obstructive sleep apnoea) that can influence its control, phenotype and response to treatment. The prevalence of comorbidities seems to be particularly high in severe asthma, and their treatment is a critical step in the therapeutic course of these patients. Chronic rhinosinusitis with nasal polyps and obesity are two major comorbidities that are often associated with severe asthma. Many studies have shown that obese patients have poorly controlled asthma and reduced response to controller therapy, probably due to mechanical and metabolic factors, and that weight loss improves asthma control. The association between chronic rhinosinusitis and asthma has been clearly established and radiologic severity of chronic rhinosinusitis is correlated with asthma severity and airway inflammation (sputum eosinophilia). Medical or surgical treatment of chronic rhinosinusitis seems to improve asthma control.

We studied 64 patients with severe asthma to investigate the influence of these two common comorbidities on pulmonary function, airway inflammation, asthma control and quality of life. In this attempt, patients performed spirometry, collected induced sputum to evaluate level and type of airway inflammation, measured exhaled nitric oxide (eNO) and performed ENT visit.

Asthma control was evaluated according to GINA guidelines and by Asthma Control Test (ACT) questionnaire, and quality of life was evaluated by Asthma Quality of Life Questionnaire (AQLQ). The percentage of patients with uncontrolled asthma according GINA guidelines was high at 46.9%. The prevalence of obesity and nasal polyps was 34.4% and 32.8% respectively. Obese asthmatics had a similar functional data than non-obese (pre-BD FEV1 77.7±23.5 vs. 77.9±14.8), but poorer asthma control (ACT score: 16 (7-25) vs. 21 (10-25), $p<0.05$; poorly controlled according GINA guidelines: 71.4% vs. 34.9%, $p<0.05$) and quality of life index (AQLQ score: 4.5 (3.0-6.2) vs. 5.1 (2.7-6.7), $p<0.05$), as well as a trend to have lower sputum eosinophilia (6.6 (0-71.2) vs. 17.6 (0-95.6), $p=0.07$), with no difference in asthma treatment. Asthmatics with chronic rhinosinusitis and nasal polyps showed similar asthma control and quality of life to asthmatics without nasal polyps, but poorer FEV1 (71.1±16.7 vs 81.0±17.3, $p<0.05$) and higher sputum eosinophilia (29.8 (0.4-95.6) vs. 8.5 (0-84.1), $p<0.05$). In a multivariate analysis taking into account age, sex, FEV1 (% predicted), obesity, nasal polyps and sputum eosinophilia, only obesity predicted the lack of asthma control (OR: 5.6, CI: 1.4-22.8 p=0.01).

We concluded that in patients with severe asthma, nasal polyposis is associated with increased eosinophilic airway inflammation and with worse lung function, but has less impact on asthma control and quality of life than obesity.

Frederica Novelli graduated in Medicine and Surgery at the University of Parma (2005) and has a postgraduate degree in Respiratory Medicine from the University of Pisa (2009). Since 2011 she has held a research grant on "Phenotyping of asthma" and currently PhD in Physiopathology and Clinical of Cardiovascular and Respiratory Diseases at the University of Pisa on severe asthma. She is author and co-author of several abstracts presented in national and international congresses and of 11 papers published in international journals.

Compensatory Lung Growth Effects on Pulmonary Mechanics of Emphysematous Rats After Bilobectomy

Francine Maria de Almeida[1], Beatriz Mangueira Saraiva-Romanholo[1], Rodolfo de Paula Vieira[2], Henrique Takachi Moriya[3], Ana Paula Ligeiro de Oliveira[2]; Fernanda Degobbi TQS Lopes[1], Thais Mauad[4], Milton de Arruda Martins[1], Rogerio Pazetti[5]

1. Clinical Medicine (LIM20), FMUSP; 2. Nove de Julho University (UNINOVE); 3. Biomedical Engineering Laboratory (LEB), USP; 4. Pathology (LIM05), FMUSP; 5. Thoracic Surgery (LIM61), FMUSP: São Paulo

Pulmonary emphysema is characterised by the permanent destruction of alveolar walls leading to airspace enlargement, loss of elastic recoil, decreased surface area for gas exchange, pulmonary hyper distension and increased respiratory effort.[1, 2] Several experimental models of pulmonary emphysema have been developed, such as cigarette smoke exposure and administration of exogenous proteinases, which induce lung parenchyma destruction as in humans.[3] Some researchers have shown that a single dose of elastase induces diffuse alveolar damage and rapid destruction of alveolar septa, resulting in airspace enlargement.[3, 4] Lung volume reduction surgery (LVRS) is one of the most performed surgical treatments for patients with moderate and/or advanced pulmonary emphysema waiting for lung transplantation.

LVRS is a palliative procedure for patients with severe emphysema whose respiratory function is severely impaired due to lungs and chest hyperinflation. The goal of surgery is to reduce hyperinflation by removing the destroyed portions of the lung, and thus, improve respiratory function, dyspnoea, exercise tolerance and quality of life.[5] Pneumonectomy (PNX) is an established model to study compensatory lung growth (CLG) in mammals. The PNX model has the advantage of mimicking the loss of functional lung units that are destroyed in lung disease: tissue loss can be defined and reproducible, the remaining lung is normal, and the compensatory response can be quantified without difficulty.[6]
We investigated the effects of CLG on pulmonary mechanics after bilobectomy (LBX) in rats with emphysema induced by elastase. Ninety-five Wistar rats were divided into four groups: saline+sham LBX (SS); saline+LBX (SX); elastase+sham LBX (ES); and elastase+LBX (EX). Forty-two days after the instillation of porcine pancreatic elastase (5UI/100g) or saline solution, animals underwent sham surgery or right bilobectomy (middle and cardiac lobes). Animals were killed at two, four or sixteen weeks after LBX.

Pulmonary mechanics and inflammatory cell counts were performed in broncoalveolar lavage (BAL) and in lung tissue. Pulmonary resistance was increased in ES at 16 weeks ($p=0.002$). Pulmonary elastance was increased in EX compared to ES after four and 16 weeks ($p<0.001$).

Total cells, macrophages and neutrophyls were increased in ES and Ex compared to SS and SO ($p<0.05$). There was less mononuclear cells in the EX in comparison with the ES ($p=0.024$) after four weeks; polimorphonuclear cells were also decreased after two weeks in the EX versus ES ($p=0.019$). Changes in lung function are a major feature of COPD. The pulmonary function tests in experimental models are less sensitive than morphometry, as they detect only more severe degrees of airway remodeling and parenchymal destruction.[7] Consequently, we found few studies in the literature reporting mechanics data in experimental elastase models of rats. We observed little difference in the parameters of mechanical ventilation in our model of emphysema.

The resistance values of the respiratory system practically did not change in this model. On the other hand, elastance of the respiratory system was increased in EX group at T4 and T16, suggesting that the LBX was beneficial in these groups. We found an increase in total number of cells, macrophages and neutrophils in BAL of all elastase-treated animals, indicating an increase in pulmonary inflammation.

However, LBX was not effective in reducing inflammation in operated animals as expected. We conclude that CLG improves pulmonary elastance after LBX in elastase-treated animals.

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Francine Maria de Almeida is a biologist and has a Master of Science from São Paulo University Medical School (FMUSP), São Paulo, Brazil. She has previously worked with clinical and experimental models of lung inflammatory diseases, including thoracic surgery in rodents. Currently, she is a doctoral student at FMUSP and is studying the effects of creatine after lung transplantation in rats.

Berlin Questionnaire For Sleep Apnoea Syndrome: Risk Factors for High Score

Cerrai Sonia[1], Maio Sara[1], Sarno Giuseppe[1], Baldacci Sandra[1], Angino Anna[1], Di Pede Francesco[1], Martini Franca[1], Fresta Martina[1], Viegi Giovanni[2]

1. Pulmonary Environmental Epidemiology Unit, CNR Institute of Clinical Physiology (IFC), Pisa; 2. CNR Institute of Biomedicine and Molecular Immunology (IBIM) "A. Monroy", Palermo

Introduction

Obstructive sleep apnoea syndrome (OSAS) is characterised by repeated episodes of upper airway obstruction during sleep. Sleep fragmentation determined by the recurrence of sleep apnoea is the cause of excessive daytime sleepiness. Each apnoea episode is associated with a reduction of the oxygen concentration in the blood and with oscillations of heart rate and of systemic arterial and pulmonary pressures, that can cause permanent breathing problems and hypertension.[1] Compared to the general population, patients with OSAS have an over two-fold risk of developing hypertension and cerebrovascular or cardiovascular diseases.[2, 3, 4]

Estimates of OSAS prevalence in the general population are in the range of 3% to 10%. Factors that increase susceptibility for the disorder include age, male sex, obesity, family history, menopause, craniofacial anomalies, and risky behaviours such as smoking habits and alcohol consumption.[5, 6]

Although public awareness of obstructive sleep apnoea has steadily increased during the last few decades, and despite the numerous advancements in our understanding of the pathogenesis and clinical consequences of the disorder, most of those affected still remain undiagnosed.[7]

For this purpose, some screening tests, with low-cost and easily reproducible procedures, have been identified. Among these, the Berlin Questionnaire is a tool that quickly indentifies the risk (low to high) of sleep-disordered breathing.

Aim and Method

We have tried to identify risk factors associated with the probability to obtain a high score at the Berlin Questionnaire for OSAS in an Italian general population sample surveyed twice (18 years apart). Detailed information on population characteristics and methodology have been previously published.[8, 9]

From 1985–1988, a general population sample of 3865 subjects, enrolled through a randomised, stratified, family cluster design and living in the urban and suburban area of Pisa (PI1), Central Italy, was investigated. A second cross-sectional study (PI2) was carried out between 1991–1993. Beside those participating in PI1, other subjects were recruited; overall, 2841 subjects were investigated. A third cross-sectional study (PI3) was carried out between 2009-2011. Beside those participating in PI1/PI2, other subjects were recruited: new spouses and subjects who were not available in PI1/PI2. Overall, 1620 subjects were studied: 73% of them had already participated in PI1/PI2 (average follow-up of 18 years).

In PI1 and PI2, information on respiratory symptoms/diseases and risk factors were obtained by a standardised interviewer-administered questionnaire developed by the National Research Council (CNR). A subsample (n=1890), aged ≤75 years, performed the spirometry test (forced vital capacity maneuver - FVC) according to the American Thoracic Society (ATS) protocol.[10]

PI3 was performed within the European IMCA2 (Indicators for Monitoring COPD and Asthma in the EU) project, using a self-administered questionnaire on socio-demographic characteristics, respiratory symptoms/diseases and risk factors designed for such a project. All questions about asthma and COPD were obtained from previously used and validated questionnaires.[11, 12] A subsample (n=689) performed the spirometry test (FVC maneuver). The probability of having OSAS was scored using the standardised Berlin Questionnaire. Such score (High vs Low) has been used as the outcome to evaluate the association with baseline (PI2) risk factors: age, sex, Body Mass Index (BMI), smoking habits, and diagnoses of asthma, COPD and rhinitis, through a Logistic Regression Model.

Results and Conclusion

In PI3 there was a 25.7% prevalence of Berlin Questionnaire High Score and such High Score was significantly associated with the following baseline characteristics: age 25-64 yrs, age ≥65 yrs, BMI 25-29 kg/m2, BMI ≥30 kg/m^2, ex-smoker, diagnoses of rhinitis and COPD.

These findings suggest that personal and anthropometric factors (age and BMI), risk factors (smoking habit) and respiratory conditions (diagnoses of COPD and rhinitis) are associated with the possibility to obtain, 18 years apart, a High Score at the Berlin Questionnaire, which is suggestive of a high

Sonia Cerrai graduated *summa cum laude* in Biology at the Faculty of Mathematical, Physical and Natural Sciences of Pisa University. Since 2007 she has worked as a Researcher at CNR Institute of Clinical Physiology for the Pulmonary Environmental Epidemiology Unit, under the direction of Dr. Giovanni Viegi.

probability of having OSAS. Primary care physicians and specialists across various medical disciplines could use such an easy tool for predictive and preventive purposes.

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TNF-α, IL-8, IL-6 Levels in Serum of Sarcoidosis Patients with Different Clinical Course

Olga Denisova[1, 2], **George Chernogoryuk**[2] and **Ksenia Egorova**[2]

1. Pulmonology Department, Tomsk Regional Clinical Hospital; 2. Hospital Therapy Department, Siberian Medical University

Introduction

Sarcoidosis is a systemic granulomatous disease of unknown etiology affecting the lung. The disease typically spontaneously remits but, in 20% of cases, progresses with severe lung dysfunction or cardiac and neurologic involvement.

Studies on the immunopathogenic origins of sarcoidosis have provided evidence of persistent antigenic stimulation at sites of inflammation that is associated with dysregulated cytokine production.[1, 2, 3] The data are the basis for the application of TNF antagonists in the treatment of sarcoidosis.[4]

Although researchers have demonstrated systemic inflammation in sarcoidosis, the prognostic significance of various cytokines and chemokines is not fully understood. The aim of the study was to investigate the influence of TNF-α, IL-8, IL-6 on the prognosis of new-onset sarcoidosis, the relationship of cytokines with clinical manifestations of the disease.

Methods

The study included 41 patients with sarcoidosis onset (stage II) and 18 healthy controls. The age of patients was 22 - 73 years (42,6 ± 13,1 years), of whom 24 (58.3%) were women and 17 (41.4%) were men. The comparison group consisted of 18 individuals without sarcoidosis, 16 (55.6%) women and 8 (44.4%) men, and median age was 40,5 ± 3 years. The diagnosis of sarcoidosis in all cases was verified by VATS biopsy.

Levels of TNF-α, IL-8, IL-6 were determined by ELISAs in the blood serum. According to the 1-3year period of observation (without systemic corticosteroid treatment) sarcoidosis group was divided into 3 groups: spontaneous regression, progression and stabilisation.

For statistics, the non-parametric method of Mann–Whitney Utest and Spearman's correlation were used. In data expressed as median, the significance level was considered significant if <0.05.

Results

The progression group is characterised by the highest levels of blood TNF-α (10.7 pg/ml), IL-6 (7.4 pg/ml). Their values were significantly higher compared to the regression group (9.2 and 7.4 pg/ml respectively). IL-8 (9.5 pg/ml), IL-6 levels were significantly higher in the blood of the progression group patients compared to control (5.3 and 3.6 pg/ml). The group of spontaneous regression expressed the highest level of IL-8 (14.1 pg/ml). In contrast, TNF-α, IL-8, IL-6 levels were significantly reduced in the healthy control. Cytokine levels in the group with stabilisation were not significantly different.

Increased serum IL-6 level was associated with reduced FVC in sarcoidosis patients ($r = -0.6$). We found positive associations of IL-6 ($r = 0.5$-0.7) with smoking, weight loss, increased peripheral lymph nodes, CIC and seromucoid levels in blood; and negative associations with the frequency of thyroid disease in patients ($r = -0.7$). TNF-α level direct correlated ($r = 0.5$-0.6) with fever, cough, weight loss, serum levels of Ig M, and TSH. IL-8 had inverse correlation with red blood count ($r = 0.4$). We have not found significant correlations between TNF-α, IL-8, IL-6 and other FVD parameters, degree of dyspnea, age, gender, presence of comorbidity rate, weakness, splenomegaly, skin lesions, sweating, and arthralgia. No relationships were found with blood biochemistry parameters (including calcium) and white blood count.

Conclusions

Serum TNF-α, IL-6 levels determine many of the clinical manifestations of the disease. TNF-α, IL-8, IL-6 appears to have a predictive value for the clinical course of sarcoidosis.

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Olga Denisova is a pulmonologist at the Consultative Diagnostic Center of the Tomsk Regional Clinical Hospital, Russia, and specialises in the field of sarcoidosis and diffuse lung diseases. She received her PhD in the Department of Hospital Therapy, Siberian State Medical University. Dr. Denisova is interested in the mechanisms of sarcoidosis development and new therapeutic approaches in the treatment of this disease.

Pulmonary Alveolar Proteinosis

Önder Öztürk

Department of Pulmonary Diseases,School of Medicine, University of Suleyman Demirel, Cunur, Isparta

Pulmonary alveolar proteinosis (PAP), first described by Rosen, Castleman, and Liebow in 1958, is an extremely rare lung disease characterised by accumulation of eosinophilic periodic acid Schiff (PAS)-positive material in the distal airways.[1] PAP is occurring worldwide with an estimated prevalence of 0.1 per 100,000 individuals and the median age at diagnosis is 39 (30–46), especially among males.[2, 3] Although the symptoms are not specific, and almost one third of patients are asymptomatic, the diagnosis of PAP is made on the basis of a combination of symptoms, high-resolution computed tomography, and bronchoscopy with PAS stain of bronchoalveolar lavage fluid; lung biopsy is rarely required.[1, 3, 4] According to etiology, PAP can be divided into two categories: (i) autoimmune PAP, accounting for approximately 90% of all PAP cases, and (ii) non-autoimmune PAP, which can be further subdivided into secondary PAP and congenital PAP. The secondary form is found in association with high levels of exposure to dust, mineral and metal particles (e.g. aluminum, titanium, indium, and silica). It is further associated with haematological malignancies and has been seen after allogeneic bone marrow transplantation for myeloid malignancies. Genetic PAP is seen especially in children, and radio-clinical presentation depends on the mutated gene.[1]

Although different treatment modalities have been applied since PAP was first described, the treatment of PAP depends on the underlying cause. Therapy for congenital PAP is supportive, but SP-B deficiency has been treated successfully by lung transplantation. Therapy for secondary PAP generally involves treating the underlying condition. Although a number of treatment approaches have been used in isolated cases, whole-lung lavage (WLL) has been the first-line of treatment. Although there are no randomised controlled studies of WLL to determine the optimal strategy,[5] an algorithm is proposed by Leth *et al*.[1] They suggest that autoimmune PAP patients should be divided into three stages by disease severity score (DSS), which is based on the presence of symptoms and degree of reduction in PaO2, as suggested by Inoue *et al*.:[3] "DSS 1 = no symptoms and PaO2 ≥ 70 mm Hg (Stage 1); DSS 2 = symptomatic and PaO2 ≥ 70 mm Hg (Stage 2); DSS 3 = PaO2 ≥ 60 mm Hg but < 70 mm Hg; DSS 4 = PaO2 ≥ 50 mm Hg but < 60 mm Hg; DSS 5 = PaO2 < 50 mm Hg. In the following [sic], DSS 3 + 4 + 5 is combined as Stage 3."

Despite significant radiographic abnormalities, 20% of primary PAP patients undergo spontaneous remission and do not require treatment. These patients should be followed up for relapse or progression in symptoms. Although there are no clear guidelines on when to start treatment, the treatment should be started when either symptoms become limiting or when the patients require oxygen or are hypoxemic at rest (Stage 3, P(A–a)O2 > 40 mm Hg or shunt fraction > 10–12%), and ground-glass opacity progresses on HRCT. Clinical response has, in one study, been defined as an improvement in one of the following parameters: > 10 mm Hg increase in (PaO2), > 12 mm Hg reduction in (P(A–a)O2), > 12% increase in DLCO, or > 7% increase in forced vital capacity.[6] If WLL fails, inhaled GM-CSF should be attempted. If WLL and inhaled GM-CSF therapy fail or are associated with unacceptable side effects, then rituximab, a monoclonal antibody directed against the CD20 antigen of B-lymphocytes, should be administered. Plasmapheresis may help patients unresponsive to WLL, but should be applied only after all other treatments, including combination therapy, have been attempted.

In conclusion, our knowledge about the pathophysiology of PAP has greatly improved in the past 20 years, but we need further studies to understand PAP's biological and immunological mechanisms, in order to define better treatment modalities.

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Önder Öztürk is an Associate Professor in the Department of Pulmonology, Faculty of Medicine, University of Süleyman Demirel and head of the Diagnosis and Treatment of Sleep Disorders Research Center. He is a member of European Respiratory Society, American Thoracic Society, American Academy of Sleep Medicine, Sleep Society, Turkish Thoracic Society, Turkish Respiratory Society, Turkish National Society of Allergy and Clinical Immunology and Turkish Society of Lung Cancer. Dr. Öztürk has special interests in sleep disorders, COPD, lung cancer, immunology and molecular biology. He has also authored numerous scientific papers published in international, peer-reviewed journals.

