ISSN: 2543-0343 Volume 5 Issue 4 October-December 2021

Pediatric Respirology and Critical Care Medicine

APPS
ASIAN PAEDIATRIC PULMONOLOGY SOCIETY

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

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

Wolters Kluwer Medknow

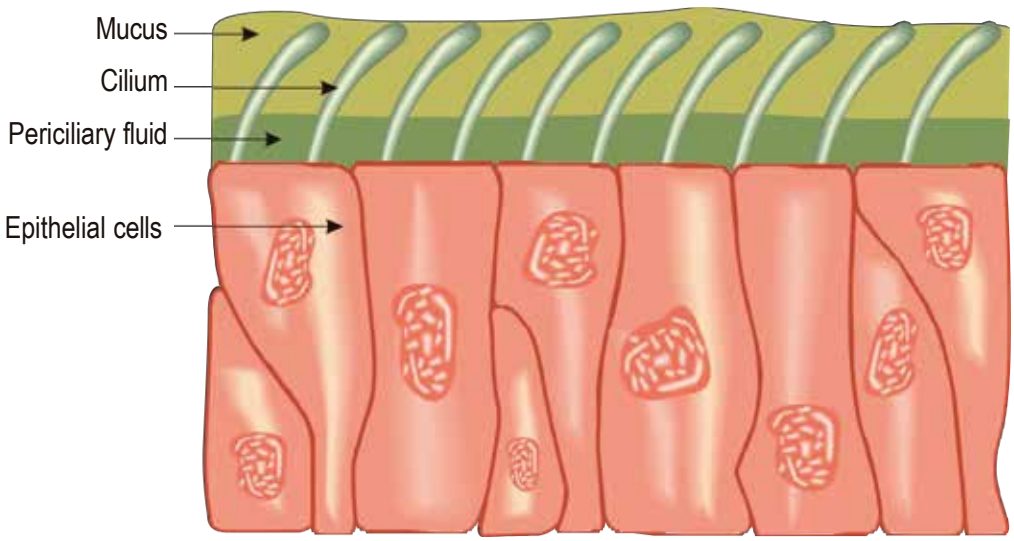
Nasal tissue.
What it is all about

Nasal tissue comprises a complex of integrated systems involving the following structures and functions.

Structures and functions at the epithelial/mucus junction

- Epithelial cell
- Mucus producing cells (goblet cells)
- Mucus
- Cilia
- Periciliary fluid
- Cellular Repair
- Cellular inflammation

Every component has a complex interaction with others and each process has complex biochemical chemistry



Ringer's solution has been shown to work more effectively than isotonic saline solutions on nasal tissue[1]. It is because there are so many different complex biochemical processes involved with all the structures. Simple saline solutions are no longer the best solution to use.

FLO® Sinus Care re-constitutes to Locke Ringer's solution so you can have confidence in recommending it to your customers.

Reference:
1. Ringer-Lactate solution versus isotonic saline solution on mucociliary function after nasal septal surgery. Unal M et al The Journal of Laryngology and Otology Oct 2001 Vol 115 pp 796-797

Further product information is available upon request from:

Sino-Asia Pharmaceutical Supplies Ltd.
Tel: (852) 2573 1400 Fax: (852) 2575 0826
WhatsApp: (852) 6127 02 06 Email: info@sinoasia.com.hk

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

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, Wanfang Data.

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.

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 5 ¦ Issue 4 ¦ October-December 2021

Contents

Editorial

This edition of the journal covers three important common respiratory childhood conditions, namely respiratory tract infections, allergic rhinitis, and obstructive sleep apnea (OSA).

Acute respiratory infections are common in young children and account for frequent visits to the doctor as well as the emergency room. It is important to be able to accurately evaluate the severity of the respiratory disease so that those with more severe diseases requiring admission can be recognized and managed early in the appropriate setting. Several respiratory severity scores have been developed with varying complexities. Examples of such scores are the Tal score, Respiratory Distress Assessment Instrument (RDAI), the Wang Respiratory score (WRS), and the Kristjansson Respiratory score (KRS). Most of the scores are quite similar to the Paediatric Severity Respiratory Score (PRESS) but WRS, KRS, Tal score, and RDAI do not use SaO_2 in the score and uses mainly the components of respiratory rate, wheezing, and retractions with/without the general condition for the score. These were designed mainly to assess bronchiolitis in children.

The utility of the PRESS as reported by Jagalamarri *et al.* in this publication has the advantage of being a simple and easy-to-use score that can be easily used in community settings as it uses five components, namely respiratory rate, wheezing, accessory muscle use, SaO_2, and feeding difficulties. SaO_2 is easy to measure in most clinical settings in this day and age. The authors showed a significantly increased need for respiratory support in those who had a severe PRESS as compared with those with a moderate score. The use of the PRESS may be useful in resource-limited countries to differentiate those children who should be admitted for management from those who can be continued to be managed in the community. To better answer that question, a larger community study should be performed. Subsequent management of the child is still dependent on an accurate diagnosis of the respiratory disease as the PRESS is a measure of respiratory distress and is not specific for any disease condition.

Another common disease in childhood is allergic rhinitis, which in Asia can affect up to 40% of children. The mainstay of treatment for allergic rhinitis is the use of intranasal steroids and antihistamines. There are still many parents who have concerns about giving their children long-term steroids due to the perceived complications with steroids. Nonsteroidal treatments are therefore very appealing to parents and especially the use of probiotics that are perceived to be harmless and beneficial to health. This article by Huang *et al.* conducted in Taiwan highlights the acceptability and tolerability of heat-killed *Lactobacillus paracasei* LCW23 in the management of allergic rhinitis. A 12-week treatment with *L. paracasei* LCW23 led to improvement in nasal symptoms. The use of probiotics for the management of allergic diseases is very species dependent and hence the results cannot be generalized to all probiotics.

The third article in this publication is on the use of pulse oximetry to screen for OSA in infants. Infants born prematurely with bronchopulmonary dysplasia, upper airway obstruction, and recurrent clinical apneas are at increased risk of OSA. The gold standard for diagnosing OSA is with polysomnography. However, polysomnography is labor intensive and is not available in many resource-limited countries. Even in countries where it is available, the wait time for a study can be very long due to limited availability. The study by Hou *et al.* is important as it targets a specific age group which are infants who are difficult to evaluate even on a sleep study. They showed that an overnight pulse oximetry had a good correlation with the polysomnogram. Their study showed that an oxygen desaturation index (ODI) < 90% of >1.3/h can detect an Obstructive Apnea-Hypopnea Index of >2/h with a sensitivity of 77% and specificity of 71%. This will allow more patients to be evaluated in a timely manner and especially in infants where doing an overnight polysomnography can be challenging.

Financial support and sponsorship

Not applicable.

Conflicts of interest

There are no conflicts of interest.

Anne Goh

Department of Paediatrics, KK Women's and Children's Hospital, Singapore

Address for correspondence: Dr. Anne Goh,
Department of Paediatrics, KK Women's and Children's Hospital,
100 Bukit Timah Road, Singapore 229899.
E-mail: Anne.goh.e.n@singhealth.com.sg

Submitted: 13-09-2022 **Accepted:** 13-09-2022 **Published:** 23-09-2022

Access this article online

Quick Response Code:

Website: www.prccm.org

DOI: 10.4103/prcm.prcm_13_22

How to cite this article: Goh A. Editorial. Pediatr Respirol Crit Care Med 2021;5:55-6.

Original Article

Utility of PRESS Score in Predicting the Outcomes of Children Admitted with Respiratory Distress: A Prospective Study

Vanitha Lakshmi Jagalamarri, Lokeswari Balleda, Sravani Kolla, Thimmapuram Chandra Sekhara Reddy
Department of Paediatrics, Sri Ramachandra Children's and Dental Hospital, Guntur, Andhra Pradesh, India

Abstract

Background: Respiratory distress in children must be promptly recognized and aggressively treated because they decompensate quickly leading to adverse outcomes. **Objectives:** To determine the outcomes of children admitted with respiratory distress based on PRESS score. **Study Design:** A prospective study which was done between September 2018 and March 2020. A total of 90 children of age group 1 month to 10 years with respiratory distress at the time of admission. **Intervention:** The PRESS scoring was done and outcomes measured which included use of Respiratory support [nasal cannula, high flow nasal cannula (HFNC), mechanical ventilation (MV)], duration of ICU and hospital stay. **Results:** Compared to moderate PRESS score, children with severe PRESS score had significantly more admission in PICU (91.30% vs 64.18%, $P = 0.016$); significantly more number of days of hospital stay (7 vs 5, $P = 0.001$); significantly more number of days of ICU stay (5 vs 3, P<.0001); significantly more median days of respiratory support (4 vs 3, P<.0001); significantly more use of respiratory support (67 vs 23patients, $P < 0.0003$) and more HFNC usage (73.91% vs 20.90%, P<.0001). However there was comparable requirement of mechanical ventilation between the two groups (8.7% vs 0%, $P = 0.063$). **Conclusion:** PRESS score can be a useful respiratory scoring system in triaging the children at the time of admission and in predicting the requirement of respiratory support and duration of hospital stay. It probably may serve as a useful tool at the community level to consider referral to an appropriate health facility in view of its simplicity.

Keywords: HFNC, respiratory distress, respiratory score, Spo2

Introduction

Respiratory distress in children, particularly in infants, must be promptly recognized and aggressively treated because they decompensate quickly due to smaller airways, increased metabolic demands and less respiratory reserves. As such profound respiratory distress in children if not treated early and appropriately leads to respiratory failure and thus to cardiac arrest.[1-5] So early recognition of respiratory distress and failure is important for implementation of non-invasive or invasive modalities to decrease mortality and morbidity.

Paediatric Respiratory Severity Score (PRESS) is one of the scores used for triaging and assessment of respiratory status.

It is crucial to evaluate the severity of respiratory distress in a timely manner at the initial bedside assessment in emergency department, so that further management can be planned. There are few scoring systems for evaluating respiratory distress at bed side. Paediatric respiratory score is one of the first score developed and used at Seattle children's hospital in 2004.[6]

Yumiko Miyaji, K. Sugai *et al.* developed PRESS score in 2010 to evaluate a new simple bedside scoring system for the rapid assessment of paediatric respiratory infections in emergency settings.[6]

Access this article online

Quick Response Code:

Website: www.prccm.org

DOI: 10.4103/prcm.prcm_1_22

Address for correspondence: Dr. Vanitha Lakshmi Jagalamarri, 13-7-1, 6th Lane Gunturuvarithota, Old Club Road, Guntur 522 001, Andhra Pradesh, India.
E-mail: dhatrichowdary44@gmail.com

Submitted: 11-02-2022 **Revised:** 24-05-2022
Accepted: 23-06-2022 **Published:** 23-09-2022

How to cite this article: Jagalamarri VL, Balleda L, Kolla S, Reddy TC. Utility of PRESS score in predicting the outcomes of children admitted with respiratory distress: A prospective study. Pediatr Respirol Crit Care Med 2021;5:57-61.

After that few studies were done basing on the PRESS score in evaluating the respiratory infections. Population group included was 1 month to 16 years.

Those studies highlighted the importance of PRESS score as a bed side scoring system for respiratory infections, need for hospitalization and need for oxygen therapy.[6-8] There are also studies comparing CRS score (Clinical Respiratory Score) with PRESS Score.[6,7] As PRESS score is very simple in its application, we preferred this for our study. It can be used in resource limited settings.

Inclusion criteria

Children of age group 1 month to 10 years with respiratory distress at the time of admission, independent of need for supplemental oxygen, HFNC, mechanical ventilation with or without fever were included in the study.

Exclusion criteria

Children of age less than one month, more than 10 years, and children with non-respiratory causes of respiratory distress were excluded from the study.

Materials and Methods

After taking informed and written consent from the parents, we conducted a prospective observational study on 90 children over a period of 18 months from September 2018 to March 2020. Approval from Ethics committee was taken before commencing the study.

PRESS scoring was done at the time of admission and children were categorized into mild, moderate and severe respiratory distress. PRESS includes five components namely, respiratory rate, wheezing, accessory muscle use, SpO2, and feeding difficulties. Respiratory rate was evaluated based on the WHO guidelines.[4] Wheezing was defined by auscultation performed by experienced paediatricians. Accessory muscle use was defined as visible retraction of one or more of the supraclavicular /suprasternal, intercostal, and subcostal muscles. SpO2 was evaluated as above or below 95% at room air. Feeding difficulties were assessed using information provided by the parents. Each component was given 0 or 1 point and the PRESS total score was classified as mild (0–1 points), moderate (2–3 points), or severe (4–5 points).

Data was collected regarding requirement and duration of respiratory support [by means of nasal oxygen therapy, high flow nasal cannula (HFNC) and mechanical ventilation (MV)], duration of ICU stay, and duration of hospital stay. Children who were given nasal oxygen were weaned off to room air. Children who required HFNC were gradually weaned off to nasal oxygen and then to room air. Likewise children who required mechanical ventilator were weaned off to HFNC and followed by nasal oxygen and subsequently to room air.

