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Pediatric Respirology and Critical Care Medicine

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Avamys is **effective** for all major nasal and ocular symptoms associated with AR[1]

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≈42% Reduction in **nasal symptoms** of seasonal AR compared with baseline
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≈38% Reduction in **ocular symptoms** of seasonal AR compared with baseline
(Mean baseline rTOSS over 2 weeks: 6.2; mean change: -2.33)[1]

* Integrated analysis was performed on data from 4 randomised, double-blind, placebo-controlled, parallelgroup, bmulticentre trials, which were designed to evaluate the efficacy and safety of FFNS, 110 µg QD for 14 days in 1141 adult and adolescent SAR patients exposed to mountain cedar, ragweed or grass pollen allergen. The primary efficacy measure for each study was the mean change from baseline over the entire treatment period in daily rTNSS.

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A reduction in growth velocity has been observed in children treated with fluticasone furoate 110 µg daily for 1 year. Therefore, children should be maintained on the lowest dose that delivers adequate symptom control.[2]

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AR: Allergic rhinitis

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1. Maspero JF, Walters RD, Wu W, et al. An integrated analysis of the efficacy of fluticasone furoate nasal spray on individual nasal and ocular symptoms of seasonal allergic rhinitis. Allergy Asthma Proc. 2010;31(6):483-492. **2.** Avamys® Hong Kong prescribing information vGDS10/IPI09 (2017). **3.** Rosenblut A, Bardin PG, Muller B, *et al.* Long-term safety of fluticasone furoate nasal spray in adults and adolescents with perennial allergic rhinitis. *Allergy.* 2007:62(9);1071-1077. 4. La Force C, Journeay GE, Miller SD, *et al.* Ocular safety of fluticasone furoate nasal spray in patients with perennial allergic rhinitis: a 2-year study. *Ann Allergy Asthma Immunol*. 2013;111:45-50.

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4/F., Duke of Windsor Social Service Building, 15 Hennessy Road, Wan Chai, Hong Kong
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Contents

Infection and Allergy

This issue brings up three very interesting articles related to pediatric pulmonology and critical care. The first article shows the authors' experience about flexible bronchoscopy (FB) and bronchoalveolar lavage (BAL). The second article provides the data of pertussis from a medical center of Singapore. The third article describes the author's study about CD3/CD46-activated T-regulatory type 1 (Tr1) cells in asthma.

BAL is a diagnostic procedure used for recovering epithelial lining fluid of the alveolar and bronchial airspaces. It is usually performed by injecting prewarmed sterile normal saline through a syringe into the working channel of an FB which has already been wedged into a target bronchus, irrigated, and then suctioned into a sputum trap and sent for investigation.[1] The major application of BAL is the diagnosis of pathogens for pulmonary disease. In general, BAL is performed in the most affected site depending on the radiologically identified involved lobe. The right middle lobe (RML) or lingula is the preferred site in a patient with diffuse infiltration due to easily accessible site with good volume recovered[1-3] whereas the right lower lobe (RLL) is more accessible location for BAL in infants.[2] BAL has also played an important role in the mucus plug removal for persistent and massive atelectasis.[1] In the first article, the authors tried to determine the proper location of BAL in infants and children. They provided evidence showing BAL performed in the right lung and RLL is associated with a higher volume recovered in infants and children. BAL sampling at the RLL and RML was recommended for infants and children with diffuse lung disease.

The incidence of pertussis has been increasing even though pertussis vaccination is included in the standard early childhood immunization programs worldwide.[4,5] The second article reported a cohort study relevant to children with hospitalization for pertussis in a tertiary maternal-pediatric hospital in Singapore. They found that majority cases were <6 months. Surprisingly, 69.7% had not received pertussis immunization. Thus, they suggested that routine maternal vaccination to confer passive immunity for a newborn baby may be a beneficial strategy. However, the effects of maternal pertussis vaccination are still not consistent. Some reports demonstrated efficient transplacental transfer of maternal antibodies in infants whose mothers were vaccinated with Tdap in pregnancy, with good evidence that this protects against disease in young infants.[6] However, a recent study by Saul *et al.* showed a three-component acellular maternal vaccination which was effective at preventing severe pertussis but not mild disease.[7] Knowing the prevalence of pertussis in different countries in Asia will be an interesting issue.

Asthma is a common allergic airway disease, with a prevalence of 4%–10% in the general population.[8,9] The house dust mites (HDMs) are the most important allergens involved in allergic asthma. Many HDM molecules can drive the IgE-dependent allergic response or activate the type 2 helper T immune response, leading to an allergic reaction.[10-12] Lin *et al*. provided interesting findings of regulatory T (Treg) cells. Treg cells play a central role in protecting against the development of allergic asthma, and interleukin (IL)-10–producing Tr1 cells contribute to the regulation of asthma. Complement regulatory protein CD46 was shown to stimulate the development of IL-10–producing Tr1 cells. Crosslinking of CD46 during CD4+ T-cell priming induces production of large amount of IL-10 and granzyme B. They found that asthmatic patients have decreased IL-10, granzyme B, and CCR 4 expression from CD3/CD46-activated Tr1 cells. Der p-specific immunotherapy enhances the suppressive function of IL-10 in CD46-mediated Tr1 cell from asthmatic patients and suppresses airway inflammation, hence suggesting that manipulation of complement activated Tr1 cells may be a therapeutic strategy for asthma in the future.

We hope readers can enjoy this issue.

Hong-Ren Yu

Department of Pediatrics, Chang Gung Memorial Hospital-Kaohsiung Medical Center, Kaohsiung County, Taiwan

Address for correspondence: Dr. Hong-Ren Yu, Department of Pediatrics, Chang Gung Memorial Hospital-Kaohsiung Medical Center, 123 Ta-Pei Road, Niao-Song Hsiang, Kaohsiung County 83301, Taiwan.
E-mail: yuu2004taiwan@yahoo.com.tw

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Review Article

Complements and Allergic Asthma

Ching-Yuang Lin[1], Yi-Giien Tsai[2]

[1]Clinical Immunology Center, China Medical University, Children's Hospital, Taichung, [2]Department of Pediatrics, Changhua Christian Hospital Children's Hospital, Changhua, Taiwan

Abstract

Regulatory T (Treg) cells play a central role in protecting against the development of allergic asthma and interleukin-10 (IL-10) producing T regulatory type 1 (Tr1) cells contribute to the regulation of asthma. Complement regulatory protein CD46 was shown to stimulate the development of IL-10 producing Tr1 cells. Crosslinking of CD46 during CD4+ T cell priming induces production of large amount of IL-10 and granzyme B. These CD46-induced regulatory T cells (Tr1) does not require pre-existing basal expression of FoxP3. Through local IL-10 and granzyme B secretion, such Tr1 cell could control T-cell-mediated inflammation. In asthmatic patients, we found that diminished IL-10, granzyme B, and CCR 4 expression from CD3/CD46-activated Tr1 cells. CD3/CD46-activated Tr1 cells from asthma patients co-cultured with BEAS-2B cells suppressed dermatophagoides pteronyssinus 2 (Der p 2)-induced nuclear factor-κB/p65 by cell contact inhibition. Decreased interaction of CD3/CD46-activated Tr1 and BEAS-2B cells from asthmatics was associated with downregulation of phosphorylation of protein kinase B expression. Decreased interaction between CD46-mediated Tr1 and lung epithelial cells with less IL-10 and granzyme B production may contribute to airway inflammation in allergic asthma. *Der p* specific immunotherapy enhances the suppressive function of IL-10 in CD46-mediated Tr1 cell from asthmatic patients and suppresses airway inflammation in these patients. Based on these results, it might be possible to design therapeutic strategies to manipulate complement activated Tr1 cells to achieve allergen tolerance and suppress airway inflammation in patients with allergic asthma.