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The Migration of Monocytes is Stimulated by Jagged-1 and DLL-4 via the Notch Pathway

Katherin Watzinger
University of Innsbruck, Innsbruck, Tyrol

Introduction

Inflammation seems to play an important role in the development of pulmonary hypertension (PH).[1] Pulmonary vessels are thought to be influenced by inflammatory cells and chemokines they produce. These chemokines and cytokines regulate growth, migration and differentiation of inflammatory cells, which leads to vascular remodelling.[2]

The Notch signaling pathway is an evolutionarily conserved pathway in multicellular organisms. It is absolutely required for normal embryonic development, regulates cell-fate determination and the maintenance of stem cells in adults.[3-7]

The human Notch family includes four receptors (Notch 1-4) and five ligands (Jagged 1-2, Delta-like 1, 3, and 4).[8-10] All Notch receptors are single pass trans-membrane proteins composed of a functional extracellular, trans-membrane and an intracellular domain.

Material and Methods

Monocytes were isolated from EDTA-anticoagulated venous blood, taken from healthy donors with their informed consent followed by subpopulation specific MACS isolation protocols. For the chemotactic assays modified 48-well microchemotaxis chambers were used. For blocking experiments monocytes were pre-incubated with specific ligands for different durations. Migration depth of the cells in the filter was quantified microscopically by measuring the distance [µm] from the surface of the filters to the leading front of the cells.

The RNA of monocytes was isolated with RNA-BEE and transcribed into cDNA with Superscript III (Fa. Invitrogen). The quantification was done by real time PCR.

Results

All known Notch receptors (1 to 4) are expressed on human monocytes but to a different amount. The highest expression was observed for Notch 2 while the lowest expression was assessed for Notch 4. The two Notch ligands Jagged-1 and DLL-4 can induce chemotaxis of monocytes *in vitro*. Also priming of cells with both ligands induced a significant migratory response. As the ligands are expressed on cell surfaces we preincubated monocytes with these ligands for different time intervals to explore how long a cell-cell interaction might be necessary to elicit migration. Interestingly, at least a 30 min preincubation period was necessary to activate migration by Notch ligands. Specific blocking of ligand-induced migration was achieved by preincubation with the metalloprotease ADAM 17.

Conclusion

Jagged-1 and DLL-4 can stimulate direct migration of human monocytes. For this migratory response a cell-cell interaction of at least 30 minutes seems to be necessary. It can be suggested that Jagged-1 and DLL-4 are involved in attracting monocytes to inflammatory sites.

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Katherin Watzinger studied molecular biology at the University of Innsbruck. Since February 2012 she has been working on her PhD thesis "Role of the DSL-family on cell – cell interaction in pulmonary inflammation" at the pulmonary research lab at the Medical University of Innsbruck with the head ao. Univ.-Prof. Dr. Christian M. Kaehler.

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

Ted Klok[1] and **Paul L. Brand**[1, 2]
1. Princess Amalia Children's Clinic, Isala klinieken, Zwolle; 2. UMCG Postgraduate School of Medicine, University Medical Centre, University Groningen, Groningen

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.

Ted Klok is Paediatric Resident in the Isala Hospital, Zwolle and at the University Medical Centre in Groningen, both in the Netherlands. He recently completed his PhD and defended his thesis entitled 'Determinants of adherence to inhaled corticosteroids in children with asthma' succesfully (www.tedklok.nl). His fields of interest comprise patient-centred care and shared decision making in paediatrics.

Paul Brand is a Consultant Paediatrician for respiratory and allergic disease at the Princess Amalia Children's Clinic, Isala hospital, Zwolle, the Netherlands, and a Professor of Clinical Medical Education at the University Medical Centre in Groningen, also in the Netherlands. His fields of research comprise diagnosis and management of asthma and allergy in children, with a special interest in adherence and shared decision making; in medical education, his research focuses on competency-based postgraduate medical education and its impact on consultants' preparedness for practice. Professor Brand is an active member of the Paediatric Assembly of the European Respiratory Society, and has been the Chair of the society's Task Force on preschool wheezing disorders. He is the Editor-in-chief of the Netherlands' national paediatric educational journal.

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

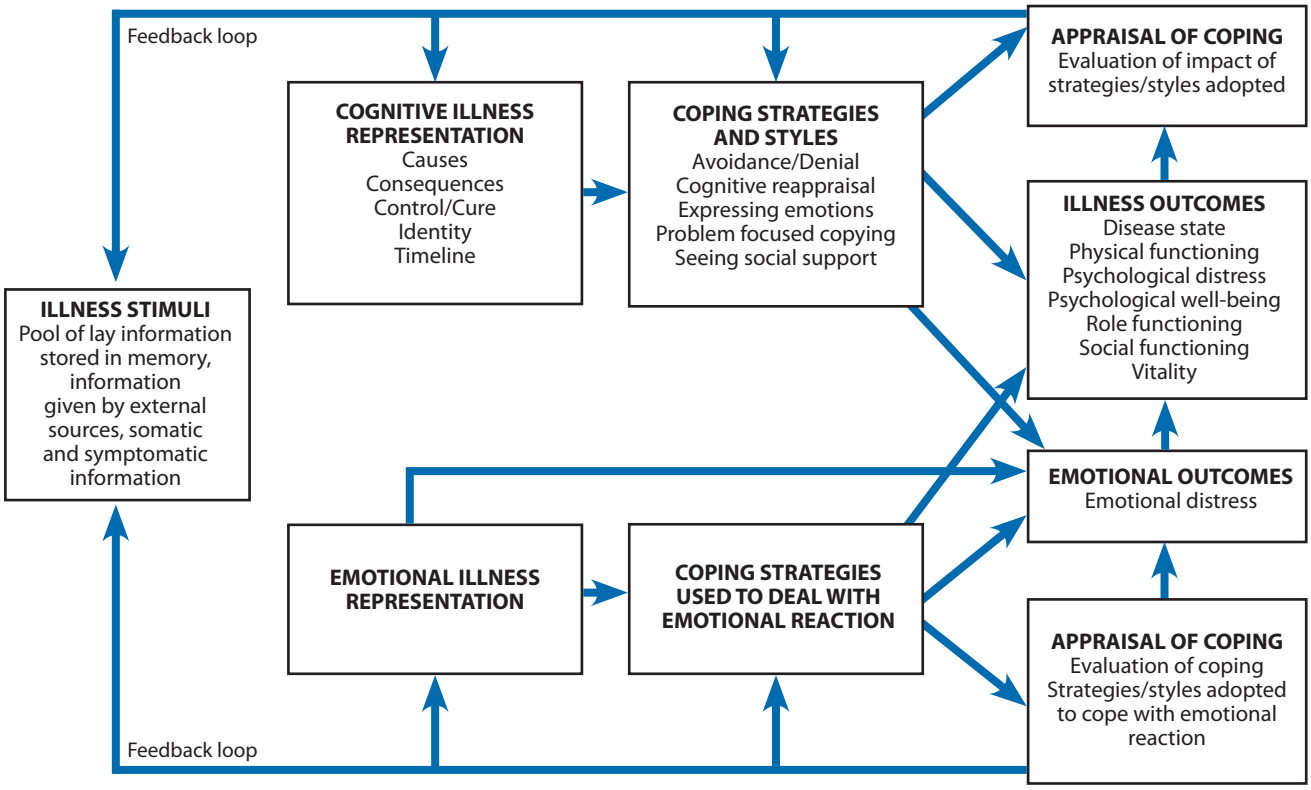

Figure 1. The Common Sense Model, (adapted by Orbell & Hagger).[10]

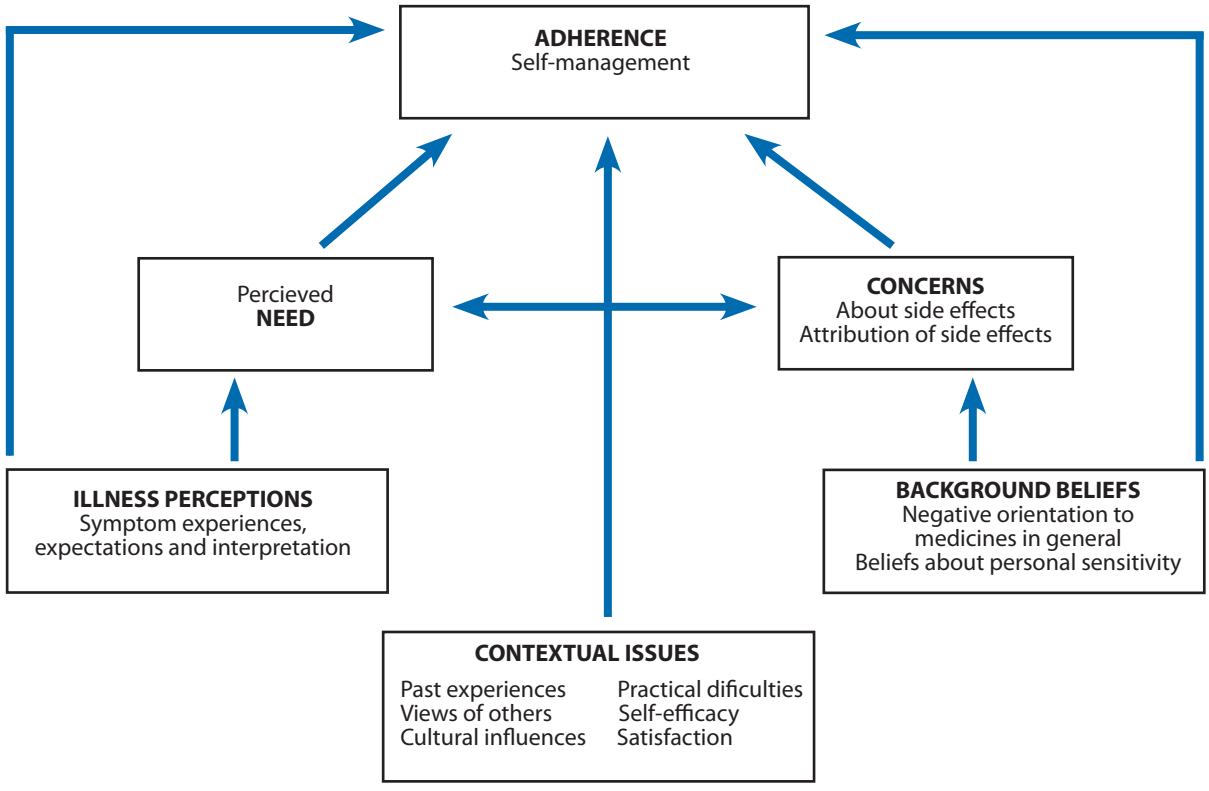

Figure 2. A theoretical model of the relationship of illness perceptions, medication beliefs and adherence as presented by Horne.[15]

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

Björn Nordlund
Karolinska Institutet, Department of Women's and Children's Health, and Astrid Lindgren Children's Hospital, Stockholm

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.

Björn Nordlund obtained his PhD at the Karolinska Institutet in Stockholm, Sweden and is a Paediatric Nurse at Astrid Lindgren Children's Hospital and Karolinska Institutet, Stockholm, Sweden. His research interests are focused on severe childhood asthma, and the project aim of his research group is to increase the understanding of children's characterisation and health-related quality of life. His research group has gathered experience and knowledge in the management, mechanisms and markers of severe asthma.

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 for 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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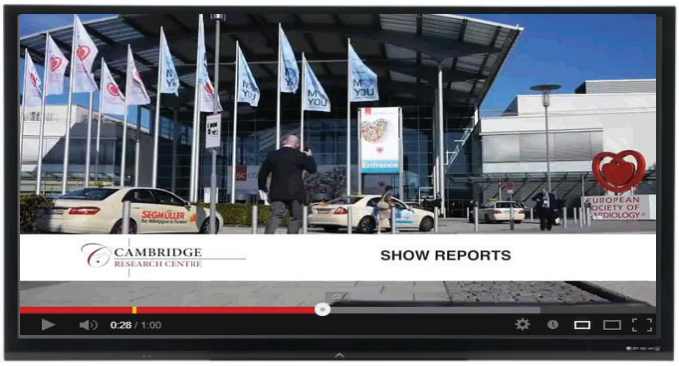

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Experimental Models to Study Cystic Fibrosis Lung Disease with Emphasis on Primary Airway Epithelial Cell Approaches

Malcolm Brodlie,[1, 2] **Jim Lordan**[3] and **Chris Ward**[1]
1. Institute of Cellular Medicine, Newcastle University, Newcastle; 2. Paediatric Respiratory Medicine, Great North Children's Hospital, Newcastle; 3. Freeman Hospital, Newcastle

Introduction

Cystic fibrosis (CF) is the most common inherited life-limiting disorder in Caucasian populations.[1] CF is associated with life-long morbidity and premature mortality, over 95% of which is associated with lung disease.[2] CF lung disease is characterised by neutrophilic inflammation, retention of mucopurulent secretions and chronic endobronchial infection with specific bacteria, most notably Pseudomonas aeruginosa. The genetic basis of the condition is known to be abnormalities in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.[3]

Promising developments in clinical care have yielded an increased survival for people with CF over recent decades.[4] However, over 20 years after the cloning of the CFTR gene, the exact pathogenesis of CF lung disease remains poorly understood.[5] It therefore follows that valid experimental models are required for use in research to further elucidate the pathogenesis of CF lung disease and to evaluate and develop novel therapeutic strategies. A shining example of this is the recent exciting discovery of a number of small molecule CFTR correctors and potentiators. The use of high throughput screening and appropriate experimental models were pivotal elements in the rapid development and translation of this approach, which has changed the therapeutic landscape for CF patients with certain genotypes.[2, 6, 7] This review describes the various cellular models and approaches available and discusses their relative merits, with a particular emphasis on primary tissue and airway epithelial cells. The article also includes a brief discussion of relevant CF animal models.

Malcolm Brodlie is an Academic Clinical Lecturer in Paediatric Respiratory Medicine at the Institute of Cellular Medicine, Newcastle University and the Great North Children's Hospital in Newcastle upon Tyne, UK. He has an interest in the pathogenesis of cystic fibrosis lung disease and in particular the development of primary bronchial epithelial cell culture models to study it.

James Lordan is a Consultant in Respiratory Medicine and Lung Transplantation at the Freeman Hospital, Newcastle upon Tyne. He is also an Honorary Senior Lecturer in Respiratory Medicine, Institute of Cellular Medicine, Newcastle University.

Christopher Ward is a Senior Lecturer in Respiratory Medicine at the Institute of Cellular Medicine, Newcastle University. His research work involves the use of primary tissue and epithelial cells to study the pathogenesis of respiratory disease, including cystic fibrosis.

Airway Epithelial Cell Models

In addition to more primitive barrier functions, airway epithelial cells are increasingly recognised to operate as 'effector' cells that produce a wide range of inflammatory and immunomodulatory cytokines and growth factors.[8-10] Such functions are not only relevant to health, where they are involved in maintaining homeostasis but also to respiratory disease, where airway epithelial cells are implicated directly in the pathogenesis of several conditions.[11]

For a number of decades it has been possible to culture human airway epithelial cells *in vitro* (Figure 1).[12, 13] Cells may be cultured most simply under submerged conditions using specialist primary airway epithelial cell medium directly on plastic or on top of a collagen matrix layer in petri dishes or flasks.[12, 14] More advanced culture techniques, such as within collagen gels, as three-dimensional spheroids or most commonly on semi-permeable membranes at an air-liquid interface, allow the development of a more accurate representation of the native airway epithelium.[15, 16] Air-liquid interface cultures have been pivotal to major advances in our understanding of the pathogenesis of CF lung disease, including the depletion of the periciliary liquid layer, and the structure and function of mucus in the airway.[17, 18]

Immortalised Airway Epithelial Cell Lines

The establishment of immortalised airway epithelial cell lines, originating from human neoplasms or produced *in vitro* by physical or chemical mutagenesis or introduction of viral oncogenes, has benefited CF research considerably.[19] Cell lines have been used extensively and have been particularly useful for the investigation of the biological effects of different CFTR mutations on cellular metabolism, biochemistry and physiology.[12, 19-22] Immortalised cells are also employed in the early stages of high-throughput screening strategies to identify novel therapeutic compounds.[22] Advantages

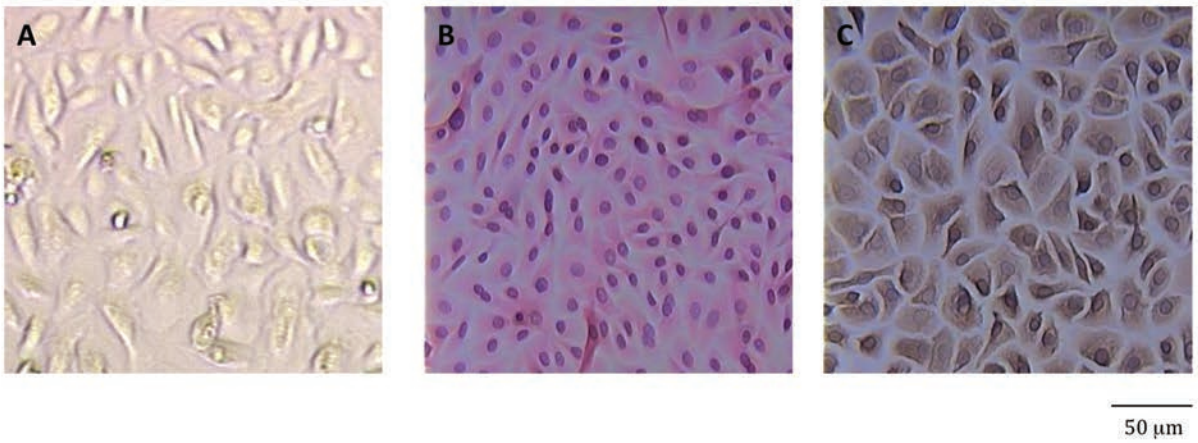

Figure 1. Light microscopy images of primary human bronchial epithelial cells cultured from the explanted lungs of a CF patient. A: Brightfield microscopy of confluent live cells in submerged culture, illustrating typical 'cobblestone' morphology. B: Haematoxylin and eosin stain of confluent fixed cells from submerged culture. C: Positive pan-cytokeratin staining of fixed cells from submerged culture indicating epithelial phenotype.

of cell lines include their widespread availability, especially when compared to the scarcity of primary CF tissue and cells, homogeneity in terms of biochemical, electrophysiological and growth characteristics and the presence of matched isogenic control cell lines with normal functioning CFTR.[19] Many cell lines are also relatively straightforward to grow in the laboratory and to cryopreserve without any requirement for expensive specialist growth media.

It should be noted, however, that the process of immortalisation may inherently generate karyotypic instability and have major effects on cellular differentiation, morphology or function compared to native cells *in vivo*.[19, 21, 23] In addition, some cell line models involve the overexpression of specific mutant forms of CFTR, and this may in itself influence cellular physiology.[24] Not all cell lines are capable of differentiating to form tight junctions, secrete mucins and form cilia either. Cell lines that are commonly used in CF research have been comprehensively reviewed.[19]

Primary Cells

Native primary cells cultured directly from people with CF represent a valuable experimental resource for research. The *ex vivo* culture of primary CF airway epithelial cells is likely to recapitulate more accurately the biology of cells *in vivo* than immortalised cell lines.[14, 25] Primary airway epithelial cells have been demonstrated to replicate in culture the *in vivo* electrophysiological profile and phenotype of the patient from whom they were sampled.[25] Indeed, primary airway epithelial cell cultures have been instrumental in several important

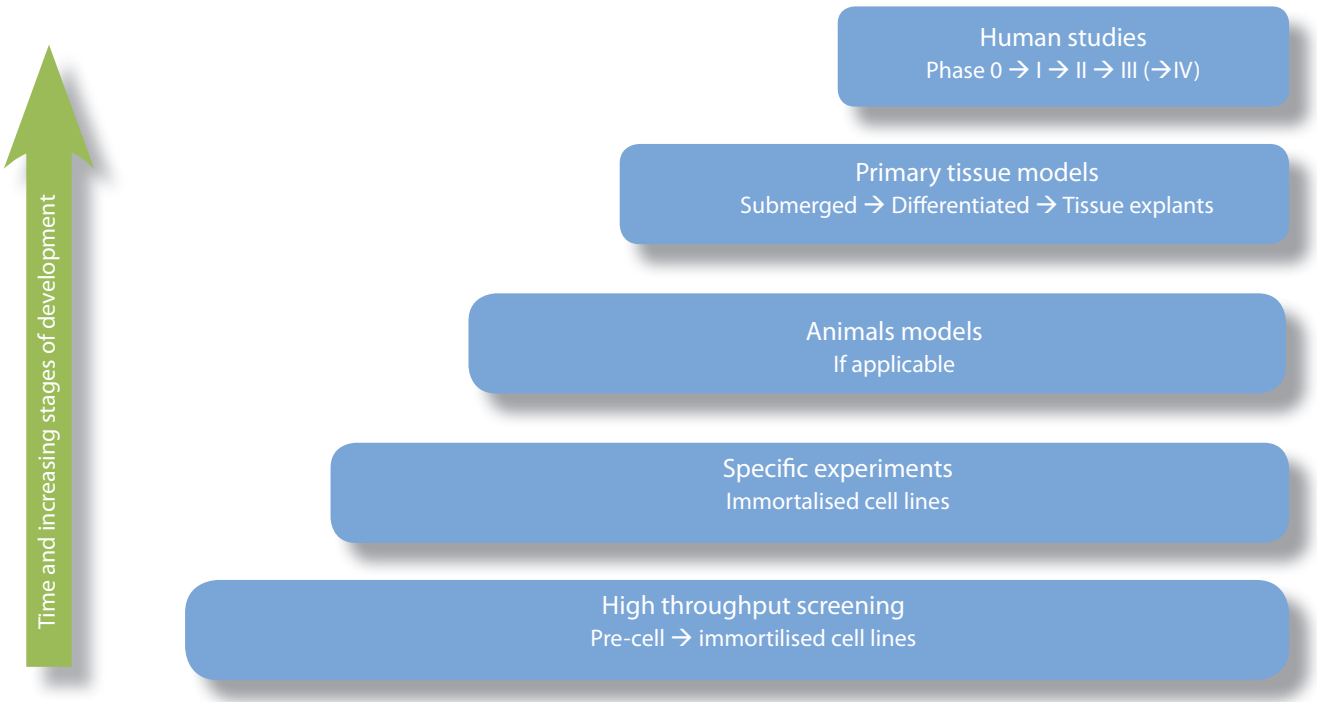

Figure 2. Schematic diagram illustrating the use of different experimental models in drug discovery for CF lung disease.