Statistical analysis

Collected data was entered in MS excel spreadsheet. Statistical tests were applied as follows-

1. Quantitative variables were compared using ANOVA / Kruskal wallis Test (when the data sets were not normally distributed.) between the severity.
2. Qualitative variables were compared using Chi-Square test / Fisher's exact test.

Analysis was done using Statistical package for social science (SPSS) version 21.0. A p value of <0.05 was considered statistically significant.

Results

Demographic data of the study subjects revealed, the mean age of the children was 12.44 ± 14.83 months with a male preponderance with 59(65.56%) males and 31(34.44%) females. . Of the 90 children, 64 (71.11%) were admitted in PICU and 26 (28.99%) were admitted in ward.

Respiratory support in the form of mechanical ventilation was required in 2 (2.22%) children, HFNC was required in 31 (34.44%) children and nasal oxygen was required in 33 (36.66%) children. Total no of children requiring respiratory support (nasal oxygen/HFNC/MV) was 66 (73.33%) and 24 (26.67%) children did not receive respiratory support in any form.

Mean PRESS score of study subjects was 3.1 ± 0.74. PRESS score was moderate in 67 (74.44%) children and severe in 23(25.56%) children. Compared to moderate PRESS score, children with severe PRESS score had more significant requirement of respiratory support (Nasal oxygen/ HFNC/ MV) [43/67(64.18%) children vs 23/23(100%) children] with a P value of <0.0003 [Table 1].

Mean number of days of requirement of respiratory support was 2.64 ± 1.87. Mean number of days of requirement of HFNC support was in 1.22 ± 1.8. Mean number of days of hospital stay was i.e. 6.28 ± 3.02. Mean number of days of ICU stay was 3.06 ± 2.13 [Table 1].

Compared to moderate PRESS score, children with severe PRESS score had significantly more admission in PICU (91.30% vs 64.18%, $P = 0.016$); significantly more number of days of hospital stay (7 vs 5, $P = 0.001$); significantly more number of days of ICU stay (5 vs 3, P<.0001); significantly more median days of respiratory support (4 vs 3, P<.0001); significantly more use of HFNC (73.91% vs 20.90%, P<.0001) and comparable requirement of ventilator (8.70% vs 0%, $P = 0.063$) [Table 1] [Figure 1].

Discussion

In our study PRESS score was moderate and severe in 67(74.44%) and 23(25.56%) of study subjects respectively. Mild cases did not require admission and hence not included in the study. In the study by Miyaji *et al*, it was

Table 1: Association of course during hospital stay with severity of PRESS score

Course during hospital stay	PRESS score		Total	P value
	Moderate(n=67)	Severe(n=23)		
Zone of admission				
PICU	43 (64.18%)	21 (91.30%)	64 (71.11%)	0.016*
Ward	24 (35.82%)	2 (8.70%)	26 (28.89%)	
Ventilator				
No	67 (100.00%)	21 (91.30%)	88 (97.78%)	0.063*
Yes	0 (0.00%)	2 (8.70%)	2 (2.22%)	
HFNC				
No	53 (79.10%)	6 (26.09%)	59 (65.56%)	<.0001#
Yes	14 (20.90%)	17 (73.91%)	31 (34.44%)	
Mean ± Stdev	0.67 ± 1.34	2.83 ± 2.04	1.22 ± 1.8	<.0001$
Median(IQR)	0(0 - 0)	3(0.500 - 4)	0(0 - 3)	
Number of days of Respiratory support				
Mean ± Stdev	2.13 ± 1.77	4.13 ± 1.29	2.64 ± 1.87	<.0001$
Median(IQR)	3(0 - 4)	4(3 - 5)	3(0 - 4)	
Number of days of hospital stay				
Mean ± Stdev	5.7 ± 2	7.96 ± 4.58	6.28 ± 3.02	0.001$
Median(IQR)	5(4 - 7)	7(6 - 8)	6(4 - 7)	
Number of days of ICU stay				
Mean ± Stdev	2.45 ± 1.96	4.83 ± 1.56	3.06 ± 2.13	<.0001$
Median(IQR)	3(0 - 4)	5(4 - 5.750)	3(1 - 5)	

*-Fisher's Exact test #-Chi square test

$-Mann Whitney test(as the data sets were not normally distributed so median was used for comparison)

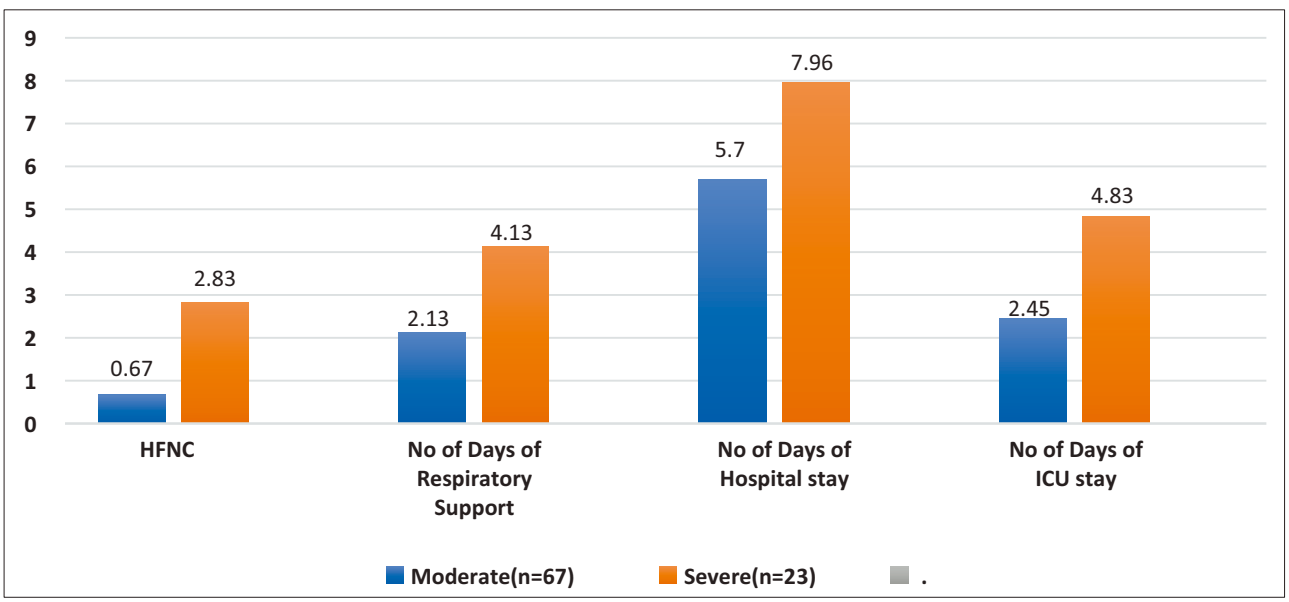


Figure 1: Association of PRESS score with course during hospital stay

found that 49.0% participants were classified as mild, 34.7% as moderate, and 16.3% as severe PRESS scores.[6] In another study by Alexandrino *et al*, revealed that 37.3% of the children had a normal respiratory health condition, 62.7% had a moderate impairment of the respiratory health condition and there were no cases of severe impairment of the respiratory health condition as per PRESS scores.[8]

In our study, on comparing children with severe PRESS score and moderate PRESS score, there was a significant requirement of PICU admission (91.30% vs 64.18%) (P = 0.016). The findings were in line with the western studies.[9-18] The PICU admission as indicated by the higher PRESS scores suggests utility value in triaging the children in ER. Also, future studies could look at ability of low PRESS to predict successful outpatient management,

and ability of high PRESS to predict children in need of early aggressive inpatient care.

On comparing children with severe PRESS score and moderate PRESS score there was significantly more median days of respiratory support (4 vs 3, P<.0001); significantly more use of HFNC (73.91% vs 20.90%, P<.0001) and there was comparable requirement of ventilation. (8.7% vs 0%, $P = 0.063$). Our findings were in line with Miyaji *et al*, who reported that oxygen therapy was longer in severe cases compared with mild and moderate cases (3.7 ± 1.8 vs 0.2 ± 0.8 vs 1.5 ± 1.8).[6] This shows higher PRESS score denotes severe respiratory dysfunction thus requiring a prolonged respiratory support in the form of HFNC or oxygen therapy. The present study shows a significant utility value of HFNC as compared to mechanical ventilation.[19] This study probably reinforces the present trend towards non-invasive respiratory management.

As expected, we noted that as compared to children with moderate PRESS score, children with severe PRESS score had significantly more number of days of hospital stay (7 vs 5, $P = 0.001$); and significantly more number of days of ICU stay (5 vs 3, P<.0001). Similar results were reported by Miyaji *et al*, who found that the hospitalization rate was 32.3% in mild cases, 91.4% in moderate cases, and 97.0% in severe cases, with significant differences between the hospitalization rates of mild and moderate cases, and between mild and severe cases. Number of days of hospital stay was highest in those with severe PRESS score than mild and moderate PRESS score.[6] This study reinforces the utility value of PRESS score in determining the duration of ICU stay and Hospital stay.

Based on our results, we can assume that the PRESS score can help in triaging the children in ER and in deciding the zone of admission and the probable clinical course. These findings may have clinical implications and usefulness in research as it could be used to determine the severity of respiratory illness. This utility may be especially true in resource limited settings but it requires community level validation.

Limitations of our study

The patients enrolled were at a single academic institution that is a referral centre for numerous local hospitals. As such children who were included in the study were probably more sick than those at other hospitals and at the community level. So the PRESS score in this study is probably skewed in favour of severe cases. Another limitation was small sample size. To offset this aberration larger community level studies and multicentric studies with larger sample size may be needed to further validate the scoring system.

Conclusion

PRESS score can be a useful respiratory scoring system in triaging the children at the time of admission and in predicting the requirement of respiratory support, zone of admission and duration of hospital stay. As it is a simple severity scoring system, healthcare providers at all levels of health care, especially in resource limited settings can apply it as a preliminary patient assessment tool for initial triaging and referral to an appropriate healthcare facility. As of now this score needs to be validated at the community level and if found good it may be applied more efficiently at the community level by health workers also. Early recognition, referral and treatment can save lives of many children. Further large scale studies can look at the ability of PRESS score in deciding the modality of respiratory support and utility value of mild PRESS score in predicting successful outpatient management.

Acknowledgement

None.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Donoghue AJ, Nadkarni V, Berg RA, Osmond MH, Wells G, Nesbitt L, *et al*.; CanAm Pediatric Cardiac Arrest Investigators. Outof-hospital pediatric cardiac arrest: An epidemiologic review and assessment of current knowledge. Ann Emerg Med 2005;46:512-22.
2. Gerein RB, Osmond MH, Stiell IG, Nesbitt LP, Burns S; OPALS Study Group. What are the etiology and epidemiology of out-of hospital pediatric cardiopulmonary arrest in ontario, canada? Acad Emerg Med 2006;13:653-8.
3. Nadkarni VM, Larkin GL, Peberdy MA, Carey SM, Kaye W, Mancini ME, *et al*.; National Registry of Cardiopulmonary Resuscitation Investigators. First documented rhythm and clinical outcome from in-hospital cardiac arrest among children and adults. JAMA 2006;295:50-7.
4. Villar J, Martínez D, Mosteiro F, Ambrós A, Añón JM, Ferrando C, *et al*.; Stratification and Outcome of Acute Respiratory Distress Syndrome (STANDARDS) Network. Is overall mortality the right composite endpoint in clinical trials of acute respiratory distress syndrome? Crit Care Med 2018;46:892-9.
5. Gattu R, Scollan J, DeSouza A, Devereaux D, Weaver H, Agthe A. Telemedicine: a reliable tool to assess the severity of respiratory distress in children. Hospital Pediatrics 2016;6:476-82. 10.1542/hpeds.2015-0272.
6. Miyaji Y, Sugai K, Kobayashi M, Niwa S, Tsukagoshi H, Kozawa K, *et al*. Paediatric Respiratory Severity Score (PRESS) for respiratory tract infections in children. Austin Virol Retrovirol 2015;2:1009.
7. Nayani K, Naeem R, Munir O, Naseer N, Feroze A, Brown N, *et al*. The clinical respiratory score predicts paediatric critical care disposition in children with respiratory distress presenting to the emergency department. Bmc Pediatr 2018;18:339.
8. Alexandrino AM, Santos RI, de Melo MC, Bastos JA, Postiaux G. Subjective and objective parameters in paediatric respiratory conditions: Cultural adaptation to Portuguese population. Fisioter Mov 2017;30:49-58.
9. Feldman AS, Hartert TV, Gebretsadik T, Carroll KN, Minton PA, Woodward KB, *et al*. Respiratory severity score separates upper versus lower respiratory tract infections and predicts measures of disease severity. Pediatr Allergy Immunol Pulmonol 2015;28:117-20.

