ISSN: 2543-0343 Volume 2 Issue 2 April-June 2018

Pediatric Respirology and Critical Care Medicine

www.appuls.org www.hkspra.org www.pedipulm.org.tw

Medknow Wolters Kluwer

Abbott
雅培

Abbott HMO# Scientifically Inspired By Breast Milk

Clinically Proven to Strengthen Immunity

Significantly Relief of Symptoms of Upper Respiratory Tract Infection[1^]

Scientific Innovation
Worldwide 1st to Launch*

Nutrients in Breast Milk

The Third Most Abundant Component in Breast Milk

HMO (Human Milk Oligosaccharide), not from human milk.

1. Marriage, B. J., R. H. Buck, K. C. Goehring, J. S. Oliver and J. A. Williams (2015). "Infants Fed a Lower Calorie Formula With 2'FL Show Growth and 2'FL Uptake Like Breast-Fed Infants." J Pediatr Gastroenterol Nutr 61(6): 649-658.

^ Compared to control formula without HMO, based on parent reported adverse events from a post-hoc analysis of a clinical study. Applies to Abbott HMO Stage 1 and 2.

* Abbott launched milk formula with HMO in the United State in September 2016. HMO has been researched in at least 13 countries worldwide.

For Healthcare Professionals Reference Only.

雅培營養專家 Abbott NUTRITION EXPERT
香港 (852) 2806 4843
中國免費直撥 4001208843

Learn more

P18-COM-HL-0432

Print ISSN: 2543-0343, E-ISSN: 2543-0351

Pediatric Respirology and Critical Care Medicine

Official Journal of Asian Paediatric Pulmonology Society, Hong Kong Society of Paediatric Respirology and Allergy, and Taiwan Society of Pediatric Pulmonology and Critical Care Medicine

Editorial Board

Editor-in-Chief

Prof. Gary Wing-kin Wong, Hong Kong

Deputy Editors

Dr. Daniel Kwok-keung Ng, Hong Kong
Dr. Kin-sun Wong, Taiwan

Associate Editors

Dr. Anne Goh, Singapore
Prof. Aroonwan Preutthipan, Thailand
Prof. Kun-ling Shen, China
Prof. Varinder Singh, India
Dr. Rina Triasih, Indonesia

Editorial Board Members

Dr. Shakil Ahmed, Bangladesh
Dr. Mahesh Babu, Singapore
Prof. Yi-xiao Bao, China
Dr. Jessie de Bruyne, Malaysia
Dr. Eric Yat-tung Chan, Hong Kong
Prof. Chung-ming Chen, Taiwan
Dr. Gary Cheok, Macau
Prof. Zen-kong Dai, Taiwan
Prof. Aye Maung Han, Myanmar
Prof. Ellis Kam-lun Hon, Hong Kong
Prof. Kai-sheng Hsieh, Taiwan
Dr. Kin-mui Ieong, Macau
Prof. ARM Luthful Kabir, Bangladesh
Prof. Sushil Kabra, India
Dr. Jin-tack Kim, Korea
Dr. Hussein Al Kindy, Oman
Dr. Carrie Ka-li Kwok, Hong Kong
Prof. Albert Martin Man-chim Li, Hong Kong
Prof. Ching-yuang Lin, Taiwan
A/Prof. Sorasak Lochindarat, Thailand
Dr. Ting-yat Miu, Hong Kong
Prof. Ashkan Moslehi, Iran
Dr. Anna Nathan, Malaysia
Dr. Nepthalie Ordonez, Philippines
A/Prof. Diem Pham, Vietnam
A/Prof. Nguyen Phung, Vietnam
Dr. Clara Rivera, Philippines
Prof. Wen-jue Soong, Taiwan
Dr. Bambang Supriyatno, Indonesia
Dr. Masato Takase, Japan
Dr. Alfred Yat-cheung Tam, Hong Kong
Prof. Saw Win, Myanmar
Prof. Li Xiang, China
Dr. Jong-seo Yoon, Korea

General Information

The journal

Pediatric Respirology and Critical Care Medicine is a journal for pediatricians to discuss the latest clinical practice and research in pediatrics and child health. It is the official Journal of Asian Paediatric Pulmonology Society, Hong Kong Society of Paediatric Respirology and Allergy, and Taiwan Society of Pediatric Pulmonology and Critical Care Medicine. The journal's full text is available online at http://www.prccm.org. The journal allows free access (Open Access) to its contents and permits authors to self-archive final accepted version of the articles on any OAI-compliant institutional/subject-based repository.

Abstracting and indexing information

The journal is registered with the following abstracting partners: Baidu Scholar, CNKI (China National Knowledge Infrastructure), EBSCO Publishing's Electronic Databases, Exlibris – Primo Central, Google Scholar, Hinari, Infotrieve, National Science Library, Netherlands ISSN center, ProQuest, TdNet.

Information for authors

The journal does not charge for submission, processing or publication of manuscripts and even for color reproduction of photographs. Please check http://www.prccm.org/contributors.asp for details. All manuscripts must be submitted online at http://www.journalonweb.com/prcm.

Advertising policies

The journal accepts display and classified advertising. Frequency discounts and special positions are available. Inquiries about advertising should be sent to Medknow Publications, advertise@medknow.com. The journal reserves the right to reject any advertisement considered unsuitable according to the set policies of the journal.

The appearance of advertising or product information in the various sections in the journal does not constitute an endorsement or approval by the journal and/or its publisher of the quality or value of the said product or of claims made for it by its manufacturer.

Copyright

The entire contents of the Pediatric Respirology and Critical Care Medicine are protected under Indian and international copyrights. The Journal, however, grants to all users a free, irrevocable, worldwide, perpetual right of access to, and a license to copy, use, distribute, perform and display the work publicly and to make and distribute derivative works in any digital medium for any reasonable non-commercial purpose, subject to proper attribution of authorship and ownership of the rights. The journal also grants the right to make small numbers of printed copies for their personal non-commercial use under Creative Commons Attribution-Noncommercial-Share Alike 3.0 Unported License.

Permissions

For information on how to request permissions to reproduce articles/information from this journal, please visit www.prccm.org.

Disclaimer

The information and opinions presented in the Journal reflect the views of the authors and not of the Journal or its Editorial Board or the Society of the Publisher. Publication does not constitute endorsement by the journal. Neither the Pediatric Respirology and Critical Care Medicine nor its publishers nor anyone else involved in creating, producing or delivering the Pediatric Respirology and Critical Care Medicine or the materials contained therein, assumes any liability or responsibility for the accuracy, completeness, or usefulness of any information provided in the Pediatric Respirology and Critical Care Medicine, nor shall they be liable for any direct, indirect, incidental, special, consequential or punitive damages arising out of the use of the Pediatric Respirology and Critical Care Medicine. The Pediatric Respirology and Critical Care Medicine, nor its publishers, nor any other party involved in the preparation of material contained in the Pediatric Respirology and Critical Care Medicine represents or warrants that the information contained herein is in every respect accurate or complete, and they are not responsible for any errors or omissions or for the results obtained from the use of such material. Readers are encouraged to confirm the information contained herein with other sources.

Addresses

Editorial Correspondence
Prof. Gary Wing-kin Wong
Hong Kong Society of Paediatric Respirology and Allergy
4/F., Duke of Windsor Social Service Building, 15 Hennessy Road, Wan Chai, Hong Kong
E-mail: wingkinwong@cuhk.edu.hk
Website: www.prccm.org

Published by
Wolters Kluwer India Private Limited
A-202, 2nd Floor, The Qube, C.T.S. No.1498A/2
Village Marol, Andheri (East), Mumbai - 400 059, India.
Phone: 91-22-66491818
Website: www.medknow.com

Pediatric Respirology and Critical Care Medicine

Volume 2 ¦ Issue 2 ¦ April-June 2018

Contents

EDITORIAL

Suppurative Lungs, Pneumothorax and 6-Min Walk Test in Children

Aroonwan Preutthipan 17

REVIEW ARTICLES

'Suppurative Lung Disease' in Children

Mark Lloyd Everard 18

Primary Spontaneous Pneumothorax in Children: A Literature Review

Ping-Yang Kuo, Bao-Ren Nong, Yung-Feng Huang, Yee-Husan Chiou 25

ORIGINAL ARTICLE

Correlation between 6-min Walk Test and Cardiopulmonary Exercise Test in Chinese Patients

Pik-Fung Wong, Eric Yat-Tung Chan, Daniel Kwok-Keung Ng, Ka-Li Kwok, Ada Yuen-Fong Yip, Shuk-Yu Leung 32

Suppurative Lungs, Pneumothorax and 6-Min Walk Test in Children

In this issue, Prof. Mark Lloyd Everard has stimulates the awareness of persistent bacterial bronchitis (PBB) and chronic suppurative lung disease (CSLD) in children. As he wrote, "if doctors do not know this disease exists, they will never diagnose it."[1] PBB and CSLD is a chronic neutrophil-predominated bronchitis. CSLD has been used to describe the clinical features of bronchiectasis when the radiographic features needed to make a diagnosis of bronchiectasis are absent.[2] He also describes the pathophysiology of this disease which is associated with the development of bacterial biofilms in the lungs and airways. Making the diagnosis is somewhat challenging, not straightforward like pneumonia or asthma. Choosing the most appropriate antibiotics and physiotherapy to eliminate bacteria and permit recovery of structure and function in most cases should result in a cure, which could prevent lifelong morbidity from bronchiectasis.[1] Since this disease entity is probably underrecognized, its exact prevalence is unknown. Early diagnosis should be emphasized to minimize long term complications.

Primary spontaneous pneumothorax (PSP) in children may lead to a life threatening condition. In the current issue of *Pediatric Respirology and Critical Care Medicine*, Ping-Yang Kuo *et al*. publish an excellent literature review of PSP in children including epidemiology, pathophysiology, clinical features, diagnosis, and management.[3] Unlike adults, the recurrent rate of PSP was much more higher in children after nonsurgical management.[3] Therefore they recommended thorax computed tomography (CT) and subsequent surgical treatment, not only for recurrent PSP but also first episode of large PSP after needle aspiration or chest tube drainage.[4] Video-assisted thoracoscopic surgery (VATS) with either mechanical or chemical pleurodesis to stop air leak is suggested for the affected side. The suggested timing of VATS after failure from tube thoracostomy was ranged from 3 to 7 days.[5-7] Wedge resection by VATS is recommended if CT scan of the chest shows bullae or blebs.[8] Practice guidelines based on adults may not be applicable to children as the situation may not be the same.

The 6-min walk test (6MWT) is the distance an individual can walk at a constant, uninterrupted, unhurried pace in 6 min. It is now used routinely to assess patients with cardiopulmonary disease in view of its simplicity and cost-effectiveness. Li *et al.* demonstrated in 2005 that the 6MWT had good correlation with maximum oxygen uptake determined by cardiopulmonary exercise test (CPET) in healthy children.[9] The correlation was confirmed again in children with various cardiopulmonary diseases by Dr. Pik-Fung Wong's study published in this issue.[10] Moreover, if the distance that the child could walk in 6 min was less than 10th percentile of height-matched reference obtained from healthy Chinese children, that child most likely had abnormal CPET. This is another convincing evidence supporting the usefulness of 6MWT, which can be performed easily in children in every parts of the world.

Aroonwan Preutthipan

Division of Pediatric Pulmonology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

Address of correspondence: Dr. Aroonwan Preutthipan, Division of Pediatric Pulmonology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok 10400, Thailand.
E-mail: aroonwan.pre@mahidol.ac.th

References

1. Everard M. 'Suppurative lung disease' in children. Pediatr Respirol Crit Care Med 2018;2:19-25.
2. Redding GJ, Carter ER. Chronic suppurative lung disease in children: Definition and spectrum of disease. Front Pediatr 2017;5:30.
3. Kuo P, Nong B, Huang Y, Chiou Y. Primary spontaneous pneumothorax in children: A literature review. Pediatr Respirol Crit Care Med 2018;2:26-32.
4. Soccorso G, Anbarasan R, Singh M, Lindley RM, Marven SS, Parikh DH. Management of large primary spontaneous pneumothorax in children: Radiological guidance, surgical intervention and proposed guideline. Pediatr Surg Int 2015;31:1139-44.
5. Zganjer M, Cizmić A, Pajić A, Cigit I, Zganjer V. Primary spontaneous pneumothorax in pediatric patients: Our 7-year experience. J Laparoendosc Adv Surg Tech A 2010;20:195-8.
6. Butterworth SA, Blair GK, LeBlanc JG, Skarsgard ED. An open and shut case for early VATS treatment of primary spontaneous pneumothorax in children. Can J Surg 2007;50:171-4.
7. Williams K, Oyetunji TA, Hsuing G, Hendrickson RJ, Lautz TB. Spontaneous pneumothorax in children: National management strategies and outcomes. J Laparoendosc Adv Surg Tech A 2018;28:218-22.
8. Noh D, Lee S, Haam SJ, Paik HC, Lee DY. Recurrence of primary spontaneous pneumothorax in young adults and children. Interact Cardiovasc Thorac Surg 2015;21:195-9.
9. Li AM, Yin J, Yu CC, Tsang T, So HK, Wong E, *et al.* The six-minute walk test in healthy children: Reliability and validity. Eur Respir J 2005;25:1057-60.
10. Wong P, Chan E, Ng D, Kwok K, Yip A, Leung S. Correlation between 6-min walk test and cardiopulmonary exercise test in Chinese patients. Pediatr Respirol Crit Care Med 2018;2:33-6.