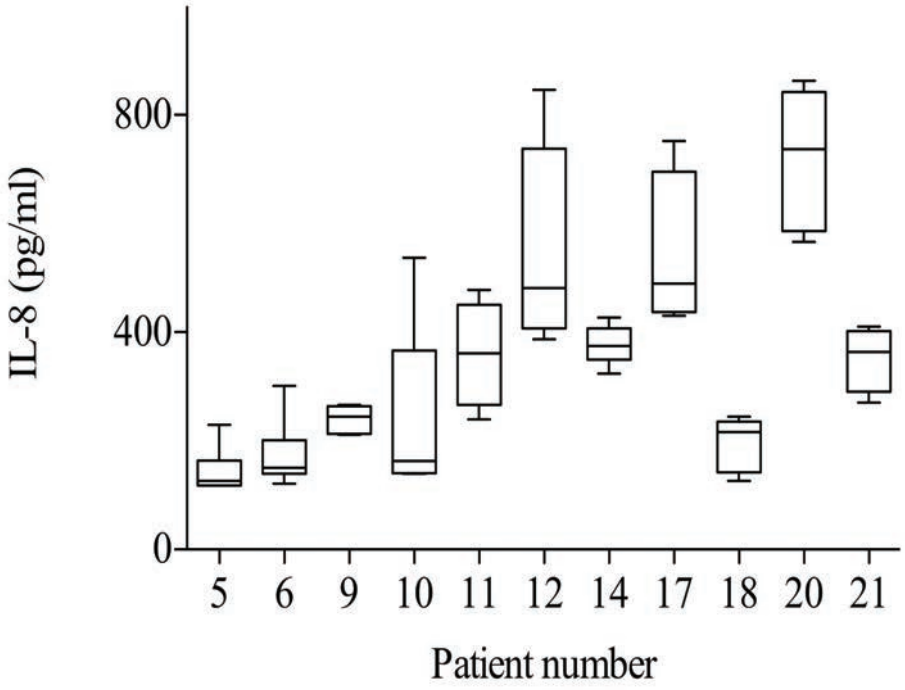

Figure 3. Variation in basal production of interleukin-8 by primary bronchial epithelial cells from people with advanced CF lung disease. Horizontal lines indicate the median basal production of interleukin-8, results from four replicate experiments. Each patient number represents a different individual.

developments in our understanding of the pathophysiology of CF lung disease.[17, 26-29] In terms of drug discovery, although immortalised cell lines are extremely valuable in the early stages of high-throughput screening as outlined above, primary cells are vital to confirm and validate any initial findings in a cell line prior to more advanced stages of analysis (Figure 2).[5, 22, 30, 31]

There are a number of limitations and disadvantages involved in the use of primary airway epithelial cells however. Firstly, access to tissue and procurement of primary cells may be difficult. Cells and tissue from rare clinical genotypes are particularly scarce. Different potential sources of primary CF airway epithelial cells are discussed below. Secondly the culture of primary airway epithelial cells is technically more challenging than immortalised cell lines and there are particular problems associated with the culture of airway cells directly from people with CF such as eradicating infection by multi-resistant microorganisms.[14] Clinically, in people with CF there is a diverse spectrum of disease and often a relatively weak correlation between genotype and clinical lung phenotype.[32] Primary airway epithelial cells from individual patients reflect this inherent biological heterogeneity in terms of their function and inflammatory responses for example.[33] Figure 3 illustrates the variation in basal interelukin-8 production by unstimulated primary bronchial epithelial cells cultured under submerged conditions from different individuals with CF. In some instances the homogeneity of an immortalised CF cell line along with isogenic control may be preferable experimentally.

Appropriate ethical approval and strict adherence with human tissue legislation are clearly essential along with the informed consent of the participants.[34-37] Equally, any research sampling must not compromise the clinical care or health of patients.[38, 39]

Explanted Lungs Removed at the Time of Transplantation

The only life-sustaining intervention for end-stage CF lung disease is transplantation.[40] Explanted lungs removed at the time of transplantation from individuals with CF represent a potential source of large numbers of primary bronchial epithelial cells. The procurement of appropriate lung tissue is logistically demanding however and is limited to a number of specialist transplant centres. Lung transplantation is also unpredictable in nature, informed consent is required in advance from patients and the co-operation of the multidisciplinary transplant team is essential. It is also imperative that the multidrug-resistant organisms, which inevitably colonise the airways of people with end-stage lung disease, are eradicated from cultures at an early stage to achieve success.[19, 41] In our experience a patient-specific combination of anti-microbials that is guided by the sensitivities of recent clinical isolates is beneficial to success rates (Figure 4).[14] Fortunately the choice of agents is not hampered by the frequent allergies encountered clinically in people with end-stage CF lung disease however.[42]

Intact sheets of bronchial epithelium may also be resected from lungs shortly after explantation and placed in perfused mini-Ussing chambers. This allows the investigation of electrophysiological responses, for example with small molecule CFTR correctors or potentiators, in the context of an intact epithelium complete with submucosal glands.[43, 44]

Primary CF airway epithelial cells sampled from explanted tissue are by definition representative of end-stage disease and may not be truly indicative of cells and the epithelium at earlier stages of disease when it is most attractive to develop interventional therapeutic strategies to ameliorate disease progression. Furthermore, primary cells from an end-stage CF airway may have been subject to epigenetic modifications during the course of disease.

Bronchial Brushings

Bronchial epithelial cells may also be cultured in smaller numbers

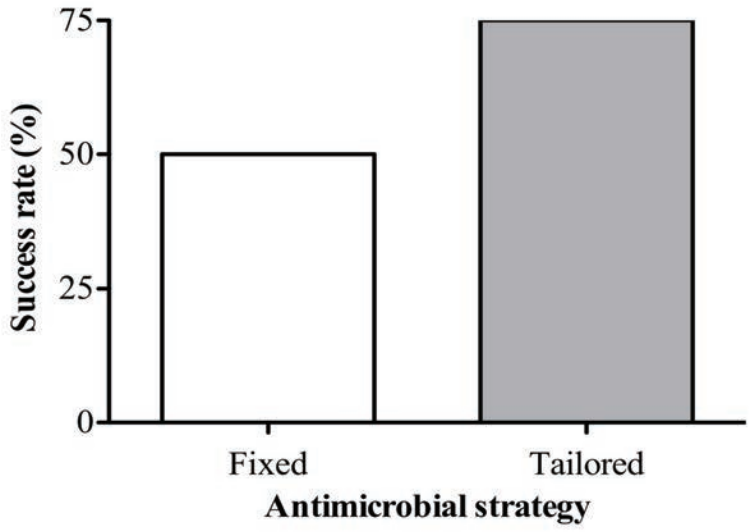

Figure 4. Success rates in achieving cultures from explanted CF lungs using fixed and tailored, patient-specific, antimicrobial strategies.

from brushings of the lower airway. Bronchial brushings may be obtained blindly from patients who are intubated by passing a cytology brush down the endotracheal tube. Alternatively, brushings may be performed under direct vision via a flexible bronchoscope in patients, including children, undergoing general anaesthesia, or in those who are undergoing bronchoscopy for a clinical indication.[45-47] McNamara *et al*. have demonstrated bronchoscopic sampling to be a quick and well-tolerated procedure in children that yields an increased number of cells compared to blind brushings via an endotracheal tube.[45]

Once the appropriate ethical approval is in place a flexible, a patient-centred approach is likely to be required from the clinical researcher to maximise the procurement of informed consent. This strategy can also maximise the collection of bronchial brushings from CF patients, for example by intercalating sampling within planned clinical procedures such as gastrostomy or totally implantable vascular access device insertion. Eradication of infection remains essential for the successful culture of cells *in vitro*.

Nasal Brushings

The nose is an alternative source of airway epithelial cells that is easily accessible. Nasal brushings may be performed in a relatively non-invasive manner in the clinic. In adults and older children the technique does not require any sedation or anaesthesia, and therefore allows repeated longitudinal sampling from the same individual, for instance with a particular CFTR genotype of interest or before and after a specific intervention or treatment. Nasal brushings may also be performed on patients that are less likely to undergo bronchoscopy clinically such as those with more established lung disease where the risks associated with bronchoscopy are increased.[48, 49] There are several published methods for the culture of nasal epithelial cells from people with CF and the feasibility of the technique has even been demonstrated in infants.[25, 48, 50]

McDougall *et al*. compared the release of proinflammatory mediators and surface expression of receptors by undifferentiated monolayers of nasal and bronchial epithelial cells from the same individuals under resting conditions and in response to cytokine stimulation.[49] They found differences in absolute mediator levels but similar responses to stimulation and comparable cell surface receptor expression, suggesting that nasal epithelial cells represent an accessible surrogate for lower airway epithelial cells to study inflammation.[49]

A further source of nasal epithelial cells are from polypectomy resection specimens from CF patients. The frequency of this procedure varies between healthcare systems however, and there may be ongoing superadded inflammatory processes as part of the pathogenesis of the polyp that may be reflected in the phenotype of the cultured cells.[25, 51]

Alternatives to Cellular Models: Animal Models

Since the cloning of the CFTR gene it has been possible to develop animal models of CF.[3] A large amount of work has been performed in this area, principally focussed on mice, that has generated over 1000 papers. Animal models of CF have been reviewed extensively elsewhere and a detailed discussion is beyond the scope of this article.[52-54] The obvious strength of animal models is that they allow the study of disease pathogenesis or the evaluation of novel therapeutic strategies with in the dynamic complexities of structurally intact organs. Once the appropriate genetic manipulation has been achieved, however, the utility of an animal model is clearly dependent on how closely the phenotype of the animal matches that observed in the human disease.

A variety of genetic approaches have been taken to generate CF mouse models including CFTR knockout, residual function, specific CFTR mutations and indirectly via ENaC overexpression.[52, 55] Many of the mice exhibit a characteristic CF electrophysiology phenotype and gastrointestinal disease that closely mimics that found in humans with CF.[56] Pancreatic disease appears to be less severe in CF mice due to lower levels of CFTR expression in the murine pancreas and the presence of an alternative secretory pathway.[57] In male mice CFTR dysfunction leads to mucoid obstruction of the vas deferens rather than complete absence as is seen in human CF. The net effect however is similarly severely reduced fertility.[52]

As mentioned above, the vast majority of morbidity and mortality in people with CF is associated with lung disease that is characterised by chronic colonisation with specific bacteria.[58, 59] Unfortunately there are significant differences between the human CF lung phenotype and that seen in CF mice. Despite promising bioelectric features of

the airway in some CF mice, establishing chronic infection with P. aeruginosa and subsequent inflammation and bronchiectatic damage has proved difficult. Possible explanations for this include inter-species differences in lung physiology, innate immunity, airway epithelial cell composition, alternative chloride channels and less widespread submucosal glands.[60-63]

The limitations of murine models to date with regard to reproducing the CF lung phenotype have led to attempts in recent years to develop other animal models. Larger animals such as pigs or ferrets have the advantage that the respiratory system more closely resembles the human situation and in particular submucosal glands are extensively distributed throughout the respiratory tract.[64] Furthermore it is possible to perform procedures such as flexible bronchoscopy and higher resolution imaging of the thorax in these animals. Most notably a porcine model has been successfully developed at the University of Iowa that is now generating important insights in to the pathophysiology of CF lung disease.[65-68] This includes pigs with the most common clinical CFTR mutation, F508del.[69] Piglets with disrupted CFTR have been observed to develop a severe gastrointestinal phenotype including meconium ileus, necessitating ileostomy, but also characteristic features of CF lung disease.[65] These early results seem very promising however the model is yet to be completely validated. Furthermore, it will be a number of years before the latest larger animal models represent a realistic mainstream tool for CF research.

Conclusions

Experimental models are critically important for use in research to advance both our knowledge of the pathogenesis of CF lung disease and to discover and evaluate novel therapeutic compounds and strategies. Immortalised airway epithelial cell lines have contributed significantly to CF research but have inherent limitations, including karyotypic instability and poor replication of behaviour *in vivo*. Primary lung tissue and airway epithelial cells harvested from nasal or bronchial brushings or explanted lungs from people with CF represent a valuable resource for the *ex vivo* study of CF lung disease. A large amount of work over the last two decades has unfortunately failed to yield a good CFTR-deficient murine model of CF lung disease. The development of larger animal models, for example porcine, remains in its infancy but is already yielding important results.

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Long-term Effects of Tobramycin Nebuliser Solutions in Patients with Cystic Fibrosis and Chronic Pseudomonas Aeruginosa Infection

Henryk Mazurek
Department of Pulmonology and Cystic Fibrosis, Pediatric Division, Institute of Tuberculosis and Lung Diseases, Rabka-Zdroj

Introduction

Cystic fibrosis (CF) is an autosomal recessive disease, where an accumulation of the mucus and subsequent infection and inflammation cause chronic, progressive bronchopulmonary disease, leading to respiratory failure and a shorter life span.

Bronchial tree infections are caused by a relatively small number of pathogens, which are harmless to healthy, immunocompetent subjects. The most prevalent and most relevant is Pseudomonas aeruginosa (PA), which is detected in about half of patients in many countries (i.e 51% in USA). The majority of adult patients are chronically infected by PA.[1]

As a result of the development of chronic infection with PA and biofilm formation, a faster deterioration of the respiratory system is observed, with more frequent exacerbations and hospitalisations, more rapid FEV1 decline and finally an earlier death. Intrabronchial antibiotic administration is often used as one element of strategy aiming to eradicate new PA infection. After chronic infection development, PA eradication is only rarely possible (even with intensive antimicrobial therapy), but long-term inhaled antibiotic therapy could limit negative infection consequences. The suppression of chronic infection by PA in patients with CF is already the most frequent indication for the use of inhaled antibiotics, targeting the airways (bronchi and bronchioles).

Henryk Mazurek completed his training in pediatrics, pulmonology and allergology in Poland, which was followed by further training in respiratory physiology at the University of Nancy I (France). He is currently Head of the Cystic Fibrosis and Pneumonology Unit at the Pediatric Division of the Institute for Tuberculosis and Lung Disease in Rabka Zdrój (Poland). His PhD research was conducted on the application of forced oscillation technique in children. Dr. Mazurek lectures and publishes in the field of respiratory disorders in childhood. Research interests include respiratory infections, cystic fibrosis and asthma. He is a member of ERS and a regular reviewer of research papers for many scientific journals.

There are 3 antibiotics approved for this indication: tobramycin, colistimethate and aztreonam. These antibiotics can be administered by nebulisation or using dry powder inhalers (tobramycin and colistimethate). However, the broadest experience and best proof of long-term efficacity and safety are observed for the tobramycin nebulised solution (TNS).[2]

Nebulised Tobramycin

Tobramycin is an antibiotic from the aminoglycoside group, produced by Streptomyces tenebrarius. It has bactericidal properties, and works by disrupting protein synthesis and altering cell wall permeability. Tobramycin is active against many bacterial species, but topical administration is only approved against PA infection in CF patients.

There are two formulations of nebulised tobramycin, both approved for long-term therapy for CF patients with chronic PA infection, aged >6 years: Tobi® and Bramitob®. Both TNS physico-chemical properties are adapted to intrabronchial delivery and differ from this for parenteral administation (by its viscosity, osmolality, pH). They are free from preservatives and have the same antibiotic doses (300 mg), but at different volumes – 5 ml or 4 ml respectively. TNS is administered twice daily using a jet nebuliser (i.e. Pari LC Plus/Pari LC Sprint, with appropriate compressor), in 28-day on-off cycles. The registered nebulisation system is inseparable from drug formulation, as different nebulisation techniques were related with 100-fold differences in peripheral lung deposition.[3] Successful lower airways drug deposition, matching pathogens location and enabling to achieve sufficient local concentration (>MIC) is most important for antimicrobial efficacity. Intermittent administration in 28-day (on -off cycles) is an empirical strategy, but other regimes were not tested in clinical trials. Repeated intermittent dosing gives the opportunity for regrowth of susceptible strains[4] and is cost-effective. It is also more friendly for patients (i.e. given twice daily, with off cycles), compared to other inhaled antibiotics: patients spend less time in therapy, using TNS only every other month. Administration of tobramycin by nebulisation allows us to obtain a

high concentration in the sputum (~25 times MIC, overcoming the antagonism from sputum), with low systemic concentrations (~100-times lower than in sputum).[5] This explains the high antibacterial efficacity and minimalises drug-related adverse events. Systemic bioavailability is estimated to be about 12% of nominal dose[5] and levels considered as ototoxic (>10 ug/ml) were not observed in clinical studies. Tobramycin is undetectable in the blood 8 hours after nebulisation[6] and there is no tobramycin accumulation during prolonged treatment.

The lower age limit of registration is related to the opportunity to measure lung function, which is an important end-point in clinical trials supporting official approval. Both TNS were tested mainly in subjects with moderate-to-severe lung impairments, with FEV1 between 25% and 75% of predicted. In this stage of disease there is room for improvement, but the disease is not so advanced so as to exclude possible lung function amelioration.

Taking into account observed good clinical results, some experts suggest also using inhaled tobramycin in children below 6 years, in patients with less advanced disease, as well in those with end-stage disorder. In patients with advanced disease, aerosol deposition is more central and there could be some lung areas where ventilation is so low that aerosol penetration is minimal (possible sputum concentration < MIC). To protect from the re-population of bacteria from those areas during the off phase, it is recommended to alternate TNS with another inhaled antibiotic, given during the off phase.

Lessons from the Long-term Studies

There are only a few controlled clinical trials of TNS with long-term observation, including patients receiving at least 3 cycles of therapy. The results of those studies consistently show beneficial effects and a low risk with this therapy.

Clinical Effects

In the first publications of key importance, data from two identical 2nd phase studies were integrated.[4, 7-9] In total, 520 patients aged at least 6 years old were included, with FEV1 between 25% and 75% of predicted, and randomised to receive TNS or a placebo. After 3 cycles of therapy (week 20), in the active group FEV1 increased by 10% of predicted relative to baseline, compared to a 2% decline in the placebo group (p<0,001). This increase was greatest in patients between 13 and 17 years of age, attaining 14.3% at week 20.[7-9] During 24 weeks of therapy, there were less exacerbations, and less antibiotic therapies in tobramycin group. Hospitalisation probability was also reduced by 26%.

After completing a blinded part study, patients had the possibility to participate in three consecutive 24-week long cycles of open-label therapy with TNS.[8] Overall, 242 patients were observed to the end of the 96-week period. At this point, patients receiving a placebo in the blinded part of the study, and who received tobramycin 24 weeks later, did not attain as high amelioration in lung functions as those who had received it earlier. The difference in mean FEV1 between subjects treated from the beginning of the blinded study and those who received the antibiotic 24-weeks later was of 4.7%. However, the long-term decline in lung function after the end of the 1st cycle of TNS was parallel in both groups. Nevertheless, a bigger increase in the active group gained throughout the blinded phase led to better spirometry results at the end of observation and potentially ameliorated prognosis. This suggests that early initiation of tobramycin therapy, as soon as possible after diagnosing chronic infection, could be very important for long-term effects.