10. Duarte-Dorado DM, Madero-Orosteguí DS, Rodriguez Martinez CE, Nino G. Validation of a scale to assess the severity of bronchiolitis in a population of hospitalized infants. J Asthma 2013;50:1056-61.
11. Chan P, Goh A. Respiratory syncytial virus infection in young malaysian children. Singapore Med J 1999;40:336-40.
12. Thokngaen J, Karoonboonyanan W. Pediatric respiratory severity score evaluates disease severity of respiratory tract infection in children. Chula Med J 2019;63:43.
13. Ducharme FM, Chalut D, Plotnick L, Savdie C, Kudirka D, Zhang X, *et al*. The pediatric respiratory assessment measure : a valid clinical score for assessing acute asthma severity from toddlers to teenagers. J Pediatr 2008;152:476-80.
14. Gold DL, Mihalov LK, Cohen DM. Evaluating the Pediatric Early Warning Score (PEWS) system for admitted patients in the pediatric emergency department. Acad Emerg Med 2014;21:1249-56.
15. Beyeng RTD, Purniti PS, Naning R. Validity of bacterial pneumonia score for predicting bacteremia in children with pneumonia. Paediatr Indones 2011;2:322-6.
16. Destino L, Weisgerber MC, Soung P, Bakalarski D, Yan K, Rehborg R, *et al*. Validity of respiratory scores in bronchiolitis. Hosp Pediatr 2012;2:202-9.
17. Reed C, *et al*. Development of the Respiratory Index of Severity in Children (RISC) score among young children with respiratory infections in South Africa. PloS One 2012;7:e27793. doi:10.1371/journal.pone.0027793.
18. Rodriguez H, Hartert TV, Gebretsadik T, *et al*. A simple respiratory severity score that may be used in evaluation of acute respiratory infection. BMC Res Notes 2016;9:85.
19. Cheng A, *et al*. Evaluating the Clinical Respiratory Score for Initiating High Flow Nasal Cannula in the Pediatric Emergency Department. Annals of Emergency Medicine 2018;72:S88-S89.

Efficacy and Safety of Orally Administered Heat-killed *Lactobacillus paracasei* LCW23 in Patients with Allergic Rhinitis: A Randomized Controlled Clinical Trial

Chung-Bin Huang, Ying-Hsiang Wang[1], Wei-Jen Chen[2], Chih-Ming Tsai[3], Chia-Hao Kang[3], Pai-Yin Lin[2], Hsin-I Lo[2], Hong-Ren Yu[3,4]

Department of Pediatrics, Kuang Tien General Hospital, Taichung, Taiwan, [1]Department of Pediatrics, Chang Gung Memorial Hospital, Chiayi, Taiwan, [2]Research and Development Department, Syngen Biotech Co., Ltd, Tainan, Taiwan, [3]Department of Pediatrics, Chang Gung Memorial Hospital, Kaohsiung, Taiwan, [4]Graduate Institute of Clinical Medical Science, Chang Gung University College of Medicine, Kaohsiung, Taiwan, ROC

Abstract

Objective: In this study, we primarily evaluated the effects of IMMUPHYLA LCW23 on symptoms of allergic rhinitis. IMMUPHYLA LCW23 is a commercial probiotic product containing the *Lactobacillus paracasei* LCW23 strain. **Materials and Methods:** Sixty 5–18-year-old children with allergic rhinitis positive for the dust mite-specific bivalent antibody and meeting the inclusion criteria were enrolled in this double-blind, randomized, placebo-controlled trial. They were administered 2–4 g of the probiotic product containing *L. paracasei* LCW23 (2.5×10^9 cells/g; n = 28) or a placebo supplement (n = 32) according to their body weights for 12 weeks. After the treatment period, a self-assessment of allergic rhinitis symptoms in the nose and eyes was performed. **Results:** This study results revealed that 12-week supplementation with IMMUPHYLA LCW23 is safe, with no side effects. In addition, the Pediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ) assessment revealed that the probiotic significantly alleviated general discomfort (P = 0.003) and common symptoms of allergic rhinitis, such as nasal congestion (P = 0.033), runny nose (P = 0.001), and blowing nose (P = 0.008). **Conclusion:** Administration of IMMUPHYLA LCW23 was safe in the long-term follow-up study. The probiotic likely reduced the risk of allergy prevalence, without any major side effects.

Keywords: Allergic rhinitis, heat-killed probiotic, IMMUPHYLA LCW23, *Lactobacillus paracasei* LCW23, PRQLQ

Introduction

Allergic rhinitis is the most common childhood illness. The prevalence of this global health concern is continuously increasing.[1] Allergic diseases are characterized by long-term nasal symptoms of obstruction, rhinorrhea, sneezing, and itching, affecting 10%–40% of the children worldwide.[2] According to the World Allergy Organization, more than 400 million individuals experience allergic rhinitis globally. In the European Union, one in every four children is affected by an allergic disease. Increasing adoption of western lifestyles and use of antibiotics cause changes in the normal microflora, which can predispose children to allergic diseases. In the USA, 10–30% of adults and up to 40% of children are affected by the condition.

Taiwan is an island region with a subtropical climate that is hot and humid. The air quality is also poor in the region. These factors are conducive to allergen prevalence. Allergic diseases in the region include allergic rhinitis, asthma, and insect-sting allergies. Contact or inhaled allergens cause allergic rhinitis, which is associated with a series of immune reactions that cause inflammation of the nasal mucosa. Children and adolescents have a considerably

Access this article online

Quick Response Code:

Website: www.prccm.org

DOI: 10.4103/prcm.prcm_2_22

Address for correspondence: Prof. Hong-Ren Yu, Department of Pediatrics, Kaohsiung Chang Gung Memorial Hospital, #123 Ta-Pei Road, Niao-Sung District, Kaohsiung 833 Taiwan, ROC. E-mail: yuu2002@cgmh.org.tw

Submitted: 10-03-2022 **Revised:** 07-08-2022
Accepted: 11-08-2022 **Published:** 23-09-2022

How to cite this article: Huang C-B, Wang Y-H, Chen W-J, Tsai C-M, Kang C-H, Lin P-Y, *et al.* Efficacy and safety of orally administered heat-killed *Lactobacillus paracasei* LCW23 in patients with allergic rhinitis: A randomized controlled clinical trial. Pediatr Respirol Crit Care Med 2021;5:62-9.

higher prevalence of allergic rhinitis than adults do. The prevalence rate decreases with age.[3] Although allergic rhinitis is considered a mild and seasonal nuisance, it leads to a considerable economic burden and affects children's social activities, school performance, and work efficiency.

Supplementation of specific probiotic bacteria is an attractive approach to reduce the risk of allergic rhinitis.[4,5] The health benefits of lactic acid bacteria were first observed by Metchnikoff in the late nineteenth century.[6] Currently, oral bacteriotherapy is accepted in the prevention and treatment of allergies.[7] Probiotics have been used effectively in allergen-mediated conditions to alleviate allergy symptoms by improving the gut ecosystem.[4] The incidence of allergic diseases has been reported to be associated with the presence of probiotics in the gut, especially *Lactobacillus paracasei*.[8] A randomized, double-blind clinical trial[9] found that the ingestion of milk fermented with *L. paracasei* reduced the severity and frequency of allergic rhinitis symptoms. The antiallergic mechanism of probiotics is related to immune regulation in which the Th1/Th2 balance is skewed toward Th1 by inhibiting Th2 cytokines.[10] Another study reported that *L. paracasei* strains may be more beneficial than other strains are in treating allergies.[11] Clinical trials on allergies in children administered *L. paracasei* supplementation reported improvement in perennial allergic rhinitis symptoms in 95% of the patients.[4] Recent evidence indicated that a combination supplement of *L. paracasei* and *L. plantarum* for 3 months is beneficial in reducing common cold infections in children.[12] Moreover, supplementation with *L. paracasei* positively and significantly improved ocular symptoms, as assessed using the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ).[13] Studies have also demonstrated the beneficial effects of *L. paracasei* LP33 on allergic rhinitis symptoms.[9,14] Huang *et al.*[15] revealed that children with asthma receiving *L. paracasei* for 12 weeks demonstrated reduced asthma severity and improved allergic rhinitis symptoms. These study results reveal the therapeutic potential and safety of *L. paracasei* supplementation.

Clinical studies have suggested that non-viable probiotic containing dead cells and their metabolites can exert relevant biological responses.[16] For instance, it can release bacterial components with key immunomodulating effects,[16,17] enhancing gene expression,[18] activated macrophages, and suppressed excessive inflammation in mice and humans.[19,20] *L. paracasei* LCW23 (commercially available as IMMUPHYLA LCW23®) was initially isolated from the intestinal tract of normal, healthy humans in Taiwan. Due to specific heat-killed process, *L. paracasei* LCW23 exert relevant biological benefit. Our animal studies have demonstrated that heat-treated *L. paracasei* LCW23 can significantly reduce immunoglobulin E (IgE) level and allergy-related cytokines such as interleukin-4 (IL-4) and IL-5. Besides, *L. paracasei* LCW23 can reduce inflammatory cell infiltration and airway obstructions when observing lung tissue in mice (data not published). Specific heat-killed process allows *L. paracasei* LCW23 to retain its immune activity without being restricted by temperature condition. In this investigation, we hypothesize that heat-killed *L. paracasei* LCW23 can improve allergic symptoms in children caused by allergic rhinitis.

Materials and Methods

Patients

This double-blind, randomized, parallel, placebo-controlled study was conducted in Taiwan. The trial was approved by the Ethics Committee of the hospital (No. 97-1580D). In total, 80 children with allergic rhinitis were recruited in this study. Signed informed consent to participate in the study was obtained from their caregivers. The children were randomly allocated to either the probiotic (n = 40) or placebo (n = 40) group. Inclusion criteria were as follows: (I) 5–18 years of age; (II) personal allergy history, (III) family allergy history, and (IV) allergy to house dust mites. Exclusion criteria were as follows: (I) use of any other steroid-containing drugs and (II) smoking. During the screening period, patient characteristics and personal histories of allergic diseases were obtained. Allergic responses were confirmed concomitantly in a positive skin prick test or specific IgE (ImmunoCAP; Pharmacia and Upjohn, Kalamazoo, MI, USA) bivalent for house dust mites.

Study design

IMMUPHYLA LCW23 and a placebo powder were prepared and coded in good manufacturing practice (GMP)-certified facilities by Syngen Biotech Co., Ltd (Tainan, Taiwan, ROC) and dispensed by a study nurse. IMMUPHYLA LCW23 comprised *L. paracasei* LCW23 (2.5×10^9 cells/g) heat killed at 70–75°C for 30 min. The probiotic and placebo (sharing the same physical appearance) products were stored at room temperature and administered to the participants orally once daily at night for 12 weeks. Children who weighed less than 30 kg were administered 2 g of the probiotic or placebo per day, whereas those weighing more than 30 kg were given 4 g of probiotic or placebo.

Each subject had five clinical visits (visits 0–4) in the protocol. At visit 0, which was the screening visit, general data of all children were recorded. A comprehensive medical and allergy rhinitis history were obtained from all children. A physical examination of vital signs (blood pressure, heart rate, body temperature, and respiratory rate) was performed at each visit. In addition, blood samples were collected at the baseline assessment visit (visit 1) and end-of-study visit (visit 4) for evaluation of the allergy markers of total IgE, absolute eosinophil count

(AEC), and related biochemical parameters. During the trial, children and caregivers received the questionnaire assessment. The children or caregivers assessed the severity of allergic rhinoconjunctivitis symptoms in the nose and eyes, quality of life, and other symptoms by using the modified Pediatric RQLQ (PRQLQ) at the baseline assessments visit (visit 1), treatment visits (visits 2 and 3), and end-of-study visit (visit 4). Adverse events (AEs) were recorded in the diary at each visit [Figure 1].

PRQLQ evaluation

The PRQLQ, developed by Juniper *et al.*,[21] is a disease-specific HRQOL instrument focussing on the physical and emotional impact of a disease. The modified PRQLQ can comprehensively evaluate the physical, psychological, and social skills of children with allergic rhinoconjunctivitis.[21] It is divided into two parts, namely, the degree and frequency of symptoms, and each part has 20 questions in 5 domains: nasal symptoms, ocular symptoms, practical problems, other symptoms, and activity limitations. Each item is scored using a 5-point scale from 0 to 4, with 0 representing no impairment and 4 maximum impairments. The participants were asked to complete the questionnaire with assistance from their parents at visits 1–4.

Biochemical analysis

Dust mite-specific IgE in total serum was measured using a fluorescence enzyme immunoassay. Peripheral blood was also sampled and measured using an automated hematology analyzer. Blood samples were analyzed for white blood cell count, red blood cell count, hemoglobin, hematocrit, glutamic oxaloacetic transaminase, and glutamic pyruvic transaminase.

Statistical analysis

Efficacy was assessed on the basis of symptoms of allergic rhinitis by using the modified PRQLQ. A χ^2 test was used for comparative analysis. The differences between the study groups were compared using an unpaired *t*-test, and differences between visits in each group were compared using a paired *t*-test. A *P*-value of less than 0.05, with a 95% confidence interval, was considered statistically significant in all tests. All values are expressed as means ± SDs.