Keywords: Allergic asthma, CD46, interleukin-10, Tr1 regulatory T cell

Introduction

The traditional concept of the complement system was an effector arm of antibody response that destroys bacteria by lysis. Complement cascade is initiated through three pathways: classical pathway, lectin pathway, and the alternative pathway. Although triggered differently, these pathways culminate in the formation of the C3 convertases (C3bBb and C4bC2a) and C5 convertase (C3bBbC3b and C4b C2aC3b) which involves cleavage of C2 and C4 in classical and lectin pathways or the serine proteases factor B and factor D in alternative pathway. Deposition of clusters of C3b or C4b on a pathogen leads either to immune adherence and subsequent ingestion by phagocytic cells (opsonization) or to lysis by engagement of the membrane attack complex.[1] The coating of the pathogen with opsonic fragments derived from C3 and C4 is a robust process and is minimally influenced by complement inhibitors.[1,2] This powerful effector system requires tight regulation. This is achieved through plasma and membrane regulatory proteins that inhibit complement activation in the fluid phase and on self. There are three major different mechanisms of regulation which are through serine protease factor I in conjunction with CD46, complement receptor 1 (CR1, CD35) or by factor H and C4b-binding protein.[1] The complement system is an important component of humoral immune response.[2] It serves as a natural adjuvant, lower the threshold for B cell activation, promotes the development of optimal B cell memory, and maintains B-cell tolerance.[3,4] Complement also can modulate T-cell responses during the induction and effector phases and contraction phase.[5] These effects arise through direct modulation of T cell itself or indirectly through the alteration of antigen presenting cells (APCs).[6] The possible roles of the complement system in asthma will be discussed here.

Complement system is activated locally and systemically to amplify inflammatory response in allergic asthma.[7-9] CD46

Address for correspondence: Prof. Ching-Yuang Lin, Clinical Immunology Center, China Medical University, Children's Hospital, No. 2, Yun-Der Road, Taichung 40402, Taiwan.
E-mail: cylin@mail.cmuh.org.tw

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are widely expressed in airway epithelial cells, leukocytes, and fibroblasts. Human lamina propria contains T cells with a cytokine expression profile that is characteristic of CD 46-induced Tr1 cell.[10-13] In the present review, we elucidated the role of CD46-induced Tr1 cells in airway mucosal immunity and mechanism for CD46 modulation of Tr1 cells. We addressed as: (i) induction of T cell proliferation, (ii) induction of Tr1 differentiation, and (iii) competition effect of interleukin-2 (IL-2) in the Th1/Tr1 balance. Cross-linking of CD46 during T-cell receptor (TCR) activation leads to strong $CD4^+$ T-cell proliferation and synthesis of large amount Il-10 and granzyme B similar to what is seen in inducible Tr1 cells.

T Cells, Interleukin-10, and Complement Regulatory Proteins

Allergic asthma is a chronic airway inflammatory disease. Recent studies reported that regulatory T cells (Treg) play a central role in protecting against the development of allergic asthma.[14] Treg cells such as IL-10 producing T regulatory type 1 (Tr1) also contribute to the regulation of asthma.[15,16] IL-10 producing Tr1 cells can be induced *in vitro*[17] and with Vitamin D3 and dexamethasone.[18] Human $CD4^+$ $CD25^+$ Tregs can induce IL-10 production via direct contact under anti-CD3/CD28 stimulation *in vitro*.[19,20] This is an important pathway for the induction of IL-10 producing Tr1 cells. Interestingly, the complement regulatory protein CD46 was shown to be physiological stimulants for the development of IL-10 producing Tr1 cells. $CD4^+$ T cells stimulated with anti-CD3/CD46 in the presence of IL-2 produced massive IL-10, confirming a Tr1 phenotype.[8] Moreover, the supernatants from $CD4^+$ T cells activated by CD3/CD46 plus IL-2 inhibited the proliferation of bystander $CD4^+$ T cells.[9] IL-10 has been shown to protect against airway hyperresponsiveness in asthma through its effects on the proliferation and cytokine production of Th2 cells, on the activation of mast cell and eosinophil, and on the IgG4:IgE ratio.[21-23]

Two membrane-bound complement regulators, CD46 and CD55 participate directly in modulating function of APCs.[17] CD46 is a measles receptor.[24] Measles infection can induce transient spontaneous remission of minimal change nephrotic syndrome in children.[25] The cross-linking of CD46 with measles virus leads to calcium flux and suppress IL-12 production.[26] It is one reason for the suppression of T-cell response during measles infection. Cross-linking of CD46 during $CD4^+$ T cell priming induces synthesis of large amounts of IL-10 and granzyme B.[19,20] However, the mechanism of CD46 modulating effect on APC and T-cell function is not fully understood.

CD46 with either of its two regularly expressed cytoplasmic tails, Cyt1 or Cyt2.[9,27] Cyt1 and Cyt2 differ in size and amino-acid sequence, and both contain motifs necessary for signaling. Mice $CD4^+$ T cells that express CD46 with the Cyt1 cytoplasmic tail proliferated strongly produced IL-10 and inhibited the contact-hypersensitivity reaction after concurrent TCR and CD46 activation. By contrast, activation of Cyt2 cytoplasmic tail on CD46 showed weak proliferation and low IL-10 production but a heightened contact-hypersensitivity reaction.[9]

Two main mechanisms for the termination of T cell response by complement are the modulation of apoptosis and induction of regulatory T cells (Treg).[13,27] CD46 has an unanticipated function in recognizing apoptotic T cells.[11,13,27] CD46 was to cluster in the apoptotic blebs and then shed in microparticles and allows engulfment by phagocytes. Treg cells are divided into natural $CD4^+$ $CD25^+$ Treg cells, originate from thymus and inducible Treg (Tr1) and TH3 cells, originate from the periphery against both self and foreign antigen.[28,29] The suppressive effect in Tr1 cell is primarily by secretion of IL-10, whereas the suppressive effect of TH3 cell is primarily by secretion of TGFβ1. Crosslinking CD46 during toll-like receptor (TLR) activation leads to the development of Tr1 cell. These CD46-induced Tr1 cells proliferate strongly and suppress the activation of bystander T cells through the secretion of IL-10. CD46-induced Tr1 also synthesize granzyme B and perforin, and develop contact-dependent cytotoxicity toward autologous immunocompetent T cells.[30]

Tolerance to environmental allergens encountered on airway mucosa could be mediated by the development of Treg cells to suppress airway inflammation.[31-33] In children with allergic asthma, the $CD4^+$ $CD25^+$ Treg cells were decreased in bronchoalveolar lavage fluid and did not inhibit pulmonary Th2 response.[33] Defective recruitment of Treg function to the airway is important in the pathogenesis of allergic asthma.[10]

Defects of Treg in Interleukin-10 Production in Asthma Patients

Human $CD4^+$ $CD25-$ T cells stimulated with anti-CD3/CD46 or anti-CD3/CD28 in the presence of IL-2 can induce IL-10 production *in vitro*. IL-10 production in undivided $CD4^+$ T cells and co-cultured $CD4^+$ $CD25^+$/$CD4^+$ CD25-and $CD4^+$ T cells under anti-CD3/CD46 stimulation in asthma patients was significantly lower than that in healthy controls; although, the levels of IL-10 under anti-CD3/CD28 stimulation were not different between asthma patients and healthy controls.[27]

Confocal microscopic analysis of human bronchial mucosa biopsy specimens revealed lower $CD4^+$ $CD46^+$ T cells in mite-sensitive asthmatics than nonatopic subjects. Peripheral blood mononuclear cells (PBMCs) were stimulated with Derp 2 then analyzed by flow cytometry for CD46 surface expression on $CD4^+$ T cells. Quantitative analysis of $CD4^+$ $CD46^+$ cell in PBMCs revealed that number of $CD4^+$ $CD46^+$ cells decreased in asthmatics compared with nonatopic controls ($P < 0.05$). The CD3/CD46-activated $CD4^+$ T cells from asthmatic patients had significantly lower IL-10 and interferon gamma (IFNr) expression compared with nonatopic controls ($P < 0.05$). When IL-10 and IFNr

was quantified from cultured soup by ELISA, a striking defect with CD46-mediated Il-10 and IFN-r production was observed in asthmatics when compared with nonatopic controls. Double immunofluorescence staining was used for CD46 and granzyme B expression in CD3/CD46-activated $CD4^+$ T cells. Significantly decreased granzyme B in CD46-activated $CD4^+$ T cells was noted in asthmatics then nonatopic control.[10]

Both cytoplasmic isoforms of CD46, Cyt1, and Cyt2 in asthmatic children were examined. Quantitative reverse transcription-polymerase chain reaction (RT-PCR) analysis of Cyt1 and Cyt2 mRNA in CD3/CD46-induced Tregs from asthmatics revealed decreased CD46-Cyt1 isoform mRNA and increased CD46-Cyt2 isoform mRNA expression compared with controls, Cyt1 inhibited the inflammatory reaction with increased IL-10 production.[33]