In another 24 week trial, 247 patients aged >6 years, with FEV1 between 25 and 75% of predicted were randomised to TNS or placebo.[10] After 3 cycles of therapy, there was significantly greater improvement in spirometry in patients receiving tobramycin with FEV1 values higher of 6.4%, compared to placebo group (p<0,001). The proportion of patients with the need of other antipseudomonal parenteral therapy was lower in TNS group (55.6% vs. 70.2%, p = 0.029), as well as hospitalisations (18.6% vs. 36.9%, p = 0,002). The number of lost school or working days was also lower (4.7 ± 9.1 vs. 10.0 ± 13.9, p<0.001). In the active group patients had a higher increase in body mass index compared to baseline and to the placebo group (p = 0.007 and <0.005 respectively).

In the third long-term study, 324 patients with FEV1 between 40 and 80% of predicted were randomised to one cycle of Bramitob or Tobi, and thereafter 209 patients entered an open-label extension phase, and received 6 additional on-off cycles of Bramitob.[11] After an initial increase in FEV1 after the first 4 weeks of therapy, small decreases in lung functions were observed during off periods, but measured values were still above baseline. Lung functions were recurrently increasing during the next on period and after 7 on-off cycles FEV1 was still higher than at baseline. After the 56-week treatment period with TNS, the improvement in FEV1% predicted was 5.7% above baseline.

Strong confirmation of TNS long-term therapy value came from retrospective CFF registry study. Sawicki *et al.*[12] analysed data of 12,740 patients from 1996 to 2008, who met recommended criteria for TNS therapy, and were followed for at least one year. In patients using TNS, they found a 21% reduction in odds ratio of death in the year subsequent to meeting indications to this therapy. This effect was even more pronounced among patients regularly using TNS. It is worth pointing out that this reduction in mortality by TNS use was even greater than observed in dornase users, which reduced risk of death by 15%.

Microbiological Effects

Inhaled tobramycin reduces colony density in lower airways. In the above mentioned trials, bacterial density behaviour mirrored lung function: diminished at the end of the on phase, and increased after the off phase. In the study of 209 patients participating in open-label extension phase with 6 cycles of Bramitob, the significant reduction

in PA bacterial density observed at the end of the first cycle, was maintained throughout the on cycles of extension (-1,13 log CFU/g).[11]

For many years there have been suggestions that traditional parenteral bacterial susceptibility breakpoints to tobramycin, important for intravenous administration, are probably irrelevant for inhaled therapy. Antibiotic concentration in sputum can be 100 times higher than serum concentration after IV administration,[9] which gives the opportunity to limit growth of less susceptible strains as well. There is only a low correlation between bacterial susceptibility and clinical and lung function improvement, which was also observed in patients colonised by strains with increased MIC values.[13] Parenteral breakpoints are usually defined as MIC >16 mg/l, but Morosini[14] suggested that if inhaled tobramycin is considered, patients with PA and intermediate susceptibility or who are resistant to tobramycin (according to parenteral breakpoints) should be retested with Etest and recategorised using MIC>128 ug/ml as a resistance breakpoint.

Some questions arise, however. First, is the matter of longevity of the clinical effectiveness in patients harbouring more resistant strains? Is clinical improvement perhaps related to suppression of other, tobramycin sensitive bacteria? Second, prolonged tobramycin administration could be a risk factor for selection of multidrug – resistant strains of PA, as well as other, emerging bacteria (e.g. Stenotrophomonas maltophilia) or fungi.[15] In patients using inhaled antibiotics, isolation of Candida or Aspergillus was already observed more often, but without increased frequency of fungal diseases.

Safety

The most common AE observed during TNS treatment were respiratory symptoms related to underlying disease (i.e. cough, increased sputum), present in 85-90% of patients. They had similar incidence in both placebo and active group. Some of those respiratory events could be related to specific drug formulation, as cough or rarely observed bronchoconstriction, with wheezing or dyspnoea. Most of these events could be easily prevented by earlier salbutamol administration.

Among adverse events related to tobramycin inhalation, only tinnitus and voice alteration were more frequent than in the placebo group in the study of Ramsey[7] (3% vs. 0% and 13% vs. 7% respectively). In the literature, there are only a few case - reports of TNS systemic effects, classic for aminoglycosides (i.e. nephrotoxicity or ototoxicity).[16]

For security reasons, baseline and periodic audiometric assessments are necessary for auditory toxicity, particularly when long-term inhaled tobramycin therapy is planned. Blood urea nitrogen and serum creatinine concentration for a renal function evaluation of patients receiving long-term therapy are suggested. This seems particularly necessary if eighth nerve toxicity is suspected (e.g. hearing loss, tinnitus or vertigo). Rarely, serum trough concentrations could be needed when systemic accumulation is suspected due to comorbidities (e.g. renal dysfunction) or concomitant systemic drug exposure (e.g. parenteral aminoglycosides).

Summary

Among inhaled antibiotics, TNS therapy has the best documented efficacity and safety, as it combines low systemic exposure (reduced toxicity) with the possibility to limit bacterial burden by high sputum concentration (efficacy). Compared to other nebulised antibiotics, TNS has more acceptable posology (i.e. twice daily, with on-off cycles). Long-term therapy studies with TNS consistently showed improvement in lung function (FEV1), which was sustained over time. It was particularly maintained during the off cycle. The decrease in exacerbations frequency, and antibiotic or hospitalisation needs were another important effect of TNS therapy. Systematic TNS therapy decreases bacterial density in the airways, and resistance development is probably not an important issue. Adverse events are rare and not serious. The early introduction of inhaled tobramycin therapy gives the opportunity to preserve better lung function than delayed the beginning of therapy. Retrospective CFF patients registry analysis documented a 21% reduction in the subsequent year mortality in patients using TNS, and was even more pronounced among patients regularly using TNS.

Well-established advantageous effects of the long-term administration of tobramycin supported the place of TNS in many guidelines (e.g.[17, 18]). TNS is widely considered as standard, first-line inhaled antibiotic therapy for patients with CF and chronic PA infection. Nevertheless, due to different reasons, inhaled antibiotics are probably underutilised by potentially eligible patients, who don't profit from the potential to improve prognosis.[19] TNS is often used as the "gold standard" comparator in clinical trials on new inhaled antibiotics, which are looking for simpler, shorter drug administration. This could improve compliance, but emerging studies will show if they have better efficacity and safety than nebulised tobramycin. The enrichment of treatment armamentarium will probably lead to many questions emerging concerning the selection of available therapies and best suitable regimens.

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R-V Graph in Whole Body Plethysmography

Hans-Juergen Smith
Marketing Research Diagnostics, Carefusion, Hoechberg

Introduction

Slow spirometry and forced spirometry (flow volume loop) are often used to measure clinically relevant lung volumes and forced expiratory and inspiratory flows. Dynamic parameters such as forced expiratory volume in one second (FEV1) or forced vital capacity (FVC) as well as static lung volumes such as expiratory reserve volume (ERV), inspiratory capacity (IC) and inspiratory vital capacity (IVC) can be derived.

The influence of patient co-operation has to be considered on the quality of spirometry test results, which are highly effort dependent. Furthermore, maximal inspiratory and expiratory manoeuvres do not specifically represent resting tidal breathing conditions, and can therefore lead to diagnostic uncertainties.

Whole body plethysmography[1, 2] allows comprehensive tidal breathing analysis based on the determination of resistance in the airways (Raw) and the lung volume at the end of a tidal volume expiration. This is the point that the lung inward and chest wall outward elastic recoil forces are at an equilibrium, which is termed as functional residual capacity (FRCpleth) or intra thoracic gas volume (ITGV). If the measured FRCpleth is then linked with an additional maximal vital capacity manoeuvre, further absolute lung volumes such as total lung capacity (TLC) and residual volumes (RV) can be determined. The ratio between lung volumes at tidal breathing and total lung capacity (FRCpleth/TLC) can be calculated.

A newly developed clinically oriented graphic report, the resistance volume graph (R-V graph), displays the course of resistance in the airways (Raw) when lung volumes are considered through the tidal breathing cycle (VT). The R-V graph is based on conventional indices such as Raw and FRCpleth, and its generation requires neither modifications in the testing procedure or changes in the application of current interpretation concepts in body plethysmography. The design also utilises predicted ranges and therefore uniquely combines all relevant body plethysmography test results for quick and reliable visual diagnosis.

sRaw Breathing Loops using Full Body Plethysmography

In the first phase of the plethysmography measurement the patient is breathing normally while sitting in a tightly sealed box. Breathing loops of the patient's specific airways resistance (sRaw loops) are recorded and compensated for body conditions (BTPS). The slope of the breathing loops can be calculated using different slope integrating lines (Figure 1).

Slope fitting according to Matthys[3] is called effective specific airways resistance (sReff). This method provides the lowest variability as it incorporates area indices of the entire breathing loop. Due to this feature sReff is often used in the clinical trending of data. Another established method for sRaw slope fitting was outlined by Ulmer,[4] which is termed as total specific airways resistance (sRtot). Ulmer defines a line between the points of maximal in- and expiratory shift volume. This method brings the advantage of improved sensitivity in end-expiratory inhomogeneity within the peripheral lung, however it is associated with increased variability.

Specific information regarding the changes in airways resistance across the entire breathing cycle as well as its direct relationship to the lung volume at any point of measurement are included in the sRaw breathing loop. However the way that this is displayed, plotting flow against shift volume, lacks details due to the nature of this flow-"shift volume"-diagram (Figure 1), which does not incorporate differentiable features of airways resistance and lung volume.

It is important to appreciate that the sRaw slope only provides an average measure throughout the breathing cycle. Therefore the degree of a ventilation inhomogeneity, expiratory flow limitation or end-expiratory closing within the airways may not be identified. Furthermore, a collapse in the peripheral lung during expiration within the tidal breath can be underestimated. The specific changes caused by obstruction during the tidal breath may also not be observed. In summary, the mechanisms of obstruction lack detail using this non-specific loop.

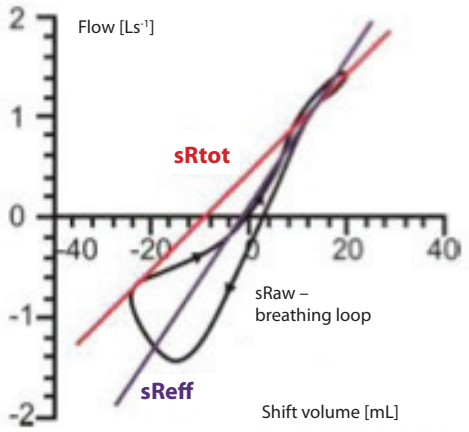


Figure 1. The sRaw breathing loop and two of its common slope integrating lines. sReff = effective specific airways resistance, sRtot= total specific airways resistance.

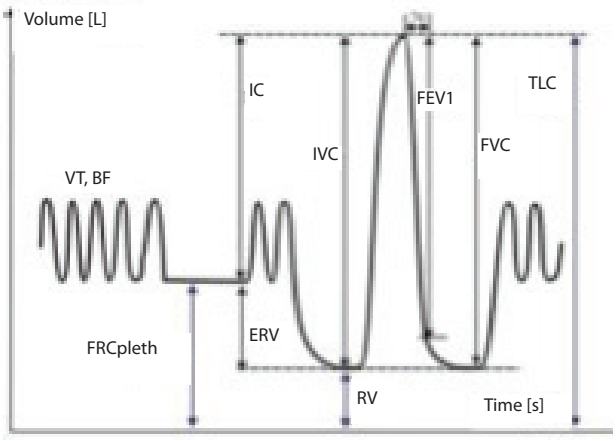


Figure 2. In the course of a "linked maneuver", the measurement of FRCpleth volume is linked with a maximal maneuver so that the following absolute volumes can be derived: FRCpleth = functional residual capacity, RV = residual volume, TLC = total lung capacity.

Measurement of Lung Volumes using Full Body Plethysmography

Absolute lung volumes such as functional residual capacity (FRCpleth), residual volume (RV) and total lung capacity (TLC) can be accurately measured using whole body plethysmography, which allows the evaluation of the peripheral lung. These volumes cannot be determined from a spirometry measurement alone and require a "linked maneuver" in which the FRC shutter measurement is linked with a maximal slow or forced spirometry breathing (Figure 2).

Airways Resistance (Raw) using Full Body Plethysmography

The effective airways resistance (Reff) and the total airways resistance (Rtot) are automatically calculated from the corresponding specific airways resistances (sReff, sRtot) relative to the mean lung volume at resting breathing. Measured FRCpleth therefore has to be increased by half of tidal volume (VT), outlined in the equation below.

$$Raw = \frac{sRaw}{FRCpleth + \frac{VT}{2}}$$

Due to how Raw is calculated from sRaw and FRCpleth, Raw is simply an average of the airways resistance throughout the tidal volume cycle. Thus, changes in total cross sectional airway caliber affecting resistance to flow within tidal breathing is dependent upon physiologic and pathophysiologic characteristics of the respiratory system which cannot be shown.

The Concept of Resistance-volume Analysis

The graphical display of the test results using whole body plethysmography today is similar to that originally outlined by DuBois and co-authors[1,2] more than 50 years ago. Islam and Ulmer[5] in 1977 suggested plotting the behaviour of airways resistance against the corresponding lung volume. They discovered that this method is both reproducible and informative. Specific patterns of flow and/or volume dependent variations in airways resistance, differentiated between inspiration and expiration, can be detected.

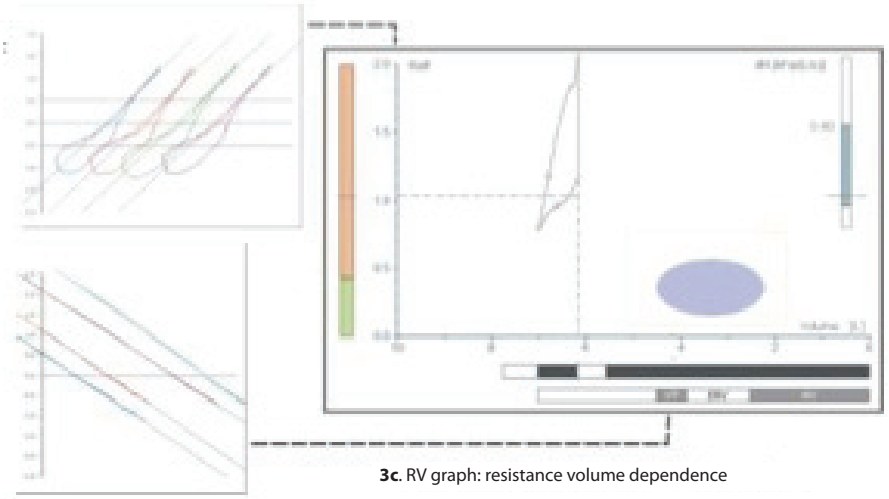
In order to allow a wider and more in-depth diagnostic image of

3a. sRaw breathing loops:

The entire courses of all valid breathing loops are averaged.

3b. FRC occlusion pressure curves:

The median of all accepted FRC recordings is used and linked with maximal breathing from RV to TLC.



3c. RV graph: resistance volume dependence

Figure 3. By means of a R-V transformation, the recordings during the first and second phases during the whole body plethysmography measurement (3a, 3b) are linked into the R-V graph (3c).

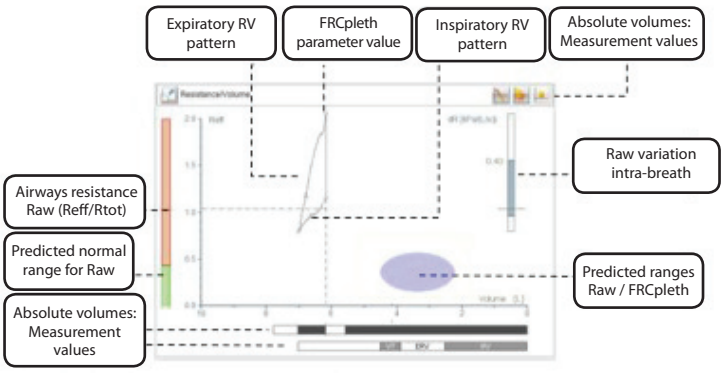


Figure 4. Description of the individual components of the RV graph. Y axis: Resistance scale with predicted normal range, X axis: Absolute volumes, measured and predicted, Right: Intra-breath variation of Raw, Centre: RV loop and predicted ranges of Raw and FRC.

airways resistance during quiet tidal breathing, the relationship between airways resistance and lung volumes with reference to predicted values can now be displayed. Using the recorded body plethysmography signals of flow, volume and shift volume with respect to absolute lung volumes of RV, FRCpleth and TLC, the R-V transformation (resistance-volume transformation) generates instantaneous loops over the course of airways resistance relative to absolute lung volume termed as the R-V graph (resistance-volume graph, Figure 3).

It is important to note that the testing procedure in clinical routine diagnostics remains unchanged as the R-V graph plots currently measured data of Raw with respect to measured lung volumes.

R-V Transformation

The R-V transformation integrates the specific airways resistance (sRaw) loops recorded during tidal breathing prior to the occlusion of the shutter (Figure 3a) with the occlusion pressure curves (FRCpleth) recorded during the occluded shutter (Figure 3b). The data is also smoothed using the average of the accepted breathing loop curves (sRaw) and the median of the valid FRCpleth slopes. A simple algorithm is then applied to generate the R-V graph (Figure 3c) by linking data from the measured signals.

The Components of the R-V Graph

There is always a relationship between airways resistance and lung volume. The Raw is never constant. During tidal breathing airway caliber, and therefore airways resistance (Raw), is affected by both airway smooth muscle tone and elastic recoil properties, resulting in airways collapse and significant increases in Raw on expiration. In COPD the peripheral collapse is largest at FRC, e.g. maximal Raw differs between the end of expiration and the beginning of inspiration. The R-V graph (Figure 4) illustrates the direct relationship between airways resistance (Raw) and lung volumes (FRCpleth +VT). In addition it offers an insight into the dynamics of the volume-dependency of airways resistance over the complete course of a representative normal breath (VT).

With reference to Figure 4, the left part of the chart outlines the resistance scale in which it is possible to detect the measured value of effective or total airways resistance (Reff or Rtot). This is displayed using a horizontal dashed line linked to the Y axis. The green area outlines the normal predicted range of airways resistance. Note: In terms of physiology, the airways resistance (Y axis) is specific to the central components of the respiratory tract.

The lower part of Figure 4 summarises measured lung capacities and volumes on the X axis using a bar diagram. In addition, a predicted value bar below allows the measured parameters (TLC, IC, FRCpleth, ERV and R-V) to be referenced against normative data. The importance of the FRCpleth parameter is highlighted by means of a vertical dashed line. Note: In terms of physiology, the X axis components of the R-V graph exclusively depend upon the peripheral characteristics of the respiratory tract.

The gray oval field combines the predicted ranges of Raw and FRCpleth. The circumference of the grey oval represents lower and upper limits of the normal ranges. The length of the bar diagram to the right of the R-V graph (Figure 4) display the variability of measured airways resistance during the tidal breaths. A higher degree of obstruction is normally associated with a greater variance of airways resistance, demonstrated by a longer bar diagram. The numerical value next to this bar outlines the difference between mean inspiratory and mean expiratory resistance across the tidal breath.

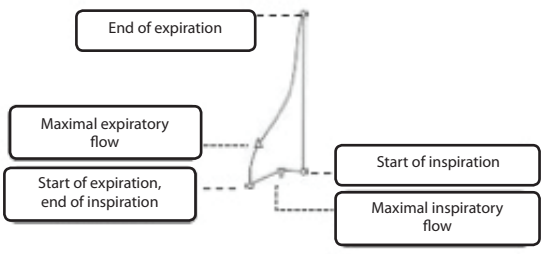


Figure 5. Markers on the R-V loop indicate key characteristic points within the breathing cycle.