Results

Demographic characteristics

A total of 80 participants were randomly and equally allocated to the probiotic and placebo groups for screening. Of the 80 screened children, 20 were excluded for the following reasons: 6 participants did not meet the acceptance criteria in visit 0 (e.g., those aged <5 or >18 years). In the baseline assessment during visit 1, three participants did not have positive allergy test results. Of these three participants, two had negative results for the house dust mite-specific antibody bivalent and one did not have baseline biochemical data from blood samples. In visit 2, 11 participants withdrew their consent during the experiment. Among them, seven withdrew their consent and four were excluded for taking steroids during the study period [Figure 2]. Finally, 60 children participated in this study, and their demographic data are provided in Table 1. No statistically significant differences were observed between the groups at baseline.

Efficacy assessment

No differences in the level of general discomfort were noted in the baseline PRQLQ scores between the probiotic and placebo groups (2.50 ± 1.32 and 2.50 ± 1.31, respectively). The symptom scores for general discomfort level ($P = 0.003$) [Table 2], frequency of nasal congestion ($P = 0.033$), runny nose ($P = 0.001$), and blowing nose ($P = 0.008$) [Table 3] in the probiotic group were significantly reduced at final visit when compared with those in the placebo group. After taking the probiotic product for 4 weeks, the participants exhibited a significant improvement in 18 of the 40 items (45%) on the questionnaire regarding symptoms of allergic rhinitis. Furthermore, 32 items (80%) were significantly improved and 38 items (95%) were improved in the symptoms of allergic rhinitis at week 12.

The percentage changes in IgE and AEC levels between baseline and visit 4 in the probiotic and placebo groups are presented in Figure 3. No significant difference in the IgE or AEC levels was noted between the groups. This was possibly due to a large variation in the level of allergen-specific IgE in serum.

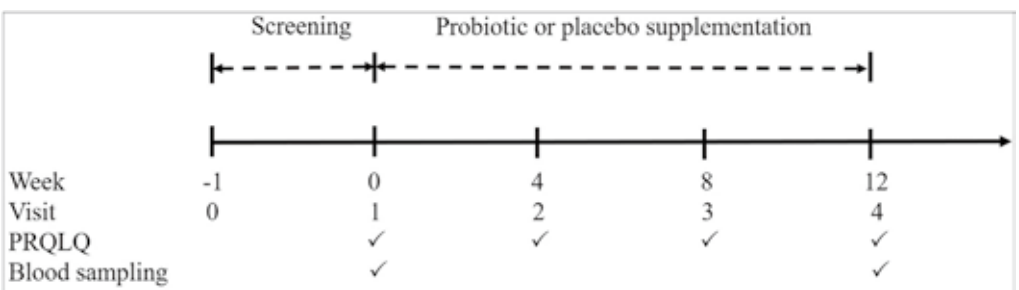


Figure 1: Schema of the experimental design

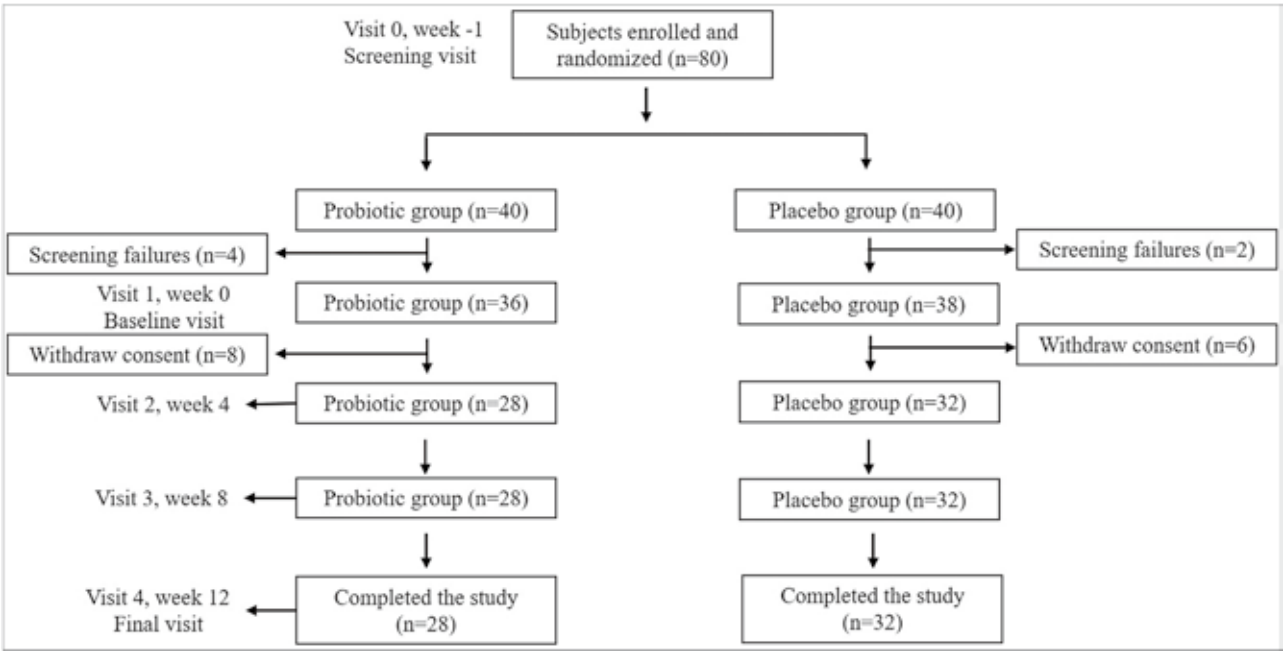


Figure 2: Flow chart of study procedures

Table 1: Baseline characteristics of participants

	IMMUPHYLA LCW23® (*n* = 28)	Placebo (*n* = 32)
Gender (F/M)	14/14	13/19
Age (years)	9.92 ± 3.00	9.19 ± 3.45
Height (cm)	138.95 ± 15.54	134.89 ± 19.26
Weight (kg)	35.92 ± 12.22	34.91 ± 14.93
BMI (kg/m^2)	18.09 ± 3.01	18.41 ± 3.36

Safety assessment

Adverse reactions were not noted in vital signs or physical examination of all systems in both groups. AEs were noted in seven children. Overall, 28 AEs of mild or moderate severity were reported. The most common AE was vomiting (21.4%), followed by headache (14.2%). The incidence of any other AE was <11%. The treating physician identified that one case of nausea and one case of vomiting were related to the probiotic, but their severities were mild. The probiotic group had a lower proportion of AEs (9.3%) than the placebo group did (12.5%).

Discussion

Inhaled allergens and specific IgE antibodies in the body may trigger an immune response, leading to allergic rhinitis. Mast cells, the body's immune cells, release inflammatory substances, such as histamine, which cause inflammation of the nasal mucosa. The three most typical symptoms of allergic rhinitis are sneezing, nasal congestion, and runny nose. If the symptoms of allergic rhinitis are not well controlled, they may affect breathing and sleep quality, even resulting in poor learning ability and weakened concentration.[22,23]

The effects of probiotics on allergic rhinitis have been widely investigated in randomized clinical trials and summarized in multiple reviews and meta-analyses.[10,24,25] Probiotics for the primary prevention of allergy have been investigated. *L. paracasei* is a member of normal human and animal gut microbiota. Previous studies have indicated that *L. paracasei* has antiallergic benefits possibly by modulating the immune response through rebalancing the Th1/Th2 pathway.[26] Our study indicated that *L. paracasei* LCW23 exerts antiallergic benefits after 3 months of supplementation. Intake of *L. paracasei* LCW23 for 8 weeks can help patients achieve up to 80% of improvement in symptoms. After 12 weeks of treatment, it can help achieve 95% improvement in allergic rhinitis symptoms, with a low incidence of AEs. After the 3-month experimental period, children in the probiotic group had significantly less frequent uncomfortable symptoms such as nasal congestion, runny nose, and blowing nose than did those in the placebo group. Our findings are consistent with results of previous studies, which demonstrated that certain probiotic strains are effective in alleviating allergic rhinitis,[9,13,14] with no serious AEs.[9,14]

L. paracasei LCW23 is a heat-killed probiotic. Heat treatment may affect the composition of the bacterial cell wall and modify the immunological properties of the bacterium, providing protection against enteropathogens and helping maintain intestinal barrier integrity.[27] Previous studies have revealed that dead bacterial cells release components with key immunomodulating effects and antagonizing properties against pathogens.[16] In a clinical study, heat-killed *L. paracasei* effectively improved the overall QoL of patients with allergic rhinitis.[14] Other investigations have shown that

Table 2: Mean severity score for individual symptom items of the Pediatric Rhinoconjunctivitis Quality of Life Questionnaire between the probiotic and placebo groups (n = 60)

Variables	IMMUPHYLA LCW23® (first visit)	Placebo (first visit)	*P*	IMMUPHYLA LCW23® (final visit)	Placebo (final visit)	*P*
Nose symptoms domains						
Stuffy	3.18±1.145	3.18±1.145	NS	2.06±1.037	2.10±1.039	NS
Sneezing	2.88±1.062	3.22±1.005	NS	2.19±0.941	2.00±0.962	NS
Runny nose	2.75±1.195	3.15±1.096	NS	2.08±0.997	2.09±0.989	NS
Itchy nose	2.81±1.139	3.18±1.158	NS	1.97±0.872	1.78±.912	NS
Eye symptoms domains						
Itchy eyes	2.56±1.320	2.53±1.190	NS	1.83±0.985	2.03±1.119	NS
Watery eyes	1.77±1.035	1.93±1.055	NS	1.45±0.711	1.50±0.970	NS
Swollen	1.78±1.291	1.63±0.960	NS	1.39±0.748	1.28±0.643	NS
Sore eyes	1.66±1.144	1.56±0.952	NS	1.41±0.729	1.37±.667	NS
Practical problems domains						
Rub nose and eyes	3.03±1.333	3.12±1.086	NS	2.00±0.909	3.12±1.086	NS
Blow nose	2.98±1.303	3.13±1.078	NS	2.03±0.942	3.13±1.078	NS
Carry Kleenex	2.67±1.322	2.71±1.270	NS	2.02±1.161	2.71±1.270	NS
Feel embarrassed	2.50±1.297	2.66±1.192	NS	1.75±0.816	2.66±1.192	NS
Other symptoms domains						
Tired	2.52±1.155	2.59±1.284	NS	1.78±0.934	1.87±0.960	NS
Irritable	2.75±1.309	2.32±1.321	NS	1.66±1.042	1.56±0.741	NS
Do not feel well all over	2.50±1.333	2.50±1.321	NS	1.41±0.583	1.85±1.040[#]	0.003
Headache	2.11±1.086	1.87±.976	NS	1.47±0.734	1.43±0.759	NS
Activities limitation domains						
Playing outdoors	2.08±1.145	2.06±1.244	NS	1.53±0.755	1.71±0.754	NS
Hard to get to sleep at night	2.75±1.309	2.85±1.319	NS	1.77±0.988	1.68±0.781	NS
Hard to pay attention	2.83±1.242	2.79±1.333	NS	2.00±1.155	1.82±0.961	NS
Wake up during the night	2.45±1.458	2.32±1.321	NS	1.58±1.051	1.46±0.762	NS

Between-group comparison, [#]NS = not significant

heat-killed *L. paracasei* produces a high-tumor necrosis factor-α secretion of stimulated monocytes.[28] Heat-killed bacteria are different from live bacteria in terms of their lipoteichoic acid (LTA), peptidoglycan (PGN), and exopolysaccharide contents.[16] Evidence has demonstrated that bacterial cell-wall components, such as PGNs and LTAs, stimulate IL-12 (p70) production[29] and activate the innate immune system through pattern recognition receptors called toll-like receptors.[30,31] PGNs are a major component of the probiotic cell wall, which interacts with TLR2 for Th1-cell activation and differentiation.[32] In addition, Li *et al.*[33] reported that PGNs in probiotics have preventive activity against allergic inflammatory response by regulating Treg/Th17 imbalance. In contrast, LTAs from the cell wall of heat-killed *L. paracasei* D3-5 can be used as a biotherapy to ameliorate leaky gut and inflammation.[34] Non-viable probiotics can provide health benefits in terms of modulating immunity. They may further act to reduce allergic rhinitis symptoms.

Allergens taken up by antigen-presenting cells lead to the activation of Th2 cells, which help regulate cellular immunity, promote isotype transformation, and produce specific IgE antibodies from B cells.[35] Theoretically, patients with allergic rhinitis are more likely to have an elevated total IgE level than healthy individuals, and *L. paracasei* may reduce IgE levels. However, previous researches showed inconsistent results. A previous study reported that *L. paracasei* CNCMI-1518 affects immune responses by inhibiting IgE-dependent human basophil and mouse mast-cell activation.[11] In a 12-month study, the *L. paracasei* group had decreased IgE levels compared with the placebo group.[15] However, other studies reported no significant difference in IgE levels between the probiotic and placebo groups, which were consistent with our study.[36-40] These inconsistent results may be explained by the difference of study groups age, probiotic strains, and the duration of treatment.

L. paracasei LCW23 did not change the biochemical parameters in the study population at the baseline or final visit. The findings indicated that the probiotic used in our study did not have any obvious side effects in children. In addition, uncomfortable symptoms in a single child were related to the test sample, but the severity of these AEs was mild. Moreover, the probiotic group had a lower proportion of AEs (9.3%) than the placebo group did. Therefore, *L. paracasei* LCW23 is considered safe for use in children.