Migration of CD3/CD46-activated Tregs migrates across the bronchial epithelial cell (human bronchial epithelial cell line BEAS-2B was used) under aeroallergen (Derp 2 was used) stimulation, as the time course of migration capacity, was examined. Using the trans-epithelial system *in vitro*, percentage of CD3/CD46-activated $CD4^+$ T cells migrating across BEAS-2B monolayer decreased in asthmatic patients. Furthermore, imaging assay was taken at intervals of 10 min for 2 h revealed higher mobility of CD3/CD46-induced T cells from healthy controls than in asthmatics.[10,33]

Der p2-Activated Bronchial Epithelial Cells and Treg Migration

Der p2-activated bronchial epithelial cells (BEAS-2B) induce nuclear factor-κB (NF-kB)/P65 in a dose-dependent manner. Transwell inset experiments (pore size 0.4 μM) demonstrated that CD3/CD46-activated $CD4^+$ migrated to *Der p* 2-activated BEAS-2B cells by cell contact. CD3/CD46-activated Tregs inhibit NF-kB activity in *Der p*2-activated BEAS-2B cells. Asthmatic patients have decreased NF-kB/p65 induction on *Der p* 2 stimulated BEAS-2B cells and suppressed CD3/CD46-activated Treg migrating to BEAS-2B cells. To test whether CD3/CD46-activated Tregs migrating suppression to *Der p* 2-activated EBAS-2B cells was through IL-10, IL-10 neutralizing antibody was added to co-cultures. Enhanced NF-kB from BEAS-2B cells in co-culture with CD3/CD46-induced Treg following treatment with neutralizing anti-IL-10 mAb was noted both in asthmatics and controls. Percentage of ICAM-1 on *Der p* 2-stimulated BEAS-2B cells when co-cultured with CD3/CD46-activated Tr1 Tregs was greater in healthy controls that than in asthmatics.[10,33]

Expression of CCR4, CCR5, CCR7, and CCR8 on Tregs might slow migration toward inflammatory sits leading to inhibition of responding cells. Percentage and expression of CCR4 on CD3/CD46-activated Tregs declined significantly in asthmatics compared with healthy controls.[10]

Decreased AKT phosphorylation was noted in *Der p*2-stimulated BEAS-2B in touch with CD3/CD46-activated Tregs in asthma patients compared with controls.[10,33]

Der p Immunotherapy and Enhance CD3/CD46 Induced Treg in Suppressing Allergic Inflammation in Asthmatics

Defects in CD3/CD46-induced Tr1 function in regulating immune responses have been shown in asthmatics [Figure 1]. We demonstrated that Dermatophyagoides pteronyssinus (*Der p*) immunotherapy activated human bronchial epithelial cells and recruit CD3/CD46-activated Tr1 cells to the airway to suppress airway inflammation. Clinically, all the asthmatic patients who received *Der p* specific immunotherapy (SIT) had improved asthma scores, increased pulmonary function (forced expiratory volume in one second) and decreased exhaled nitric oxide after 1 year of SIT.[6-8,34-36] The number of $CD4^+$ $FoxP3^+$ T cells increase and $CD4^+$ $IL\text{-}4^+$ cells decreased after 1 year of SIT. Increased IL-10 and IFNr expression in CD3/CD46-induced Treg were noted after 1 year of SIT in asthmatic patients. IL-10, IFNr, GM-CSF, and soluble CD40 ligand production from CD3/CD46-induced Treg was increased in asthmatic patients after 1 year of SIT. Quantitative RT-PCR analysis of Cyt1 and Cyt2 mRNA in the CD3/CD46-induced Treg from asthmatic patients after 1 year of SIT revealed a reciprocal change in the increase in CD46-induced Cyt1 mRNA expression associated with decreased CD46-induced Cyt2 mRNA expression. *Der p*

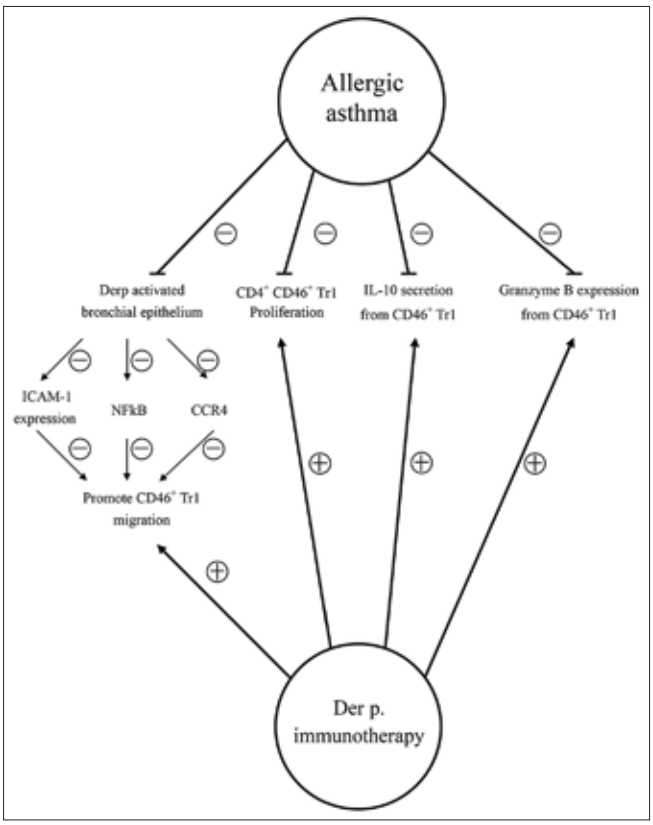

Figure 1: Airway inflammation pathway and their link to $CD46^+$ Tr1 cells. Airway epithelial cell overaction by aeroallergen has been implicated in airway inflammation. Allergic asthma patients defect in recruit $CD46^+$ Tr1 cells to suppress airway inflammation. Derp specific immunotherapy can enhance the suppressive function in $CD46^+$ Tr1 cells from asthmatic patients.

SIT also increased CD3/CD46-induced T-cell suppression of CD25-depleted $CD4^+$ T-cell proliferation.[7]

Down regulation of the effector T cell response through the development of a T-cell lineage with suppressive properties might be a novel role for complement in the contraction of an immune response.[7,8,33] CD46 can induce the development of a distinct immune-modulatory T cell population to produce IL-10 and granzyme B. CD3/CD46-activated Tr1 cell can suppress airway inflammation in asthmatic patients [Figure 1]. Further understanding of how CD46 activates IL-10 producing Tr1 cell during *Der p* SIT, and the dose of mite allergen might be important.

CD3/CD46-activated Tr1 cell permit dendritic cell activation through their simultaneous secretion of GM-CSF and soluble CD40 leading to mucosal tolerance.

Conclusion

Asthmatic patients have dysfunctional $CD46^+$ Tr1 cell that fail to suppress mite-induced airway epithelial cell inflammation. *Der p* SIT can rescue the suppressive function of $CD46^+$ Tr1 cells and achieve allergen tolerance for asthmatic patients.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Original Article

Location of Bronchoalveolar Lavage in Children

Natcha Sakrajai, Panida Srisan

Department of Medical Services, Division of Pulmonology and Critical Care, Queen Sirikit National Institute of Child Health, Ministry of Public Health, Bangkok, Thailand

Abstract

Background: Bronchoalveolar lavage (BAL) is a useful procedure in the diagnosis and treatment of several respiratory diseases. The right middle lobe or lingula is the preferred location of BAL in diffuse lung disease. The aim of this study was to determine the proper location of BAL in infants and children. **Design:** This was prospective, observational study at Queen Sirikit National Institute of Child Health between January and December 2017. **Materials and Methods:** Children, aged 1 month to 15 years, who underwent BAL were enrolled for this study. BAL was performed with the flexible bronchoscope under general anesthesia. The total instilled volume was generally 2–3 ml/kg, divided into 2–6 aliquots. The location of BAL was the most affected area in chest radiography. In diffuse lung disease, BAL was performed in all lobes. The volume and percentage of fluid recovered from various lobes were compared. **Statistical Analysis:** Statistical analysis was performed using SPSS version 23. The value of $P < 0.05$ was considered statistically significant. **Results:** A total of 66 patients with a median age of 1.6 years were enrolled. The total volume recovered was 20% of the instilled volume (interquartile range [IQR] 13.4, 31.8). The volume recovered from the right lung (23%, IQR 13.4, 32.58) was significantly higher than from the left lung (18.9%, IQR 12.5, 30, $P = 0.019$). There was no significant difference between volume recovered from various lobes. However, there was a trend toward higher volume recovered from the right lower lobe (RLL) (25%, IQR 13.1, 33.75). **Conclusions:** In infants and children, BAL performed in the right lung and RLL is associated with a higher volume recovered.