R-V Loop in Detail

The R-V loop (resistance-volume loop) outlined in Figure 4 is detailed in Figure 5. The R-V loop trace utilises markers (triangles, circles) which help to characterise and identify the subcomponents of the R-V loop between the inspiratory and expiratory cycle. These markers allow quantitative evaluation of breathing dynamics during the breathing cycle and measure changes that occur due to dysfunction. The triangles (Δ) indicate the flow dependency of airways resistance. Within the breathing cycle the values of airways resistance are

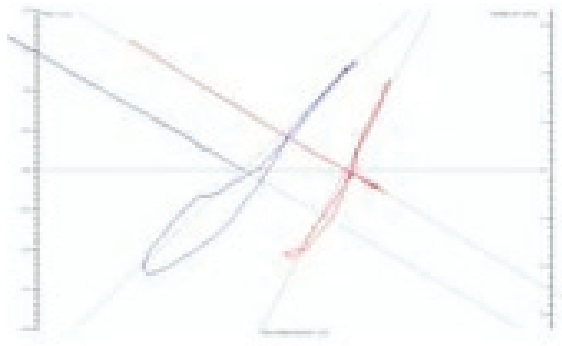


Figure 6a. Conventional graphic report of the sRaw breathing loops and FRC occlusion pressure curves of a pre-post assessment. Pre-measurement displayed in blue, post-measurement in red.

marked at the points where the maximal inspiratory and expiratory flow occurs. Note: Flow-dependency (flow type), i.e. the increase of resistance at maximal flow within the tidal breath is usually caused by the large central airways.

Conversely, the circles (o) indicate the values of airways resistance at the zero flow phases:

- At the start of inspiration.
- At the transition from inspiration to expiration.
- At the end of expiration.

If the resistance of the airways at the start of the expiration differs largely between the airways resistance at the end of expiration, a volume dependent component within airways resistance can be concluded. Note: The volume dependency of airways resistance (volume type) is usually caused within the lungs elastic recoil properties mediated by changes in peripheral lung parenchyma affecting the forces around the peripheral airways, as well as reducing airway caliber causing peripheral obstruction and inhomogeneity within the airway itself.

Comparison of a Conventional Report and the R-V Graph in a Pre-post Assessment

The R-V graph is particularly informative within pre- and post-assessments using a bronchodilator, as it clearly demonstrates the differentiated response to the bronchodilator within the bronchial system. Figure 6a shows a common graphic report using a bronchodilator by means of the sRaw breathing loops and FRC occlusion pressure curves with the pre-measurements (blue) compared with the post-measurements (red). Looking at the graph it is hard to see how much reduction in airways resistance may have occurred and also how much change may have occurred in lung volumes in relation to their predicted values.

At a glance it is possible to deduce clear information regarding the most important clinical issues with changes in resistance and volumes post-bronchodilator. Significant reductions in the post-measurement have occurred where Reff is within normal limits and FRCpleth is now just above the normal range. The intra-breath variation of Reff is significantly reduced. Residual volume (RV) is reduced but still remains increased above normal limits.

The same bronchodilatation examination displayed using R-V graph (Figure 6b) clearly outlines that the airways resistance (Reff) is within the predicted range in the post-measurement as it falls within the normal (green) range of the vertical resistance scale (left). The functional residual capacity (FRCpleth) is reduced, falling closer to the gray FRC predicted normal range in the post-measurement. It is therefore clear to observe increases in the inspiratory capacity (IC) post-bronchodilator.

The X axis of the R-V graph summarises absolute volumes of the pre- and post-measurements in comparison to their predicted values (gray bar). Even though the degree of hyperinflation is reduced, visible in a reduction in residual-volume (R-V) and RV/TLC%, these hyperinflation parameters are still significantly above predicted values when compared to the gray reference bar (Figure 6b). The chart clearly shows that the R-V curve (red) has moved downwards and to the right compared of the pre-measurement (blue). Due to the effects of bronchodilation, the patient does not only benefit from a reduction of the airways resistance but also from a decrease of the hyperinflation. The

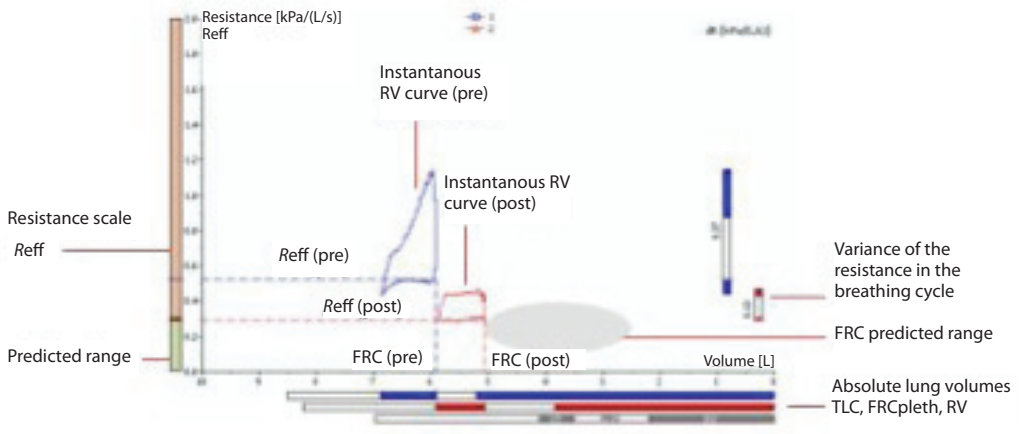


Figure 6b. R-V graph of the bronchodilatation from Figure 6a. Pre-measurement is shown in blue and the post-measurement in red. At a glance it is possible to deduce clear information regarding the most important clinical issues with changes in resistance and volumes post bronchodilator. Significant reductions in the post-measurement have occurred where Reff is within normal limits and FRCpleth is now just above the normal range. The intra-breath variation of Reff is significantly reduced. Residual-volume (R-V) is reduced but still remains increased above normal limits.

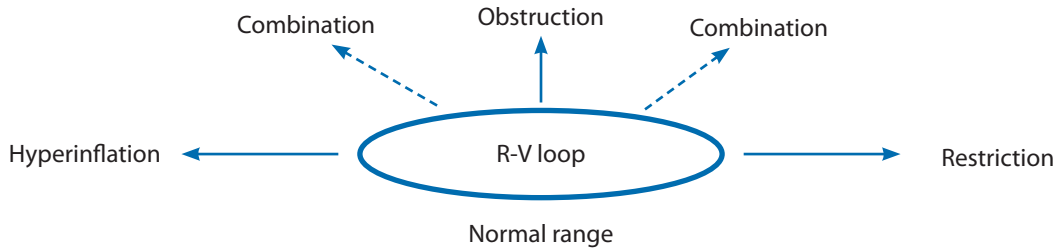


Figure 8. The arrows show the moving direction of the R-V loop according to the disease pattern.

variance of resistance (dR) in the post-measurement displayed in the right part of the report has fallen significantly.

The R-V graph allows for a fast and comprehensive diagnosis by merely evaluating the vertical and horizontal position of the R-V loop compared to predicted ranges for airways resistance and static lung volumes. The full potential of the R-V graph becomes clear when performing pre- and post-measurements. Here, the R-V graph explicitly displays the complexity and diversity of the bronchial reaction to a bronchodilator.

Conclusion

The R-V graph clearly illustrates the relationship between airways resistance and lung volume not only in single measurements but also after bronchodilation (Figure 7). In addition, it offers an insight into the dynamics of airways resistance during the complete breathing cycle of spontaneous tidal breathing. The possible conclusions with regard to the flow- and volume-dependency of the airway resistance are expected to be helpful in providing a more detailed classification and phenotyping of obstruction. Furthermore, abnormal changes in the relationship between airways resistance and lung volume are clearly and definitively illustrated.

The R-V graph identifies changes in the airways resistance (Y axis) as specific to the central components and changes in lung volumes exclusively depending upon the peripheral characteristics of the respiratory tract. Generally the R-V graph can be considered a simplified and clinically oriented summary of the whole body plethysmography measurement results, which illustrate the direct relationship between airways resistance and lung volume.

Acknowledgements

The author is grateful to Darren Murray for his thorough and critical review of the manuscript.

Appendices

List of exclusive whole body plethysmography parameters		
sRaw	kPa.s /cmH2O.s	common term for specific airways resistance
Note: In various areas the term sRaw is used as synonym for sRcenter or sRmid. It is recommended to replace both approximations by sReff with the advantage that the latter has lower variability.		
sReff	kPa.s /cmH2O.s	effective specific airways resistance
sRtot	kPa.s /cmH2O.s	total specific airways resistance
Raw	kPa.s.L-1 /cmH2O.s.L-1	commen term for airways resistance
Note: In various areas the term Raw is used as synonym for Rcenter or Rmid. It is recommended to replace bot approximations by Reff with the advantage that the latter has lower variability.		
Reff	kPa.s.L-1 /cmH2O.s.L-1	effective specific airways resistance
Rtot	kPa.s.L-1 /cmH2O.s.L-1	total specific airways resistance
FRCpleth	L	functional residual capacity
ITGV	L	synonym for FRCpleth
RV	L	residual volume
TLC	L	total lung capacity
RV/TLC	%	fraction of RV in TLC

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Management with Erythropoietic Agents of Chemotherapy-induced Anaemia in Patients with Lung Cancer

Angelica Tiotiu and **Yves Martinet**
Department of Respiratory Medicine, Nancy University Hospital

Background

Anaemia is a common haematological complication in cancer patients, especially in lung cancers (LC).[1] Its etiology is multifactorial, due to myelosuppressive therapy, bone marrow tumour invasion, nutritional deficiency, tumour bleeding and platinum-based chemotherapy renal toxicity.[1, 2] Anaemia prevalence in LC patients is 37.6% and 83.3% in patients receiving chemotherapy.[3]

Fatigue, as a clinical manifestation of anaemia, is particularly common in LC,[1] interfering with daily activities in about 50% of patients with advanced disease.[1, 4] Co-morbidities, such as chronic obstructive pulmonary disease (COPD), heart disease and other smoking-related complications exacerbate anaemia symptoms in LC patients. As a result, the impact of fatigue is often more severe in LC than in other tumour types[1, 4] and their quality of life (QoL) is markedly reduced.

Haemoglobin (Hb) levels below 11-13 g/dl are associated with poor prognosis in LC patients, indicating that a proactive approach of anaemia management may improve the overall quality of treatment. Therefore, early and effective anaemia management in LC is required,[1] and several guidelines for the management of chemotherapy-induced anaemia (CIA) are currently available.[5-8]

Angelica Tiotiu is a MD in the Department of Respiratory Medicine, Nancy University Hospital, France. Her clinical interests include asthma, allergical and immunological diseases, lung cancer, sleep apnoea, pulmonary hypertension, COPD and supportive care. She achieved her formation in allergology in 2012 (Strasbourg, France) and graduated as a pneumologist in 2009. She achieved a Master's Degree in Clinical Pharmacology (2004) and graduated the Cluj Napoca University, Romania in 2003 with an award for the best scientific activity, and has completed fellowships in Pneumology (Bruxelles, Belgium 2006-2007), Internal Medicine (Tours, France, 2002) and Radiology (Pecs, Hungary, 2001). Dr. Tiotiu's membership in professional societies includes European Respiratory Society, European Academy of Allergology and Clinical Immunology, Belgian Society of Pulmonology, and the Romanian Society of Pulmonology.

Treatment Guidelines

In UK, an audit of blood/red blood cells transfusion (RBCT), using the classical treatment of severe or symptomatic CIA, showed that patients with LC had the highest rate (43%) of blood transfusion among all solid tumours.[9] Blood transfusion risks include transfusion adverse reactions (haemolytic, febrile, non-haemolytic, lung injury, etc), congestive heart failure, virus transmission (hepatitis, HIV, etc), bacterial contamination, iron overload, increased thrombotic events and decreased survival. Its benefits are a rapid increase of Hb and haematocrit levels and a rapid improvement of fatigue.[8]

The introduction of recombinant human erythropoietin has significantly improved the management of anaemia. Actually, erythropoiesis-stimulating agents (ESAs) are commonly used for symptomatic CIA in adult patients with non-myeloid malignancies, in order to prevent RBCTs and their possible complications, and to improve health-related QoL.

The European Medicines Agency (EMEA) recommends the use of ESAs in patients treated with chemotherapy with Hb levels ≤10g/dl, in order to increase Hb by 2g/dl or to prevent Hb further decline. In patients not treated with chemotherapy, there is no indication for ESAs, and when administered with a target Hb of 12-14g/dl it even might increase the risk of death. In patients treated with curative intent, ESAs should be used with caution.

ESAs should be administered at the lowest possible dose to avoid transfusions, and adapted according to the response. After 4 weeks of treatment, if Hb increases at least 1g/dl, the dose may remain the same or can be decreased by 25%-50%; if it increases less than 1g/dl, the dose of ESA should be increased by 25-50%. After 6 weeks of treatment, in no responders (<1 g/dl increase or no diminution of transfusion requirements) ESAs should be discontinued; in responders, ESAs should be discontinued if Hb exceeds 13 g/dl until it falls below 12 g/dl.[5, 6]

Specific recommendations are not yet available for anaemic LC

patients treated by chemotherapy. However, the effectiveness and safety of several types of ESAs (epoetin beta, alpha, darbepoetin alpha) have already been proved by studies on LC patients with CIA. Concerning more recent ESAs (epoetin theta, zeta, HX575), their efficacy and safety are proved in overall solid cancer patients with CIA, but not yet specifically for LC.

Epoetin beta is a recombinant human erythropoietin with the same biochemical structure and biological function as the endogenous hormone. Epoetin beta therapy (subcutaneously 30,000 IU once weekly or 150 IU/kg three times weekly) effectively increases Hb levels, reduces transfusion requirements, is well tolerated and improves QoL compared to standard care in anaemic patients with solid tumour.[10, 11] The first study in LC was published by Kunikane[12] proving its effectiveness (two groups treated by 100 or 200 UI/kg three times weekly) in non-small cells lung cancer (NSCLC) patients treated by cisplatin-based chemotherapy. After 8 weeks, Hb levels had decreased in the placebo group but increased in the two epoetin beta groups. In addition, the Hb level at the nadir during the second cycle of chemotherapy was significantly greater in both epoetin groups than in the placebo group.

In 102 patients with LC (NSCLC 64% and small cells lung cancer - SCLC 36%), epoetin beta 450 IU/kg once weekly (approximately 30,000 IU) prevented severe anaemia in LC patients receiving platinum-based chemotherapy. An Hb positive response (increase >1g/dl) was observed in 60% patients, and a stable level in 30%. Only 9% of the patients required transfusions. QoL improved significantly in patients with Hb response ($p<0.01$) and was maintained in non-responders ($p\geq0.578$).[13]

Early intervention with epoetin beta is effective in anaemic patients with LC and well-tolerated despite chemotherapy, as observed in a study on 40 patients, in which 72.5% of them required epoetin by the second chemotherapy cycle (mean baseline Hb 10.4 ± 1.2 g/dl). Epoetin beta 30,000 IU was associated with a rapid increase in mean Hb levels by 1.3 g/dl after 4 weeks. Most patients (95%) remained transfusion-free throughout the study and epoetin beta was well tolerated.[14]

Epoetin beta (150 IU/kg s.c, three times weekly) appears to have a significant, beneficial impact on performance status score and Hb levels in LC patients undergoing concurrent chemoradiation after neoadjuvant chemotherapy.[15]

Epoetin alfa is the first ESAs who proved its effectiveness in CIA. Administrated subcutaneously 40,000 IU once weekly, an adjustment of doses after 4 weeks is recommended in order to optimise the treatment. Epoetin alfa prevents anaemia and reduces transfusion requirements in SCLC patients receiving platinum-based chemotherapy as shown by Thatcher.[16] Significantly fewer epoetin alfa treated patients ($p<0.05$) experienced anaemia (Hb<10 g/dl) during chemotherapy (300 IU/kg, 39%; 150 IU/kg, 48%; untreated, 66%) with a significantly lower number of treated patients transfused [300 IU/kg, 20% ($p<0.001$); 150 IU/kg, 45% ($p<0.05$); untreated, 59%]. Epoetin alfa effectiveness seems to be greater in SCLC anaemic patients treated by platinum-based chemotherapy.[17]

Crawford *et al*. performed a retrospective subgroup analysis of 1748 LC patients, 93% of them receiving platinum-based chemotherapy. Mean Hb level increase was 1.9g/dl, with a significant reduction of transfusions from month 2 onwards. QoL parameters increase during epoetin treatment was correlated with Hb improvement magnitude from baseline.[18] Another study including 216 patients with NSCLC proved that epoetin alfa, 40,000 IU weekly administrated immediately after chemotherapy initiation, was well-tolerated, effective in maintaining increased Hb levels, and determined a reduced transfusion incidence versus patients receiving epoetin alfa 8 weeks after chemotherapy initiation. QoL score improved with early epoetin alfa intervention without negative effect on overall survival.[19] The same results were found in a dutch observational study on 343 LC patients. Thus, epoetin alfa treatment corrects chemotherapy-related anaemia in both NSCLC and SCLC patients, and early epoetin alfa intervention seems advantageous both in terms of maintaining adequate Hb levels during chemotherapy as well as reducing transfusions.[20]

In patients with limited disease SCLC receiving concurrent chemo-hyperfractionated radiotherapy, epoetin alfa administrated 10,000 IU sc 3 times weekly has a potential benefit in preventing severe anaemia.[21]

Darbepoetin alfa is an erythropoiesis-stimulating glycoprotein with greater sialic acid content, and therefore, a threefold longer half-life than epoetin alfa, allowing less frequent administration (every 3 weeks), while stimulating erythropoiesis with the same efficacy and safety when administered every 1, 2 or 3 weeks to cancer patients.[22]

The administration of Darbepoetin alfa once weekly for 12 weeks to 320 anaemic LC patients (Hb≤11g/dl)[23] significantly increased Hb levels (66% of patients with haematopoietic responses defined as an increase in Hb concentration by ≥ 2 g/dl or a Hb concentration of ≥12 g/dl in the absence of red blood cell transfusions within the previous 28 days), decreased blood transfusion requirements (27% treated patients required transfusions vs 54% in the placebo group) and improved FACT-fatigue scores in 56% of treated patients. Darbepoetin alfa had no negative effect on disease outcome and patients did not develop antibodies against the drug. Adverse events were similar between groups.

In 600 extensive-stage SCLC patients receiving first-line platinum-chemotherapy,[24] darbepoetin alfa did not improve survival, but Hb levels were significantly higher in the treated group ($p<0.001$), and transfusion requirement was lower vs placebo (hazard ratio=0.4; CI95%, 0.29 to 0.55).

These results demonstrate the benefit of these 3 ESAs in the treatment of

symptomatic CIA in LC patients. More recently, other erythropoietins (Epoetin theta) and biosimilars agents (Epoetin zeta, HX575) have been developed for symptomatic CIA treatment, but only a few studies on patients with solid cancers are available. Studies including more LC patients are necessary before final conclusions can be made regarding the effectiveness and safety of these agents on this subgroup of patients.

A new recombinant human erythropoietin, Epoetin theta (20,000 IU weekly) was compared to Epoetin beta (450 IU/kg per week) and placebo in adult cancer patients receiving platinum-based chemotherapy (7.2% LC). Doses were adjusted at week 4 according to haematological response. Epoetin theta initial dose was based on recent evidence that lower doses of "classical" ESAs were as efficient as recommended doses to achieve a comparable Hb response. Both Epoetin theta and beta were safe and effective in treating symptomatic anaemia due to platinum-based chemotherapy (theta responders 65.8%, beta responders 71.2% vs placebo 20.3%, p<0.0001). The mean weekly dose at the time of complete Hb response was lower in the Epoetin theta group (30,000 UI) vs Epoetin beta group (42,230 UI).[25]

HX575 (Binocrit®, Sandoz Biopharmaceuticals) is the first epoetin alfa biosimilar approved by the EMEA for treatment of symptomatic CIA in adult patients with solid tumours. Its effectiveness and safety were assessed by two multicentre studies, in 2009[26] and 2012,[27] including 114 patients (40 LC), and 152 patients (32 LC). Biosimilar ESAs HX575 seems as effective and safe as Epoetin alfa in this indication. In the 2012 study, 79% patients achieved an Hb response (an increase of ≥1g/dl at 4 weeks, or Hb in the range 10-12 g/dl) and response rates were similar for patients who received Binocrit® 30,000 IU/week or 40,000 IU/week (81% vs 78%). The Hb response rate was significantly greater in patients supplemented with intravenous iron vs not supplemented.[27]

Another alfa epoetin biosimilar, Epoetin zeta (Retacrit®, Hospira), was evaluated on 216 patients with solid tumours or non-myeloid haematological malignancies receiving chemotherapy.[28] 81.5% patients achieved a response by week 8 (increase in Hb ≥1 g/dL or reticulocyte count ≥40,000 cells/μL) and a significant increase in mean Hb levels (1.8 g/dL, p < 0.0001) was observed at week 12. A clinically significant thrombotic event within the first 12 weeks of epoetin zeta treatment was reported in 4.2% patients. No transfusions were necessary in 81% of the patients, no patients developed anti-erythropoietin antibodies and QoL improved over the study.[28]

Safety and Tolerability

Erythropoietin has a thrombogenic potential, independently of Hb levels. Few meta-analyses reported an increase in relative risk of thrombotic events associated with ESAs use (relative risk between 1.48 and 1.69).[29-32] The absolute risk of venous thromboembolism concerns 7.5% of patients treated with ESAs vs 4.9% of control patients.[29] Thus, the use of ESAs should be carefully reconsidered in patients with a high risk of thromboembolic events suggested by a previous history of thrombosis, heritable mutation, hypercoagulability, elevated pre-chemotherapy platelet count, recent surgery, prolonged immobilisation, hypertension, treatment with steroids and hormonal agents[6, 8] Other adverse effects of ESAs are rare: arterial hypertension, pure red cell aplasia, hypersensitivity (dyspnoea, skin rash and urticarial).