Table 3: Mean frequency score for individual of symptoms items of the Pediatric Rhinoconjunctivitis Quality of Life Questionnaire between the probiotic and placebo groups ($n = 60$)

Variables	IMMUPHYLA LCW23® (first visit)	Placebo (first visit)	*P*-value	IMMUPHYLA LCW23® (final visit)	Placebo (final visit)	*P*-value
Nose symptoms domains						
Stuffy	3.59±1.231	3.66±0.971	NS	2.30±0.987	2.68±1.029[#]	0.033
Sneezing	3.07±0.919	3.00±0.909	NS	2.34±0.930	2.38±0.792	NS
Runny nose	2.88±0.890	2.66±1.087	NS	2.03±0.942	2.54±0.818[#]	0.001
Itchy nose	2.99±1.000	2.70±1.064	NS	2.06±0.941	2.26±0.940	NS
Eye symptoms domains						
Itchy eyes	2.27±0.930	2.41±0.950	NS	1.84±0.979	1.93±0.869	NS
Watery eyes	1.91±1.050	1.79±0.890	NS	1.44±0.710	1.50±0.820	NS
Swollen	1.63±0.826	1.71±0.830	NS	1.39±0.704	1.41±0.696	NS
Sore eyes	1.72±1.061	1.59±0.738	NS	1.38±0.655	1.46±0.679	NS
Practical problems domains						
Rub nose and eyes	2.83±1.135	3.10±0.917	NS	2.00±0.816	2.15±0.778	NS
Blow nose	3.10±0.917	2.86±1.167	NS	2.09±0.955	2.50±0.782 [#]	0.008
Carry Kleenex	2.93±1.188	2.97±1.321	NS	1.95±1.133	2.06±1.244	NS
Feel embarrassed	2.50±1.113	2.50±1.357	NS	1.86±1.006	1.90±1.095	NS
Other symptoms domains						
Tired	2.72±1.188	2.69±1.175	NS	1.88±1.016	2.03±1.007	NS
Irritable	2.70±1.094	2.43±1.163	NS	1.89±1.071	1.75±0.904	NS
Do not feel well all over	2.56±1.167	2.59±1.136	NS	1.58±0.773	1.85±0.996	NS
Headache	2.19±0.990	2.00±0.993	NS	1.50±0.735	1.49±0.763	NS
Activities limitation domains						
Playing outdoors	2.20±1.115	2.24±1.024	NS	1.81±1.111	1.94±0.844	NS
Hard to get to sleep at night	2.75±1.098	2.59±1.026	NS	1.81±1.052	1.74±0.908	NS
Hard to pay attention	2.97±1.272	2.93±1.297	NS	2.13±1.228	2.06±1.006	NS
Wake up during the night	2.33±1.222	2.19±1.200	NS	1.67±1.024	1.60±0.900	NS

Between-group comparison, [#]NS = not significant

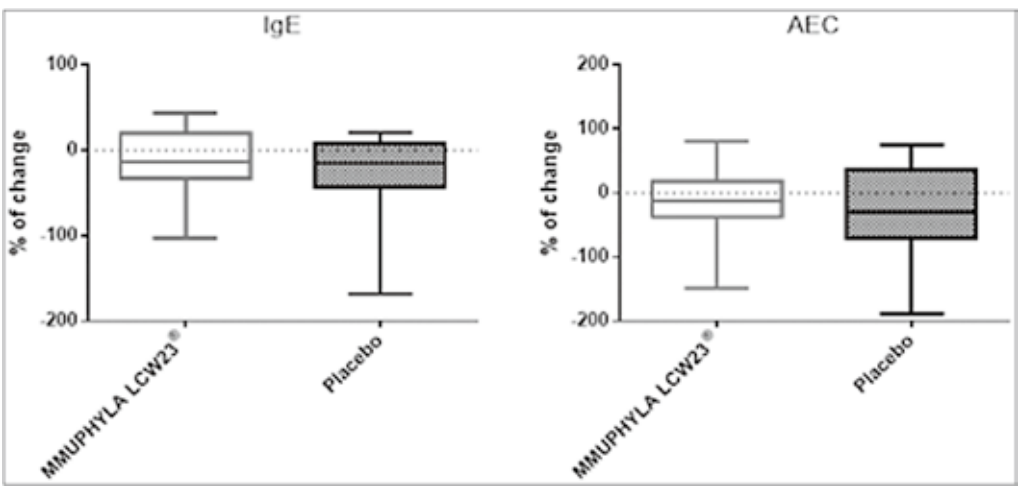


Figure 3: Change in IgE and AEC levels between baseline and visit 4 in the placebo and the IMMUPHYLA LCW23 groups

Conclusion

Supplementation with the probiotic product for 12 weeks significantly improved individual symptoms, such as frequency of uncomfortable symptoms and nasal concerns, compared with placebo supplementation. The benefits of heat-killed bacteria can be exploited in a commercial product. There are several advantages for such a product including the absence of risks for immunocompromised children, increased stability compared to products containing live bacteria, and therefore easier to ship and store. *L. paracasei* LCW23 appears to be safe, with potential therapeutic value in allergy alleviation.

Acknowledgments

We are grateful to Dr. Shiuan-Huei Wu and Dr. Pei-Yu Chu for discussion and comments of this article. We also thank all the participants for their contribution in this study.

Financial support and sponsorship

This study was financially supported by the Syngen Biotech Co., Ltd in Taiwan, ROC.

Conflicts of interest

The authors have no conflicts of interest. This manuscript was edited by Wallace Academic Editing.

References

1. Mastrorilli C, Posa D, Cipriani F, Caffarelli C. Asthma and allergic rhinitis in childhood: What's new. Pediatr Allergy Immunol 2016;27:795-803.
2. Chong SN, Chew FT. Epidemiology of allergic rhinitis and associated risk factors in Asia. World Allergy Organ J 2018;11:17.
3. Hwang CY, Chen YJ, Lin MW, Chen TJ, Chu SY, Chen CC, *et al*. Prevalence of atopic dermatitis, allergic rhinitis and asthma in Taiwan: A national study 2000 to 2007. Acta Derm Venereol 2010;90:589-94.
4. Ahmed M, Billoo AG, Iqbal K. Efficacy of probiotic in perennial allergic rhinitis under five year children: A randomized controlled trial. Pak J Med Sci 2019;35:1538-43.
5. Fassio F, Guagnini F. House dust mite-related respiratory allergies and probiotics: A narrative review. Clin Mol Allergy 2018;16:15.
6. Mackowiak PA. Recycling Metchnikoff: Probiotics, the intestinal microbiome and the quest for long life. Front Public Health 2013;1:52.
7. Tang ML, Ponsonby AL, Orsini F, Tey D, Robinson M, Su EL, *et al*. Administration of a probiotic with peanut oral immunotherapy: A randomized trial. J Allergy Clin Immunol 2015;135: 737-44. e738.
8. Inamine A, Sakurai D, Horiguchi S, Yonekura S, Hanazawa T, Hosokawa H, *et al*. Sublingual administration of *Lactobacillus paracasei* KW3110 inhibits Th2-dependent allergic responses via upregulation of PD-L2 on dendritic cells. Clin Immunol 2012;143:170-9.
9. Wang MF, Lin HC, Wang YY, Hsu CH. Treatment of perennial allergic rhinitis with lactic acid bacteria. Pediatr Allergy Immunol 2004;15:152-8.
10. Wang HT, Anvari S, Anagnostou K. The role of probiotics in preventing allergic disease. Children (Basel) 2019;6:24.
11. Cassard L, Lalanne AI, Garault P, Cotillard A, Chervaux C, Wels M, *et al*. Individual strains of *Lactobacillus paracasei* differentially inhibit human basophil and mouse mast cell activation. Immun Inflamm Dis 2016;4:289-99.
12. Lazou Ahrén I, Berggren A, Teixeira C, Martinsson Niskanen T, Larsson N. Evaluation of the efficacy of *Lactobacillus plantarum* HEAL9 and *Lactobacillus paracasei* 8700:2 on aspects of common cold infections in children attending day care: A randomised, double-blind, placebo-controlled clinical study. Eur J Nutr 2020; 59:409-17.
13. Costa DJ, Marteau P, Amouyal M, Poulsen LK, Hamelmann E, Cazaubiel M, *et al*. Efficacy and safety of the probiotic *Lactobacillus paracasei* LP-33 in allergic rhinitis: A double-blind, randomized, placebo-controlled trial (GA2LEN study). Eur J Clin Nutr 2014;68:602-7.
14. Peng GC, Hsu CH. The efficacy and safety of heat-killed *Lactobacillus paracasei* for treatment of perennial allergic rhinitis induced by house-dust mite. Pediatr Allergy Immunol 2005;16:433-8.
15. Huang CF, Chie WC, Wang IJ. Efficacy of Lactobacillus administration in school-age children with asthma: A randomized, placebo-controlled trial. Nutrients 2018;10:1678.
16. Piqué N, Berlanga M, Miñana-Galbis D. Health benefits of heat-killed (Tyndallized) probiotics: An overview. Int J Mol Sci 2019;20:2534.
17. Kotani Y, Shinkai S, Okamatsu H, Toba M, Ogawa K, Yoshida H, *et al*. Oral intake of *Lactobacillus pentosus* strain b240 accelerates salivary immunoglobulin A secretion in the elderly: A randomized, placebo-controlled, double-blind trial. Immun Ageing 2010;7:11.
18. van Baarlen P, Troost FJ, van Hemert S, van der Meer C, de Vos WM, de Groot PJ, *et al*. Differential NF-kappaB pathways induction by *Lactobacillus plantarum* in the duodenum of healthy humans correlating with immune tolerance. Proc Natl Acad Sci USA 2009;106:2371-6.
19. Iwabuchi N, Yonezawa S, Odamaki T, Yaeshima T, Iwatsuki K, Xiao JZ. Immunomodulating and anti-infective effects of a novel strain of *Lactobacillus paracasei* that strongly induces interleukin-12. FEMS Immunol Med Microbiol 2012;66:230-9.
20. Morita Y, Jounai K, Sakamoto A, Tomita Y, Sugihara Y, Suzuki H, *et al*. Long-term intake of *Lactobacillus paracasei* KW3110 prevents age-related chronic inflammation and retinal cell loss in physiologically aged mice. Aging (Albany NY) 2018;10:2723-40.
21. Juniper EF, Howland WC, Roberts NB, Thompson AK, King DR. Measuring quality of life in children with rhinoconjunctivitis. J Allergy Clin Immunol 1998;101:163-70.
22. Blaiss M. Current concepts and therapeutic strategies for allergic rhinitis in school-age children. Clin Ther 2004;26:1876-89.
23. Liu J, Wu Y, Wu P, Xu Z, Ni X. Analysis of the impact of allergic rhinitis on the children with sleep disordered breathing. Int J Pediatr Otorhinolaryngol 2020;138:110380.
24. Güvenç IA, Muluk NB, Mutlu FŞ, Eşki E, Altıntoprak N, Oktemer T, *et al*. Do probiotics have a role in the treatment of allergic rhinitis? A comprehensive systematic review and meta-analysis. Am J Rhinol Allergy 2016;30:157-75.
25. Zajac AE, Adams AS, Turner JH. A systematic review and meta-analysis of probiotics for the treatment of allergic rhinitis. Int Forum Allergy Rhinol 2015;5:524-32.
26. Wang X, Hui Y, Zhao L, Hao Y, Guo H, Ren F. Oral administration of *Lactobacillus paracasei* L9 attenuates PM2.5-induced enhancement of airway hyperresponsiveness and allergic airway response in murine model of asthma. PLoS One 2017;12:e0171721.
27. Zyrek AA, Cichon C, Helms S, Enders C, Sonnenborn U, Schmidt MA. Molecular mechanisms underlying the probiotic effects of *Escherichia coli* Nissle 1917 involve ZO-2 and PKCzeta redistribution resulting in tight junction and epithelial barrier repair. Cell Microbiol 2007;9:804-16.
28. Haller D, Bode C, Hammes WP. Cytokine secretion by stimulated monocytes depends on the growth phase and heat treatment of bacteria: A comparative study between lactic acid bacteria and invasive pathogens. Microbiol Immunol 1999;43:925-35.
29. Sashihara T, Sueki N, Ikegami S. An analysis of the effectiveness of heat-killed lactic acid bacteria in alleviating allergic diseases. J Dairy Sci 2006;89:2846-55.
30. Hopkins PA, Sriskandan S. Mammalian toll-like receptors: To immunity and beyond. Clin Exp Immunol 2005;140:395-407.
31. Lien E, Ingalls RR. Toll-like receptors. Crit Care Med 2002;30:S1-11.
32. Sun J, Shi YH, Le GW, Ma XY. Distinct immune response induced by peptidoglycan derived from *Lactobacillus* sp. World J Gastroenterol 2005;11:6330-7.
33. Li AL, Sun YQ, Du P, Meng XC, Guo L, Li S, *et al*. The effect of *Lactobacillus actobacillus* peptidoglycan on bovine β-lactoglobulin-sensitized mice via TLR2/NF-κB pathway. Iran J Allergy Asthma Immunol 2017;16:147-58.
34. Wang S, Ahmadi S, Nagpal R, Jain S, Mishra SP, Kavanagh K, *et al*. Lipoteichoic acid from the cell wall of a heat killed *Lactobacillus paracasei* D3-5 ameliorates aging-related leaky gut, inflammation and improves physical and cognitive functions: From *C. elegans* to mice. Geroscience 2020;42:333-52.