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

Access this article online

Quick Response Code:

Website: www.prccm.org

DOI: 10.4103/prcm.prcm_8_18

How to cite this article: Preutthipan A. Suppurative lungs, pneumothorax and 6-min walk test in children. Pediatr Respirol Crit Care Med 2018;2:17.

Review Article

'Suppurative Lung Disease' in Children

Mark Lloyd Everard

Division of Paediatrics and Child Health, Perth Children's Hospital, University of Western Australia, Nedlands, Western Australia, Australia

Abstract

A chronic neutrophil dominated bronchitis also known variously as PBB and CSLD is relatively common in childhood. There are numerous risk factors that may contribute to the development of a chronic bronchitis [inc viral LRTIs, malacia, aspiration, poorly controlled asthma etc.]. In most cases a specific significant on-going risk factor such as CF is not identified. It is under-diagnosed due to lack of awareness (if you do not know something exists you will never diagnose it). It is commonly mis-diagnosed as 'asthma' or 'recurrent chest infections'. Diagnosis is based on pattern recognition and response to treatment analogous to accurate diagnosis of asthma. Response to treatment must be dramatic and unequivocal to make a definite diagnosis. Beware regression to the mean PBB is a biofilm disease leading to challenges in treatment. A PBB is the cause of most cases of 'bronchiectasis'. Bronchiectasis is a radiological or pathological appearance, not a disease. Most cases are curable in the absence of a major underlying risk factor such as cystic fibrosis, PCD or significant immunodeficiency. Hence bronchiectasis is a largely preventable radiological appearance.

Keywords: Biofilms, chronic bacterial bronchitis, chronic cough, neutrophils, persistent bacterial bronchitis

Introduction

Suppurative lung disease will have accompanied humankind from the earliest times. The physical consequences of chronic suppurative lung disease (CSLD) were first described by Rene Laennec some 200 years ago in his classic, original description of bronchiectasis, correctly identifying the role of the chronic purulent secretions in its aetiology (though bacteria had not been identified as the cause of the purulent secretions).[1] Equally importantly, he used the term bronchiectasis to describe a physical appearance and *not* a disease. The disease was the consequence of the chronic endobronchial infection resulting in a range of symptoms that included chronic cough, chronic expectoration of sputum and malaise accompanied by intermittent exacerbations. Severity ranged from a troublesome productive cough to cachexia and respiratory failure. Death might result from a severe episode of bronchopneumonia (an exacerbation characterised by areas of pneumonia accompanying chronic bronchitis) or terminal respiratory failure and wasting. In the following 150 years, the condition remained a major cause of ill health in childhood.[2-7]

By the early C20th, the usual suspects regarding pathogenic bacteria had been identified[8] and an understanding of the role of chronic infection and impaired airways clearance became established over the subsequent 50 years.[9-16] With the advent of effective antibiotics in the second half of the C20th, the quality of life of those with a chronic endobronchial infection was transformed[17] and many in more affluent countries coming to believe that 'bronchiectasis' had largely disappeared attributing this to improved hygiene and vaccinations as much as to the use of antibiotics.[18,19] The focus on asthma (in part driven by pharma who were starting to develop products in portable inhalers that they could sell in vast quantities such as β-agonists and then, from the early 1979's, inhaled corticosteroids [ICS])[20] further marginalised interest in chronic bacterial infection outside the chronic bronchitis that was typically associated with smokers. The mantra that '*asthma should not be treated with antibiotics*' was, as with so much in medicine, rolled out for the best of reasons. The intention was to try and ensure *exacerbations* of asthma were not treated with antibiotics for a 'chest infection'

Address for correspondence: Prof. Mark Lloyd Everard, Division of Paediatrics and Child Health, Perth Children's Hospital, University of Western Australia, Winthrop Avenue, Nedlands, 6009 Western Australia, Australia.
E-mail: mark.everard@uwa.edu.au

Access this article online

Quick Response Code:

Website: www.prcm.org

DOI: 10.4103/prcm.prcm_6_18

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Everard ML. 'Suppurative lung disease' in children. Pediatr Respirol Crit Care Med 2018;2:18-24.

but managed appropriately with β-agonists and if necessary corticosteroids.[21] This further helped solidify in the minds of many the concept that bacteria produced acute pneumonic illnesses and occasionally produce an acute infection of the conducting airways such as a staphylococcal tracheitis but did not cause chronic bronchitis in children.

As a result, the concept of a 'chronic bronchitis' in children faded from the collective memory of many resulting in a self-fulfilling outcome. If one is not aware a condition exists, it is impossible to recognise or diagnose it and if it is not being diagnosed and recognised, it effectively ceases to exist.

While the vast majority of paediatric opinion leaders were saying that chronic bronchitis did not exist in children and that it was really all unrecognised asthma, adult physicians were refining the long-held concept that 'bronchiectasis', in most but not all cases, was the result of a vicious cycle of impaired mucociliary clearance and/or impairment of immunity leading a persistent infection associated with chronic inflammation that resulted in damage to the epithelium, and in time, the structure of the airway that further impaired mucociliary clearance promoting infection with the inflammation.[11-16] Over a variable period ranging from months to decades, this would lead to the dilation of proximal airways evident on CT scans as bronchiectasis and as Laennec almost uniquely observed, obliteration of smaller more distal airways which presumably accounts for the fall in forced vital capacity over time.[1,22]

This of course gave rise to a largely unrecognised period of cognitive dissonance– individuals believing that children did not get a chronic bronchitis (despite all the historical evidence to the contrary) while at the same time holding the belief that chronic infection of the conducting airways was the cause of bronchiectasis. To resolve this, they convinced themselves that really it was only those with cystic fibrosis (CF), primary ciliary dyskinesia (PCD), significant immunodeficiencies and those damaged by conditions such as whooping cough or measles who developed to 'CSLD'.[23] Many presumed the bronchiectasis following whooping cough or measles was a consequent of damage wrought during the acute illness without understanding that these infections could, in a minority of patients, initiate persistent bacterial bronchitis (PBB).

The recognition that children experienced chronic endobronchial infection in the absence of the major risk factors outlined above did not disappear completely in the 1980s and 1990s,[24] but our understanding was muddled[25,26] as reflected in the wide range of terms being used to describe the same condition including 'bronchiectasis' (inappropriately being used to denote a disease), pre-bronchiectasis, chronic bronchitis, chronic juvenile bronchitis, persistent endobronchial infection, a protracted or persistent bronchitis and suppurative lung disease.[27] As interest in the condition was reignited in the early C21st, at least in developed countries,[27-35] some even suggested that a chronic (or 'protracted') bacterial bronchitis was a 'new disease' and tried to differentiate it from 'CSLD'.

For the purposes of this review, the term PBB will be used since it describes the chronic nature of the condition and clearly describes an on-going inflammation of the conducting airways resulting from a persistent bacterial infection. The ability of a patient to expectorate or for there to be sufficient damage to demonstrate bronchiectasis on computed tomography scan are simply features of the condition that may or may not be present. This is analogous to the child with asthma who may have a dry night time cough without wheeze or have such a severe exacerbation that they have a 'silent chest' – both still have asthma.

The Importance of Bacterial Biofilms in Pulmonary Disease

The recognition that has come in the last couple of decades that most bacteria exist not as rapidly dividing planktonic organisms but as highly organised communities within biofilms finally provided a mechanism for persistence of bacteria in the conducting airways. Bacteria have been forming communities held together by an extracellular matrix, thus forming biofilms, for more than 3.5bn years.[35] As part of this process, it is now clear that bacteria communicate with each other using quorum-sensing molecules that influence their behaviour and metabolism. A range of strategies are adopted by bacteria in biofilms to facilitate their persistence and resist environmental threats such as host responses, antibiotics, other micro-organisms and nutrient-poor environments. These include the physical barrier provide by the extracellular matrix, the ability to down regulate metabolism, low rates of replication, the ability to share genes such as antibiotic resistance gene within members of the community and the development of collective strategies for eliminating threats such as antibiotics.[27-41]

This survival strategy permits them to persist very effectively in potentially hostile environments. Over the past 10 years, it has been increasingly recognised that a PBB is both relatively common and a major cause of respiratory morbidity. The relevant bacteria persist in biofilms driving a sustained, but ineffective neutrophilic bronchitis with most of the symptoms attributable to this chronic bronchitis. However, the concepts still have not reached much of the respiratory community including many, but not all, of those interested in chronic obstructive pulmonary disease (COPD).

Much of our understanding of the behaviour of biofilms and their role in respiratory illness comes from the ear, nose and throat world and chronic otitis media and to a lesser extent, chronic sinusitis. The interplay of microorganisms within a given ecological niche is complex with competition for dominance and/or collaboration being key to their success.[42-48]

Conventionally, acute febrile bacterial illnesses have been associated with rapidly dividing organisms such as the *Streptococcus pneumoniae* in an acute pneumonia or *E Coli* in an acute urinary infection. Both of these are generally 'commensals' living with the host but not causing illness.

During an acute illness caused by planktonic, rapidly dividing organisms, they can be identified if an appropriate sample is obtained using conventional (i.e., >100-year-old) microbiological techniques using culture plates (though this is rapidly being augmented by the use of matrix-assisted laser desorption ionisation time-of-flight). As the organisms in these acute diseases are planktonic and are dividing very rapidly 'rules,' such as it is likely to be a 'real' result if a pure growth of a likely suspect is obtained at levels of $>1 \times 10^5$/ml, were adopted for diagnostic purposes. Such 'rules' do not apply to more chronic biofilm diseases.

In a biofilm, the organisms turn over very slowly and hence such 'rules' are inappropriate[40] giving rise to debate regarding their value when assessing bronchoalveolar lavage (BAL) fluid, the guidelines being written before the recognition that biofilms were directly relevant to respiratory health. Consequently, some laboratories continue to produce qualitative results while others produce qualitative results such as scanty, few, moderate or heavy growths. Some authorities suggest if the organism should not be there and it is cultured then it is highly relevant while others argue that some degree of quantification is required to eliminate the effect of upper airways contamination of the sample. To complicate the issue further there is evidence to suggest that 'pathogens' can be cultured in BAL samples from healthy children (Craven personal communication) and certainly they are observed in all 16S microbiome studies. This adds a further layer of complexity to the interpretation of BAL results.

Intercurrent viral infections commonly cause exacerbations through the release of increased numbers of planktonic bacteria. This may simply result in increased symptoms as they colonise other areas of the conducting airway, but if the organisms extend into the respiratory portion of the lung, the patient may present as a 'bronchopneumonia'. The exact mechanism that leads to the release of planktonic bacteria and the change in the bacterial behaviour is unclear but the enzymatic degradation of the surface of the biofilm matrix appears to contribute to the process.[49] In the past, bronchopneumonia was considered to be a more potent killer than acute pneumonia in all age groups. In some COPD and otitis media studies, an exacerbation has been associated in many cases with the appearance of an apparently new strain or pathogen.[50] It is unclear whether these have been newly acquired or just happen to be the organism identified on that occasion or even simply represent gene switching in malleable organisms such as non-typeable haemophilus influenzae (NTHi).

The 'Lung Microbiome'

Further challenges to our understanding of microbial events in the lower airway come from our recognition that the lower airways are not sterile but have a normal microbiota.[51-54] In disease states such as PBB, the diversity of this community is greatly reduced with increased density of certain operational taxonomic units, that is bacteria characterised on sequence similarity.[51] It appears that the pathogens that appear to cause PBB are also present in the 'healthy' microbiome of the conducting airways.[51-54] 'Pulmonary disease' appears to result from a disruption of a 'healthy' dynamically changing community probably mediated through the formation of biofilms. It is the ability of one or more organisms to dominate the local environment through establishing biofilms that initiate the chronic inflammation characteristic of PBB and other related diseases. 16S RNA techniques have also confirmed that organisms such as certain Neisseria species, usually dismissed as 'oral commensals,' probably do drive disease and account for a significant proportion of 'negative' BAL samples.[51]

Quite how the 'healthy' microbiome of the conducting airway is maintained is unclear. A 'wash in, wash out' concept in which continual clearance through mucociliary clearance and macrophages is matched by replenishment by microaspiration is favoured by some,[52,53] but others believe that there is a stable local community that remains in equilibrium unless disturbed by events such as antibiotic therapy or acquisition of a pathogen.

Criteria for diagnosing biofilm-related disease remain challenging[39,40] and the implications of positive and 'negative' cultures will be discussed below.

Persistent bacterial bronchitis is neutrophil-dominated bronchitis

A neutrophil polymorphonuclear neutrophil (PMN)-dominated response leads to release of mediators such as elastase, myeloperoxidase and metalloproteases which drives mucus production and cough.[55] The inability of the PMNs to clear the bacteria biofilms leads to a chronic and persistent neutrophilic bronchitis which over time damages the conducting airways. Macrophages fail to cope with the intensity and persistence of the neutrophilia resulting in products such as DNA and myeloperoxidase from PMN nets and necrotic PMNs mixing with mucus altering it rheology and colour (the greater the neutrophil influx and death through necrosis the deeper the colour of the sputum ranging from yellow through to dark green).[56] The 'phlegm' resulting from this chronic suppuration maybe expectorated but more commonly is swallowed due to inability to expectorate in younger children and often due to embarrassment in older children (especially girls) who learn to quietly huff and swallow rather than cough loudly and expectorate.