The effects of ESAs on survival are controversial. Three meta-analysis on cancer patients survival indicate an increased mortality risk when using ESAs,[29-31] while two other meta-analyses suggest no significant effect on mortality or disease progression,[32, 33] and three recent pharmacovigilance trials have reported no adverse effects on survival in cancer patients with CIA receiving ESAs.[34-36]

In LC, up to now, only small-scale studies have evaluated the impact of ESAs on survival. A study of 51 patients with SCLC or NSCLC undergoing cisplatin-based chemotherapy plus radiotherapy suggested that higher nadir Hb levels (≥10g/dl) and Hb level improvements during epoetin treatment were associated with longer survival.[15] The progression-free survival[23] and overall survival at 1-year in a placebo-controlled study of darbepoetin alpha in 314 patients with SCLC or NSCLC and CIA, showed a longer median survival in the darbepoetin alfa group versus controls (46 vs 34 weeks). No increase in mortality with ESAs use was observed in two recent randomised studies in patients receiving chemotherapy for SCLC.[24, 37]

These results suggest that treating anaemia with erythropoietic agents in patients with LC does not have a negative effect on long-term outcome, but they need to be confirmed further in larger-scale, prospective trials specifically addressing the impact of anaemia treatment on patient's survival.

Conclusions

When concurrently administered with chemotherapy in patients with LC, ESAs are effective to maintain Hb levels, increase QoL, and reduce the need for emergency blood transfusions. Erythropoietin therapy should be initiated in patients with symptomatic CIA, after taking into consideration individual risks and benefits. Hb level target should be about 12 g/dl. In order to decrease the risk of serious cardiovascular and thromboembolic reactions, the lowest dose needed to avoid red blood cell transfusion should be used. Pharmacokinetic characteristics of Darbepoetin alfa allow a reduced administration frequency and might increase patient's acceptance of treatment. There is currently no published evidence about the effectiveness and tolerance of biosimilars epoetins and epoetin theta in the treatment of CIA for patients with LC.

Finally, the influence of ESAs on tumour response to anticancer therapy and overall survival in anaemic LC patients remains to be determined. Thus, well-designed trials are still required to evaluate the safety of ESAs for lower target Hb levels.

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The Child with Recurrent Pneumoniae: A Challenging Issue in Paediatrics

Serena Moser and **Giorgio Piacentini**
Paediatric Department, University of Verona, Verona

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

María Teresa Romero Rubio,[1] Raquel Lucas Sendra,[1] and **Amparo Escribano Montaner[2]**
1. Pediatric Pulmonology, Hospital de Denia, Alicante; 2. Pediatric Pulmonology and Cystic Fibrosis Unit, University Clinical Hospital and University of Valencia

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.

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Bronchial Carcinoid Tumours in the Paediatric Population

Giovanna Rizzardi, Luca Bertolaccini, Andrea Viti and **Alberto Terzi**
Thoracic Surgery Unit, S. Croce Hospital, Cune

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?

Adam J. Sybilski
Department of the Prevention of Environmental Hazards and Allergology, Medical University of Warsaw, Warsaw;
Department of Paediatric and Neonatology, Central Clinical Hospital of Ministry of Internal Affairs, Warsaw

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.

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Pulmonary Hypertension in the Course of Lung Diseases: The Diagnostic Pathway and Treatment Considerations

Monika Szturmowicz
I Department of Lung Diseases, National Institute of Tuberculosis and Lung Diseases, Warsaw

Classification of Pulmonary Hypertension in the Course of Lung Diseases (PH-LD)

According to the currently used classification of pulmonary hypertension (PH), lung diseases associated with PH are found in three different groups.[1] Pulmonary disorders leading to PH by the mechanism of hypoxia, hypoventilation and/or parenchymal pathologic changes, such as chronic obstructive pulmonary disease (COPD), obstructive sleep apnoea syndrome (OSAS), idiopathic pulmonary fibrosis (IPF), are included in group 3. Lung diseases with multifactorial mechanisms of PH, such as sarcoidosis, pulmonary Langerhans cell histiocytosis (PLCH), lymphangioleiomiomatosis (LAM), are classified in group 5. Collagen tissue diseases (CTD) with predominant vascular involvement are found in group 1 (pulmonary arterial hypertension – PAH).

There are many controversial aspects such as:

1. How to classify PH in the course of collagen tissue disease with predominant parenchymal lung pathology?
2. How to classify PLCH with predominant vascular lesions and high pulmonary hypertension?

Some of these controversies are caused by the fact that the pathogenesis of PH in the majority of lung diseases is complex. Lung biopsy specimens are usually lacking due to the high risk of bleeding in PH. Thus it is sometimes very difficult to recognise the dominating cause of PH on clinical grounds only. These problems have been addressed by many authors, and future progress seems to be combined with defining various phenotypes of PH in the course of respiratory disorders.

Monika Szturmowicz is a Professor of Medicine affiliated at I Department of Lung Diseases, National Tuberculosis and Lung Diseases Research Institute, Warsaw, Poland. She is also the Editor-in Chief of *Polish Pneumonology and Allergology*, the peer-reviewed, official journal of the Polish Respiratory Society. Dr. Szturmowicz is an active member of ACCP (FCCP since 2003), ERS and IASLC and is directly involved in clinical research concerning pulmonary hypertension in lung diseases. She is the author of 80 papers published in peer-reviewed international journals, IF 35, Hirsh Index 9. Dr. Szturmowicz is also a happy wife, a mother of three children, and a grandmother of Anthony (6), Sophie (3) and Johnny (3 months). She loves travelling, swimming, and gardening.

Recognition of PH-LD

Pulmonary hypertension is diagnosed during right heart catheterisation (RHC), when mean resting pulmonary artery pressure (mPAP) is equal or higher than 25 mmHg.[2] PH-LD belongs to the category of precapillary PH, recognised when pulmonary capillary wedge pressure is equal or lower than 15 mmHg.[2] RHC is the only reliable method of diagnosing PH, nevertheless due to its invasiveness it should be performed only when the obtained results are expected to change the treatment plan. The most undisputable indications for RHC are:

1. Evaluation for lung transplantation in patients with end-stage lung disease.
2. Suspicion of out-of-proportion PH-LD, in a patient who is a potential candidate to PH-specific treatment.

Screening of PH-LD

Respiratory disorders are the second most frequent cause of PH, thus it is important to consider PH as one of the causes of dyspnoea in the course of lung diseases. The parameters most indicative are: profound hypoxemia requiring the supplement of oxygen and low diffusion capacity for carbon monoxide (DLCO), usually less than 40% of the predicted value.[3,4] Short 6MWT distance with substantial desaturation are suggestive of PH, nevertheless the sensitivity and specificity of this finding is uncertain.[5,6] Swigris *et al*. proposed the additional parameter – heart rate recovery in the first minute after 6MWT.[7] A recovery rate equal or lower than 13 beats was a strong predictor of PH assessed by RHC.

The European Society of Cardiology recommend transthoracic echocardiography (TTE) as the best method of non-invasive screening for PH.[2] Pulmonary artery systolic pressure (PASP) is calculated from the maximal velocity of tricuspid regurgitation jet. PH is likely if PASP is higher than 50 mmHg.[2] Nevertheless, the diagnostic value of TTE in predicting PH-LD is low.[8,9] Nathan *et al*. found the 50% of sensitivity and 68% of specificity of PASP>50 mmHg for predicting PH confirmed by

RHC in the group of the patients with interstitial lung diseases.[9] Devaraj *et al*. proposed the model of PH prediction based on echocardiographic assessment of PH combined with the ratio of the main pulmonary artery to ascending aorta diameters on chest CT scan.[10]

The additional parameters that can be taken into consideration assessing the possibility of PH are serum concentrations of brain natriuretic peptides (NT-proBNP and BNP), hormones indicative of heart strain. NT-proBNP cut off value used by Takkar *et al*. for PAH screening in scleroderma was 209.9 pg/ml.[11] The role of NT-proBNP in PH LD screening is uncertain due to its dependence on age and left heart insufficiency.

Epidemiology of PH-LD

The prevalence of PH-LD depends on the type and stage of lung disease. In IPF, PH on RHC was found in 10% of early stages,[12] 31-46% of advanced disease[3, 13] and even 86% of patients at the time of referral for lung transplantation.[14] In the majority of patients, mPAP was within 25-40 mmHg. High mPAP, exceeding 40 mmHg, was found in 2-9% only.[3, 13] The prevalence of PH is probably the highest in the distinct IPF phenotype - combined pulmonary emphysema and fibrosis (CPFE).[15]

In sarcoidosis, the overall prevalence of PH was 6%,[16] and in stage IV disease it was 38-40%.[17] In the patients referred for lung transplantation, the overall prevalence of PH was 73.8%.[4]

In PLCH, PH was very common in late stages of disease (92-100%),[18, 19] however there was little data concerning the early stages of disease.

In COPD, the prevalence of mild PH on RHC (mPAP 25-35 mmHg), in the end-stage disease was 36-50%.[20, 21] High PH, exceeding 40 mmHg was found in 1-5% of patients only.

Prognosis of PH-LD

The prognosis of the patients with PH-LD is worse than in those without PH. The significant decrease of survival in the patients with mPAP>40 mmHg was noted in COPD patients by Chaouat *et al*.,[21] and in IPF by Lettieri *et al*.[3] Baughman *et al*. demonstrated that, in sarcoidosis patients, the worse prognosis was in the group with precapillary PH, as compared to those with postcapillary PH.[17] In most respiratory diseases, the presence of PH is an additional recommendation for lung transplantation.

Out-of-proportion PH-LD

The consensus definition of out-of-proportion PH-LD is not available. Most investigators agree that out-of-proportion PH-LD should be recognised in a patient with severe PH [mPAP> 40(45) mmHg], despite preserved lung function parameters. Out-of-proportion PH in COPD was recently described by Chaouat and Minai[22] as "any PH in the patient with FEV1>=50% pred. value or PH>=40 mmHg irrespective of COPD stage, in the absence of comorbid illness". The characteristic clinical features of COPD patients with out-of-proportion PH are: severe hypoxemia requiring oxygen treatment, low DLCO and normo or hypocapnia. The last feature was seen in most analysed cases. The frequency of out-of proportion PH in COPD is 1-3%.[21] The genetic predisposition for vascular involvement in COPD was recently suggested.[23, 24]

The phenotype of out-of-proportion PH is less well described in the interstitial lung diseases (ILDs), but the common findings are: profound hypoxemia and low DLCO (< 40 mmHg) despite well preserved lung volumes (TLC>60% pred.). The reported frequency of out-of-proportion PH in the course of ILDs was 2-10% in IPF[3, 12, 13] and 10% in sarcoidosis.[17]

Differential Diagnosis of PH-LD

Excluding comorbidities influencing pulmonary pressure is of great importance, especially in the group of out-of-proportion PH-LD.

The most frequent comorbidity is left heart insufficiency in the patients with coexisting coronary heart disease, systemic arterial hypertension and diabetes, resulting in postcapillary (venous) PH. Venous PH may also be the result of direct heart involvement in sarcoidosis and scleroderma. The reported frequency of venous PH in ILDs was 15-16%.[14, 17]

The suspicion of postcapillary PH is often based on TTE indicating the left heart chambers dilatation, thickened left ventricular (LV) wall and intraventricular septum, low LV ejection fraction, the mitral or aortic valve pathology. RHC is the best way to confirm or exclude postcapillary PH as precipitating factor in PH-LD.

The other common precipitating factor in PH-LD is pulmonary thromboembolic disease (PTD). The increased predisposition for PTD in lung diseases is mainly observed in IPF, CTD and COPD. In CTD, a procoagulative state may be due to the presence of antiphospholipid syndrome. Sprunger *et al*. found PTD as the cause of death in 3% of IPF patients.[25]

Established Treatment in PH-LD

The principles of PH-LD treatment consist of:

1. Long-term oxygen therapy (LTOT) in case of PaO2<60 mmHg.
2. Best available therapy of underlying disease, including immunosuppressive treatment when indicated.
3. Rehabilitation (patients with mild and moderate PH).
4. Referral for lung transplantation (LTx) in end stage disease (according to recommendations).

The data concerning the effectiveness of LTOT are available only in COPD. The stabilisation of PH was observed in COPD patients receiving LTOT > 15 hours/day.[26] In the patients with ILDs, the LTOT influence on PH was not proved. Nevertheless the ESC recommend oxygen use in

Author (ref) Type of analysis	Type of LD (No of pts)	PFT % pred.	DLCO % pred.	RHC mPAP [mmHg]	Type of treatment (No of pts)	Treat. duration	Treatment results (No of pts)
Barnett[38] retrospective	Sarcoidosis (22)	TLC 60%	38%	46	Bosentan (12), Sildenafil (9), Combined (8) Epoprost. (1)	11 months	Improvement of: NYHA, 6MWT (18) mPAP (12), PVR (12)
Judson[44] prospective	Sarcoidosis (21) (48% evaluated)	FVC 61.5%	33+/-11%	32.7+/- 7.28	Ambrisentan	24 weeks	Improvement of: NYHA, quality of life No change of: 6MWT, dyspnea
Milman[39] retrospective	Sarcoidosis (25)	FVC 41%	24(10-60)%	48+/-15	Sildenafil (12)	4 months (1-12)	Decrease of: mPAP(9), PVR(6), No change: 6MWT
Baugham[43] prospective	Sarcoidosis (22)	FVC 50%	nd	36 (22-62)	Iloprost inh.(15)	16 weeks	Increase of: 6MWT(3), Decrease of: PVR(6), life quality -cough
Baugham[42] retrospective	Sarcoidosis (7)	FVC 66%	59%	53.4+/-13.4	Bosentan (4), epoprostenol(1), Combined (1) CCB(1)	4-8 months	Decrease of : mPAP(4)
Fisher[45] retrospective	Sarcoidosis (8)	FVC 59%	30%	55(47-66)	Epoprostenol iv (7)	29 months	Decrease of: PVR(6)
Collard[37] prospective	IPF (14)	FVC 71+/-5%	32%	10 pts>25 mmHg	Sildenafil	3 months	Increase of: 6MWT – 57%
Cottin[40] retrospective	LAM (20)	FEV1 42+/-25%	29+/-13%	32+/-6	Bosentan (5) Sildenafil (1)	38 months	Decrease of: mPAP, PVR No change: NYHA
Le Pavec[41] prospective	PLCH (29)	TLC 84+/-19%	29+/-10%	52+/-14	ERA (10) Sildenafil (5) Iloprost (1)	5.5+/-2.5 months	Decrease of: mPAP, PVR Improvement: NYHA(8), 6MWT(5)
Rietema[34] retrospective	COPD (15)	FEV1 49+/-24%	48+/-16%	22+/-9	Sildenafil	12 weeks	No change: SV
Valerio[35] prospective	COPD (16)	Gold III-IV	nd	37.5+/-5	Bosentan	18 months	Decrease of: mPAP, PVR, BODE Increase of: 6MWT
Held[36] prospective	COPD (4)	FEV1 39-63%	26-79%	38-50	Bosentan	18 months	Decrease of: mPAP, Increase of: 6MWT

Table 1. PH-specific treatment in PH-LD – up-to-date results. PFT – pulmonary function test, DLCO – diffusion lung capacity for carbon monoxide, RHC - right heart catheterisation, TLC – total lung capacity, FVC – forced vital capacity, FEV1 – forced expiratory volume in 1 second, IPF – idiopathic pulmonary fibrosis, LAM – lymphangioleiomiomatosis, PLCH – pulmonary Langerhans cell histiocytosis, COPD – chronic obstructive pulmonary disease, 6MWT – 6 minute walk test, mPAP – mean pulmonary artery pressure, PVR – pulmonary vascular resistance, SV – stroke volume, nd – no data.

the patients with PaO2<60 mmHg.

Some of the patients with PH in the course of ILDs respond to steroids treatment. Such effects may be observed in sarcoidosis, in case of vascular obstruction due to enlarged lymph nodes or due to sarcoid granulomas developing in vessels' wall. Załęska *et al*. observed the regression of PH in the course of corticotherapy of sarcoidosis-associated fibrosing mediastinitis.[27] Miamishi-Yamamoto *et al*. described CTD patients in whom mPAP decrease was achieved in the course of immunosuppressive therapy.[28] The patients with PH and end-stage or progressing lung disease should be referred for LTx, if they are within age limit and suitable otherwise.

PH-specific Treatment in PH-LD: Up-to-date Results

The first attempts to use PH specific drugs in PH-LD were reported in the end of 90-ties by Olszewski *et al*.[29] Despite numerous publications addressing this problem, the investigators are far from recommending such treatment in PH-LD. The phenomenon, observed by Ghofrani *et al*. during intravenous prostacyclin administration in IPF, was worsening of patients' hypoxemia and

decreasing quality of life due to increased perfusion of relatively poorly ventilated areas.[30] Nevertheless such effect was not observed in the patients receiving sildenafil or inhalation of nitric oxide.[30] Blanco *et al*. investigated the acute effect of sildenafil in COPD.[31] The haemodynamic improvement was observed at the expense of worsening of resting hypoxemia. Nevertheless, during exercise no further decrease in oxygen saturation was noted. This trial was described as negative, but contained important messages. The PH specific drugs are capable of improving haemodynamic parameters in PH-LD and the increased cardiac output during exercise may compensate the hypoxemia due to increased shunting.

The most important studies of PH-specific drugs use in the patients with respiratory diseases, contained no data concerning RHC assessment and their results were negative.[32, 33] On the other hand, many groups reported the results of retrospective or prospective observational studies of PH-specific treatment in small groups of PH-LD patients and found such treatment effective in terms of improving exercise capacity and/or haemodynamic indices (Table 1).[34-45] The improvement was observed in most reported groups after at least 16 weeks of treatment. No significant desaturation was noted in the majority of these trials, nevertheless the intravenous prostanoids were used only in single patients. The most troublesome side effect was a cough associated with iloprost inhalation, worsening the quality of life.[43]

Promising preliminary data were published recently on soluble guanylate cyclase stimulator (Riociguat) use in PH ILDs[46] and in COPD.[47]

How to Move Forward?

To determine clear indications for PH specific treatment in PH-LD in the future, the following suggestions should be taken into account:

1. The target groups for RCT should include only the patients with out of proportion PH, confirmed with RHC.
2. The other precipitating causes of PH, especially venous PH have to be ruled out in the candidates to PH-specific treatment.
3. The proper duration of open phase of RCT is important, as the influence of PH-specific drugs on pulmonary vessels in PH-LD may develop after several months of treatment.
4. The PH-LD patients not responding to PH specific therapy should be listed for LTx if they are suitable otherwise, in the same way as PAH patients are.

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Causal Factors of Multidrug Resistant and Extensively Drug Resistant Tuberculosis: Regional and National Response in the WHO European Region

Colleen Denise Acosta,[1] Sevim Ahmedov,[2] Andrei Dadu,[1] Martin van den Boom,[1] Hans Henri Kluge,[1] and **Masoud Dara[1]**

1. World Health Organization Regional Office for Europe, Copenhagen; 2. USAID, Infectious Diseases Division, Office of Health, Infectious Diseases and Nutrition, Washington DC

Introduction

Tuberculosis (TB) is an archetypal disease of poverty. It remains a leading cause of death and life-threatening illness disproportionately in low and middle-income countries around the world. In 2011, there were approximately 8.7 million new cases of TB and 1.4 million people died from the disease.[1] Although encouragingly global rates of new TB cases have been falling since 2005 in line with Millennium Development Goal targets, the global burden remains enormous, and the increasing prevalence of multidrug-resistant TB (MDR-TB) and extreme drug-resistant TB (XDR-TB) is of urgent concern. In 2011, there were an estimated 310,000 cases of MDR-TB amongst notified TB patients.[1] Fifteen of the 27 countries with a high M/XDR-TB burden were in the World Health Organization (WHO) European Region.[2] This review, therefore, will focus on the current burden of M/XDR-TB in the WHO European Region, factors contributing to drug-resistance, national treatment policies, and the strategic role of the Green Light Committee/Europe in supporting high-priority countries to improve treatment of M/XDR-TB.