35. Wang K, Pramod SN, Pavase TR, Ahmed I, Lin H, Liu L, *et al*. An overview on marine anti-allergic active substances for alleviating food-induced allergy. Crit Rev Food Sci Nutr 2020;60:2549-63.
36. Chen YS, Jan RL, Lin YL, Chen HH, Wang JY. Randomized placebo-controlled trial of *Lactobacillus* on asthmatic children with allergic rhinitis. Pediatr Pulmonol 2010;45:1111-20.
37. Giovannini M, Agostoni C, Riva E, Salvini F, Ruscitto A, Zuccotti GV, *et al*.; Felicita Study Group. A randomized prospective double blind controlled trial on effects of long-term consumption of fermented milk containing *Lactobacillus casei* in pre-school children with allergic asthma and/or rhinitis. Pediatr Res 2007;62:215-20.
38. Ishida Y, Nakamura F, Kanzato H, Sawada D, Hirata H, Nishimura A, *et al*. Clinical effects of *Lactobacillus acidophilus* strain L-92 on perennial allergic rhinitis: A double-blind, placebo-controlled study. J Dairy Sci 2005;88:527-33.
39. Lin J, Zhang Y, He C, Dai J. Probiotics supplementation in children with asthma: A systematic review and meta-analysis. J Paediatr Child Health 2018;54:953-61.
40. Lin WY, Fu LS, Lin HK, Shen CY, Chen YJ. Evaluation of the effect of *Lactobacillus paracasei* (Hf.A00232) in children (6-13 years old) with perennial allergic rhinitis: A 12-week, double-blind, randomized, placebo-controlled study. Pediatr Neonatol 2014;55:181-8.

Original Article

Use of Pulse Oximetry to Screen for Infant Obstructive Sleep Apnoea

Andy Cheuk-ting Hou, Eric Yat-tung Chan, Ka-li Kwok, Mei-yee Lau, Shuk-yu Leung
Department of Paediatrics, Kwong Wah Hospital, Hong Kong SAR, China

Abstract

Introduction: Pulse oximetry is currently used to screen for obstructive sleep apnoea (OSA) in children. However, its use in infant has not yet been well studied. **Aim:** The aim of this study was to develop a screening criterion using pulse oximetry to identify infant with probable OSA. **Materials and Methods:** This was a retrospective cross-sectional study including infants <1 year of age with features of upper airway obstruction or requiring home oxygen to find associations between obstructive apnoea hypopnoea index (OAHI) in infant polysomnography (PSG) and parameters in pulse oximetry by Spearman Rho's correlation. The factor with the strongest correlation is further analysed by receiver-operating characteristic (ROC) curve to identify a cutoff with highest Youden index to screen for probable OSA (OAHI >2 per hour). **Results:** A total of 27 infants were studied. The index of oxygen desaturation with SpO2 <90% per sampled hour (ODI<90%) had the best correlation with OAHI (r = 0.52, P = 0.005). Using the cutoff of ODI<90% more than 1.3 per hour, the sensitivity and specificity for identifying OAHI >2 per hour was 77% and 71%, respectively. **Conclusion:** Infant pulse oximetry can be a useful tool to screen for probable infant OSA especially for paediatric units not offering infant PSG service.

Keywords: Infant, obstructive sleep apnoea, oximetry

Introduction

Obstructive sleep apnoea (OSA) has been reported to be associated with sudden infant death syndrome long ago.[1-3] Recent studies reported infants with snoring or OSA had poorer neurocognitive outcomes.[4-7] Polysomnography (PSG) remains the gold standard to diagnose infant with OSA.[8,9] Yet the availability of infant PSG in paediatric units is limited due to its sophisticated and labour-intensive nature. Pulse oximetry was introduced as a screening test for OSA in children in 2000.[10] It gains popularity in research and clinical use in the past decades.[11,12] Recent research further focuses on its simplicity and accuracy.[13,14] However, publications on pulse oximetry to screen for infant OSA and its clinical use is very limited.[15] The aim of this study was to develop a screening criterion using pulse oximetry to identify infant with probable OSA for earlier referral to diagnosis and intervention.

Materials and Methods

This was a retrospective cross-sectional study conducted in Kwong Wah Hospital (Hong Kong) from December 2019 to December 2020. The study included infants aged 12 months or below. These subjects simultaneously underwent a PSG and a separate pulse oximetry study. Infants with cyanotic heart diseases or severe hypoxic ischemic encephalopathy were excluded from the study.

PSG was performed by qualified sleep technologists in sleep laboratory with a digitized system (Siesta, Profusion 3 Software, Compumedics, Australia).[16] The standard infant montage was used and the following parameters were recorded during the study: electroencephalogram (EEG) F3-M2, F4-M1, O1-M2, O2-M1, C4-M1, C3-M2; electrooculogram (EOG); submental, tibial, and intercostal electromyogram (EMG); electrocardiography (ECG); airflow with nasal pressure transducer and

Access this article online

Quick Response Code:

Website: www.prccm.org

DOI: 10.4103/prcm.prcm_3_22

Address for correspondence: Dr. Andy Cheuk-ting Hou, Department of Paediatrics, Kwong Wah Hospital, 25 Waterloo Road, Hong Kong SAR, China.
E-mail: hct741@ha.org.hk

Submitted: 31-03-2022 **Revised:** 27-05-2022
Accepted: 13-06-2022 **Published:** 23-09-2022

How to cite this article: Hou AC, Chan EY, Kwok KL, Lau MY, Leung SY. Use of pulse oximetry to screen for infant obstructive sleep apnoea. Pediatr Respirol Crit Care Med 2021;5:70-6.

oral thermal sensor; oxygen saturation and pulse waveform by build-in pulse oximeter; carbon dioxide level by transcutaneous carbon dioxide monitor (TCM 4, Radiometer, Copenhagen, Denmark); rib cage and abdominal volume changes using respiratory inductance plethysmograph (RIP); sleep characteristics by position sensor, snoring microphone and video monitoring using an infrared video camera. Infant and paediatric sleep staging rules of American Academy of Sleep Medicine (AASM) manual version 2.4 were observed.[17] Infants staging was done in children younger than 2 months and the child staging to older children. AASM criteria for obstructive apnoea and obstructive hypopnoea were employed.

Pulse oximetry study was recorded by Masimo Radical-7 pulse-oximeter. Data were downloaded to PROFOX software for analysis. Periods with low Signal IQ (Signal Identification and Quality indicator) were excluded from interpretation as artefacts. Awake periods when the infant's eyes were opened or during crying or feeding were manually excluded. This is done by one same independent observer, not involved in PSG interpretation, using 5–10 min, to quickly screen through the video captured by the infrared camera recorded during the pulse oximetry study and PSG.

Several oximetry parameters were analysed and are listed in Table 1. These included $ODI4_0$: index of oxygen desaturation ≥4% from baseline (ODI4) for events lasting more than 0 s per sampled hour; $ODI4_{10}$: ODI4 for events lasting more than or equal to 10 s per sampled hour; $ODI3_0$: index of oxygen desaturation ≥3% from baseline (ODI3) for events lasting more than 0 s per sampled hour; $ODI3_{10}$: ODI3 for events lasting more than or equal to 10 s per sampled hour; ODI<90%: index of oxygen desaturation with SpO2 <90% per sampled hour; cluster of 5: ≥5 drops of SpO2 ≥4% from baseline within 30 min; cluster of 3: ≥3 drops of SpO2 ≥4% from baseline within 30 min; McGill score by Nixon in 2004.[18]

All statistical analyses were performed by using IBM SPSS Statistics for Windows, Version 25.0. Separate Spearman Rho's correlation for each mentioned oximetry parameters with OAHI were determined. Receiver-operating characteristic (ROC) curves were plotted for the oximetry parameter with the most significant Spearman's Rho's correlation to OAHI. The cutoff level with the optimal combination of sensitivity and specificity was calculated using the Youden index. The area under curve (AUC) reflects the accuracy of the oximetry parameters in predicting OAHI >2 per hour and >5 per hour in PSG. A value of $P < 0.05$ was considered statistically significant.

This study was approved by the Hong Kong Hospital Authority Kowloon Central Cluster Ethics Committee.

Results

This study included 27 infants consisted of 17 boys and 10 girls, of which 17 were ex-preterm infants. The median chronological age was 122 days and the median corrected age was 105 days. The indications for PSG were moderate-to-severe bronchopulmonary dysplasia (BPD) (n = 13), upper airway obstruction (n = 13), and recurrent clinical apnoea (n = 1).

Median total sleep time, study time, and sleep efficiency of the PSGs were 174 min, 219 min, and 80.5%, respectively. The median obstructive apnoea hypopnoea index (OAHI) of the subjects was 1.8 per hour.

For pulse oximetry, the median study time was 244 min, the median time excluded as artefacts, and awake period was 12 min. The median of $ODI4_0$ was 13.2 per hour; $ODI4_{10}$ was 5.1 per hour; $ODI3_0$ was 24.0 per hour; $ODI3_{10}$ was 10.0 per hour; ODI<90% was 1.4 per hour; cluster of 5 was 0.8 per hour; and cluster of 3 was 1.2 per hour. Using McGill scoring, 9 infants scored 1; 11 infants scored 2; and 7 infants scored 3. These are summarized in Table 2.

The Spearman's Rho correlation between each oximetry parameter and OAHI (with p-value <0.05) were as follows: 0.498 for $ODI4_0$; 0.413 for $ODI4_{10}$; 0.427 for $ODI3_0$; 0.520 for ODI<90%; 0.493 for cluster of 5 per hour; and 0.414 for McGill score. The results of $ODI3_{10}$ and cluster of 3 per hour were statistically insignificant. These are summarized in Table 3. ODI <90% had the highest correlation with OAHI (r = 0.52, P = 0.005). This is shown in Figure 1.

ROCs were derived from logistic regression models with OAHI >2 per hour and >5 per hour as response variables and ODI<90% as covariate. The AUC for OAHI >2 per

Table 1: Oximetry parameters analysed and their abbreviations

$ODI4_0$	Index of oxygen desaturation ≥4% from baseline for events lasting more than 0 s per sampled hour
$ODI4_{10}$	Index of oxygen desaturation ≥4% from baseline for events lasting more than or equal to 10 seconds per sampled hour
$ODI3_0$	Index of oxygen desaturation ≥3% from baseline for events lasting more than 0 s per sampled hour
$ODI3_{10}$	Index of oxygen desaturation ≥3% from baseline for events lasting more than or equal to 10 seconds per sampled hour
ODI<90%	Index of oxygen desaturation with SpO2 <90% per sampled hour
Cluster of 5	≥5 drops of SpO2 ≥4% from baseline within 30 min
Cluster of 3	≥3 drops of SpO2 ≥4% from baseline within 30 min
	McGill score

Table 2: Demographics; infant polysomnography and pulse oximetry parameters

Variables	Total (n = 27) Median (IQR)	OAHI<=2 (n = 14) Median (IQR)	OAHI>2 (n = 13) Median (IQR)	*P* Value
Maturity, *n*(%):				
Term (>=37 week)	10 (37%)	6 (43%)	4 (31%)	0.695
Preterm (<37 week)	17 (63%)	8 (57%)	9 (69%)	
Gender, *n*(%):				
Female	10 (37%)	4 (29%)	6 (46%)	0.345
Male	17 (63%)	10 (71%)	7 (54%)	
Indications, *n*(%):				
BPD	11 (41%)	5 (36%)	6 (46%)	0.581
Upper airway obstruction	15 (55%)	9 (64%)	6 (46%)	0.343
Recurrent clinical apnoea	1 (4%)	0 (0%)	1 (8%)	0.481
Chronological age, days	122 (94 to 162)	127 (71 to 173)	114 (99 to 157)	0.734
Corrected age, days	105 (62 to 124)	112 (58 to 125)	94 (63 to 124)	0.734
Infant PSG parameters:				
Study time, min	219 (198 to 239)	232 (202 to 242)	208 (197 to 226)	0.133
Total sleep time, min	174 (160 to 194)	190 (160 to 206)	169 (160 to 175)	0.069
Sleep efficiency, %	81 (75 to 90)	83 (77 to 92)	77 (74 to 84)	0.159
OAHI/h	1.8 (1.1 to 4.3)	**1.1 (0.0 to 1.6)**	**4.3 (2.6 to 5.2)**	**<0.001**
CAI/h	2.3 (1.2 to 4.3)	1.6 (1.1 to 3.5)	3.7 (1.4 to 7.0)	0.099
SpO2 nadir, %	82 (79 to 86)	83 (80 to 87)	80 (78 to 85)	0.158
Pulse oximetry parameters:				
Study time, min	244 (220 to 257)	250 (224 to 266)	220 (210 to 253)	0.085
Artefacts time, min	12 (5 to 25)	10 (3 to 13)	19 (12 to 43)	0.085
$ODI4_0$/h	13.2 (8.9 to 18.8)	9.4 (7.0 to 15.5)	17.1 (11.3 to 22.3)	0.037
$ODI4_{10}$/h	5.1 (3.3 to 8.4)	3.9 (1.9 to 7.1)	6.6 (4.7 to 8.9)	0.094
$ODI3_0$/h	24.0 (14.0 to 33.0)	17.0 (13.5 to 30.3)	29.0 (19.5 to 37.5)	0.126
$ODI3_{10}$/h	10.0 (7.7 to 16.9)	9.5 (7.0 to 15.0)	14.5 (8.0 to 18.7)	0.264
ODI<90%	1.4 (0.9 to 3.5)	**1.2 (0.5 to 1.7)**	**2.8 (1.2 to 4.6)**	**0.016**
Cluster of 5/h	0.8 (0.4 to 1.2)	0.6 (0.3 to 1.3)	0.9 (0.6 to 1.5)	0.120
Cluster of 3/h	1.2 (0.9 to 1.4)	1.2 (0.7 to 1.4)	1.2 (0.9 to 1.6)	0.480
McGill classification, *n*(%):				
Score 1	9 (33%)	6 (43%)	3 (23%)	0.069
Score 2	11 (41%)	7 (50%)	4 (31%)	
Score 3	7 (26%)	1 (7%)	6 (46%)	