Clinical symptoms – pattern recognition

The symptoms of a persistent bacterial endobronchial infection include a chronic cough, sleep disturbance and in many, a significant malaise due to both lack of high-quality sleep resulting from the coughing and the effects of chronic suppuration are attributable to the chronic inflammation.[27,31-33] They are often reported to 'wheeze' but this a typical misuse of the term.[27,57,58] Older individuals they may produce sputum but pre-school children general swallow any sputum. Just because they are young, it does not mean they have a different disease.

Recognising the condition is largely pattern recognition, as indeed it is for most conditions. History can suggest the likely diagnosis but is far from infallible.[27,30] The clinical features have been discussed elsewhere and hence will not be discussed in detail in this article.

Diagnosis

Diagnosis is confirmed in much the same way as a robust asthma diagnosis is established. A diagnosis of possible or probable asthma or endobronchial infection is made on the basis of the history and examination (though examination is often not particularly helpful). The diagnosis is only confirmed and becomes definite when there is a dramatic and unequivocal response to therapy.

For a diagnosis of asthma, the response may be an increase of >12%–15% in forced expiratory volume in one second following a selective β-agonist or complete resolution of wheeze and significant increased work of breathing within 10 min of a dose of a β-agonist. Similarly, a dramatic and unequivocal change in a child's symptoms after 6 weeks of an ICS should be sufficient. That is not *'they are coughing a bit less' 'they seem to be sleeping a bit better'* all of which may simply regression to the mean.

The parents report '*he is a new child*' '*I have my cheerful little girl back and we are all sleeping'*! Unfortunately, as much of diagnosis is based on an inadequate history and failure to truly understand the nature of the response if any to a given treatment, over- and under-diagnosis of asthma are still common place.[59,60]

For PBB, the typical response to treatment is slow when compared to the dramatic lysis with resolution of fever that occurs within 24 h of starting antibiotics in most patients with pneumococcal pneumonia (excepting those developing an empyema or necrotising pneumonia). Often there is a discernible difference at around a week, but the cough does not usually resolve until around 10–14 days. As such the point of review should be 14 days with the same criteria as for asthma – a dramatic change such that the parents report something along the lines of '*its amazing, he is not 'coughing for the first time in 9 months*', 'she is sleeping through the night and is so much happier, it is wonderful'.

Regression to the mean and other potential catches

The reason for seeking a dramatic and unequivocal response is that parents will generally seek help during an escalation of symptoms which with respiratory symptoms are generally associated with an intercurrent illness. If the physician chooses to do nothing other than reassure the mother and then reviews the patient in a couple of weeks, the patient will almost certainly have improved due to them *'regressing to the mean'* irrespective of whether they have asthma, PBB, both of these conditions or simply have a virus. For an asthmatic, this will be towards the day-to-day 'bother' commensurate with their normal level of control and severity;[61] for PBB, it will be towards their baseline level of coughing and sleep disturbance and for an otherwise healthy individual it will be to normal respiratory health unless they contract another respiratory virus in the interval.

It is all too easy to take credit for the improvement if one prescribes an intervention and thus be misled if we are not critical and demand a dramatic and unequivocal change to support our presumed diagnosis.

Recurrent chest infections

Physicians frequently fail to take an adequate history when a child is admitted with 'pneumonia' or 'recurrent chest infections'. One of the most important questions in the former is *'when was your child last completely well without any respiratory symptoms, in particular a cough'*, and in the latter *'was* he/she *completely well between episodes or did they get better but still have cough every day'*.

In the former, the 'pneumonia' may be an acute exacerbation of a chronic bronchitis (hence a 'bronchopneumonia') and later, when the child has developed bronchiectasis, the 'cause' will be attributed to 'post-pneumonic' bronchiectasis when in fact the problem was an on-going bacterial bronchitis that preceded and persisted after treatment of the 'pneumonia'. In those with recurrent 'chest infections,' the damage is much more likely to be attributable to the chronic inflammation manifest by the chronic cough than the acute flare-ups as is the case in patients with CF.

If the cough and symptoms completely resolve between episodes without aggressive antibiotic therapy, this makes PBB much less likely with recurrent viral infections and relatively mild asthma much more likely (mild asthma often presenting with viral-induced exacerbations which do not induce severe shortness of breath but whose symptoms can drag on for many weeks).

Timing and quality of cough

A 'wet' or 'productive' sounding cough suggest secretions within the airways. While those with a chronic bacterial bronchitis will typically have a 'wet' cough that can be compared with that of a chronic smoker *('does your child sound like a 60 a day smoker first thing in the morning?'* is often a much more informative question that is their cough dry or wet?), they can on occasions have a dry cough despite the presence of large amounts of secretions at bronchoscopy. Parental reporting of the quality of cough appears to be unreliable (unpublished data) and listening to the child cough where possible is the most important part of the examination. A wet cough is not entirely specific as it just indicates secretions and poorly controlled asthmatic or one recovering from a viral exacerbation may have a wet cough though typically the asthmatic cough is said to be dry and non-productive. Many children with viral infections will develop a wet sounding cough, but equally many appear to have a dry irritating cough with respiratory viruses. A persistent dry cough as assessed by both parents and physicians being likely to resolve over time.

The timing of a cough is also potentially informative with those having a chronic endobronchial infection typically worse when they first go to bed and first thing in the morning – the parents are aware they have woken up because of the coughing that precedes breakfast. However, a poorly controlled asthmatic whose symptoms are worse in the early hours may still be symptomatic as they get up from a disturbed nights' sleep.

As noted above, undue shortness of breath on exercise with some coughing is more common amongst asthmatics while severe coughing leading to difficulty catching one's breath is more likely to be due to airways suppuration, but the history can again be misleading.

Investigation and Management

Confirming the diagnosis

As noted above a clear, complete resolution of symptoms, including cough, at 14 days after commencing an appropriate antibiotic makes the diagnosis highly likely. For some, there is an incomplete response which maybe attributable to more severe disease (uncommon but does occur and occasionally symptoms require 2 weeks of intravenous antibiotics to resolve), poor adherence which appears to be relatively uncommon (parents are often desperate to find a solution and are highly motivated) or there is a comorbidity resulting in on-going symptoms.

For example, asthma and a persistent endobronchial infection can and do exist. Poor control of asthma results in impaired mucociliary clearance and thus predisposes to a PBB. Hence, the persistence of a 'wet' cough should raise the specter that either it is not asthma or if the patient has clearly been correctly diagnosed with asthma such as demonstrating marked reversibility but still has a persistent wet cough PBB should be considered as a possible co-morbidity.

'Difficult asthma' is due to one or more of three possibilities in the vast, vast majority of cases – (1) it is not asthma (2) it is asthma and something else that also causes respiratory symptoms (3) the patient is not taking their inhaled steroids effectively either because they are not taking >80% of doses or are not using their inhaler effectively-that is poor regimen and/or poor device adherence.

Investigations

There is no general consensus as to when and what to investigate. Given that the majority of cases resolve without sequel if treated aggressively, it would appear reasonable to defer investigations in an otherwise apparently healthy individual until the condition has relapsed two or three times after a prolonged course of antibiotics *providing* there are no other reasons for concern such as failure to thrive, unusually severe non-respiratory infections, history of inhaled foreign body, suspicion of aspiration or concern about airways abnormality with symptoms from birth or soon afterward. Significant conditions such as x-linked agammaglobulinaemia and other antibody deficiencies, variants of CF (particularly in countries without neonatal screening) and PCD can present in older pre-school and school-aged children and hence appropriate investigations should be considered when the setting appears atypical. Timing of investigations is also, in part influenced by parental wishes, some parents wanting investigations at the outset and others preferring to wait to see if the condition will resolve with treatment. Approaches to investigation have been discussed previously.

Treatment

This, as with so much in this neglected field, is largely an evidence-free zone. Treatment is aimed at eliminating the bacteria and permitting recovery of structure and function using antibiotics and physiotherapy which in most cases should result in a cure. The lung disease associated with CF is in large part due to the development of a persistent bacterial bronchitis. Unlike most patients with a PBB the underlying defect currently prevents a cure though with aggressive therapy the airways can often be kept free from significant suppuration for many years.

As noted above perhaps, the best guide to treatment is 'coughing is a clinical marker of inflammation'. If there is on-going inflammation at best the airways will not be repairing themselves and more at worst; there will be slowly progressive damage. If a child has an intercurrent viral the illness, any wet cough should have resolved within 10–14 days. The only published trial to date utilised a 2-week course with a number of those on placebo becoming cough free, and many of those on active treatment did not becoming cough free[62] calling into question the diagnosis. In long-term retrospective reports, relapse is common even if a longer initial course of 6 or 8 weeks is used.[27,63] These longer treatment courses are largely empirical being chosen as they appear to cover the period taken for cilia to recover following a viral respiratory tract infection.[63] However, in many cases the inflammation has persisted for months or years so recovery times for cilia obtained from previous health infants may not be relevant and longer courses may be optimal. The risk of not curing the bronchitis is long-term morbidity with the risk of treatment being largely the side effects of the antibiotics. Clearly prevention with early intervention is the goal, but this requires large community-based studies to determine whether advice such as *'do not give antibiotics for a cold but if the child still has a wet cough at 14 or 21 days treat with a 5 or 7 days course of antibiotics and ensure the cough resolves'* would strike the right balance.

Immunologists have long used 'prophylactic' antibiotics for prolonged periods presumably based on experience that their patients seem healthier on these without really understanding the role of the biofilm disease. Which antibiotic should be used is again unclear. Co-amoxiclav is widely used as the 'usual suspects', namely *S. pneumoniae*, NTHi and *Moraxella catarrhalis* are generally sensitive. In some areas, a macrolide such as azithromycin is widely used for 'convenience' in that once loaded some prescribe it 3x per week such as Monday/Wednesday/Friday to aid adherence, and others are attracted

by its 'anti-inflammatory' properties. However, resistance is a major issue in countries using relatively high quantities of macrolides, and this remains a concern for the individual as well as society.[64]

It is well known that adherence with treatment is poor in most therapeutic areas. This is one in which my experience is that parents do not delay contacting the medical team at the recurrence of a cough and this is presumably because the difference between the child with symptoms and the same child when cough free is so dramatic the parents are highly motivated.

The role of physiotherapy is unclear. In theory, it should be very helpful, but it requires greater commitment from parents than the antibiotic regimen. Some parents find it very helpful though usually it is only introduced if the cough reoccurs after one or two courses of treatment.

Natural history

The natural history of PBB and ill health associated with bronchiectasis has been discussed elsewhere.[31-33]

Summary

On-Going chronic bronchitis due to a persistent bacterial infection is a relatively common cause of chronic respiratory symptoms and morbidity in childhood[65,66] though its true prevalence in any setting is unclear due to lack of any robust prevalence data based on accurate diagnosis (the same is true of asthma). The lack of a simple diagnostic test means that pattern recognition and unequivocal response to treatment form the basis of a robust diagnosis (again this is no different to asthma). If a clinician is not aware of the condition, they can never make the diagnosis and failure to make an accurate diagnosis can result in chronic, often lifelong and unnecessary morbidity.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest

References

1. Laënnec RT. A Treatise on the Disease of the Chest. Paris: Brosson et Chande; 1819.
2. Weatherhead GH. Disease of the lungs. Considered Especially in Relation to the Particular Tissues Affected Illustrating the Different Kidns of Cough. London: John Churchill; 1823. p. 12-8.
3. West C. Lectures on the Diseses of Infancy and Childhood. London: Longmans, Green & Co.; 1875. p. 337-42.
4. Day WH. Disease of Children. London: J & A Churchill; 1885. p. 389-96.
5. Young FH. Chronic non-tuberculous infection of the lungs in children. Br Med J 1932;1:604-6.
6. Banks HS. Chronic pulmonary catarrh and fibrosis in school children. Tubercle 1933;14:385-9.
7. Smith TF, Ireland TA, Zaatari GS, Gay BB, Zwiren GT, Andrews HG, *et al.* Characteristics of children with endoscopically proved chronic bronchitis. Am J Dis Child 1985;139:1039-44.
8. Hastings TW, Niles WL. The bacteriology of sputum in common non-tuberculous infections of the upper and lower respiratory tracts, with special reference to lobar and broncho-pneumonia. J Exp Med 1911;13:638-51.
9. Gloyne SR. Pathology of bronchiectasis. Postgrad Med J 1926;1:174-5.
10. Patterson D, Moncrieff A. Diseases of Children. 4th ed., Vol. 1. London: Edward Arnold & Co.; 1947. p. 648-62.
11. Engel S. The pathogenesis of bronchial catarrh and of acute and chronic bronchitis. J Clin Pathol 1958;11:302-5.
12. Field CE. Bronchiectasis in childhood; clinical survey of 160 cases. Pediatrics 1949;4:21-46.
13. Field CE. Bronchiectasis in childhood; aetiology and pathogenesis, including a survey of 272 cases of doubtful irreversible bronchiectasis. Pediatrics 1949;4:231-48.
14. Field CE. Bronchiectasis in childhood; prophylaxis, treatment and progress with a follow-up study of 202 cases of established bronchiectasis. Pediatrics 1949;4:355-72.
15. Cole PJ. Inflammation: A two-edged sword – The model of bronchiectasis. Eur J Respir Dis Suppl 1986;147:6-15.
16. Cole P. The damaging role of bacteria in chronic lung infection. J Antimicrob Chemother 1997;40 Suppl A:5-10.
17. Field CE. Bronchiectasis. Third report on a follow-up study of medical and surgical cases from childhood. Arch Dis Child 1969;44:551-61.
18. Callahan CW, Redding GJ. Bronchiectasis in children: Orphan disease or persistent problem? Pediatr Pulmonol 2002;33:492-6.
19. Kolbe J, Wells AU. Bronchiectasis: A neglected cause of respiratory morbidity and mortality. Respirology 1996;1:221-5.
20. Everard ML. 'Recurrent lower respiratory tract infections' – Going around in circles, respiratory medicine style. Paediatr Respir Rev 2012;13:139-43.
21. Speight AN, Lee DA, Hey EN. Underdiagnosis and undertreatment of asthma in childhood. Br Med J (Clin Res Ed) 1983;286:1253-6.
22. Reid LM. Reduction in bronchial subdivision in bronchiectasis. Thorax 1950;5:233-47.
23. Nikolaizik WH, Warner JO. Aetiology of chronic suppurative lung disease. Arch Dis Child 1994;70:141-2.
24. Phelan PD, Landau LI, Robertson CF. Suppurative lung disease. In: Respiratory Illness in Children. 4th ed. Oxford, UK: Blackwell Scientific; 1994. p. 295-6.
25. Taussig LM, Smith SM, Blumenfeld R. Chronic bronchitis in childhood: What is it? Pediatrics 1981;67:1-5.
26. Seear M, Wensley D. Chronic cough and wheeze in children: Do they all have asthma? Eur Respir J 1997;10:342-5.
27. Donnelly D, Critchlow A, Everard ML. Outcomes in children treated for persistent bacterial bronchitis. Thorax 2007;62:80-4.
28. De Schutter I, De Wachter E, Crokaert F, Verhaegen J, Soetens O, Piérard D, *et al.* Microbiology of bronchoalveolar lavage fluid in children with acute nonresponding or recurrent community-acquired pneumonia: Identification of nontypeable *Haemophilus influenzae* as a major pathogen. Clin Infect Dis 2011;52:1437-44.
29. De Baets F, De Schutter I, Aarts C, Haerynck F, Van Daele S, De Wachter E, *et al.* Malacia, inflammation and bronchoalveolar lavage culture in children with persistent respiratory symptoms. Eur Respir J 2012;39:392-5.
30. Marchant JM, Masters IB, Taylor SM, Cox NC, Seymour GJ, Chang AB, *et al.* Evaluation and outcome of young children with chronic cough. Chest 2006;129:1132-41.
31. Craven V, Everard ML. Protracted bacterial bronchitis: Reinventing an old disease. Arch Dis Child 2013;98:72-6.
32. Kantar A, Chang AB, Shields MD, Marchant JM, Grimwood K, Grigg J, *et al.* ERS statement on protracted bacterial bronchitis in children. Eur Respir J 2017;50. pii: 1602139.
33. Ishak A, Everard ML. Persistent and recurrent bacterial bronchitis – A paradigm shift in our understanding of chronic respiratory disease. Front Pediatr 2017;5:19.
34. Verhagen LM, de Groot R. Recurrent, protracted and persistent lower respiratory tract infection: A neglected clinical entity. J Infect 2015;71 Suppl 1:S106-11.
35. Noffke N, Christian D, Wacey D, Hazen RM. Microbially induced sedimentary structures recording an ancient ecosystem in the ca

3.48 billion-year-old Dresser Formation, Pilbara, Western Australia. Astrobiology 2013;13:1103-24.
36. Flemming HC, Wingender J, Szewzyk U, Steinberg P, Rice SA, Kjelleberg S, *et al.* Biofilms: An emergent form of bacterial life. Nat Rev Microbiol 2016;14:563-75.
37. Flemming HC. EPS-then and now. Microorganisms 2016;4. pii: E41.
38. Kyd JM, McGrath J, Krishnamurthy A. Mechanisms of bacterial resistance to antibiotics in infections of COPD patients. Curr Drug Targets 2011;12:521-30.
39. Koo H, Allan RN, Howlin RP, Stoodley P, Hall-Stoodley L. Targeting microbial biofilms: Current and prospective therapeutic strategies. Nat Rev Microbiol 2017;15:740-55.
40. Høiby N, Bjarnsholt T, Moser C, Bassi GL, Coenye T, Donelli G, *et al.* ESCMID guideline for the diagnosis and treatment of biofilm infections 2014. Clin Microbiol Infect 2015;21 Suppl 1:S1-25.
41. Cuthbertson L, Rogers GB, Walker AW, Oliver A, Green LE, Daniels TW, *et al.* Respiratory microbiota resistance and resilience to pulmonary exacerbation and subsequent antimicrobial intervention. ISME J 2016;10:1081-91.
42. Lysenko ES, Ratner AJ, Nelson AL, Weiser JN. The role of innate immune responses in the outcome of interspecies competition for colonization of mucosal surfaces. PLoS Pathog 2005;1:e1.
43. Pettigrew MM, Gent JF, Revai K, Patel JA, Chonmaitree T. Microbial interactions during upper respiratory tract infections. Emerg Infect Dis 2008;14:1584-91.
44. Murphy TF, Bakaletz LO, Smeesters PR. Microbial interactions in the respiratory tract. Pediatr Infect Dis J 2009;28:S121-6.
45. Weiser JN. The pneumococcus: Why a commensal misbehaves. J Mol Med (Berl) 2010;88:97-102.
46. Weimer KE, Armbruster CE, Juneau RA, Hong W, Pang B, Swords WE, *et al.* Coinfection with *Haemophilus influenzae* promotes pneumococcal biofilm formation during experimental otitis media and impedes the progression of pneumococcal disease. J Infect Dis 2010;202:1068-75.
47. Bakaletz LO. Bacterial biofilms in the upper airway – Evidence for role in pathology and implications for treatment of otitis media. Paediatr Respir Rev 2012;13:154-9.
48. Reimche JL, Kirse DJ, Whigham AS, Swords WE. Resistance of non-typeable *Haemophilus influenzae* biofilms is independent of biofilm size. Pathog Dis 2017;75. pii: ftw112.
49. Chattoraj SS, Ganesan S, Jones AM, Helm JM, Comstock AT, Bright-Thomas R, *et al.* Rhinovirus infection liberates planktonic bacteria from biofilm and increases chemokine responses in cystic fibrosis airway epithelial cells. Thorax 2011;66:333-9.
50. Jensen RG, Johansen HK, Bjarnsholt T, Eickhardt-Sørensen SR, Homøe P. Recurrent otorrhea in chronic suppurative otitis media: Is biofilm the missing link? Eur Arch Otorhinolaryngol 2017;274:2741-7.
51. Cuthbertson L, Craven V, Bingle L, Cookson WO, Everard ML, Moffatt MF, *et al.* The impact of persistent bacterial bronchitis on the pulmonary microbiome of children. PLoS One 2017;12:e0190075.
52. Dickson RP, Erb-Downward JR, Huffnagle GB. Homeostasis and its disruption in the lung microbiome. Am J Physiol Lung Cell Mol Physiol 2015;309:L1047-55.
53. Bassis CM, Erb-Downward JR, Dickson RP, Freeman CM, Schmidt TM, Young VB, *et al.* Analysis of the upper respiratory tract microbiotas as the source of the lung and gastric microbiotas in healthy individuals. MBio 2015;6:e00037.
54. Marsh RL, Kaestli M, Chang AB, Binks MJ, Pope CE, Hoffman LR, *et al.* The microbiota in bronchoalveolar lavage from young children with chronic lung disease includes taxa present in both the oropharynx and nasopharynx. Microbiome 2016;4:37.
55. Gompertz S, Stockley RA. Inflammation – Role of the neutrophil and the eosinophil. Semin Respir Infect 2000;15:14-23.
56. Stockley RA, Bayley D, Hill SL, Hill AT, Crooks S, Campbell EJ, *et al.* Assessment of airway neutrophils by sputum colour: Correlation with airways inflammation. Thorax 2001;56:366-72.
57. Elphick H, Shirlock P, Foxall G, Primhak RA, Everard ML. Respiratory noises in early childhood – Misuse of the term wheeze by parents and doctor. Arch Dis Child 2001;84:35-9.
58. Elphick HE, Ritson S, Rodgers H, Everard ML. When a "wheeze" is not a wheeze: Acoustic analysis of breath sounds in infants. Eur Respir J 2000;16:593-7.
59. Looijmans-van den Akker I, van Luijn K, Verheij T. Overdiagnosis of asthma in children in primary care: A retrospective analysis. Br J Gen Pract 2016;66:e152-7.
60. Yang CL, Simons E, Foty RG, Subbarao P, To T, Dell SD, *et al.* Misdiagnosis of asthma in schoolchildren. Pediatr Pulmonol 2017;52:293-302.
61. Reddel H, Ware S, Marks G, Salome C, Jenkins C, Woolcock A, *et al.* Differences between asthma exacerbations and poor asthma control. Lancet 1999;353:364-9.
62. Marchant J, Masters IB, Champion A, Petsky H, Chang AB. Randomised controlled trial of amoxycillin clavulanate in children with chronic wet cough. Thorax 2012;67:689-93.
63. Pritchard MG, Lenney W, Gilchrist FJ. Outcomes in children with protracted bacterial bronchitis confirmed by bronchoscopy. Arch Dis Child 2015;100:112.
64. Hare KM, Grimwood K, Chang AB, Chatfield MD, Valery PC, Leach AJ, *et al.* Nasopharyngeal carriage and macrolide resistance in indigenous children with bronchiectasis randomized to long-term azithromycin or placebo. Eur J Clin Microbiol Infect Dis 2015;34:2275-85.
65. Faniran AO, Peat JK, Woolcock AJ. Measuring persistent cough in children in epidemiological studies: Development of a questionnaire and assessment of prevalence in two countries. Chest 1999;115:434-9.
66. Cook DG, Strachan DP. Health effects of passive smoking 3. Parental smoking and prevalence of respiratory symptoms and asthma in school age children. Thorax 1997;52:1081-94.

Friso 美素佳兒

FRISO® with Natural Nutrient* Support Digestion

FRISO® Gold with LockNutri®

Lower levels of glycated and aggregated protein which supports healthy gut to maintain its role as immune barrier of the body[1-7]

Native protein

FRISO® use LockNutri® to preserve the native structure of protein

Aggregated protein

FRISO® assists digestion by containing lower levels of aggregated and glycated protein

* Natural nutrient refers to protein, one of the main nutrients in milk

References: 1. Data on file. FrieslandCampina Global Development Nutrition, Scientific product substantiation paper, MBW_019, 1.0, March 2015. **2.** Rudloff S, Lönnerdal B. J Pediatr Gastroenterol Nutr. 1992;15(1):25-33. **3.** Lindberg T, et al. J Pediatr Gastroenterol Nutr. 1998;27(1):30-36. **4.** Pischetsrieder M, Henle T. Amino Acids 2012;42(4):1111-1118. **5.** Dupont D, et al. Food Dig. 2010;1:28-39. **6.** Seiquer I, et al. Am J Clin Nutr. 2006;83(5):1082-1088. **7.** Internal data from FrieslandCampina. 2014.

Breastfeeding is the best nutrition for healthy growth and development of babies.

For medical professionals' reference only.

NEW

nose friendly®

Nose Friendly Products

Superior nasal function - no harmful preservatives - no stinging or burning

ALL PRESERVATIVE FREE

New formulations to optimise nasal epithelial function

flo® Sinus Care Starter Kit

- Recommended for congestion from Acute Sinusitis, Chronic Sinusitis and Allergies
- Also ideal for Post Operative care
- **Preservative and Medication FREE**
- Isotonic - No Sting formula
- More gentle than concentrated salt solutions
- May be used during pregnancy

flo® Baby Saline+ Nasal Spray

- Recommended for Infants' blocked nose
- 15mL pack size
- **Sterile and Preservative FREE**
- Isotonic - No Sting formula
- **Sprays at any angle**
- Quick and easy to use
- Comfy for baby and parents

flo® Refill 50

- Recommended for congestion from Acute Sinusitis, Chronic Sinusitis, Allergies and Post Operative care
- Refill pack - 50 sachets pack size for on-going and long term use
- **Preservative and Medication FREE**
- Isotonic - No Sting formula
- More gentle than concentrated salt solution

flo® Kids Saline+ Nasal Spray

- Recommended for children from 5 years of age and older with blocked nose
- 15mL pack size
- **Sterile and Preservative FREE**
- Isotonic - No Sting formula
- **Sprays at any angle**
- Quick and easy to use
- Children who are involved in their own treatment are often happier and more operative, making them easier to treat

flo® CRS Starter Kit

- Specially formulated
  - Xylitol: high grade hydration for airway surface
  - low in sodium & potassium factors in nasal & sinus tissue
- Suitable for people concern about chronic sinusitis.
- **Preservative and Medication FREE**
- Isotonic - No Sting formula
- May be used during pregnancy

flo® Saline+Plus Nasal Spray

- Recommended for Colds and Flu, Rhinitis, Sinusitis, Hay fever, Blocked nose caused by pregnancy.
- Post Operative use
- 30mL pack size
- **Sterile and Preservative FREE**
- Isotonic - No Sting formula
- Includes added minerals

You Tube : How to wash your sinuses with FLO Sinus Care

You Tube : How to clear baby's blocked nose with FLO Baby

Further product information is available upon request from:

Sino-Asia Pharmaceutical Supplies Ltd.