Burden of M/XDR-TB in the European Region

MDR-TB is caused by Mycobacterium Tuberculosis which is resistant to at least isoniazid and rifampicin, the two most potent TB drugs. XDR-TB is a type of MDR-TB, resistant to isoniazid and rifampicin plus any fluoroquinolone and at least one of three injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin).[1, 3, 4] Rates of M/XDR-TB are geographically and socioeconomically disparate in the WHO European Region; currently, all high-burden MDR-TB countries are eastern former Soviet states (plus Bulgaria), and 99% of the MDR-TB cases in the WHO European Region occur in these countries.[4] The estimated annual incidence and proportion of MDR-TB amongst new and retreatment TB cases in the high-burden MDR-TB countries are shown in Table 1. Rates of MDR-TB amongst new and retreatment cases are significantly higher in these countries compared to the top three high-burden MDR-TB countries in other WHO Regions, with rates reaching 32 and 76% respectively in Belarus.[5] Although drug-susceptibility testing (DST) with second-line drugs for XDR-TB remains low (11% coverage[4]), XDR-TB is estimated to account for more than 10% of drug-resistant cases,[6] with the majority (92%) also disproportionately in the 15 high-burden eastern countries.[4] Additionally, treatment success rates of MDR-TB have decreased from 72.5 and 50 % in 2005, to 67.2 and 49.2 % in 2011 amongst new and previously treated cases, respectively.[4]

TB Treatment and Drug Resistance

Misuse of anti-TB drugs is the single most important factor leading to drug resistance in Europe.[7-9] Patient non-adherence to drug regimens,[10] monotherapy, the addition of single drugs to failing regimens,[11] or substandard and falsified anti-tuberculosis drugs[12] lead to acquired resistance. Drug resistant strains can then be passed to susceptible contacts, particularly HIV infected individuals[13, 14] or previously treated TB patients,[14, 15] resulting in infection and primary resistance. Failure to detect drug-resistant TB leads to inappropriate drug regimens, treatment failure and further transmission of resistant strains.[16] The same mechanisms also lead to the emergence and transmission of XDR-TB.

The factors leading to misuse are complex and interconnected, particularly in low income, high-TB burden countries (Figure 1). Misuse of anti-tuberculosis drugs and detection failure largely stem from suboptimal TB case management[17] due to system-level weaknesses associated with poor socioeconomic development. Within the European Region, system level barriers were identified amongst the 15 high-burden MDR-TB countries (Figure 2).[2] Ten out of the fifteen countries (67%) reported deficiencies in human resources to manage MDR-TB, whilst programme management problems and inconsistent access to quality assured anti-TB drugs were identified by 53 and 47% of countries, respectively. Other barriers reported were: weak infection control, recording and reporting technical limitations, insufficient laboratory capacity or quality, insufficient financing, sub-optimal case-finding (identified in some countries as due to weak integration between primary care or private healthcare and the national TB programme), and insufficient social support or involvement such as alcohol or injecting-drug addiction counselling.[2]

	Estimated Annual Incidence of MDR-TB	Estimated % of TB cases with MDR-TB out of the total notified	
	Cases (95% CI)	Newly treated (95% CI)	Previously treated (95% CI)
High MDR-TB burden countries in WHO European Region			
Armenia	250 (220-280)	9.4 (7.1-12)	43 (38-49)
Azerbaijan	3400 (3200-3700)	22 (19-26)	55 (52-60)
Belarus	2000 (1900-2100)	32 (30-35)	76 (72-79)
Bulgaria	120 (90-150)	2.0 (1.1-3.2)	26 (19-33)
Estonia	100 (83-120)	23 (17-29)	58 (43-71)
Georgia	760 (700-820)	11 (9.6-12)	32 (28-35)
Kazakstan	8200 (8000-8400)	30 (29-32)	51 (50-53)
Kyrgyzstan	1500 (1400-1700)	26 (23-31)	52 (45-58)
Latvia	120 (96-140)	13 (10-16)	29 (20-40)
Lithuania	360 (320-390)	11 (9.2-13)	49 (44-54)
Republic of Moldova	1600 (1500-1700)	19 (17-22)	64 (60-67)
Russian Federation	44000 (40000-48000)	20 (18-22)	46 (41-52)
Tajikistan	1000 (910-1200)	13 (9.8-16)	54 (48-59)
Ukraine	9300 (8500-10000)	16 (14-18)	44 (40-49)
Uzbekistan	3000 (2700-3400)	23 (18-30)	62 (53-71)
High MDR-TB countries in other WHO Regions (top 3)			
India	66000 (58000-73000)	2.1 (1.5-2.7)	15 (13-17)
China	61000 (54000-68000)	5.7 (4.6-7.1)	26 (22-30)
Philippines	11000 (8000-13000)	4.0 (2.9-5.5)	21 (14-29)

Table 1. Estimated annual incidence of MDR-TB and estimated proportion of new and previously treated TB cases with MDR-TB amongst 15 high-MDR-TB countries in the European Region compared to the top three high-MDR-TB countries in other WHO Regions.[1, 5]

Inconsistent access to appropriate anti-TB drugs is particularly problematic, as most other barriers to control efforts presuppose that therapy is available. Whilst treatment (drugs and care) is free of charge for patients in all high-burden countries in the European Region, stock-outs of second-line drugs have been reported in Azerbaijan, the Russian Federation and Ukraine.[2] Azerbaijan additionally reported stock-outs for first-line drugs, worryingly citing lack of funding for this basic TB treatment.[2]

Inconsistent access to second-line drugs was also reported by Armenia, Belarus, Kyrgyzstan and Lithuania due to weak drug management and inefficient decentralised drug procurement systems.[2] Drug registration procedures, whilst high in cost, potentially prevent marketing and prescription of poor quality drugs.[18] Comprehensive information on anti-TB drug registration is not available, however a recent clinical audit found that all first-line drugs and most second-line drugs were not registered in at least one country from the former Soviet Union.[18] Another study found that substandard and falsified drugs, particularly amongst non-registered drugs, were readily available in pharmacies in Turkey and the Russian Federation.[12] A prerequisite to ensure effective treatment and control of primary TB and M/XDR-TB is the continuous availability of quality-controlled drugs,[19, 20] not only for patients but also for their close contacts with latent TB infection.[11, 21-23] Therefore registration and procurement processes must continue to be streamlined particularly in high-burden countries with the inclusion of new anti-TB drugs.[24, 25]

Airborne infection control is another important factor in the prevention of M/XDR-TB transmission. However, WHO-recommended control measures have only been implemented in four of the 15 high-burden European countries; assessments have been carried out in 10 countries.[2] Both appropriate drug administration and effective airborne infection control in diagnostic and healthcare facilities is dependent upon rapid diagnosis of drug-resistant TB. GeneXpert MTB/RIF, an automated rapid nucleic acid amplification test for TB detection and rifampicin resistance,[26] was endorsed by the WHO in 2010. The relatively high cost of the test (including the machine, test-cartridges and maintenance) has, however, limited its availability in high-burden countries in the region.[2] The introduction of this technology and other rapid diagnostic methods are urgently needed. In addition to ensuring proper airborne infection control, a critical challenge upon the availability of rapid diagnostics, will be to ensure capacity and resources to manage newly diagnosed M/XDR-TB patients.[27] Given that 'insufficient human resources to manage MDR-TB' was the most cited bottleneck by high-burden countries, it is clear that barriers are interconnected and must continue to be addressed in a comprehensive or crosscutting manner.

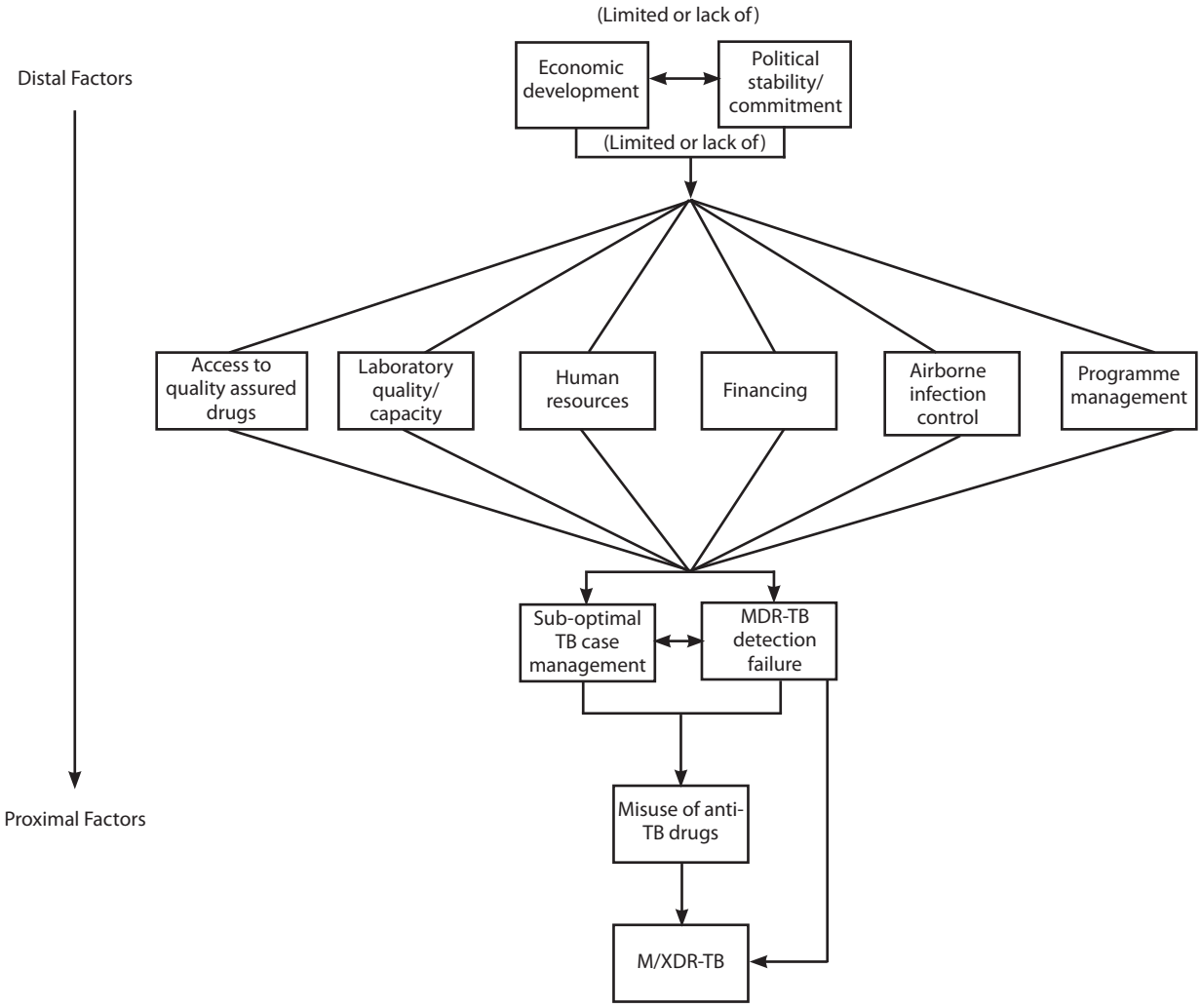

Figure 1. Conceptual model of distal to proximal risk factors forming a causal pathway leading to drug resistance.

National Policies and TB Control

National treatment policies may also unwittingly lead to amplification of drug resistance. For example, several high-MDR-TB countries in the region require that previously treated patients fail the 'category II regimen' (first-line treatment plus streptomycin with extension of treatment to eight months) before being considered for MDR-TB treatment.[28] WHO TB treatment guidelines recommend treatment be guided by DST using rapid, molecular tests where possible for all previously treated patients, particularly in areas with high MDR-TB prevalence.[29, 30] Georgia, a high-MDR-TB country, has since eliminated the requirement in favour of DST.[31] Several countries also have policies that promote excessive hospitalisation of patients and TB suspects.[28, 32, 33] This policy, as opposed to ambulatory or outpatient care for patients without severe clinical conditions and those that are sputum smear-negative, increases the risk of nosocomial infection and transmission of TB and M/XDR-TB.

Some policies are country-specific. In Armenia, TB treatment can only be initiated by a specialist TB physician in one of ten district hospitals, even if the patient is diagnosed as sputum smear-positive for pulmonary TB in another facility.[32] This policy introduces the additional difficulty of self-referring to another centre (with potential for repeat laboratory examination), further delaying treatment and increasing risk of transmission.[32] In addition, until recently, second-line drugs were not prohibited (and thus often prescribed) for drug-susceptible TB patients.[32] In Uzbekistan, in addition to an adequate TB regimen, an extra first-line drug as well as 7–8 non-TB drugs (which was a standard component of TB treatment in the former Soviet Union) were regularly prescribed.[34] This policy may indirectly promote resistance by introducing the risk of further side-effects and patient non-adherence.

National policies for TB treatment for migrants and prisoners also have a profound effect on TB and M/XDR-TB control. Both populations are typically at increased risk of active TB as they have a high incidence of latent TB infection,[23] limited access to healthcare services, including anti-TB therapy, and reside in crowded conditions that favour rapid TB transmission. The International Union Against Tuberculosis and Lung Disease recommends that undocumented migrants receive access to TB testing and that they are not deported until the end of treatment.[35] Norway and Kazakhstan have adopted this policy,[2] however, in many countries deportation of individuals diagnosed with TB is enforced.[36] This causes treatment delays and intermittency, thereby increasing the risk for development of drug resistance and TB transmission in the

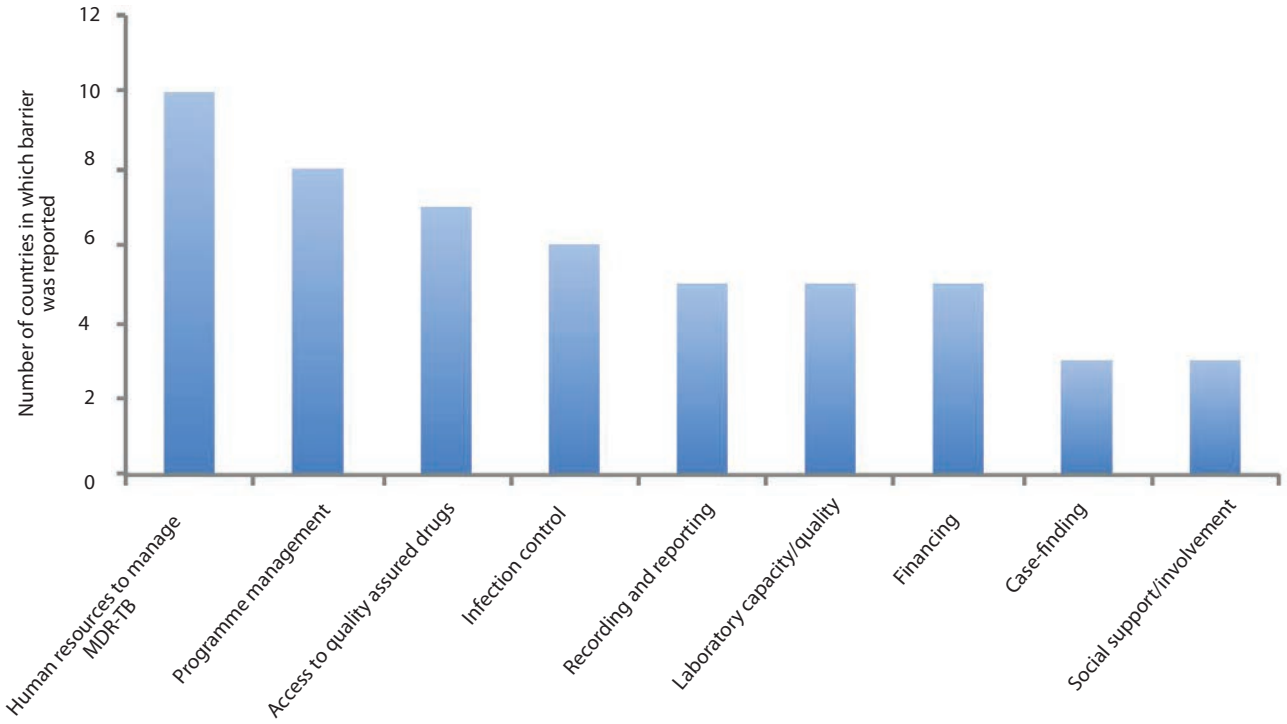

Figure 2. Bottlenecks reported by the 15 high-MDR-TB countries in the European Region.[2]

community. Amongst inmates, the incidence of TB is 5 to 70 times higher than within the general population[37] and inadequate follow-up of released prisoners with TB can undermine national control efforts.[38] For example, TB treatment for released prisoners in Azerbaijan is facilitated by non-governmental organisations, which is not guaranteed to be sustainable.[39]

Two key recommendations for European Regional policy on TB treatment for migrants and prisoners have been recently introduced. A consensus statement from the Wolfheze[40] 2011 conference put forth a minimum package for cross-border TB control and care in the WHO European Region and called for national health authorities to adopt it.[36] The package includes recommendations for a legal framework for TB cross-border collaboration, financial mechanisms and adequate health service delivery in the form of prevention, infection control, contact management, diagnosis and treatment, and psychosocial support.[36] The International Union Against Tuberculosis and Lung Disease has also recommended that national health authorities and partner organisations adopt and implement the internationally recommended Stop TB strategy in penitentiary settings in addition to measures for screening, infection control and TB management in prisons.[38]

Response Plans and Green Light Committee/Europe

In order to address alarming M/XDR-TB trends, causal determinants and barriers to TB control in the WHO European Region, a Consolidated Action Plan to Prevent and Combat M/XDR-TB (2011-2015) was developed for all 53 member states. The goal of the plan is to contain the spread of drug-resistant TB by achieving universal access to prevention, diagnosis and treatment of M/XDR-TB in all member states in the WHO European Region by 2015.[2] The plan, which has six strategic directions and seven areas of intervention are aligned with the Global Plan to Stop TB 2011-2015 with the following specific targets to be met by the end of 2015: decrease by 20% the proportion of MDR-TB amongst retreatment patients, diagnose at least 85% of all estimated MDR-TB patients, and successfully treat at least 75% of all patients notified of having MDR-TB. Endorsement and implementation of the plan began in 2011.

The WHO European Office has also assisted 18 high priority countries (the 15 high-burden MDR-TB countries in Table 1, plus Romania, Turkey and Turkmenistan) to develop national M/XDR-TB response plans based on their TB drug resistance surveys, resource availability, HIV burden and other national specificities. All high-priority countries, with the exception of the Russian Federation, have prepared and finalised their national M/XDR-TB action plans, however Ministries of Health in some countries have yet to officially endorse these plans.

A strategic and integral partner in achieving the comprehensive goals of the Consolidated Action Plan and the national M/XDR-TB response plans is the Green Light Committee/Europe (GLC/Europe). The GLC initiative was formed in 2000 upon recognition by key stakeholders, including the WHO and the Stop TB Partnership, that expansion of access to treatment for MDR-TB worldwide was moving too slowly. The GLC, therefore, was formed as a technical advisory body to enable countries to access affordable, high-quality, second-line drugs for the treatment of MDR-TB.[41] The GLC/Europe was formed in 2011 to carry out the goals of

the GLC initiative and further provide assistance for developing national capacity to scale-up programmatic management of M/XDR-TB.[42]

Currently the GLC/Europe provides assistance to 18 countries in the European Region including all 15 high-burden MDR-TB countries.[41s] It provides technical assistance for implementation of the Consolidated Action Plan and the national M/XDR-TB response plans. To date, the GLC/Europe has reviewed and provided expert input into the national M/XDR-TB action plans of 15 high-priority countries. In these countries, GLC/Europe has additionally provided further assessment of wider health system, governance and finance issues hindering M/XDR-TB control, such as those discussed above. The GLC/Europe has also assisted several high-priority countries at the national policy level to introduce specialised clinical teams to manage M/XDR-TB patients, which is recommended by the WHO. These specialised teams, known as Consilia in former Soviet countries, are multidisciplinary, comprising of specialists in both adult and paediatric medicine, surgery, radiology, public health, psychology, nursing, etc.[43]

Implementation of Consilia is a prerequisite to apply for international funding and concessionally priced M/XDR-TB drugs.[43] However, in many high-burden countries, clinical expertise is limited. To address this barrier, WHO/Europe and the European Respiratory Society (ERS), with support from the European Centre for Disease Prevention and Control (ECDC), launched the ERS-WHO Electronic Consilium (e-Consilium) in 2012. The aim of the this initiative is to provide internet-based, peer-to-peer consultation to national Consilia and individual clinicians for M/XDR-TB and other difficult-to-treat TB cases, including TB/HIV and paediatric cases.[43] Expert consultation, however, can only be a truly effective component of a comprehensive TB control plan if patients are properly and expeditiously diagnosed. In order to address limitations in second-line anti-TB DST, especially within high-priority countries, the European Tuberculosis Laboratory Initiative (ELI) was recently launched to improve and expand second-line DST in the 18 high-priority countries through scale-up of diagnostic capacity by 2015.[44]

With the compliment of e-Consilium and ELI, the GLC/Europe is able to assist countries with access to quality-assured second-line anti-TB drugs and liaise with global partners, donors and technical agencies to streamline efforts to meet the 2015 targets. Taking a patient-centred approach, the GLC/Europe also provides support for food packages, transport vouchers, counselling/ psychosocial support, hygiene packets, education, housing and financial incentives (depending on country and patient situation) to over 30,000 approved MDR-TB patients in the region.[2, 41] It has been shown that patient-level socioeconomic interventions can reduce TB risk factors and improve health-seeking behaviours.[45-49] The combination, therefore, of national and patient-level assistance from the GLC/Europe, ERS-WHO e-Consilium and ELI, offer a powerful method of addressing many of the factors along the causal pathway of drug-resistance, and most importantly enables effective treatment for MDR-TB patients. On-going monitoring and evaluation will reveal the full impact of these initiatives on MDR-TB control in the region.