BPD = bronchopulmonary dysplasia, PSG = polysomnography, OAHI = obstructive apnoea hypopnoea index, CAI = central apnoea index, SpO2 = oxygen saturation, $ODI4_0$ = index of oxygen desaturation ≥4% from baseline (ODI4) for events lasting more than 0 s per sampled hour, $ODI4_{10}$ = ODI4 for events lasting more than or equal to 10 s per sampled hour, $ODI3_0$ = index of oxygen desaturation ≥3% from baseline (ODI3) for events lasting more than 0 s per sampled hour, $ODI3_{10}$ = ODI3 for events lasting more than or equal to 10 s per sampled hour, ODI = oxygen desaturation index

Cluster of 5: ≥5 drops of SpO2 ≥4% from baseline within 30 min

Cluster of 3: ≥3 drops of SpO2 ≥4% from baseline within 30 min

Frequencies and percentages [*n* (%)], or medians and interquartile range (median [IQR]) are shown.

P Values were calculated with chi-square test or Mann–Whitney *U* test.

hour was 0.77 (P = 0.016). Using the cutoff of ODI<90% more than 1.3 per hour, the sensitivity and specificity for identifying OAHI >2 per hour was 77% and 71%, respectively. This is shown in Figure 2A and Table 4A. The AUC for OAHI >5 per hour was 0.98 (P = 0.008). Using the cutoff of ODI<90% more than 3.8 per hour, the sensitivity and specificity for identifying OAHI >5 per hour was 100% and 91.7%, respectively. This is shown in Figure 2B and Table 4B.

Discussion

This study showed that video-adjusted infant pulse oximetry had a significant correlation with in-hospital PSG. Index of oxygen desaturation with SpO2 <90% per sampled hour (ODI<90%) had the best correlation with OAHI. Non-video adjusted oximetry with automatic artefacts exclusion may still resulted in SpO2 drops and SpO2 nadir much lower than the baseline leading to questionable preciseness.

Yet there is not a consensus on defining infant OSA. American Thoracic Society (ATS) suggested that an infant found to have an apnoea–hypopnoea index (AHI) greater than 2 per hour should alert physicians as to the probable presence of significant OSA.[19] European Respiratory Society practice statement for obstructive sleep disordered breathing in 1- to 23-month-old children defined OSA with OAHI ≥1 per hour.[20] Kato and Schlüter reported obstructive apnoea was rarely seen in healthy term infants in their publications in early 2000s.[21,22] However, hypopnoea index (HI) was not reported in both studies. Kato explained that their PSG recording techniques in 1991 to 1993 did not allow for identification of such events. In 2013, 2015 and 2019, Brockmann, Duenas-Meza and Daftary, respectively, published new reference values for infant PSG from 'healthy' term subjects.[23-25] Data on HI were included in these three studies. The median OAHI ranged from 0.5 per hour to 7.7 per hour, in which younger infants has higher median OAHI. The significant diversified findings between earlier and later publications were partly contributed by the advancement in technology and equipment sensitivity nowadays compared to the first infant PSG in Jan 1989 by Schlüter.[26] Moreover, there had been changes in the AASM scoring criteria for defining an obstructive apnoea event and an obstructive hypopnoea event throughout the past two decades.[27-30] Some otorhinolaryngologists has been using OAHI ≥1.5 to define infant OSAS in their publications.[31-33] Up till now, we still lack a universally adopted cutoff for defining OSAS in infants. From current evidence, we can predict the 'normal' OAHI in infant is likely represented by an inverse proportion curve, and join as a continuum with the cutoff of OAHI <1 in children. This study hence adopted a fixed cutoff of OAHI >2 to screen for presence of probable OSA among infants.

Table 3: Correlation between OAHI and pulse oximetry parameters

Variables	*r*	*P* Value
$ODI4_0$/hour	0.498	0.008
$ODI4_{10}$/hour	0.413	0.032
$ODI3_0$/hour	0.427	0.027
$ODI3_{10}$/hour	0.356	0.068
ODI<90%	**0.520**	**0.005**
Cluster of 5/hour	0.414	0.032
Cluster of 3/hour	0.241	0.226
McGill score	0.493	0.009

OAHI = obstructive apnoea hypopnoea index, $ODI4_0$ = index of oxygen desaturation ≥4% from baseline (ODI4) for events lasting more than 0 s per sampled hour, $ODI4_{10}$ = ODI4 for events lasting more than or equal to 10 s per sampled hour, $ODI3_0$ = index of oxygen desaturation ≥3% from baseline (ODI3) for events lasting more than 0 s per sampled hour, $ODI3_{10}$ = ODI3 for events lasting more than or equal to 10 s per sampled hour, ODI = oxygen desaturation index

Cluster of 5: ≥5 drops of SpO2 ≥4% from baseline within 30 min

Cluster of 3: ≥3 drops of SpO2 ≥4% from baseline within 30 min

r values were correlation coefficients and *P* value were calculated using Spearman Rho's correlation analysis

Ehsan included 38 infants over their 8-year study period.[15] They have shown that ODI from home- or hospital-based oximetry has a significant positive correlation with OAHI in PSG for young infants with symptoms or risk factors for sleep disordered breathing. An average of 3 hours data were excluded due to artefact in each oximetry of their subjects. They reported $ODI4_0$ >3 is useful to screen for OAHI>5 in symptomatic infants (noisy breathing/snoring or history of ALTE/BRUE) with a sensitivity of 100%, specificity of 35%. They showed that $ODI4_0$ was not a good parameter to screen for milder OSA.

In this study, ODI<90%, McGill score and cluster of 5 per hour are good predictors of probable OSA. Why ODI<90% is chosen for further analysis is because of its

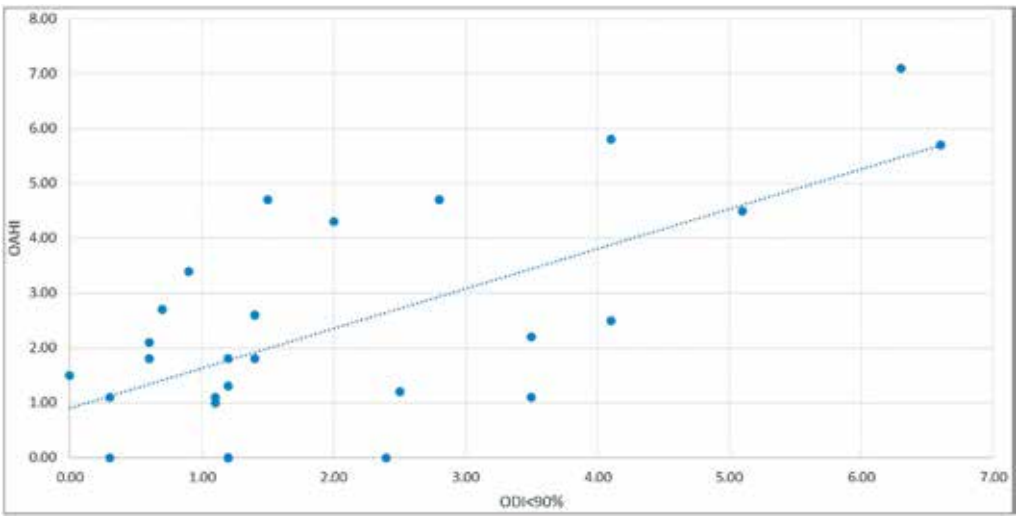


Figure 1: Spearman's rho correlation analysis between ODI<90% and OAHI

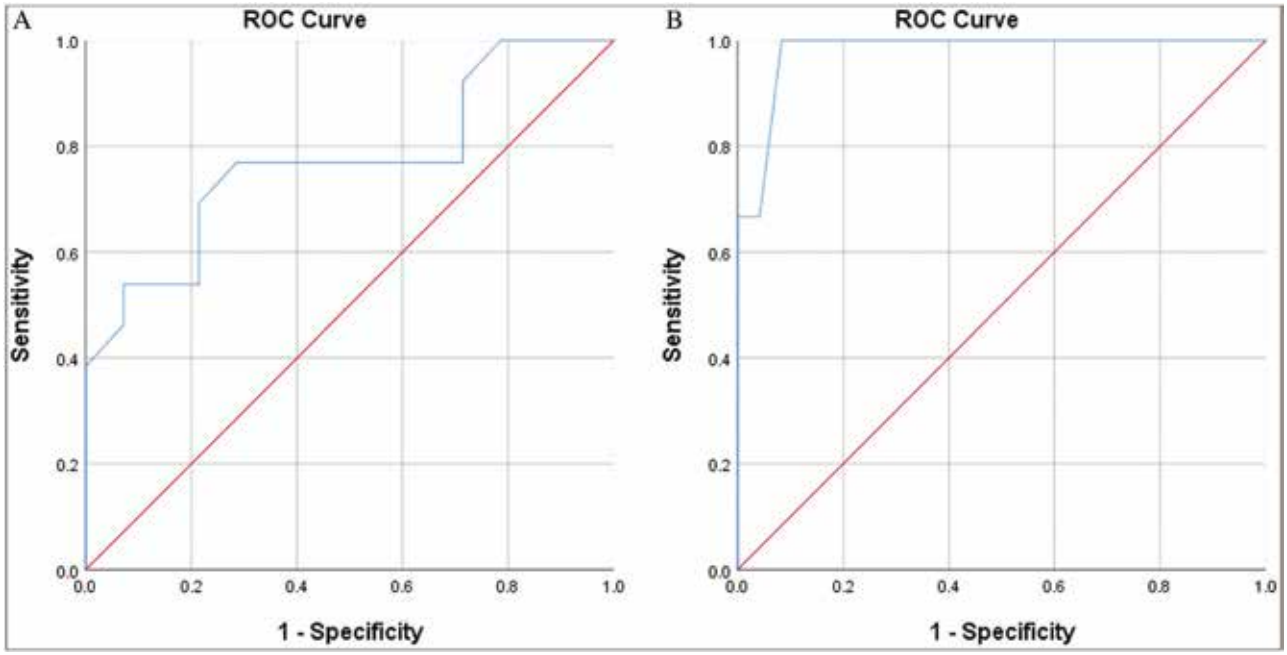


Figure 2: (A) ROC curves with OAHI >2 and ODI<90%. (B) ROC curves with OAHI >5 and ODI<90%

Table 4A: Receiver-operating characteristic (ROC) curve analysis of ODI<90% for detecting OAHI>2/h

Cutoff point, ODI<90%, >/h	Sensitivity	Specificity	Youden index
1.00	0.769	0.286	0.055
1.15	0.769	0.429	0.198
1.30	**0.769**	**0.714**	**0.484**
1.45	0.692	0.786	0.478
1.75	0.615	0.786	0.401
2.20	0.538	0.786	0.324

Youden index = sensitivity + specificity – 1

Table 4B: Receiver-operating characteristic (ROC) curve analysis of ODI<90% for detecting OAHI>5/h

Cutoff point, ODI<90%, >/h	Sensitivity	Specificity	Youden Index
1.00	1.000	0.292	0.292
1.15	1.000	0.375	0.375
1.30	1.000	0.542	0.542
1.45	1.000	0.625	0.625
1.75	1.000	0.667	0.667
2.20	1.000	0.708	0.708
2.45	1.000	0.750	0.750
2.65	1.000	0.792	0.792
3.15	1.000	0.833	0.833
3.80	**1.000**	**0.917**	**0.917**
4.60	0.667	0.958	0.625
5.70	0.667	1.000	0.667

Youden index = sensitivity + specificity – 1

highest correlation coefficient and its simplicity in data collection. This study showed that ODI<90% of >1.3 per hour, can detect OAHI >2 per hour with a sensitivity and specificity of 77% and 71%, respectively. The strength of this current study is standardization, simultaneousness and conveniency. All our infant PSGs were performed and scored by a standardized protocol in accordance to AASM manual version 2.4.[17] The interpretation is done

by the same group of qualified Paediatric Respiratory Medicine specialist with a decade or more experience in sleep medicine. Both PSG and oximetry of each subject were performed simultaneously but independently. Our oximetry recording technically started earlier and ended later than PSG; this is represented by the discrepancy in the reported study time. In daily practice, most pulse oximetry machines can automatically count for the number of times that SpO2 drops below 90%. Thus, it is convenient to use the suggested ODI<90% cutoff as a screening tool.