Tel: (852) 2573 1400 Fax: (852) 2575 0826 Whatsapp: (852) 6127 0206

Email: info@sinoasia.com.hk website: http://www.sinoasia.com.hk

Review Article

Primary Spontaneous Pneumothorax in Children: A Literature Review

Ping-Yang Kuo[1], Bao-Ren Nong[2,3], Yung-Feng Huang[2,3], Yee-Husan Chiou[2]

[1]Department of Pediatrics, Kaohsiung Veterans General Hospital, [2]Division of Pediatric Allergy, Immunology and Rheumatology/Pulmonology, Department of Pediatrics, Kaohsiung Veterans General Hospital, Zuoying District, Kaohsiung City, [3]Department of Pediatrics, National Defense Medical Center, Tri-Service General Hospital, Taipei, Taiwan

Abstract

Studies about primary spontaneous pneumothorax (PSP) in pediatric patients are not as many as in adult patients since the incidence of PSP is lower in children than in adults. There are evidence-based guidelines for the management of PSP in adults, whereas, in children, the approach of PSP is mainly extrapolated from the adult guideline. In this article, aspects of incidence rate, epidemiology, and pathophysiology, diagnosis, management, and recurrence rate about pediatric PSP are discussed.

Keywords: Children, primary spontaneous pneumothorax, recurrence, Video-Assisted Thoracic Surgery(VATS)

Introduction

Pneumothorax is defined as the accumulation of air in pleural cavity that results in partial or complete collapse of lung. It is an uncommon disorder in children under 18 years of age. The peak age of occurrence in pediatric population is either in neonatal period or late adolescent period. Pneumothorax can be categorized into spontaneous or traumatic. Spontaneous pneumothorax can be further divided into primary and secondary type. Secondary spontaneous pneumothorax arises from preexisting lung disease, such as asthma, cystic fibrosis, or interstitial lung disease [Table 1].[1]

Compared to adults, studies of primary spontaneous pneumothorax (PSP) in pediatric population are scarce. Furthermore, there is no consensus about the management of PSP in children. The aim of this article is to give a literature review of PSP in children under 18 years of age, mainly focused on its epidemiology, diagnosis, management strategy, and recurrence rate in pediatric population.

Epidemiology

The incidence of PSP in the pediatric population is 3.4/100,000 children.[2] There is a male predominance in this disorder, with a male-to-female ratio ranging from 2:1 to 9:1.[3,4] In pediatric studies, the peak age of incidence occurs between 14 and 17 years of age, mainly in late teenagers. The affected patients typically showed tall, thin habitus. In some previous studies, the mean Body Mass Index (BMI) was around 18 kg/m^2, which is classified as underweight.[5] It may be explained by that these tall, slim children tend to have higher transpulmonary pressure at lung apex, and their rapid growth relative to pulmonary vasculature may result in ischemia and thus blebs formation at these regions.[6] In a retrospective study including 171 adolescents, only 34% had underweight BMI.[3] Meanwhile, Noh *et al*. showed that there was no apparent relationship between BMI and PSP recurrence rate.[7]

Pathophysiology

In spontaneous pneumothorax, the air leaks through visceral pleural, which may be caused by an acute increase in transpulmonary pressure or defects in visceral pleural. Apical bullae and subpleural blebs are found in the majority of PSP patients.[8-11] In adult studies, subpleural bleb or bullae (usually on the apical portion of the upper lobe) are found in

Address for correspondence: Dr. Bao-Ren Nong, Department of Pediatrics, Kaohsiung Veterans General Hospital, No.386, Dajhong 1st Rd., Zuoying Dist., Kaohsiung City 81362, Taiwan.
E-mail: brnong@gmail.com

Access this article online

Quick Response Code:

Website: www.prccm.org

DOI: 10.4103/prcm.prcm_3_18

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Kuo PY, Nong BR, Huang YF, Chiou YH. Primary spontaneous pneumothorax in children: A literature review. Pediatr Respirol Crit Care Med 2018;2:25-31.

Table 1: Causes of secondary pneumothorax in children

Etiology	Disease
Airway disease	Asthma
	Cystic fibrosis
	Chronic obstructive pulmonary disease
Infection	Necrotizing pneumonia, tuberculosis
	Pneumocystis jirovecii
Congenital malformations	Congenital cystic adenomatoid malformation
	Congenital lobar emphysema
Connective tissue disease	Marfan syndrome
	Ehlers–Danlos syndrome
Interstitial lung disease	Sarcoidosis
	Langerhans cell granulomatosis
Malignancy	Lung cancer, metastasis
Aspiration	Foreign body aspiration
endometriosis	Catamenial pneumothorax

76%–100% of patients during VATS and in nearly all patients during thoracotomy.[6] In the study of Shih *et al*., 91.3% (21 of 23) PSP were found to have apical blebs in operation. Lopez *et al*., 98% (59 of 60) identified blebs/bullae during the operation.[6,8] While the exact pathogenesis of PSP remains unclear, rupture of blebs/bullae in lung tissue that causing air to leak into pleural space may be the possible reasons.

While many reports revealed that smoking is a major risk factor in adults PSP, the situation is not the same in children. The study of Chiu *et al*. found that only 22% of adolescent patients with PSP were smokers in their study.[3] This may be explained by the prevalence of smokers in children is low, compared to adults.[3]

Clinical Features

PSP occurred most often when the patient was at rest. A small pneumothorax may be asymptomatic, whereas large pneumothorax may present with acute chest pain, dyspnea, chest tightness, cough, back pain, and ipsilateral shoulder pain. Physical examination usually revealed diminished breath sounds and hyper-resonant percussion over the affected side of the lung. If signs of hemodynamic comprise such as tachycardia, hypotension, and cyanosis were noted, tension pneumothorax showed be considered, and emergent needle decompression may be needed.

Diagnosis

Pneumothorax is mainly diagnosed by symptoms, physical examination, and chest radiography. The size of pneumothorax can be measured from X-ray film. In adults, a large pneumothorax is defined as ≥3 cm of air between the pleural line and apical chest wall (apex-to-cupola distance), or ≥2 cm between the entire lateral lung edge and the chest wall, at the level of hilum.[12,13]

To calculate the volume of pneumothorax, Light method, Rhea method, and Collins method were used in adult patients.[14-16]

Till date, no standard method had been developed for measuring the size of pneumothorax in the pediatric population. Guideline from the British Thoracic Society (BTS), American College of Chest Physicians (ACCP), and the foresaid methods may be suitable for adolescent patients. For younger children, small or large pneumothorax is usually determined by the relative size of pneumothorax compared to the whole chest cavity.

Management

While the ACCP and the BTS had published guidelines for the management of pneumothorax in adult patients, management of pneumothorax in children has not been standardized. We summarized the management of pneumothorax in children based on several retrospective studies.

Management of pneumothorax includes observation, supplemental oxygen, needle aspiration, thoracostomy tube, and surgical intervention with either video-assisted thoracic surgery (VATS) or open thoracotomy plus pleurodesis.

According to BTS 2010 guideline, observation is the treatment of choice for small PSP without significant breathlessness.[12] Up to 80% of pneumothoraces estimated as smaller than 15% have no persistent air leak.[12] Supplemental oxygen may accelerates the reabsorption of air by the pleura.[17]

PSPs that are large (involving ≥15% of the hemithorax) or progressive may be drained by simple aspiration with a plastic intravenous catheter, thoracentesis catheter, or small-bore (7–14 French) catheter or by the insertion of a chest tube.[17] In a study by Lee *et al*., the success rates of needle aspiration and chest tube as primary treatments for PSP (small and large) in children were 78% and 67%, respectively, indicating comparable success rates with both interventions. Besides, the overall success rate of conservative treatment (including observation, needle aspiration, and chest tube insertion) for the first episode of PSP was 80% in the foresaid study. Thus, the authors concluded that for most patients with the first episode PSP, conservative treatment with either observation thoracocentesis or tube thoracostomy were suitable.[18]

However, Soccorso *et al*. suggested that for large PSP in children, initially tube thoracostomy may be better than needle aspiration because 53% initially managed with needle aspiration eventually required chest tube drainage.[19]

Even though most PSP can be initially managed successfully with conservative treatment like needle aspiration or tube thoracostomy, several studies showed that children had a higher recurrence rate than adults after nonoperative treatment of PSP [Table 2]. In adult study, the recurrence rate of PSP was 30%.[17] However, for pediatric PSP, 40%–60% recurrence rate after nonoperative treatment was reported.[18,13,26,27-31] William *et al*. showed that for patients initially managed with chest tube, 49.7% ultimately require operative intervention.[24,32] Soccorso *et al*. found that most cases with large PSP were identified to have blebs/bulla as their cause for their PSP, and the recurrence rate was high after nonoperative management.

Table 2: Data of reported case series of pediatric primary spontaneous pneumothorax

Study	Institution	*n* Males/female ratio	Periods of study	Age (years of age)	Side of pneumothorax *n*=Right/left/both	Percentage of blebs or bulla identified during CT scan or operation (VATS)	BMI (kg/m^2)	Recurrence rate after nonoperative treatment	Recurrence rate after VATS treatement
Cook *et al.*, 1999[5]	Departments of Surgery, The Ohio State University Hospitals and Columbus Children's Hospitals	*n*=15 4:1	6 years (1991-1996)	Mean: 14.8	67% left side pneumothorax	N/A	Mean: 18	57%	9%
Qureshi *et al.*, 2005[20]	Division of Pediatric Surgery, Children's Hospital of Pittsburgh and the School of Medicine	*n*=43 4:1	13 years (1991-2003)	Mean: 15.9	Right: left=4:5	OP: 80% blebs	N/A	54%	11.7%
Butterworth *et al.*, 2007[21]	the British Columbia Children's Hospital	*n*=31 (male=24, female=7) 3.4:1	11 years (1993-2003)	Mean: 14.3 (range: 7-17)	N/A	N/A	N/A	61%	10%
Bialas *et al.*, 2008[10]	Division of Pediatric Surgery, Department of Surgery, University of North Carolina	*n*=32 3.6:1	9 years (1999-2007)	Mean: 16.5	Right: left=14:18	CT: 76% blebs VATS: 95% blebs	Mean: 20.2	N/A	5%
Zganjer *et al.*, 2010[9]	Department of Pediatric Surgery, Children's Hospital Zagreb, Zagreb, Croatia	*n*=16 (male=12, female=4) 3:1	7 years	Mean: 15.4 (range: 11-18)	9/6/1	CT scan: 75% (apical bulla predominant)	N/A	N/A	9%
Lee *et al.*, 2010[18]	United Christian Hospital, Kwun Tong, Hong Kong: Department of Pediatrics and Adolescent Medicine	*n*=77 10:1	8 years (1999-2007)	Mean: 16 (range 14-18)	N/A	VATS found 70%	N/A	27%	11%
Shih *et al.*, 2011[6]	Division of Pediatrics, Cheng Ching General Hospital, Taichung, Taiwan	*n*=78 7.7:1	6 years (2004-2009)	Mean: 16.76 (range: 15-18)	34/43/1	Among 23 patients received VATS, apical blebs in 21 patients (91.3%) 2 patients had blebs over lower lobe	Mean: 18.2	35.9%	21.7%

Contd...

Table 2: Contd...

Study	Institution	*n* Males/female ratio	Periods of study	Age (years of age)	Side of pneumothorax *n*=Right/left/both	Percentage of blebs or bulla identified during CT scan or operation (VATS)	BMI (kg/m^2)	Recurrence rate after nonoperative treatment	Recurrence rate after VATS treatement
Choi *et al.*, 2013[22]	Department of Thoracic and Cardiovascular Surgery, Uijeongbu St. Mary's Hospital, The Catholic University of Korea, College of Medicine, Seoul, Korea	Children group (under 17 years) *n*=126 (8.7:1) Young adult group (18-29 years) *n*=155 (7.6:1)	6 years (2005-2011)	Children group (under 17 years) Mean: 15.9 year Young adult group (18-29 years) Mean: 21.9 year	N/A	N/A	Children group (under 17 years) Mean: 18.6 Young adult group (18-29 years) Mean: 19.8	N/A	Children group (under 17 years) 10.6% Young adult group (18-29 years) 3.9%
Chiu *et al.*, 2014[3]	Department of Pediatrics, Chang Gung Memorial Hospital, Keelung, Taiwan	*n*=171 9:1	13 years (2000-2012)	Mean: 17.6	37/57/6%	CT: 53% had bulla	34% had underweight BMI	18%	4%
Lopez *et al.*, 2014[8]	Division of Pediatric Surgery, Michael E. DeBakey Department of Surgery, Baylor College of Medicine, Houston, TX, USA	*n*=96 4:1	6 years (2005-2011)	Mean: 16.4	N/A	CT: 60% blebs OP: 98% blebs	Mean: 18.8	40%	14.6%
Matuszczak *et al.*, 2015[11]	Pediatric Surgery Clinic, Medical University of Bialystok, Poland	*n*=22 (male=18, female=4) 4.5:1	10 years (2004-2014)	Mean: 16 (range: 14-17)	13/9/0	CT scan: Apical blebs (6/11) (54.5%)	Mean: 20.1	48%	N/A
Noh *et al.*, 2015[7]	Department of Thoracic and Cardiovascular Surgery, Gangnam Severance Hospital, Yonsei University, College of Medicine, Seoul, Republic of Korea	*n*=517 10:1 Group A: 114 (≤16 years) Group B: 180 (17-18 years) Group C: 223 (≥19 years)	5 years (2006-2010)	N/A	Group A Nonsurgical: 14:32 Surgical: 36:31 Group B Nonsurgical: 36:41 Surgical: 56:82	N/A	Group A Nonsurgical: 18.78 Surgical: 18.33 Group B Nonsurgical: 18.61 Surgical: 24.02	Group A (≤16 years) 45.7% Group B, (17-18 years) 51.9% Group C (≥19 years) 47.7%	Group A (≤16 years) 27.9% Group B, (17-18yrs) 16.5% Group C (≥19 years) 13.2%

Contd...