Keywords: Bronchoalveolar lavage, flexible bronchoscopy, pediatric bronchoscopy

Introduction

Bronchoalveolar lavage (BAL) has been accepted as a valuable procedure in the diagnosis and treatment of airway and pulmonary diseases in adults and children.[1-4] Generally, BAL is performed in the most affected site depending on the radiologically identified involved lobe. The right middle lobe (RML) or lingula is the preferred site in a patient with diffuse infiltration due to the easily accessible site with good volume recovered.[3-8] Whereas the right lower lobe (RLL) is more accessible location for BAL in infants.[6] Regarding the amount of fluid and the number of aliquots that should be used in children, the technique is not fully standardized. In adult, the total instilled volume is between 100 and 300 ml, divided into 3–5 aliquots.[3] Several studies in children used 2–4 aliquots of the same volume as in adults: 10 ml for children <6 years of age and 20 ml for children over 6 years of age,[5] or 5–20 ml irrespective of the body weight and age. Others adjust instilled volume to body weight: Using 1 ml/kg/aliquot for three times in children weighing <20 kg and 20 ml/aliquot instilled up to a total volume of 3 ml/kg in children weighing >20 kg. Some adjust instilled volume to 10% of the functional residual capacity with 5–20 ml/aliquot depending on the patient's size.[5-11] The aim of this study was to determine the appropriate location of BAL in infants and children with regard to the volume recovered from different lobes of the lung.

Materials and Methods

Study setting and subject

This study was a prospective, observational study at Queen Sirikit National Institute of Child Health, Bangkok. All children aged 1 month to 15 years who were admitted for BAL between January and December 2017 were enrolled. The study was approved by the Institutional Review Board.

Address for correspondence: Dr. Natcha Sakrajai, Department of Medical Services, Division of Pulmonology and Critical Care, Queen Sirikit National Institute of Child Health, Ministry of Public Health, 420/8 Rajavithi Road, Rajatevee, Bangkok 10400, Thailand.
E-mail: aom68@outlook.co.th

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Bronchoalveolar lavage protocol

BAL was performed with the flexible bronchoscope (FB) under general anesthesia in an operating room. The size of FB, diameter of which ranged from 2.8 to 3.6 mm, with a 1.2 mm working channel (Olympus Medical Systems Corp., Tokyo, Japan) varied according to the patient's age and body weight. The type of artificial airway used (e.g., laryngeal mask airway, endotracheal tube, or tracheostomy) depended on the patient's clinical status and the anesthesiologist's opinion. Topical lidocaine was applied into larynx, trachea, and bronchi through the FB before BAL.

The sterile isotonic saline was instilled with a total volume of 2–3 ml/kg, divided into 2–6 aliquots. The instilled volume, the number of the aliquots, and the location of BAL varied depending on the patient's body weight, clinical status, radiological, and endoscopic findings. BAL was performed once in each lobe. In a patient with diffuse infiltration, the instilled volume was 0.5 ml/kg/aliquot for 5–6 times. In patients with localized or patchy infiltration, the instilled volume was 3–10 ml/aliquot for 2–4 times. Removal of fluid was done after each instillation by mechanical wall suction using negative pressures of 100–150 mmHg. The percentage of volume recovered was calculated as the volume recovered × 100/the volume instilled. The amount and percentage of volume recovered from different locations were compared.

Statistical analysis

All descriptive data were expressed as a median and interquartile range (IQR) or number (percentage). Comparison of volume recovered from various locations was calculated using the Mann–Whitney U-test and Kruskal–Wallis test as appropriate. The $P < 0.05$ was considered statistically significant. Statistical analyses were performed using the SPSS Statistical software version 23 (SPSS: International Business Machines Corp., New York, USA).

Results

A total of 66 consecutive patients underwent BAL during the study period. The median age was 1.6 years (IQR 0.83–5.1). Thirty-nine patients (59%) were male. The most common indication for BAL was recurrent pneumonia (65%), followed by bronchiectasis (9%) [Table 1]. There was no serious complication from FB and BAL in this study, except for a low-grade fever in 10 patients which was resolved spontaneously.

Forty-seven patients (71.2%) with diffuse infiltration underwent BAL in 5–6 lobes. The total instilled volume was 19 ml (IQR 15, 24), with an average of 2 ml/kg. The total volume recovered was 4.3 ml (IQR 2.78, 6.22) or 20.67% (IQR 13.45, 31.78) of the instilled volume [Table 2].

The volume recovered from the right lung was significantly higher than the volume recovered from the left lung (23% vs. 18.89%, $P = 0.019$). The volume recovered from the RML, the usual recommended location was 23.3% (IQR 13.33, 40.0).

Table 1: Patient characteristics

Patient characteristics ($n = 66$)	
Age (years), median (IQR)	1.6 (0.83,5.1)
Male, *n* (%)	39 (59)
Weight (kg), median (IQR)	10 (7.0,16.7)
Indication for BAL, *n* (%)	
Recurrent pneumonia	43 (65.0)
Bronchiectasis	6 (9.0)
Persistent pneumonia	4 (6.0)
Atelectasis	4 (6.0)
Aspiration pneumonia, GERD	4 (6.0)
Recurrent wheezing	2 (3.0)
Chronic productive cough	2 (3.0)
Pulmonary hemorrhage	1 (1.5)

IQR: Interquartile range, BAL: Bronchoalveolar lavage, GERD: Gastroesophageal reflux syndrome

Table 2: Bronchoalveolar lavage data

BAL data ($n = 66$)	
Instilled volume (ml), median (IQR)	19.0 (15.0,24.0)
Volume recovered (ml), median (IQR)	4.3 (2.78,6.22)
Percentage volume recovered (%), median (IQR)	20.67 (13.45,31.78)
Number of patients underwent BAL at different location, *n* (%)	
6 lobes	15 (22.7)
5 lobes	32 (48.5)
4 lobes	10 (15.1)
3 lobes	7 (10.6)
<3 lobes	2 (3.0)

IQR: Interquartile range, BAL: Bronchoalveolar lavage

The volume recovered from the RLL was 25% (IQR 13.1, 33.75). There was no statistically significant difference in the volume recovered from all lobes in either side of the lung [Table 3].

All children were allocated to two groups based on body weight: Group A <10 kg, and Group B >10 kg. Among Group A, 31 patients, the percentage of fluid recovered from the RLL was the highest (25%, IQR 12.50, 33.33), followed by the lingula (22.50%, IQR 7.08, 30.00). Among 35 patients in Group B, the highest volume recovered was from the RML (25%, IQR 18.10, 40.0), followed by the RLL (23.33%, IQR 13.33, 36.25). In both groups, the total volume recovered from the right lung was higher than the left lung. However, there was no significant difference in the volume recovered from all lobes in both groups [Table 4].

Discussion

This study demonstrated that the volume recovered from BAL at the right lung (23%, IQR 13.4, 32.58) was higher than BAL at the left lung (18.89%, IQR 12.50, 30.00) ($P = 0.019$). The volume recovered from BAL at the RLL tended to be higher than BAL at the RML and right upper lobe (RUL) in infant and children ($P = 0.275$). To the best of our knowledge, the

Table 3: Comparison of bronchoalveolar lavage data performed in different location

Location	Instilled volume (ml)	Volume recovered (ml)	Percentage volume recovered	*P*
RUL	4.0 (3.0-5.0)	0.80 (0.40-1.27)	21.25 (11.56-29.37)	0.275[a]
RML	4.0 (3.0-4.0)	0.90 (0.50-1.30)	23.33 (13.33-40.00)	
RLL	4.0 (3.0-4.0)	0.90 (0.50-1.50)	25.00 (13.10-33.75)	
LUL	4.0 (3.0-5.0)	0.70 (0.40-1.00)	16.70 (11.67-26.67)	0.351[a]
Lingula	4.0 (3.0-4.0)	0.65 (0.40-0.98)	18.33 (10.60-31.88)	
LLL	4.0 (3.0-4.5)	0.80 (0.50-1.40)	18.75 (15.00-31.87)	
Right lung	12.0 (9.0-13.5)	2.50 (1.50-3.75)	23.00 (13.4-32.58)	0.019[b]
Left lung	8.0 (6.0-12.0)	1.70 (1.00-2.60)	18.89 (12.50-30.00)	

Data are expressed as median (IQR). [a]Kruskal-Wallis test, [b]Mann-Whitney U-test. RUL: Right upper lobe, RML: Right middle lobe, RLL: Right lower lobe, LUL: Left upper lobe, LLL: Left lower lobe, IQR: Interquartile range