Conclusions

Rates of M/XDR-TB have increased to alarming levels in the European Region, fundamentally caused by misuse of anti-TB drugs as a result of proximal and distal determinant factors. The WHO Consolidated Action Plan to Prevent and Combat M/XDR-TB (2011-2015) facilitated by the GLC/Europe (amongst other integral partners and initiatives) offer a comprehensive and integrated approach to controlling this urgent problem in the region. Implementation of existing strategies, policies and response plans, however, remains crucial. There is a clear need for continued support to the TB Programmes in the region to implement their national M/XDR-TB response plans and scale up programmatic management of drug-resistant TB. An even closer collaboration between partners, donors and stakeholders will be critical in mounting an effective public health response, and winning the battle against this archetypal disease of poverty.

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Non-invasive Ventilation in Stable Chronic Obstructive Pulmonary Disease

Eduardo Márquez-Martín,[1, 2] **Jose Luis López-Campos,**[1, 2, 3] and **Francisco Ortega Ruiz**[1, 2, 3]
1. Medical Surgical Unit of Respiratory Disease, University Hospital Virgin del Rocio. Seville; 2. Institute of Biomedicine of Seville (IBIS), Seville University, Seville; 3. CIBER of Respiratory Diseases

Introduction

Chronic obstructive pulmonary disease (COPD) is currently one of the major health problems due to the high number of patients suffering from this disease and the need for resources required. Besides the high prevalence, we must also consider the deterioration of the quality of life experienced by patients in the advanced stages of the disease.[1]

From a medical point of view, what we were able to offer these patients were bronchial anti-inflammatory drugs, bronchodilators, oxygen therapy and antibiotics, at both clinical stability phase and exacerbations.

Randomised clinical trials have shown that respiratory rehabilitation improves dyspnoea, exercise tolerance and quality of life.[2] This has made the respiratory rehabilitation one of the main concerns in the treatment of COPD. Other treatments, such as transplantation or lung volume reduction surgery, are useful for only a small number of highly selected patients.[3]

Different studies have shown that the application of non-invasive ventilation (NIV) is a therapeutic strategy of choice in severe exacerbations of COPD, and may be an alternative to endotracheal intubation and optimising resources to extubation in patients who require it.[4]

In recent years various studies have been, and are currently being conducted to assess the usefulness of NIV in COPD patients in stable phase, evaluating the benefit of parameters such as blood gases, spirometry, clinical, number of hospitalisations, etc.

Non-invasive Ventilation with Negative Pressure

Early studies that attempted to evaluate the usefulness of NIV in stable COPD patients were performed with negative pressure between the years 1984-1992 (Table 1). Five studies showed beneficial results,[5-9] but only three of these used a control group.[7, 9, 10] The number of patients was small and its duration was not more than a week. Moreover, three controlled studies showed negative results,[10-12] two of them with a reasonably long follow-up time.[10, 12] In these studies only Shapiro *et al*.[12] recruited an adequate number of patients and simulated NIV employed in the control group. The study argued that muscle fatigue in patients with COPD would be favourably treated with rest providing NIV. However, tolerance was poor and most of the patients used respirators for less time than planned.

Therefore studies with negative pressure ventilators do not allow the use of this technique for any of the following reasons: lack of control or placebo group, the goals were not met because of poor tolerance to NIV and were probably used in a appropriate group of patients (patients with positive studies had levels of arterial pressure carbon dioxide, PaCO2, significantly higher than patients in the study where the results were negative).

Non-invasive Ventilation with Positive Pressure

In later years, studies were being published that assessed the usefulness of positive pressure ventilation, PPV (Table 2). Elliot *et al*.[13] tested the night home PPV in a group of 12 patients with COPD and hypercapnic respiratory failure. After 6 months of treatment, blood gas and improved sleep efficiency increased, although its architecture and number of arousals unchanged. In this study, the quality of life did not change with the PPV but, at one year, the gasometric improvement was maintained in 7 patients. The authors proposed that the PPV was effective for the treatment of patients with stable COPD. Strumpf *et al*.[14] used the PPV in 23 patients with COPD in stable phase for 3 months in a randomised crossover study. Only 7 patients completed both arms of the study, which concluded that the home PPV was not well tolerated and that the improvement was not clinically valuable registered. The paper of Gay *et al*.[15] provides similar results in 7 COPD patients nocturnally ventilated over a period of 3 months. There was avaluable gasometric improvement and treatment rejection rate was high (43%). Lin[16] did not show that the PPV would improve gas exchange in COPD which was stable after three months of nocturnal home ventilation. A controlled study by Casanova *et al*.,[17] in 26 patients with COPD in

Author	Year	Design	Num.	Hours/day	Duration	$PaCO_2b$	$PaCO_2a$	Result
Braum	1984	No controlled	16	5	5 m	54	45	Positive
Cropp	1987	Controlled	8	3-6	3 d	50	42	Positive
Gutierrez	1988	No controlled	5	8 h/week	4 m	60	52	Positive
Scano	1990	Controlled	6	4	7 d	61	51	Positive
Ambrosino	1990	Controlled	10	6	7 d	56	51	Positive
Zibrak	1988	Controlled, crossed	9	4	3 m	47	50	Negative
Celli	1989	Controlled	16	5	13 d	45	42	Negative
Shapiro	1992	Controlled	184	5	3 m	44	44	Negative

Table 1. NIV published studies with negative pressure. $PaCO_2b$: arterial pressure carbon dioxide before; $PaCO_2a$: arterial pressure carbon dioxide after; d: day; m: month; Num: number.

stable phase treated at home for 1 year with VPP, did not detect a significant difference in terms of respiratory lung function or survival.

By contrast, in a similar design study, Meecham-Jones *et al*.[18] provided more encouraging results. After ventilating 14 patients, combination therapy of conventional oxygen therapy and PPV significantly improved blood gas, total time and sleep efficiency, quality of life and nocturnal PaCO2. Similar results have been provided by Clini *et al*.,[19] who concluded that home PPV and oxygen therapy decrease the number of admissions and hospital stays, but without demonstrating increased survival.

Although no studies have compared the response to NIV between hypercapnic and normocapnic patients, the evidence indicates that those that are hypercapnic could benefit from its use. However, the recommendation of this therapy is based on a study of level B.[19] Furthermore, the mode of application NIV has not yet been established, which explains the different levels of inspiratory pressure applied. This is clearly due to ignorance of the possible mechanisms of action. Although three mechanisms of action have been proposed, (relief from a chronic state of inspiratory muscle fatigue, increased sensitivity of the respiratory centre to CO2 and improved quality of sleep[19] and decreased lung hyperinflation), none has been clearly demonstrated.

Indications

A meta-analysis has been published[20] that assessed the potential benefits of the night PPV for 3 months in patients with COPD and hypercapnia in stable phase. Spirometric parameters were evaluated (forced expiratory volume in one second, forced vital capacity), blood gases (PaCO2, PaO2), sleep efficiency and distance walked in 6 minutes. Of the 164 publications found, only 4 papers[15, 16, 18, 19] met the requirements requested by the authors of the meta-analysis. All had an insufficient sample size (between 19 and 26 participants in each), and so the results do not show adequate statistical power, however, the application of nocturnal PPV in COPD patients in a stable situation becomes clinically relevant, primarily in those patients with baseline hypercapnia.

From this we can deduce that the home mechanical ventilation (HMV), with both positive and negative pressure, has not proved useful in the treatment of COPD, unlike in the field of chest wall diseases and obstructive sleep apnoea. Furthermore, the number of intolerance to treatment is far superior compared to that observed in these diseases. The still unexplained causes must respond to the underlying pathophysiology of these diseases and also the perception of the patient about the effects of NIV. But we can identify a number of indications for the use of home NIV in COPD patients (summarised in Table 3)[21, 22] although these have not yet been established in the relevant clinical guidelines because of the need for multicentre studies that analyse survival data, exacerbations and hospital admissions for assessing long-time effects of this therapy.[23]

Conclusions

Studies evaluating the efficacy of long-term mechanical ventilation in

Author	Year	Design	Num.	Hours/day	Duration	$PaCO_2b$	$PaCO_2a$	Result
Elliot	1992	No controlled	12	6-10	6 m	58	51	Positive
Strumpf	1991	Controlled	23	6.7	3 m	46	50	Negative
Gay	1996	Controlled	7	5.1	3 m	54	58	Negative
Lin	1996	Controlled	12	4.3	14 d	51	50	Negative
Casanova	2000	Controlled	26	6.2	12 m	51	49	Negative
Meechan-Jones	1995	Controlled	14	7	3 m	56	53	Positive
Clini	1996	Controlled	17	-	18 m	54	54	Positive

Table 2. Positive Pressure Ventilation studies. $PaCO_2b$: arterial pressure carbon dioxide before; $PaCO_2a$: arterial pressure carbon dioxide after; d: day; m: month; Num: number.

1. Symptoms: Fatigue, hypersomnolence, dyspnoea.
2. Gas exchange alterations: PaCO2> 55 mmHg PaCO2> 50 mmHg and O2 Sat> 88%.
3. Unresponsive to optimal therapy: corticosteroids and bronchodilator therapy with oxygen.
4. No response to CPAP therapy if Obstructive Sleep Apnoea.

Table 3. Indications NIV in stable COPD.

stable COPD show variable results and have controversial conclusions, although there is evidence that selected patients may benefit from this therapy.[14, 15, 17, 19, 24-26] There is a group of patients with severe COPD, posing significant nocturnal ventilatory abnormalities with consequent deterioration blood gases, hypercapnia maintained and respiratory muscle dysfunction, that do not improve with conventional treatments, including home oxygen therapy. These alterations may contribute to the progressive deterioration that these patients present with frequent hospitalisations and increased mortality. The HMV would take effect on the one hand as life support, preventing or reversing respiratory acidosis situations and secondly providing respiratory muscle rest and thereby allowing a recovery of function. It has been shown that the HMV decreases respiratory muscle activity, although the effect on the strength and resistance is variable, improving in some studies but not in others.[14, 15]

According to this, HMV could usefully contribute to improving muscle functionalism, to reduce the number of income and consequently to improve the quality of life of these patients, and may even increase survival.[27] The combination of nocturnal nasal HMV with oxygen therapy in hypercapnic COPD in stable situation can provide an improvement in the quality and quantity of sleep, both gas exchange in night-time and daytime, the symptoms linked to hypercapnia and consequently their quality of life.[28] In these patients the nutritional status and hyperinflation prognostic markers seem to be related more to survival.[29]

We could consider the use of mechanical ventilation in patients with severe COPD in which, despite conventional treatment being applied correctly, continue having nocturnal desaturations and hypercapnia with frequent episodes of chronic respiratory acidosis requiring repeated hospitalisations.

HMV is currently not a treatment that should be raised in a generalised way in stable COPD, and so further studies are needed to determine the true role of this therapy. These studies should aim to better define the characteristics of patients who may benefit, evaluate potential benefits in dyspnoea, exercise capacity, quality of life and survival.

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Upcoming Congresses and Meetings

British Thoracic Society Winter Meeting 2013

04 - 06 December 2013

London, United Kingdom

The British Thoracic Society was formed in 1982 by the amalgamation of the British Thoracic & Tuberculosis Association and the Thoracic Society. Members include doctors, nurses, respiratory physiotherapists, scientists and other professionals with an interest in respiratory disease. The BTS' main objective is to improve the care of people with respiratory disorders. The Winter Meeting is the UK's primary respiratory scientific meeting, with a focus upon presenting updates on current research and symposia from leading researchers.

The Intensive Care Society (ICS) State-of-the-Art Meeting 2013

16 - 18 December 2013

London, United Kingdom

The Intensive Care Society is the representative body in the UK for intensive care professionals and patients, and is dedicated to the delivery of the highest quality of critical care to patients. The State-of-the-Art meeting is the UK's largest gathering for intensive care professionals, and will feature both international experts and speakers from the UK, as well as an exhibition, poster presentations and research awards and grants. Topics this year will include controversies in critical care, ventilation and organ donation amongst others.

11th Annual British Thoracic Oncology Group Conference 2013

29 - 31 January 2014

Dublin, Ireland

BTOG aims to improve the care of patients with thoracic malignancies through multidisciplinary education and clinical and scientific research. BTOG represents all the disciplines involved in the care of lung cancer and mesothelioma throughout the UK, and includes medical and clinical oncologists, respiratory physicians, surgeons, radiotherapists, radiologists, nurses, pharmacists and scientists. The annual conference features scientific symposiums, plenary sessions, state-of-the-art presentations and workshops. 2012 saw attendees and submissions increase, and this year's event looks set to be even bigger.

Association for Respiratory Technology and Physiology (ARTP) Annual Conference 2014

30 January - 01 February 2014

Blackpool, United Kingdom

The Association for Respiratory Technology and Physiology (ARTP) are the professional guardians of physiological measurement issues in respiratory medicine in the UK. The Conference will once again offer a comprehensive programme aimed at healthcare professionals with an interest in respiratory and sleep physiology and medicine. Highlights of the programme include a keynote lecture focusing on the links between cardiology and respiratory, as well as lectures on paedatric issues, palliative care and sleep.

15th European Congress: Perspectives in Lung Cancer

14 - 15 March 2014

Amsterdam, The Netherlands

The 15th European Congress: Perspectives in Lung Cancer will focus upon the new findings, techniques, and research in the therapeutic management of lung cancer, and will explore the changing focus within this area to an individualised approach. Exciting presentations and lively debates will provide important clinical updates in lung cancer management, and an increased use of technology will ensure that attendees are able to keep up-to-date with all of the latest news and findings.

12th ERS Lung Science Conference

21 - 23 March 2014

Estoril, Portugal

The theme for the 12th ERS Lung Science Conference is 'Lung inflammation and immunity', and the scientific programme will provide up-to-date sessions on topics including new trends in immunology and asthma, immune responses in chronic lung diseases and the genesis of allergy and asthma. The Conference will also feature poster sessions and oral presentations, as well as debates and a Young Invesigator session, where the Willian MacNee award will be given.

4th European Lung Cancer Conference (ELCC)

26 – 29 March 2014

Geneva, Switzerland

The ELCC has been jointly organised by the European Society for Medical Oncology (ESMO) and the International Association for the Study of Lung Cancer (IASLC), where attendees will benefit from updates from thoracic oncology specialists and clinical practise in the field of lung cancer. Key topics will include molecular testing in advanced non-small cell lung cancer, mesothelioma and oncogenic-driven diseases. Meet-the-expert sessions, interactive workshops and in-depth

lectures make this the thoracic conference of 2014. The meeting also encourages interaction and debae between participants and speakers.

WCA-2014

29 March – 01 April 2014

Mexico City, Mexico

The World Congress of Asthma (WCA) 2014 will be organised by INTERASMA, the Global Association of Asthma, who have prepared an exciting scientific programme featuring basic and clinical science and new insights into epigenetics, proteomics, mechanisms, risk factors and new therapeutic tools. The programme will include three tracks: paediatrics, primary care clinicians and asthma specialists.

Association of Respiratory Nurse Specialists (ARNS) Annual Conference 2014

09 - 10 May 2014

Warwick, United Kingdom

The ARNS Annual Conference promises something for all those working in respiratory nursing and health professional roles. The conference will feature a variety of workshops and sessions covering a wide range of areas within respiratory illness. This course is aimed at doctors, nurses and physiotherapists who would like to feel more confident with managing end of life issues in respiratory disease.

7th International Primary Care Respiratory Group (IPCRG) World Conference

21 - 24 May 2014

Athens, Greece

The International Primary Care Respiratory Group is hosting its 7th World Conference in partnership with ELEGEIA, the Greek Association of General Practitioners, and have created a thought-provoking programme which focuses upon the challenges of multiple morbidity and integrated care. Highlights of the programme include symposia on prevention, primary care case-finding and diagnosis, which will be delivered by internationally-renouned speakers, as well as sessions which focus on how to integrate patient care for patients with respiratory problems who have multiple morbidities. Practical workshops and cutting-edge primary care research and oral and poster presentations also feature heavily within the conference. The 7th World Conference is an excellent event at which to network with colleagues from around the globe and improve your understanding of primary care issues.

EAACI 2014

07 - 11 June 2014

Copenhagen, Denmark

The European Academy of Allergy and Clinical Immunology is a non-profit organisation which aims to promote basic and clinical research, as well as collect, assess and disseminate scientific information. It further aims to encourage and provide training and continuous education. This year, the Congress' main theme is 'Challenging Dogmas', a crucial part of the scientific process and the source of much innovation. The programme will not only provide delegates with a comprehensive and broad understanding of the basic and clinical research within the field, but also with many opportunities to discuss and debate this research with both renouned experts and colleagues. Indeed, networking is a key componant of the congress, and is encouraged throughout the 5-day event. Attendees will return home with new skills for treating patients, new ideas and new inspiration.

37th European Cystic Fibrosis Conference

11 - 14 June 2014

Gothenburg, Sweden

The European Cystic Fbrosis Society aims to facilitate the acquisition and distribution of knowledge and research in the field of cystic fibrosis. The Conference will provide a forum for the discussion of the best basic and applied science, and facilitate translation of the latest knowledge into daily clinical practice. The programme will reflect these priorities and bring together scientific and clinical teams. You can expect a high quality programme of plenary sessions, symposia and workshops, with international experts in cystic fibrosis presenting the lectures. The Conference will provide a social platform and a great opportunity for making or renewing contacts with colleagues in the field.

European Respiratory Society Annual Conference (ERS) 2014

06 - 10 September 2014

Munich, Germany

The ERS is the leading professional organisation in its field in Europe, and has around 10,000 members from over 100 countries. It is broad-based, and covers both basic science and clinical medicine. ERS seeks to alleviate suffering from respiratory disease and promote lung health through research, sharing of knowledge and through medical and public education. The ERS congress adheres closely to these principles, and offers a range of sessions including symposia, workshops, seminars and abstract presentations, as well as lectures given by leading experts in the field.

WISC 2014

06 – 09 December 2014

Rio de Janerio, Brazil

The WAO International Scientific Conference 2014 and the 41st Annual Meeting of the Brazilian Association of Alergy and Immunopathy (ASBAI) join together at WISC 2014. The theme of the Conference is Advancing the Borders of Allergy: Treatment and Prevention by Targeting the Environment, Infection and the Susceptible Patient, and will feature the latest research, a review of current theory and practice and hands-on, problem-based learning. The Conference aims to give participants an insight into the most effective advances in treatment and prevention of allergic and immunologic diseases, and attendees will find a programme which is both varied and stimulating.

European Respiratory Society Congress 2014

6 – 10 September 2014

Munich, Germany

The European Respiratory Society (ERS) will meet at the Internationales Congress Center München from 6 – 10 September, turning Munich into the respiratory medicine capital once again.

Physicians, scientists, nurses and many other representatives of the healthcare sector are will be in attendance.

The programme of events includes a wealth of lectures and symposia. focusing on the latest research findings, techniques and strategies for the treatment of respiratory diseases.

The Cambridge Research Centre
Coppergate House
16 Brune Street
London
E1 7NJ

www.cambridgeresearchcentre.co.uk