Table 2: Contd...

Study	Institution	*n* Males/female ratio	Periods of study	Age (years of age)	Side of pneumothorax *n*=Right/left/both	Percentage of blebs or bulla identified during CT scan or operation (VATS)	BMI (kg/m^2)	Recurrence rate after nonoperative treatment	Recurrence rate after VATS treatement
Soccorso *et al.*, 2015[19]	Department of Paediatric Surgery, Birmingham Children's Hospital	*n*=50 6:1	11 years (2004-2015)	Mean: 14	N/A	CT: 75% had apical blebs (37/49) Visible blebs/bulla at thoracoscopy: 78% (43/55) Histology confirmed blebs/bulla: 100% (55/55)	N/A	36%	11%
Ciriaco *et al.*, 2016[23]	1 Department of Thoracic Surgery, Scientific Institute and University VitaSalute O San Raffaele, Milan, Italy.	*n*=58 5:1	17 years (1998-2014)	Mean: 16.6	18/40	N/A	N/A	N/A	12.1%
Williams *et al.*, 2018 (multicenter review including 36 pediatic hospitals)[24]	Division of Pediatric Surgery, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, Illinois.	*n*=1040 4:1	5 years (2010-2014)	Mean: 15.7	N/A	N/A	N/A	N/A	N/A
Williams *et al.*, 2017[25]	Ann and Robert H. Lurie Children's Hospital of Chicago	*n*=46 9:1	9 years (2007-2015)	Mean: 16.1	70% left side	CT: 79% had blebs	N/A	N/A	N/A

N/A: Not available, VATS: Video-assisted thoracic surgery, BMI: Body mass index, CT: Computed tomography, OP: Operation

The author concluded that recurrent or first episode of large PSP requires computed tomography (CT) evaluation and surgical treatment after initial management with needle aspiration/tube drainage.[19]

Furthermore, for patients managed initially with chest tube alone, the probability of subsequent surgery was >50% if they were hospitalized for over 4 days.[25] In the treatment algorithm for PSP in children by Zganjer *et al*., they started with intercostals tube catheter drainage, aspiration, and observation. If there was a significant air leak that did not stop for 5–6 days, VATS with mechanical pleurodesis was indicated.[9]

The ACCP recommends surgery for adults with air leaks lasting longer than 4 days and for recurrent spontaneous pneumothorax. The optimal timing to shift from tube thoracostomy to VATS in the management of pediatric PSP remains unclear, 3–7 days were reported.[9,21,24] Butterworth *et al*. suggested that air leaks that persist for longer than 3 days are unlikely to close spontaneously, and thus VATS may be indicated in these patients.[21] Noh *et al*. suggested that if air leaks persisted for 4 days, bullae or blebs were seen on CT scans, or ipsilateral pneumothorax recurred, wedge resection by VATS was performed.[7]

Chiu *et al*. showed that a large-size pneumothorax with a persistent air leak was the most significant factor for proceeding to VATS surgery. In addition, it was a significant factor for the recurrence of PSP (P = 0.014).[3] Thus, for children with PSP initially managed with tube thoracostomy, early surgical intervention like VATS is needed for persistent air leak. VATS is a safe and effective procedure for PSP in pediatric patients.[25] A retrospective study showed early VATS decreases hospital length of stay, charges, and readmissions.[24]

While CT scan can help to identify the pathology of lung such as blebs/bullae, causes of PSP in most patients, the correlation with intraoperative findings and role in guiding management remains unclear.[8] In a study by Lopez *et al*., blebs were detected only in 60% of patients who underwent CT scan, whereas 98% of patients who underwent operations were found to have blebs during operation.[8] There was no evidence to support prophylactic VATS in asymptomatic patients with blebs detected during CT scan.[8] For CT scan, radiation exposure and cost also need to be considered. Currently, most studies showed that routine use of HRCT in adolescent patients with PSP was not necessarily.[3] For large PSP or recurrent PSP, CT scan may be indicated to verify possible pathological structure of lung, and help to guide surgical management.[32]

Considering the high recurrence rate of PSP in children managed with conservative treatment, some advocated surgical intervention with VATS as the initial treatment plan, rather than performed after the failure of tube thoracostomy, may bring the benefit of shorter length of stay with lower cost and recurrence rate. However, some studies did not support this point of view.[20]

In the study by Cook *et al*., the author concluded that a cost-effective treatment strategy for pediatric PSP is tube thoracostomy at first presentation, followed by VATS with thoracoscopic bleb resection. This approach can minimize the number of unnecessary operations.[5]

Qureshi *et al*. in 2005 revealed that morbidity from recurrent pneumothorax after VATS occurred more frequently after primary VATS (VATS performed as initial treatment) than secondary VATS (VATS performed after nonoperative treatment failure), and the overall cost is higher in primary VATS. The authors concluded that the increased morbidity and cost did not justify a of primary VATS blebectomy/pleurodesis in children with spontaneous pneumothorax.[20]

Lopez *et al*. also suggested initial management with pleural catheter drainage, and early surgical intervention in the setting of failure of conservative management to achieve full resolution of persistent air leaks in pediatric patients with spontaneous pneumothorax.[8]

The recurrence rate of PSP in children after VATS procedure was reported as 4%–20% [Table 2], and it appeared that recurrence of PSP after surgery was more frequent in children than in adolescents or young adults.[33] Choi *et al*. reported that the recurrence rate of PSP after VATS was significantly higher in the children's group (<17 years) than the young adult group (10.6 vs. 3.9%, P = 0.032).[33] Noh *et al*. also showed that the recurrence rate after wedge resection in patients aged ≤16 years was higher than that in older patients, and suggested that wedge resection might be delayed in children.[7] This finding may be due to the fact that children are still growing, and are more likely to have newly formed blebs/bullae in lung tissue, compared to adults.[33]

For PSP management, VATS with either mechanical or chemical pleurodesis is often performed by the surgeon. Pleurodesis can prevent postoperative air leak from staple lines, and help to prevent future pneumothorax by producing adherence of the lung and pleural cavity.[10]

Preventive operation for the contralateral blebs or bulla in asymptomatic patients remains controversial since the risk of development of PSP in these patients was unknown in pediatric practice. Martinez-Ramos *et al*. did not find an association between the presence or absence of bullae and the recurrence of PSP.[34] Sahn *et al*. concluded that the presence of bullae should not guide decision-making regarding prevention of recurrence.[17] Ciriaco *et al*. also suggested that VATS should be considered only for the affected side.[23]

However, in the study of Soccorso *et al*., 20% (number 10/49) of patients had asymptomatic contralateral blebs/bulla detected on CT scan. Among these children, 40% developed pneumothorax within 6 months.[19] Thus, there was a degree of risk in these patients if contralateral blebs/bulla was detected, and patients should be well-informed about this situation.

Conclusion

The incidence of PSP in pediatric population was 3.4/100,000 children, with male predominance.

In pediatric studies, the peak age of incidence occurs between 14 and 17 years of age. Apical bullae or subpleural blebs are found in the majority of PSP among teenagers and adults. Routine use of HRCT in adolescent patients with PSP is not necessarily. CT should be reserved for large or recurrent PSP.

The recurrence rate of PSP in children after nonoperative treatment is 40%–60%. The optimal timing to shift from tube thoracostomy to VATS in the management of pediatric PSP remains unclear, from 3 to 7 days had been reported. The recurrence rate of PSP in children after VATS was reported as 4%–20%. The recurrence of PSP after surgery is more frequent in children than in adolescents or young adults. Preventive operation for the contralateral blebs or bulla in asymptomatic patients remains controversial. Currently, experts suggest VATS should be considered only for the affected side.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Taussig LM. Pediatric Respiratory Medicine. 2nd ed. St. Louis: Mosby-Year Book Inc.; 2008.
2. Dotson K, Timm N, Gittelman M. Is spontaneous pneumothorax really a pediatric problem? A national perspective. Pediatr Emerg Care 2012;28:340-4.
3. Chiu CY, Chen TP, Wang CJ, Tsai MH, Wong KS. Factors associated with proceeding to surgical intervention and recurrence of primary spontaneous pneumothorax in adolescent patients. Eur J Pediatr 2014;173:1483-90.
4. Robinson PD, Cooper P, Ranganathan SC. Evidence-based management of paediatric primary spontaneous pneumothorax. Paediatr Respir Rev 2009;10:110-7.
5. Cook CH, Melvin WS, Groner JI, Allen E, King DR. A cost-effective thoracoscopic treatment strategy for pediatric spontaneous pneumothorax. Surg Endosc 1999;13:1208-10.
6. Shih CH, Yu HW, Tseng YC, Chang YT, Liu CM, Hsu JW, *et al*. Clinical manifestations of primary spontaneous pneumothorax in pediatric patients: An analysis of 78 patients. Pediatr Neonatol 2011;52:150-4.
7. Noh D, Lee S, Haam SJ, Paik HC, Lee DY. Recurrence of primary spontaneous pneumothorax in young adults and children. Interact Cardiovasc Thorac Surg 2015;21:195-9.
8. Lopez ME, Fallon SC, Lee TC, Rodriguez JR, Brandt ML, Mazziotti MV, *et al*. Management of the pediatric spontaneous pneumothorax: Is primary surgery the treatment of choice? Am J Surg 2014;208:571-6.
9. Zganjer M, Cizmić A, Pajić A, Cigit I, Zganjer V. Primary spontaneous pneumothorax in pediatric patients: Our 7-year experience. J Laparoendosc Adv Surg Tech A 2010;20:195-8.
10. Bialas RC, Weiner TM, Phillips JD. Video-assisted thoracic surgery for primary spontaneous pneumothorax in children: Is there an optimal technique? J Pediatr Surg 2008;43:2151-5.
11. Matuszczak E, Dębek W, Hermanowicz A, Tylicka M. Spontaneous pneumothorax in children – Management, results, and review of the literature. Kardiochir Torakochirurgia Pol 2015;12:322-7.
12. MacDuff A, Arnold A, Harvey J; BTS Pleural Disease Guideline Group. Management of spontaneous pneumothorax: British Thoracic Society Pleural Disease Guideline 2010. Thorax 2010;65 Suppl 2:ii18-31.
13. Baumann MH, Strange C, Heffner JE, Light R, Kirby TJ, Klein J, *et al*. Management of spontaneous pneumothorax: An American College of Chest Physicians Delphi consensus statement. Chest 2001;119:590-602.
14. Noppen M, Alexander P, Driesen P, Slabbynck H, Verstraete A; Vlaamse Werkgroep voor Medische Thoracoscopie en Interventionele Bronchoscopie, *et al*. Quantification of the size of primary spontaneous pneumothorax: Accuracy of the light index. Respiration 2001;68:396-9.
15. Rhea JT, DeLuca SA, Greene RE. Determining the size of pneumothorax in the upright patient. Radiology 1982;144:733-6.
16. Collins CD, Lopez A, Mathie A, Wood V, Jackson JE, Roddie ME, *et al*. Quantification of pneumothorax size on chest radiographs using interpleural distances: Regression analysis based on volume measurements from helical CT. AJR Am J Roentgenol 1995;165:1127-30.
17. Sahn SA, Heffner JE. Spontaneous pneumothorax. N Engl J Med 2000;342:868-74.
18. Lee LP, Lai MH, Chiu WK, Leung MW, Liu KK, Chan HB, *et al*. Management of primary spontaneous pneumothorax in Chinese children. Hong Kong Med J 2010;16:94-100.
19. Soccorso G, Anbarasan R, Singh M, Lindley RM, Marven SS, Parikh DH, *et al*. Management of large primary spontaneous pneumothorax in children: Radiological guidance, surgical intervention and proposed guideline. Pediatr Surg Int 2015;31:1139-44.
20. Qureshi FG, Sandulache VC, Richardson W, Ergun O, Ford HR, Hackam DJ, *et al*. Primary vs. delayed surgery for spontaneous pneumothorax in children: Which is better? J Pediatr Surg 2005;40:166-9.
21. Butterworth SA, Blair GK, LeBlanc JG, Skarsgard ED. An open and shut case for early VATS treatment of primary spontaneous pneumothorax in children. Can J Surg 2007;50:171-4.
22. Choi SY, Kim YH, Jo KH, Kim CK, Park JK, Cho DG, *et al*. Video-assisted thoracoscopic surgery for primary spontaneous pneumothorax in children. Pediatr Surg Int 2013;29:505-9.
23. Ciriaco P, Muriana P, Bandiera A, Carretta A, Melloni G, Negri G, *et al*. Video-assisted thoracoscopic treatment of primary spontaneous pneumothorax in older children and adolescents. Pediatr Pulmonol 2016;51:713-6.
24. Williams K, Oyetunji TA, Hsuing G, Hendrickson RJ, Lautz TB. Spontaneous pneumothorax in children: National management strategies and outcomes. J Laparoendosc Adv Surg Tech A 2018;28:218-22.
25. Williams K, Lautz TB, Leon AH, Oyetunji TA. Optimal timing of video-assisted thoracoscopic surgery for primary spontaneous pneumothorax in children. J Pediatr Surg 2017. pii: S0022-3468(17)30767-4.
26. Sadikot RT, Greene T, Meadows K, Arnold AG. Recurrence of primary spontaneous pneumothorax. Thorax 1997;52:805-9.
27. Chiu HY, Hsiao KF, Huang SC, Tsai LY, Lin CY. Clinical study of primary spontaneous pneumothorax in children. Changhua J Med 2005;10:82-5.
28. Withers JN, Fishback ME, Kiehl PV, Hannon JL. Spontaneous pneumothorax. Suggested etiology and comparison of treatment methods. Am J Surg 1964;108:772-6.
29. Poenaru D, Yazbeck S, Murphy S. Primary spontaneous pneumothorax in children. J Pediatr Surg 1994;29:1183-5.
30. Wilcox DT, Glick PL, Karamanoukian HL, Allen JE, Azizkhan RG. Spontaneous pneumothorax: A single-institution, 12-year experience in patients under 16 years of age. J Pediatr Surg 1995;30:1452-4.
31. Choudhary AK, Sellars ME, Wallis C, Cohen G, McHugh K. Primary spontaneous pneumothorax in children: The role of CT in guiding management. Clin Radiol 2005;60:508-11.
32. O'Lone E, Elphick HE, Robinson PJ. Spontaneous pneumothorax in children: When is invasive treatment indicated? Pediatr Pulmonol 2008;43:41-6.
33. Young Choi S, Beom Park C, Wha Song S, Hwan Kim Y, Cheol Jeong S, Soo Kim K, *et al*. What factors predict recurrence after an initial episode of primary spontaneous pneumothorax in children? Ann Thorac Cardiovasc Surg 2014;20:961-7.
34. Martínez-Ramos D, Angel-Yepes V, Escrig-Sos J, Miralles-Tena JM, Salvador-Sanchís JL. Usefulness of computed tomography in determining risk of recurrence after a first episode of primary spontaneous pneumothorax: therapeutic implications. Arch Bronconeumol. 2007; 43:304-8.