Table 4: Comparison of bronchoalveolar lavage data in children weighed <10 kg and ≥10 kg

	Instilled volume (ml)	Return volume (ml)	Percentage return volume	*P**
Group A (BW <10 kg) (*n*=31)				
RUL	4.0 (3.0-6.0)	0.75 (0.40-1.50)	21.25 (11.77-26.67)	0.374
RML	3.0 (3.0-4.0)	0.70 (0.47-1.22)	19.38 (11.87-32.50)	
RLL	4.0 (3.0-4.0)	0.90 (0.50-1.30)	25.00 (12.50-33.33)	
LUL	4.0 (3.0-4.0)	0.60 (0.40-1.00)	15.83 (10.41-26.25)	0.376
Lingula	4.0 (3.0-4.0)	0.80 (0.25-0.95)	22.50 (7.08-30.00)	
LLL	4.0 (3.0-4.0)	0.80 (0.50-1.22)	21.25 (16.67-34.37)	
Right lung	11.0 (8.75-12.0)	2.55 (1.27-3.40)	22.33 (12.9-31.66)	0.307
Left lung	8.0 (6.0-10.0)	1.60 (0.90-2.50)	17.50 (13.33-30.63)	
Group B (BW ≥10 kg) (*n*=35)				
RUL	4.0 (3.0-4.0)	0.80 (0.42-1.20)	21.25 (10.60-33.10)	0.453
RML	4.0 (3.0-4.0)	1.00 (0.60-1.35)	25.00 (18.10-40.00)	
RLL	4.0 (3.0-4.5)	0.90 (0.50-1.50)	23.33 (13.33-36.25)	
LUL	4.0 (3.0-6.0)	0.70 (0.50-1.30)	17.50 (12.50-30.0)	0.822
Lingula	4.0 (3.0-4.0)	0.60 (0.40-1.10)	16.67 (12.50-35.00)	
LLL	4.0 (3.0-6.0)	0.70 (0.50-1.50)	18.75 (12.50-31.25)	
Right lung	12.0 (9.0-16.0)	2.50 (1.90-3.90)	23.33 (13.75-32.67)	0.207
Left lung	9.0 (6.0-12.75)	1.70 (1.00-3.00)	19.44 (12.43-30.63)	

Data are expressed as median (IQR). *Kruskal-Wallis test. RUL: Right upper lobe, RML: Right middle lobe, RLL: Right lower lobe, LUL: Left upper lobe, LLL: Left lower lobe, IQR: Interquartile range, BW: Body weight

RML or lingula was the preferred location for BAL in patients with diffuse lung diseases.[1-11] In infants, the BAL was easily performed in the RLL.[6] Rosell *et al*. found that the volume recovered from the anterior part of the lung (anterior segments of RUL, left upper lobe [LUL], lingula, and RML) was greater than the volume recovered from other segments due to effect of gravity.[12] Previous airway studies in children have shown that the right main bronchus was significantly larger than the left main bronchus, and the RLL bronchus was significantly larger than the LLL bronchus.[13,14] This might explain the greater volume recovered from the right lung and RLL in our study. However, while the higher volume recovered was from the RLL in the patients weighing <10 kg, the RML was associated with higher volume recovered in the patients weighing >10 kg.

There is no standardization for BAL procedure in children. The instilled volume in children is generally 1 ml/kg or maximum of 10–20 ml/aliquot for 3 times.[5-9] In this study, a single-aliquot BAL from each lobe was performed by normal saline instillation 0.5 ml/kg (or 3–5 ml) up to 5–6 lobes. However, the actual total instilled volume was only 2 ml/kg. The volume recovered in this study was only 20% (IQR 13.45, 31.78) which was technically unacceptable.[3,5,6,8] Nevertheless, this was not our primary concern. BAL in infant and young children tends to be associated with low volume recovery due to the small and collapsible bronchus which closed easily during suction.[7] The majority of our patients were infants with a median age of 1.6 years. Our prior observation, using instilled volume >1 ml/kg or 10 ml/aliquot for 2–3 times had negligible impact on the volume recovered.

Most BAL procedures (86%) were performed in 4–6 lobes. The BAL sample from one or two lobes was insufficient in evaluation of the lower airway infection in children with cystic fibrosis because of the interlobar differences in BAL microbiological findings.[15,16] In patient with suspected aspiration, it may be optimal to perform BAL in the dependent lung segments.[2] In the current study, the RLL and the RML provided higher volume recovered than the others.

Conclusions

The current study suggests that BAL performed at the right lung is associated with the greatest fluid recovery. BAL sampling at the RLL and RML were recommended for infants and children with diffuse lung disease.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Original Article

Pertussis in Children in an Era of Vaccination

Alison Marion Snodgrass, Anne Goh Eng Neo
Department of Paediatric Medicine, KK Women's and Children's Hospital, Singapore

Abstract

Background: Pertussis incidence has been increasing despite high early childhood vaccination coverage. Various strategies have been recommended to combat this problem which includes cocooning, booster doses for adolescents and young adults, and more recently maternal intrapartum vaccination. A previous report had highlighted an increase in pertussis in infants. This review was done to evaluate if there has been any change in the prevalence in the subsequent 10 years. **Materials and Methods:** Retrospective cohort study of admissions for pertussis in patients aged 0–18 years in a single-center tertiary maternal-pediatric hospital in Singapore from January 1, 2008, to October 31, 2017. **Results:** There were 221 cases identified. The majority were infants <6 months (89%) and of Malay (46%) ethnicity. About 54% were male and 81% were delivered term. Nearly, 69.7% had not received pertussis immunization. 64.2% had exposure to an unwell family member with respiratory symptoms. Cough was the most common presenting complaint (100%). High dependency or intensive care treatment was required in 21 cases (9.5%). Length of stay was significantly longer for infants under 6 months of age compared to those aged 6 months or older (additional 1.63 days, 95% confidence interval 0.57–2.68, $P = 0.003$). Coinfection was found in 23 cases, associated comorbidities in 22 cases, and both conditions in 3 children. There were 2 deaths and 11 readmissions. **Conclusions:** Pertussis in young infants in Singapore remains a significant healthcare burden despite current immunization strategies. Routine maternal vaccination to confer passive immunity on the newborn child may be beneficial to address this problem.

Keywords: Infants and children, morbidity, pertussis, vaccination

Introduction

The incidence of pertussis has been increasing despite the widespread availability of vaccination and inclusion in standard early childhood immunization programs worldwide.[1,2] Various strategies to address the problem of waning immunity against pertussis after vaccination have included additional booster doses of pertussis vaccination to adolescents and young adults, as well as vaccination to individuals in close contact with infants such as healthcare workers, infant care workers, and family members (cocooning strategies). A prior retrospective review[2] of patients diagnosed with pertussis in KK Women's and Children's Hospital from 2004 to 2007 noted a resurgence of pertussis in recent years with high morbidity in children who had not been vaccinated and recommended consideration of a booster with Tdap vaccine for young adults and healthcare workers. In Singapore's national childhood immunization schedule, 2 booster doses of pertussis vaccination are given at 18 months and 11 years of age, following the initial 3 doses at ages 2, 4, and 6 months (as part of a combination vaccine that includes inactivated poliovirus, *Haemophilus influenza* B, and possibly hepatitis B). Singapore revised the immunization schedule to include a booster dose of pertussis at age 11 years for schoolgoing children since 2009, and healthcare workers have been offered booster doses of pertussis. Maternal vaccination in the third trimester of pregnancy, which aims to protect vulnerable infants from pertussis by providing passive immunity in those too young to be immunized, is effective[3] but was only recently approved at a national level in Singapore in November 2017. This review was done to look at the efficacy of the new strategies implemented since 2009 with the exception of maternal intrapartum immunization as this was initiated too recently to show effectiveness.