Correlation between 6-min Walk Test and Cardiopulmonary Exercise Test in Chinese Patients

Pik-Fung Wong, Eric Yat-Tung Chan, Daniel Kwok-Keung Ng, Ka-Li Kwok, Ada Yuen-Fong Yip, Shuk-Yu Leung

Department of Pediatrics, Kwong Wah Hospital, Hong Kong SAR, China

Abstract

Aim: The aim of the study was to evaluate the correlation between the 6-min walk test (6MWT) and the cardiopulmonary exercise test (CPET) in Chinese pediatric patients. **Methods:** A retrospective review was undertaken for Chinese patients with exercise intolerance who had undergone both 6MWT and CPET on the same day over 21 months. Pearson's correlation analysis was used to examine the correlation between the 6-min walk distance (6MWD) and the maximum oxygen uptake ($VO2_{max}$). The 6MWD was defined as abnormal if <10th percentile of height-matched reference, and the $VO2_{max}$ was defined as abnormal if <80% predicted. **Results:** Twenty-nine patients with a mean age of 14.3 ± 3.6 years were included in the study. The correlation coefficient (r) between the 6MWD and the $VO2_{max}$ was 0.457 with $P = 0.013$. Twenty-six (three excluded as no reference for $VO2_{max}$ was available for age <10 years) patients were analyzed. Using CPET as the gold standard for functional exercise capacity, 6MWT had a positive predictive value (PPV) of 92%, negative predictive value of 29%, sensitivity of 52%, specificity of 80%, and accuracy of 58% for assessing exercise capacity. **Conclusion:** 6MWT had a high PPV for abnormal CPET. It could still be used as a simple tool to evaluate patients with exercise intolerance.

Keywords: 6-min walk test, child, exercise test

Introduction

The objective evaluation of functional exercise capacity provides clinicians with a composite assessment of the respiratory, cardiac, hematopoietic, neuropsychological, and skeletal muscle systems. The current gold standard for assessing aerobic exercise capacity is the maximal incremental cardiopulmonary exercise test (CPET),[1] which requires laboratory testing with exercise equipment to assess the maximum oxygen uptake ($VO2_{max}$).

Traditionally functional capacity is assessed by patient recall of the flights of stairs they can climb before shortness of breath occurs. However, this is imprecise. Patients may overestimate or underestimate their true functional capacity. Balke developed a simple field test to examine the functional capacity by measuring the distance walked over a defined period of time.[2] This was then modified by Cooper into a 12-min run fitness test for evaluating the physical fitness of US Air Force male officers.[3] McGavin *et al*. further modified Cooper's test into a 12-min walk test, with the objective of evaluating exercise tolerance of patients with chronic bronchitis.[4] To make allowance for patients with respiratory disease who do not have the capacity to walk for an extended period, a 6MWT was devised with the aim of achieving equally indicative results.[5] A review of functional walking tests by Solway *et al*. concluded that the 6MWT is easier to administer, better tolerated, and more reflective of daily activities than the other walk tests.[6]

The 6MWT is a simple practical test that can be executed in a 100-foot hallway, without any exercise equipment or highly trained technicians. This test measures the distance that a patient could walk on a flat, hard surface in 6 min.[7] Most studies involving the 6MWT were performed on adult participants with a spectrum of cardiopulmonary diseases such as heart failure or chronic obstructive pulmonary disease.[8,9] There was only a limited number of pediatric studies on 6MWT. However, they were mostly confined to a specific

Address for correspondence: Dr. Pik-Fung Wong, Department of Paediatrics, Kwong Wah Hospital, Waterloo Road, Hong Kong SAR, China.
E-mail: pikpik_wong@yahoo.com.hk

Access this article online

Quick Response Code:

Website: www.prccm.org

DOI: 10.4103/prcm.prcm_24_17

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Wong PF, Chan EY, Ng DK, Kwok KL, Yip AY, Leung SY. Correlation between 6-min walk test and cardiopulmonary exercise test in Chinese patients. Pediatr Respirol Crit Care Med 2018;2:32-5.

chronic disease.[10-14] A strong correlation between the 6-min walk distance (6MWD) and $VO2_{max}$ was found in children with cystic fibrosis,[10] congenital heart disease,[12] and obesity.[13] Another study in severely ill children awaiting heart–lung or lung transplantation showed that the 6MWT was an useful alternative screening tool for assessing exercise tolerance.[14] However, few local studies had been performed, one of which by Li *et al*. concluded that the 6MWT was a valid and reliable functional test for assessing exercise tolerance and endurance in healthy children.[15] Standard reference was established for the 6MWT in Chinese healthy children.[16]

In this study, we aimed to evaluate the functional exercise capacity among Chinese patients with different underlying diseases and to access the correlation between the simpler 6MWT and the more complex and resource demanding CPET.

Methods

This was a retrospective study in which records of all patients with exercise intolerance who had performed CPET at the author's department from November 2014 to July 2016 were reviewed. Patients were included for analysis if they had performed both CPET and 6MWT on the same day. CPET was performed 1 h after the 6MWT to allow the patients to rest. The baseline anthropometric parameters including body weight and height were recorded.

The 6MWT was performed by physiotherapists according to the protocol outlined by the American Thoracic Society.[7] The hallway distance of the test was modified from 30 m to 20 m due to space constraints. No "warm up" period before the test was allowed, and the patients had to rest on a chair for 10 min before commencement. The test was self-paced and the patients could rest at his or her own wish. Words of encouragement spoken to patients throughout the test were standardized as per protocol. The distance walked over 6 min (6MWD) was recorded in meters. The 6MWT was regarded as abnormal if the 6MWD was less than the 10th percentile of height-matched reference.[16]

The CPET was performed by trained technicians according to the guideline published by the American Thoracic Society,[1] with a treadmill, with a Medgraphics oxygen analyzer (Ultima Series™ Cardiorespiratory Diagnostics Systems, Medical Graphics Corp., St. Paul, MN, USA).

Data including baseline heart rate, blood pressure, carbon dioxide, and oxygen content of the respiratory gas were measured. The patient then ran on the treadmill with increasing speed according to the incremental Bruce Exercise Protocol.

The results of CPET was regarded as abnormal if the $VO2_{max}$ was <80% predicted.[17]

Statistical analysis

The mean and standard deviation for age, body weight, height, and body mass index (BMI) z-score were calculated. The respiratory exchange ratio (RER) and maximal heart rate in the CPET were also recorded. Shapiro–Wilk test was used to test for normality on datasets. Pearson's correlation analysis was used to calculate the correlation coefficient (r) between variables. The 6MWT and CPET results were represented in a 2 × 2 table. All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Inc., Armonk, NY, USA) and $P < 0.05$ was taken as statistically significant. Sensitivity, specificity, accuracy, and positive predictive value (PPV) and negative predictive value (NPV) were calculated.

The study was approved by the Research Ethics Committee of Hospital Authority Kowloon West Cluster (reference: KW/EX-17-031[108-10]).

Results

Patient demographics

Twenty-nine patients, 17 male (59%) and 12 female (41%), were included in this study. The mean age was 14.3 ± 3.6 years old, mean body weight was 51.6 ± 19.3 kg, mean height was 156.6 ± 16 cm, mean BMI was 20.6 ± 6.1 kg/m^2, and mean BMI Z-score was 0.23 ± 1.5 [Table 1]. Underlying diseases were listed in Table 2.

Relationship between 6-min walk test and cardiopulmonary exercise test

Data from all 29 Chinese patients who had completed both the CPET and 6MWT were included in the analysis. The mean $VO2_{max}$ was 32.1 ± 7.5 ml/kg/min and the mean of 6MWD was 574.3 ± 98.7 m.

The mean RER was 1.08 ± 0.11 (range 0.82–1.27) and the mean percentage of predicted maximal heart rate was

Table 1: Patient demographics

Demographic	Mean	SD	Range
Gender (male) (%)	17 (59)		
Age (years)	14.3	3.6	7.7-21.9
Height (cm)	156.6	16	121.2-178
Body weight (kg)	51.6	19.3	22.9-94.7
BMI (kg/m^2)	20.6	6.1	12.5-37
BMI Z-score	0.23	1.5	−4.14-2.61

SD: Standard deviation, BMI: Body mass index

Table 2: Patients disease types

Disease	*n*
Asthma	15
Obesity	6
Obstructive sleep apnea syndrome	4
Bronchiolitis obliterans	3
History of decortication for empyema	1
MELAS with cardiomyopathy	1
Tracheomalacia	1
Scoliosis	1

MELAS: Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes

85% ± 8.7% (range 65%–100%), indicating most patients had performed maximal exercise effort.[18]

In view of the small number of patients in our study, the Shapiro–Wilk normality test on datasets for both 6MWD and $VO2_{max}$ was used. The *P* values of the normality test for 6MWD and $VO2_{max}$ were 0.419 and 0.478, respectively, meaning there is no statistically significant difference from a normal distribution for both datasets.

The 6MWD showed a significant correlation with $VO2_{max}$ ($r = 0.457$, $P = 0.013$). A scatterplot of the relationship between 6MWD and $VO2_{max}$ was shown in Figure 1.

Analysis based on the results of the tests was performed as shown in the 2 by 2 table [Table 3]. In the calculation for sensitivity, specificity, PPV, and NPV, there were five patients with normal CPET and 21 patients with abnormal CPET.

Using CPET as the gold standard for functional exercise capacity, 6MWT had a PPV of 92%, NPV of 29%, sensitivity of 52%, specificity of 80%, and accuracy of 58% [Table 3]. Three patients were excluded as they were under 10 years old and there was no reference value for $VO2_{max}$ for this age group to define abnormality.[17] The positive and negative likelihood ratios were 2.62 and 0.59, respectively. Among the patients with an abnormal CPET, 10 cases were due to deconditioning, 9 cases were due to respiratory causes, and 3 cases were due to cardiac causes. We interpreted the abnormal results and classified their causes according to the ATS guideline.[1]

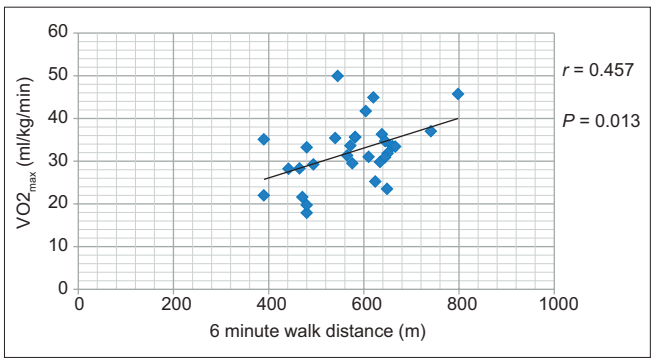


Figure 1: Scattergram of 6-min walk distance and maximum oxygen uptake.

Table 3: Results of cardiopulmonary exercise test and 6-min walk test

6MWT	CPET		Total	Likelihood ratio
	Abnormal	Normal		
Abnormal	11	1	12	LR+=2.62
Normal	10	4	14	LR−=0.59
Total	21	5	26	
Sensitivity	0.52			
Accuracy	0.58			
Specificity		0.8		

Positive predictive value=0.92, Negative predictive value=0.29, LR+: Positive likelihood ratio, LR−: Negative likelihood ratio, CPET: Cardiopulmonary exercise test, 6MWT: 6-min walk test

Discussion

This was the first local study to evaluate the correlation of the 6MWT with maximal CPET in Chinese patients who complained of exercise intolerance. Previous studies on adult patients with diverse cardiopulmonary disease all showed statistically significant correlations between 6MWD and $VO2_{max}$, with correlation coefficient (*r*) ranging from 0.21 to 0.7.[19-21] The 6MWT was shown to be an independent predictor of mortality in adult patients with primary pulmonary hypertension[21] or heart failure.[22] Within the pediatric population, previous studies evaluating the correlation were either in healthy Chinese children,[15,16] or in children with specific diseases,[11] for example, children with cystic fibrosis ($r = 0.76$, $P < 0.001$),[10] severely cardiopulmonary disease awaiting heart or lung transplant ($r = 0.7$, $P < 0.01$),[14] and congenital heart disease ($r = 0.76$, $P < 0.01$).[12]

The current study assessed whether the 6MWT was useful for identifying abnormal exercise capacity in Chinese patients with exercise intolerance.

The current study confirmed a statistically significant correlation between the 6MWT and the CPET in Chinese patients. Being a submaximal exercise test, the 6MWT is valuable in patients with moderately or severely impaired exercise tolerance because a full CPET could put them at risk of clinical deterioration. The 6MWT may be used as a quick test as it is easy to perform, less time-consuming, well tolerated by patients, and is a good reflection of daily activity performance compared to the CPET which is more expensive and time-consuming.

In view of the high PPV of 6MWT, it is a convenient and simple tool to identify patients with abnormal CPET. The main drawback of the 6MWT is its low sensitivity. The main limitation of the current study was the small number of patients.

Conclusion

6MWT has a high PPV for an abnormal CPET result and can be used as a simple tool to confirm impaired aerobic exercise capacity even though the sensitivity was low.

Financial support and sponsorship

This work was financially supported by the Tung Wah Group of Hospitals' Research Fund 2016/2017.

Conflicts of interest

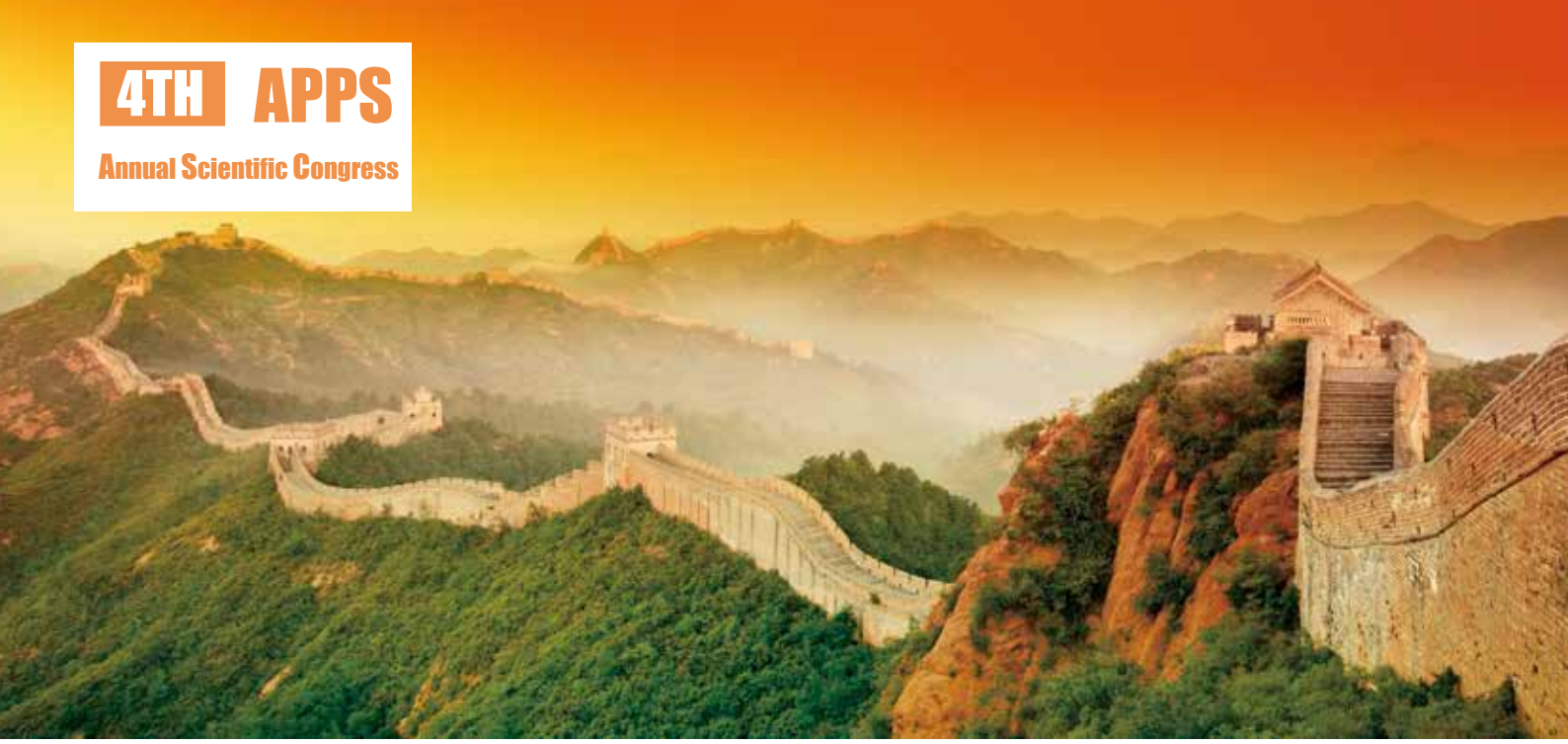
There are no conflicts of interest.

References

1. American Thoracic Society; American College of Chest Physicians. ATS/ACCP Statement on cardiopulmonary exercise testing. Am J Respir Crit Care Med 2003;167:211-77.
2. Balke B. A simple field test for the assessment of physical fitness. Civ Aeromed Res Inst US 1963; 63:1-8.

3. Cooper KH. A means of assessing maximal oxygen intake. Correlation between field and treadmill testing. JAMA 1968;203:201-4.
4. McGavin CR, Gupta SP, McHardy GJ. Twelve-minute walking test for assessing disability in chronic bronchitis. Br Med J 1976;1:822-3.
5. Butland RJ, Pang J, Gross ER, Woodcock AA, Geddes DM. Two-, six-, and 12-minute walking tests in respiratory disease. Br Med J (Clin Res Ed) 1982;284:1607-8.
6. Solway S, Brooks D, Lacasse Y, Thomas S. A qualitative systematic overview of the measurement properties of functional walk tests used in the cardiorespiratory domain. Chest 2001;119:256-70.
7. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: Guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002;166:111-7.
8. Paggiaro PL, Dahle R, Bakran I, Frith L, Hollingworth K, Efthimiou J, *et al.* Multicentre randomised placebo-controlled trial of inhaled fluticasone propionate in patients with chronic obstructive pulmonary disease. International COPD Study Group. Lancet 1998;351:773-80.
9. O'Keeffe ST, Lye M, Donnellan C, Carmichael DN. Reproducibility and responsiveness of quality of life assessment and six minute walk test in elderly heart failure patients. Heart 1998;80:377-82.
10. Gulmans VA, van Veldhoven NH, de Meer K, Helders PJ. The six-minute walking test in children with cystic fibrosis: Reliability and validity. Pediatr Pulmonol 1996;22:85-9.
11. Bartels B, de Groot JF, Terwee CB. The six-minute walk test in chronic pediatric conditions: A systematic review of measurement properties. Phys Ther 2013;93:529-41.
12. Moalla W, Gauthier R, Maingourd Y, Ahmaidi S. Six-minute walking test to assess exercise tolerance and cardiorespiratory responses during training program in children with congenital heart disease. Int J Sports Med 2005;26:756-62.
13. Elloumi M, Makni E, Ounis OB, Moalla W, Zbidi A, Zaoueli M, *et al.* Six-minute walking test and the assessment of cardiorespiratory responses during weight-loss programmes in obese children. Physiother Res Int 2011;16:32-42.
14. Nixon PA, Joswiak ML, Fricker FJ. A six-minute walk test for assessing exercise tolerance in severely ill children. J Pediatr 1996;129:362-6.
15. Li AM, Yin J, Yu CC, Tsang T, So HK, Wong E, *et al.* The six-minute walk test in healthy children: Reliability and validity. Eur Respir J 2005;25:1057-60.
16. Li AM, Yin J, Au JT, So HK, Tsang T, Wong E, *et al.* Standard reference for the six-minute-walk test in healthy children aged 7 to 16 years. Am J Respir Crit Care Med 2007;176:174-80.
17. Sheng LW, Ye JC, Qing ZY, Z Ivic Njak M, Xin SL, Jie GM, *et al.* Maximal aerobic power in children and adolescents of Beijing, China. Am J Hum Biol 1996;8:497-503.
18. Fox SM, Haskell WL. The exercise stress test: Needs for standardization. Cardiology: Current Topics and Progress. New York: Academic Press; 1970. p. 149-54.
19. Ross RM, Murthy JN, Wollak ID, Jackson AS. The six minute walk test accurately estimates mean peak oxygen uptake. BMC Pulm Med 2010;10:31.
20. Prichard RA, Juul M, Gazibarich G, Davidson PM, Mason C, Keogh AM, *et al.* Six-minute walk distance predicts VO_2 (max) in patients supported with continuous flow left ventricular assist devices. Int J Artif Organs 2014;37:539-45.
21. Miyamoto S, Nagaya N, Satoh T, Kyotani S, Sakamaki F, Fujita M, *et al.* Clinical correlates and prognostic significance of six-minute walk test in patients with primary pulmonary hypertension. Comparison with cardiopulmonary exercise testing. Am J Respir Crit Care Med 2000;161:487-92.
22. Bittner V, Weiner DH, Yusuf S, Rogers WJ, McIntyre KM, Bangdiwala SI, *et al.* Prediction of mortality and morbidity with a 6-minute walk test in patients with left ventricular dysfunction. SOLVD investigators. JAMA 1993;270:1702-7.

4TH APPS
Annual Scientific Congress



Beijing, China
December 7 – 9, 2018

APPS2018.medmeeting.org

Deadlines

* Early-bird Registration: July 31, 2018
* Call for Abstracts: July 31, 2018

Scientific Program

Workshops:

* Airway Endoscopy: Diagnostic & Therapeutics
* Exhalation NO Detection
* Single Gene Diagnosis of Respiratory System
* Allergen Detection & Immunization Therapy
* Pulmonary Function
* Sleep & Breathing: Diagnosis & Treatment

Keynote Lectures & Symposia:

* Allergy & Asthma
* Critical Care
* Imaging
* Infection
* Interventional Endoscopy
* Pulmonology
* Sleep

HOSTS

Asian Paediatric Pulmonology Society

China Medicine Education Association, Committee on Pediatrics

ENQUIRY

Secretariat of 4th APPS Annual Scientific Congress
E-mail: cmea_pediatrics@163.com
Tel: +86 10 8432 0382

English

Chinese

香港兒童呼吸及過敏學會
Hong Kong Society *of*
PAEDIATRIC RESPIROLOGY AND ALLERGY

Enquiry
ICC Ltd.
Tel: (852) 2559 9973
Email: hkspra2018@icc.com.hk
Website: www.hkspra.org

Mark Your Diary!
Please stay tuned for further updates!

21st HKSPRA Annual Scientific Meeting

20 – 21 October 2018 | Cordis Hong Kong

Courses and Workshops

- A Crash Course on Radiology in Paediatric Respiratory Medicine
- Basic Workshop in Bedside Ultrasound
- Dentistry and Sleep Disordered Breathing – An Introduction
- NIV Workshop
- Nutrition, Allergy and Respirology Diseases

Plenary Lectures and Symposia

- Allergy
- Critical Care
- Home Respiratory Support
- Nutrition and Respiratory Health
- Pulmonology
- Sleep Disordered Breathing

Academic Accreditations

CME, CNE and CPD points will be applied for the meeting.

Confirmed Speakers

Prof. Jonathan Bernstein (USA)
Dr. Mei-ching Chan (Kwong Wah Hospital)
Ms. Wenus Chan (Hong Kong)
Mr. Gordon Cheung (Kwong Wah Hospital)
Ms. Pui-shan Chow (The University of Hong Kong)
Ms. Karre Chung (Kwong Wah Hospital)
Prof. Koert de Waal (Australia)
Dr. Siu-chung Fung (United Christian Hospital)
Prof. Min Gu (The University of Hong Kong)
Prof. Christian Guilleminault (USA)
Dr. Marco Ho (Queen Mary Hospital)
Prof. Ellis Hon (The Chinese University of Hong Kong)
Prof. S. K. Kabra (India)
Dr. Sigmund Kharasch (USA)
Dr. Virginia Kharasch (USA)
Ms. Sandy Ko (Kwong Wah Hospital)
Dr. Carrie Kwok (Kwong Wah Hospital)
Dr. Charlotte Kwong (Kwong Wah Hospital)
Dr. Catherine Mak (Kwong Wah Hospital)
Dr. Daniel Ng (Kwong Wah Hospital)
Prof. Su-yun Qian (Beijing)
Dr. Augusto Sola (USA)
Prof. Ruurd van Elburg (The Netherlands)
Ms. Selena Wang (Taichung)
Dr. Ricky Wong (United Christian Hospital)
Ms. Ling-ling Yang (Taipei)
Dr. Audrey Yoon (USA)

Supporting Organizations

Asian Paediatric Pulmonology Society
Chinese Paediatric Interventional Pulmonology Society
Hong Kong College of Paediatricians
Hong Kong Dental Association
Hong Kong Institute of Allergy
Hong Kong Medical Association
Hong Kong Neonatal Society
Hong Kong Society of Orthodontists
Hong Kong Society of Sleep Medicine
Hong Kong Nutrition Association
Hong Kong Paediatric Nurses Association
Paediatric Home Respiratory Support Society

APPS
ASIAN PAEDIATRIC PULMONOLOGY SOCIETY

Airway Endoscopy Course 2018

15 -17 August 2018

Thai-Training & Education Centre (T-TEC)

Enquiry: www.appuls.org
apps.medisociety@gmail.com

OLYMPUS