Materials and Methods

Cases of pertussis in pediatric patients aged 0–18 years over an approximately 10-year period from January 1, 2008,

Address for correspondence: Dr. Alison Marion Snodgrass, KK Women's and Children's Hospital, 100 Bukit Timah Road, 229899 Singapore.
E-mail: snodgrass.alison.marion@singhealth.com.sg

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to October 31, 2017 were obtained via diagnostic search of the online pediatric patient database (using the search terms "pertussis" and "whooping cough, unspecified") with the assistance of the hospital's Department of Document Management Services. Confirmation of the coded diagnosis was performed in all cases by computerized database review of the results of real-time polymerase chain reaction assay targeting the insertion sequence IS 481,[4] used as described by Kösters *et al*. in the hospital's microbiology laboratory. The assay was optimized on the Rotorgene (Corbett Research, Australia). These cases were reviewed and analyzed using Microsoft Excel version 2013 and SPSS version 19.0 (IBM Corp. IBM SPSS Statistics for Windows, Armonk, NY: USA). Descriptive statistics was presented as n (%) for categorical variables and as mean (range) for quantitative variables. Statistical significance was set at $P < 0.05$ for the comparison of length of stay between the two age groups (<6 months vs. 6 months or more) using the 2-sample *t*-test if normality or homogeneity assumptions were satisfied, otherwise the nonparametric Mann–Whitney U-test was used. Ethics approval for the study was obtained from the Central Institutional Review Board of Singapore Health Services before commencement.

Results

A total of 221 admissions for pertussis were identified during the study period [Figure 1].

The biodata of the study population is summarized in Table 1. Most individuals were aged <6 months (89%), male (54%), of Malay ethnicity (46%), and delivered at term gestation (82%). The majority (69.7%) had not received any immunizations against pertussis [Figure 2]. Of the 2 fully vaccinated children, one was a 10 years, 4-month-old girl with a background history of allergic rhinitis and eczema, and the other an 18 years, 9-month-old boy with preexisting epilepsy, attention-deficit hyperactivity disorder, and mental retardation. Both these children presented with cough and fever without any significant contact history and had mild disease responding to supportive treatment in the general ward with no need for ventilation.

Exposure to an unwell family member with respiratory symptoms occurred in 142 cases (64.2%) – the patient's mother in 58 cases (26.2%), father in 23 cases (10.4%), sibling in 43 cases (19.5%), and other adult caregiver in 18 cases (8.1%). There were fourteen individuals (6.3%) who reported contact with an ill person outside the family, while 65 (29%) had no history of contact. In none of the patients was there a history suggestive of transmission from a healthcare provider.

Cough was the most common presenting complaint (100%), followed by cyanosis in 70 children (31.7%). Fever was present only in 55 children (24.9%). Fifty-one children (23.1%) presented with poor feeding requiring nasogastric tube feeding or intravenous hydration and 28 children (12.7%) with apnea.

Table 1: Study population demographics

Demographics	Category	*n* (%)
Total number of individuals	-	221 (100)
Age (months)	<6	197 (89)
	6-12	9 (4)
	>12	15 (7)
Gender	Male	119 (54)
	Female	102 (46)
Ethnicity	Chinese	85 (38)
	Malay	102 (46)
	Indian	15 (7)
	Others	19 (9)
Gestational age at birth	Term*	180 (82)
	Preterm†	38 (17)
	Missing	3 (1)
Coinfections	Total	23 (10.4)
	<6 months	18
	6 months or older	5
Comorbidities	Total	22 (10)
	<6 months	16
	6 months or older	6
Both coinfection and comorbidity	Total	3 (1.4)
	<6 months	3
	6 months or older	-
HD/ICU admissions	Total	21 (9.5)
	<6 months	21
	6 months or older	-

*37-42 weeks' gestation; †<37 weeks' gestation. HD: High dependency, ICU: Intensive care unit

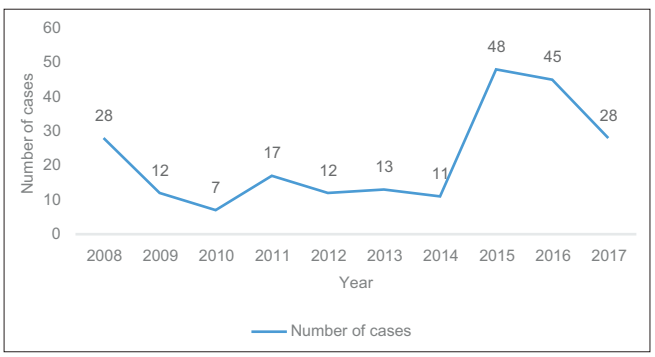

Figure 1: Number of pediatric admissions for pertussis by year.

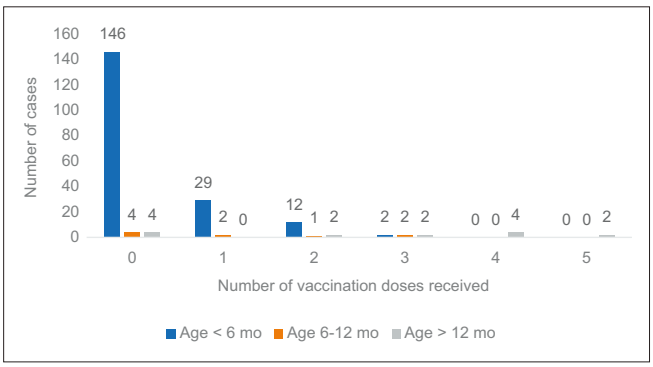

Figure 2: Age distribution of individuals by number of vaccination doses received.

All 21 cases requiring admission to high dependency unit (HDU) (5%) and intensive care unit (ICU) (5.9%) were <6 months of age. Most (8 cases, 38%) were ventilated for <1 day, and the majority (15 cases, 71.4%) did not experience any complications.

Coinfection with other organisms occurred in 23 cases. The majority of the children with coinfection (78.3%) were aged <6 months. The most common coinfecting organism was respiratory syncytial virus (RSV) in 44.4% of cases. Other organisms identified were *Metapneumovirus*, adenovirus, *Parainfluenza type 1 virus,* rhinovirus, *Staphylococcus aureus* (in sputum culture), *Enterovirus* (causing meningitis), and *Citrobacter freundii* (causing urinary tract infection). Pertussis remained the primary diagnosis in all these cases. These children were more symptomatic at presentation. Besides cough, 25% had apnea, 33.3% had cyanosis, 58.3% had fever, 50% had poor feeding requiring supplemental nasogastric tube feeding or IV hydration, and 50% had recurrent desaturation requiring supplemental oxygen. Despite the more severe disease, 77.8% recovered well in the general ward. One child required continuous positive airway pressure (CPAP) support in the HDU, and 3 children were admitted to the ICU where 1 child required CPAP ventilation and 2 children were intubated for ventilator support. Only 1 child in this age group presented with cyanosis. Culprit organisms in this older age group included RSV, *Metapneumovirus*, *Mycoplasma pneumoniae*, and *Rotavirus*.

Comorbid conditions were present in 22 children. These included a suspected immunodeficiency syndrome, congenital structural airway anomaly such as laryngomalacia, atopic respiratory disease, neurological conditions including epilepsy and focal seizures, congenital renal disorders including duplex kidneys and hydronephrosis, and gastrointestinal conditions such as gastroesophageal reflux disease. Of these, the majority (72.7%) were <6 months of age, and these children were more symptomatic at presentation. There was an increased requirement for supportive care with 7 cases (43.8%) requiring supplemental feeding or hydration and 6 cases (37.5%) requiring supplemental oxygen. These young children with comorbid conditions were more likely to be admitted to HDU and ICU for ventilator support (33.3%).

Three children had an underlying comorbid condition as well as coinfection with another organism besides *Bordetella pertussis*. All were children below 6 months of age. The first child had conjugated hyperbilirubinemia and coinfection with RSV, while the second had an inborn error of metabolism and an atrial septal defect with influenza A. These two cases had mild disease and responded well to supportive treatment in the general ward. The third child had *Parainfluenza type 2 virus* infection as well as *Candida* peritonitis. This child was very unwell and was suspected to have an underlying immunodeficiency. After a prolonged course, this child eventually died.

The average length of stay was significantly longer for children <6 months old compared to those older (4.38 ± 4.994 days vs. 2.75 ± 1.917 days; 95% confidence interval 0.57–2.68, $P = 0.003$) [Figure 3].

Admissions exceeding 10 days [range 11–44 days, depicted as outliers in Figure 3] were seen in fifteen individuals. All these children were younger than 6 months of age and unvaccinated (66.7%). All required supplemental oxygen and/or assisted feeding or intravenous hydration. The majority required a higher level of care, with 26.7% needing ICU admission and 40% in HDU. Of those requiring higher level care, 26.7% had coinfection and 20% had comorbid conditions. Children who stayed longer in the general ward were due to recurrent desaturations and coinfection with respiratory viruses as well as parental inability to cope with the child postdischarge.

There were two deaths in this review. Both were female and <6 months of age at the time of presentation. The first child was an unvaccinated preterm baby aged 2 months who presented with cough, cyanosis, and poor feeding, as well as a positive contact history (mother). She required admission to ICU for invasive ventilation due to severe respiratory distress resulting in pulmonary hypertension. Hyperleukocytosis was present. Multiorgan failure developed after 8 days despite treatment with oral clarithromycin and the child eventually succumbed.

The second child was a term infant aged 1.5 months born in a neighboring country who presented with apnea in addition to cough, fever, and poor feeding. The child was commenced on oral erythromycin. She died after 12 days from severe pertussis complicated by septic shock with suspected underlying immunodeficiency. She developed jejunal perforation and candida peritonitis as well as coinfection with *Parainfluenza type 2 virus* infection. She succumbed despite being supported on extracorporeal membrane oxygenation and hemodialysis in the ICU.

Readmission was required in eleven cases. All were unvaccinated young infants aged <6 months. Four cases

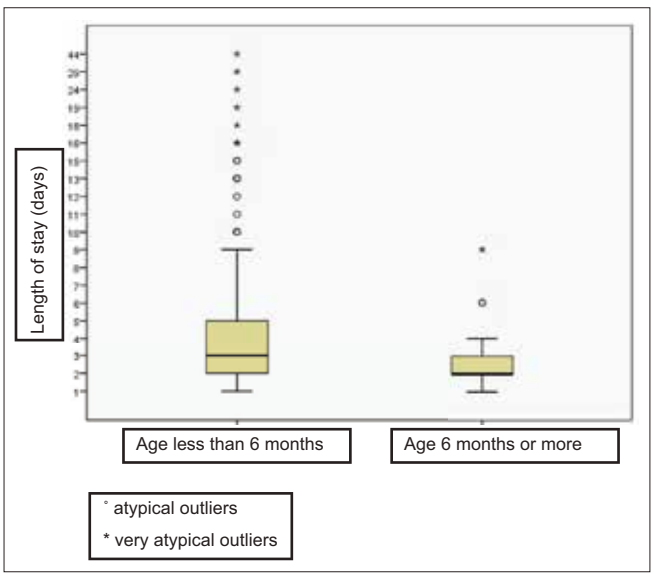

Figure 3: Length of stay with respect to age.

were male and 3 were born premature. The reasons for readmission were for persistent cough, cyanosis, and apneic episodes. Most readmissions were to the general ward, but two cases required admission to HDU and ICU for ventilatory support (noninvasive and invasive ventilation, respectively). Besides the 2 children who required ventilator support, most recovered well with supportive treatment including nasogastric feeding or intravenous hydration. Four children received a second course of macrolide treatment.

There were four cases transferred to our institution for management. One was from a local hospital and the other 3 were from a neighboring country. All were young-term infants aged <6 months with a positive contact history and were either unvaccinated or their vaccination status was not known. Clinical presentation in all cases involved severe symptoms such as cyanosis or required significant supportive care; 2 cases were placed on noninvasive ventilation in HDU and 2 cases were intubated and cared for in ICU. Only one case from overseas had coinfection with RSV, and none of the cases had any known comorbidities. Two cases survived to discharge; the status of the other 2 cases are not known as they were transferred back to their home country by specialized medical transport services for continuation of treatment.

Discussion

The prevalence of pertussis is still high in children in Singapore, with higher rates occurring every few years. Over the last 3 years, the number of cases increased from about 21 cases in 2014 to 57 cases in 2015, 84 cases in 2016, and 77 cases in 2017.[5] These numbers may still be an underestimate as laboratory tests for pertussis were only done when clinical suspicion was high. The high prevalence of Malays in our study does not follow the ethnic distribution in Singapore, where Chinese form the majority at 74.3%, followed by Malays (13.4%), Indians (9%), and other ethnic groups (3.2%).[6] This reflects the choice of healthcare utility in the country as our hospital serves the public; the more affluent Chinese population may be utilizing healthcare providers from the private sector. In 64% of the cases, there was a history of contact with a family member who was coughing, most often the mother. This contrasts with the findings of the study conducted by Kowalzik *et al*.,[7] where pertussis in household contacts was found in only 36% of cases.

While DPT vaccine coverage in infants in Singapore remains very good, with 96% of children completing their primary course of pertussis immunizations,[8] undue delay between shots was noted in this study and may have contributed to pertussis infection, especially since a single dose of pertussis vaccination is not protective as demonstrated in the previous report by Goh *et al*.[3] Our study reaffirms the significant morbidity and mortality of this age-old infection in children, with the youngest being the most vulnerable. Renewed efforts at public education that emphasize the importance of timely vaccination in obtaining optimal disease protection, as well as the significant possibility of pertussis resurgence should such vaccination be omitted, may help to ensure that parents avoid delaying their childrens' immunizations.

Many reasons for the resurgence of pertussis in recent times have been proposed, including clinical underrecognition of the diagnosis, especially in adolescents and adults where the disease is usually mild, insufficient vaccine uptake or incomplete vaccination,[9] the possibility that the current vaccines do not provide optimal protection due to the evolution of vaccine escape mutants[10-13] and the contribution of other *Bordetella* species[14,15] to clinical symptoms, lack of awareness of the importance of the specific timing of vaccination and waning immunity following immunization. While the cyclical pattern of pertussis epidemics is well known, improvement in laboratory techniques and epidemiological surveillance has also likely contributed to the increased identification and detection of pertussis cases. The widespread use of acellular vaccines induce high titers against vaccine components as measured by antibody levels, as opposed to whole-cell vaccines which have been shown to induce a TH1 response that gives better infection clearance although antibody levels may be lower than that measured with acellular vaccines. The use of acellular vaccines has resulted in an increased number of pertactin-negative mutation strains.[16]

Prevention in the form of booster immunization in adults, especially pregnant women and caregivers of infants, as well as older siblings who are frequent sources of infection to these children too young to be immunized, is vital. This is because vaccine-induced immunity does weaken over time.[17,18] This phenomenon has been documented in Singapore, where the seroprevalence rate was shown to decline with age from 92% in children aged <5 years to 63% in children from 5 to 9 years, 51% in those with 10–14 years of age, 50% in those with 15–19 years of age, and 60% in adulthood.[19] The apparent rise in seropositivity between adolescence and adulthood may be partly due to naturally occurring pertussis infection conferring natural immunity. Lai *et al*. assessed the seroepidemiology of pertussis in a cohort of 1092 highly immunized Singaporean children aged 1–17 years and found an overall pertussis seroprevalence of 60.8%; this figure fell from 85% among the individuals who had completed three doses of pertussis vaccination by the age of 2 years to 75%, then 63.1%, and finally remaining around 50% in those who had the last vaccination 1 year, 2 years, and 4 or more years before the study, respectively.[20] Adding an additional booster dose at late adolescence may potentially further boost immunity in this age group.

The current national adult immunization schedule in Singapore aims to provide passive immunity to the fetus as well as protect the mother from becoming a possible source of pertussis infection to her infant after delivery. Maternal immunization has recently been introduced in Singapore since November 2017. The impact of this strategy can only be evaluated in the next few years. It is also worth considering offering Tdap

immunization to fathers and other adult caregivers (such as grandparents, childcare, and kindergarten teachers) in this regard. Widespread implementation of this cocooning strategy may be difficult as it depends on the patient's family members voluntarily coming forward to be vaccinated, and effectiveness may vary as nonhousehold sources of infection are also well documented.[21] Vaccination of healthcare workers has been regularly offered in our hospital, and this may account for the absence of nosocomial transmission of pertussis noted in this study.

The deaths, extended length of inpatient stays, and readmissions in our study illustrate the persisting vulnerability of the infant to pertussis, particularly those too young to be immunized. In 2017, Chong *et al*. reviewed patients admitted for pertussis over a 10-year period and reported that the risk factors for admission to the ICU and HD were age ≤3 months, comorbid conditions, cyanosis, pneumonia, and leukocytosis on multivariate analysis.[22] Risk factors identified by univariate analysis in the same study for ICU/HD admissions were absent DTaP vaccination, contact history, prematurity, and laboratory abnormalities such as lymphocytosis and hyperleukocytosis (white blood cells $\geq 50 \times 10^9$/L). All the children that were admitted to the ICU/HD had never received pertussis vaccination as they were too young. Prior DTaP vaccination with at least 1 dose had a vaccine effectiveness of 86.5% in preventing ICU and HD admissions and 82.1% in preventing intubation and noninvasive ventilation.

Conclusions

Pertussis in young children remains a significant healthcare burden despite current immunization strategies. Routine maternal vaccination to confer passive immunity on the newborn child may be beneficial to address this problem.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Pulmonary Function Abnormalities in Nigerian Children with Sickle Cell Anemia: Prevalence, Pattern, and Predictive Factors

Sir,

It is worthy to comment on the interesting study by Kuti and Adegoke[1] published in the October–December 2018 issue of the *Pediatric Respirology and Critical Care Medicine*. The authors nicely determined, in a case–control study, the prevalence, pattern, and factors associated with pulmonary function abnormalities in Nigerian children with sickle cell anemia (SCA). On employing spirometry, the authors measured various components of pulmonary function tests (PFTs). They found that SCA children had lower lung volumes and capacities and higher prevalence of abnormal pulmonary function parameters compared to the controls, and a restrictive ventilatory pattern (22.1%) was the most common type.[1] I presume that such results ought to be cautiously interpreted. The authors mentioned few study limitations, namely, the absence of total lung capacity, functional residual volume, and diffusion capacity of carbon monoxide which could have further characterize the type of abnormalities of pulmonary function noticed in the studied cohort.[1] I presume that the following methodological limitation could cast additional suspicions on the study results. The authors mentioned that they referred to the reference values by Knudson *et al*.[2] to interpret the recorded spirometric readings. It is obvious that population-specific standard could yield a better idea of the pulmonary function status than using a foreign population reference standard. Actually, the reference values by Knudson *et al*.[2] is old dated back to 1983 and was constructed for Mexican-American ethnic population. It is neither valid nor worthy to be employed for Nigerian population. This is based on the observation that applying prediction formula derived for Caucasian population always overestimated the values for African ethnic population.[3] To my knowledge, spirometric standards for healthy Nigerian children and adolescents have been already constructed to be employed in the clinical settings and researches.[4] I wonder why the authors did not refer to the national standards in the methodology. I presume that if they employed that standards, different results might be obtained. Interestingly, new Nigerian spirometric values for healthy pediatric population has recently been launched.[5] Implementing that new standards in futures studies to better delineate the prevalence, type, and factors controlling pulmonary function in the SCA population is suggested. Despite the aforementioned limitations, the reported abnormal PFT in one-third of the studied SCA cohort[1] is high, necessitating routine assessment of lung function to preserve pulmonary health and improve quality of life.

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Conflicts of interest

There are no conflicts of interest.

Mahmood Dhahir Al-Mendalawi

Department of Paediatrics, Al-Kindy College of Medicine, University of Baghdad, Baghdad, Iraq

Address for correspondence: Prof. Mahmood Dhahir Al-Mendalawi, Department of Paediatrics, Al-Kindy College of Medicine, University of Baghdad, P. O. Box 55302, Baghdad Post Office, Baghdad, Iraq.
E-mail: mdalmendalawi@yahoo.com

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Authors' Response – Pulmonary Function Abnormalities in Nigerian Children with Sickle Cell Anemia: Prevalence, Pattern, and Predictive Factors

Sir,

Thank you for the interest in our article titled, "Pulmonary Function Abnormalities in Nigerian Children with Sickle Cell Anemia: Prevalence, Pattern, and Predictive Factors" published in the October–December 2018 issue of the *Pediatric Respirology and Critical Care Medicine*. We are particularly delighted with the suggestions and points raised by the correspondent and hereby wish to respond to the issues.

While we totally agree with the fact that Knudson reference equation used for our population may not be the most appropriate for Nigerian children. We however quickly want to call the attention of the correspondent to the nonavailability of an ideal standard nationwide reference equation for our population. Nigeria is a multiethnic nation, and a population-based spirometry reference equation that takes into account the various ethnic groups in the country is needed, which is unfortunately not available at present.

The reference values suggested by Njoku and Anah[1] were suggested in adults and they only gave values for peak expiratory flow rates, so are not applicable to our pediatric population.

Spirometry standard suggested by Olanrewaju[2] about 30 years ago was also not representative of Nigeria population, and the number of children assessed for the study was too few to be used as a standard reference value. Akhiwu and Aliyu[3] gave their reference equation by studying 710 children in Kano, Northwest part of the country, who were predominantly Hausa/Fulani ethnic group and the equation may not be representative of the other ethnic groups in the country. In addition, the number of children studies was too small to represent the entire child population of the country. Moreover, the age group covered by their study (6–11 years) excluded the age range of our population of interest (6–16 years), so the equation may not be appropriate for the interpretation of our lung function values. Similarly, other suggested normative values in Nigerian children are given as pilot study because of the small sample size and are nonrepresentative of the various ethnic populations in the country.[4]

We decided to use Knudson reference value for our population because our study compared the lung function values for our cases (sickle cell anemic [SCA] children) with age- and sex-matched comparative group (children with Hb genotype AA). Although Knudson reference values (done in Caucasian population) may overestimate lung function abnormalities in our population and there is a need to switch to modern spirometry equation,[5,6] the fact that lung function abnormalities were not equally observed in apparently healthy children compared to the SCA children (3.7% vs. 29.8%)[7] clearly shows that its application to our population is justifiable.

No doubt, there is a need for a modern, all-inclusive reference equation for Nigerian population; however, the need for routine assessment of lung functions in children with SCA, particularly adolescents and those with acute chest syndrome and multiple vaso-occlusive crises (VOC), which our study[6] clearly highlight, should not be overlooked.

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Conflicts of interest

There are no conflicts of interest.

Bankole Peter Kuti, Samuel A Adegoke

Department of Paediatrics and Child Health, Obafemi Awolowo University, Ile-Ife, Nigeria

Address for correspondence: Dr. Bankole Peter Kuti, Department of Paediatrics and Child Health, Obafemi Awolowo University, P.M.B. 013, Ile-Ife, Nigeria.
E-mail: kutitherapy@yahoo.com

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Understanding the Phospholipids

Phospholipids are structural components of cell membranes in human body including brain cells[1]

There are 5 major phospholipids in human milk, which are:[2]

Phosphatidylethanolamine (PE)
Found particularly in neural tissues including white matters of brain, spinal cord and nerves[3]

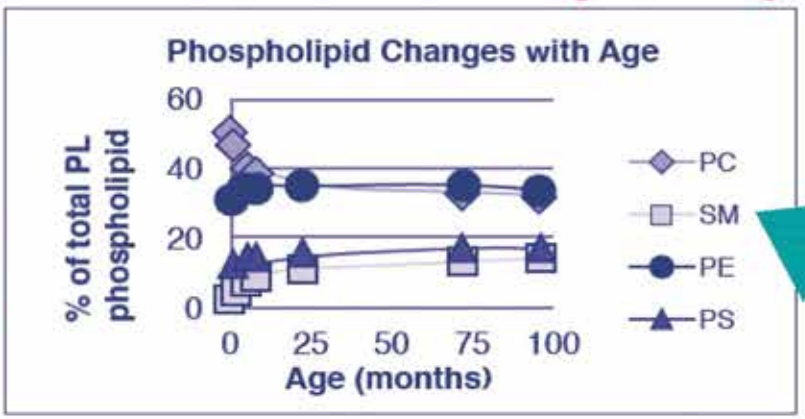
Sphingomyelin (SM)
Contributes to the formation of myelin sheaths that facilitate efficient signal transmission[4,5]

Phosphatidylcholine (PC)
The most abundant phospholipids in membrane bilayers[6]

Phosphatidylserine (PS)
Brain PS has a high content of DHA[7]

Phosphatidylinositol (PI)
Acts as a substrate of Phosphatidylserine (PS) synthesis[7]

The content of phospholipids including PC, PE, PS and SM in human brain changes with age:[8]



Sphingomyelin (SM) levels in the brain increase drastically from 2% to 15% postnatally, timing coincided with its role in the myelin sheath and mature membranes[8]

Food sources of phospholipids:[9]
Eggs, organ meats, lean meats, fish, shellfish, cereal grains, etc.

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References: **1.** SINGULAIR® (montelukast sodium) tablets product circular. Hong Kong. **2.** Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. 2018. **3.** Drug Office | 藥物辦公室 [Internet]. Hong Kong: Department of Health; c2018 [updated 2018 Sep 14; cited 2018 Sep 21]. Available from: http://www.drugoffice.gov.hk/eps/drug/productDetail/en/healthcare_providers/90746#. **4.** Knorr B, Matz J, Bernstein JA, et al. Montelukast for Chronic Asthma in 6- to 14-Year-Old Children: A Randomized, Double-blind Trial. JAMA. 1998; 279: 1181-6.

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