There are several limitations in this study. First, the small sample size of 27 infants. Second, our PSG recorded a total sleep time close to the lower margin of the median range (2.5 to 6 hours) reported in those normal value studies;[20-22,24] however, each of our PSG has included portions of REM and non-REM (active and quiet) sleep. Third, we only recruited infants <1 year of age with features of upper airway obstruction or requiring home oxygen in this study, this may cause selection bias in our findings. Hence generalization of its utility to healthy infants may not be congruent.

Galway reported that 59% of children screened positive by pulse oximetry for OSA on at least one of the three nights compared with 38% if only one night had been performed.[34] If oximetry is abnormal on the first night there is no requirement to do further recordings on subsequent nights. They also found that reducing the threshold duration for technically adequate oximetry traces to a minimum of 4 h increased the number of patients who would have been screened positive for OSA by McGill classification.

For screening infant at risk of OSA, we suggest a video-taped pulse oximetry of 3–4 hours with accurate artefact exclusion. Obvious awake periods where the infant is crying or feeding should be manually excluded by quick screening through the recorded video. Repeat pulse oximetry in screened negative but clinically high-risks patient may help to reduce the possible 'first night effect' though this phenomenon has not been studied in infants.[35,36] Any screened positive infants should be referred to have a formal infant PSG for OSA confirmation and further management.

Home oximetry screening for OSA in Hong Kong children is not as popular as foreign countries. Infant home oximetry screening is even rare. Unobserved pulse oximetry in young infants usually posted us with great difficulty to distinguish motion artefacts from genuine desaturation events.[37,38] The aim of this study was to provide a solution to paediatric units without infant PSG service to identify babies at risk of OSA by employing observed in-hospital oximetry. A video-taped home oximetry allowing accurate artefact exclusion may be considered as an alternative, although further study with similar methodology should be carried out in home setting for verification. Directly applying the result of this study for unobserved oximetry to screen for OSA in infants may not be accurate.

In conclusion, video-assisted pulse oximetry using ODI<90% is a simple parameter to predict probable OSA with a relatively good sensitivity and specificity. Although more effort is spent in editing a video adjusted oximetry, less-sophisticated tools and time is required in performing and reporting an infant PSG.

Financial support and sponsorship

This study was supported by the Tung Wah Group of Hospitals Research Fund 2020/2021.

Conflicts of interest

The authors declare that they have no conflicts of interests.

Ethical approval

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Hong Kong Hospital Authority Kowloon Central Cluster Ethics Committee.

Informed consent

Not applicable to this study.

References

1. Guilleminault C, Ariagno R, Korobkin R, Nagel L, Baldwin R, Coons S, *et al*. Mixed and obstructive sleep apnea and near miss for sudden infant death syndrome: 2. Comparison of near miss and normal control infants by age. Pediatrics 1979;64:882-91.
2. Kahn A, Groswasser J, Rebuffat E, Sottiaux M, Blum D, Foerster M, *et al*. Sleep and cardiorespiratory characteristics of infant victims of sudden death: A prospective case-control study. Sleep 1992;15:287-92.
3. Kato I, Groswasser J, Franco P, Scaillet S, Kelmanson I, Togari H, *et al*. Developmental characteristics of apnea in infants who succumb to sudden infant death syndrome. Am J Respir Crit Care Med 2001;164:1464-9.
4. Montgomery-Downs HE, Gozal D. Snore-associated sleep fragmentation in infancy: Mental development effects and contribution of secondhand cigarette smoke exposure. Pediatrics 2006;117:e496-502.
5. Piteo AM, Kennedy JD, Roberts RM, Martin AJ, Nettelbeck T, Kohler MJ, *et al*. Snoring and cognitive development in infancy. Sleep Med 2011;12:981-7.
6. Smith CB, Walker K, Badawi N, Waters KA, MacLean JE. Impact of sleep and breathing in infancy on outcomes at three years of age for children with cleft lip and/or palate. Sleep 2014;37:919-25.
7. Bandyopadhyay A, Harmon H, Slaven JE, Daftary AS. Neurodevelopmental outcomes at two years of age for premature infants diagnosed with neonatal obstructive sleep apnea. J Clin Sleep Med 2017;13:1311-7.
8. Crowell DH, Brooks LJ, Colton T, Corwin MJ, Hoppenbrouwers TT, Hunt CE, *et al*. Infant polysomnography: Reliability. Collaborative home infant monitoring evaluation (Chime) steering committee. Sleep 1997;20:553-60.
9. Crowell DH, Kulp TD, Kapuniai LE, Hunt CE, Brooks LJ, Weese-Mayer DE, *et al*.; CHIME Study Group. Infant polysomnography: Reliability and validity of infant arousal assessment. J Clin Neurophysiol 2002;19:469-83.

10. Brouillette RT, Morielli A, Leimanis A, Waters KA, Luciano R, Ducharme FM. Nocturnal pulse oximetry as an abbreviated testing modality for pediatric obstructive sleep apnea. Pediatrics 2000;105:405-12.
11. Álvarez D, Alonso-Álvarez ML, Gutiérrez-Tobal GC, Crespo A, Kheirandish-Gozal L, Hornero R, *et al*. Automated screening of children with obstructive sleep apnea using nocturnal oximetry: An alternative to respiratory polygraphy in unattended settings. J Clin Sleep Med 2017;13:693-702.
12. Crespo A, Álvarez D, Kheirandish-Gozal L, Gutiérrez-Tobal GC, Cerezo-Hernández A, Gozal D, *et al*. Assessment of oximetry-based statistical classifiers as simplified screening tools in the management of childhood obstructive sleep apnea. Sleep Breath 2018;22:1063-73.
13. Vaquerizo-Villar F, Álvarez D, Kheirandish-Gozal L, Gutiérrez-Tobal GC, Barroso-García V, Crespo A, *et al*. Wavelet analysis of oximetry recordings to assist in the automated detection of moderate-to-severe pediatric sleep apnea-hypopnea syndrome. PLoS One 2018;13:e0208502.
14. Jiménez-García J, Gutiérrez-Tobal GC, García M, Kheirandish-Gozal L, Martín-Montero A, Álvarez D, *et al*. Assessment of airflow and oximetry signals to detect pediatric sleep apnoea-hypopnoea syndrome using adaboost. Entropy (Basel) 2020;22:670.
15. Ehsan Z, He S, Huang G, Hossain MM, Simakajornboon N. Can overnight portable pulse oximetry be used to stratify obstructive sleep apnea risk in infants? A correlation analysis. Pediatr Pulmonol 2020;55:2082-8.
16. Kline C, Krupski T. Infant and toddler polysomnography. Respir Care Clin N Am 2006;12:1-10.
17. Berry RB, Brooks R, Gamaldo C, Harding SM, Lloyd RM, Quan SF, *et al*. Aasm scoring manual updates for 2017 (version 2.4). J Clin Sleep Med 2017;13:665-6.
18. Nixon GM, Kermack AS, Davis GM, Manoukian JJ, Brown KA, Brouillette RT. Planning adenotonsillectomy in children with obstructive sleep apnea: The role of overnight oximetry. Pediatrics 2004;113:e19-25.
19. Katz ES, Mitchell RB, D'Ambrosio CM. Obstructive sleep apnea in infants. Am J Respir Crit Care Med 2012;185:805-16.
20. Kaditis AG, Alonso Alvarez ML, Boudewyns A, Abel F, Alexopoulos EI, Ersu R, *et al*. ERS statement on obstructive sleep disordered breathing in 1- to 23-month-old children. Eur Respir J 2017;50:1700985.
21. Kato I, Franco P, Groswasser J, Kelmanson I, Togari H, Kahn A. Frequency of obstructive and mixed sleep apneas in 1,023 infants. Sleep 2000;23:487-92.
22. Schlüter B, Buschatz D, Trowitzsch E. Polysomnographic reference curves for the first and second year of life. Somnologie 2001;5:3-16
23. Brockmann PE, Poets A, Poets CF. Reference values for respiratory events in overnight polygraphy from infants aged 1 and 3months. Sleep Med 2013;14:1323-7.
24. Duenas-Meza E, Bazurto-Zapata MA, Gozal D, González-García M, Durán-Cantolla J, Torres-Duque CA. Overnight polysomnographic characteristics and oxygen saturation of healthy infants, 1 to 18 months of age, born and residing at high altitude (2,640 meters). Chest 2015;148:120-7.
25. Daftary AS, Jalou HE, Shively L, Slaven JE, Davis SD. Polysomnography reference values in healthy newborns. J Clin Sleep Med 2019;15:437-43.
26. Hirshkowitz M. Polysomnography: Understanding this technology's past might guide future developments. Ieee Pulse 2014;5:26-8.
27. Sleep-related breathing disorders in adults: Recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. Sleep 1999;22:667-89.
28. Wiater A, Niewrth HJ, Pediatric Task Force in the German Sleep Society (DGSM). Polysomnographic standards for infants and children. Somnologie 2000;4:39-42.
29. Iber C, Ancoli-Israel S, Chesson AL, Quan SF. for the American Academy of Sleep Medicine. The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications. 1st ed. Westchester, IL: American Academy of Sleep Medicine; 2007.
30. Berry RB, Budhiraja R, Gottlieb DJ, Gozal D, Iber C, Kapur VK, *et al*.; American Academy of Sleep Medicine. Rules for scoring respiratory events in sleep: Update of the 2007 AASM manual for the scoring of sleep and associated events. Deliberations of the sleep apnea definitions task force of the American academy of sleep medicine. J Clin Sleep Med 2012;8:597-619.
31. Muntz H, Wilson M, Park A, Smith M, Grimmer JF. Sleep disordered breathing and obstructive sleep apnea in the cleft population. Laryngoscope 2008;118:348-53.
32. Robison JG, Wilson C, Otteson TD, Chakravorty SS, Mehta DK. Increased eustachian tube dysfunction in infants with obstructive sleep apnea. Laryngoscope 2012;122:1170-7.
33. Leonardis RL, Robison JG, Otteson TD. Evaluating the management of obstructive sleep apnea in neonates and infants. Jama Otolaryngol Head Neck Surg 2013;139:139-46.
34. Galway NC, Maxwell B, Shields M, O'Donoghue D. Use of oximetry to screen for paediatric obstructive sleep apnoea: Is one night enough and is 6 hours too much? Arch Dis Child 2021;106:58-61.
35. Agnew HW Jr, Webb WB, Williams RL. The first night effect: An EEG study of sleep. Psychophysiology 1966;2:263-6.
36. Scholle S, Scholle HC, Kemper A, Glaser S, Rieger B, Kemper G, *et al*. First night effect in children and adolescents undergoing polysomnography for sleep-disordered breathing. Clin Neurophysiol 2003;114:2138-45.
37. Fletcher J, Page M, Jeffery HE. Sleep states and neonatal pulse oximetry. Sleep 1998;21:305-10.
38. Wellington G, Elder D, Campbell A. 24-hour oxygen saturation recordings in preterm infants: Editing artefact. Acta Paediatr 2018;107:1362-9.

Similac®
Total Comfort

LEADING THROUGH HMO INNOVATION

SIMILAC® TOTAL COMFORT

WITH 2′-FL HMO

FOR A BROAD SPECTRUM OF INTOLERANCE ISSUES

DUAL IMMUNE BLEND

UNIQUE COMBINATION OF PHF AND DUAL IMMUNE BLEND DESIGNED FOR **REDUCING ALLERGENICITY**[2††] AND **OPTIMIZING IMMUNE RESPONSE**[3,4]

UNIQUE DUAL-PATHWAY CARBOHYDRATE BLEND

Non-competing carbohydrate pathways improve digestion and absorption[1]

CLINICALLY PROVEN

FOR A FAST RELIEF OF GI INTOLERANCE SYMPTOMS IN **1 DAY**[5] & SUSTAINED THE IMPROVEMENT OVER **28 DAYS**[5]

Similac Mom®	Similac®	Similac® Total Comfort	PediaSure®
LACTATION COMPLETE NUTRITION FORMULA THAT HELPS UPLIFT LACTATION POWER^	REWRITING IMMUNITY STANDARD‡ 5 HMOs[§] + BB-12®[¶] FORMULA	4X WITH 2′-FL HMO+ SPECIALIZED FORMULA FOR A BROAD SPECTRUM OF INTOLERANCE ISSUES	CLINICALLY PROVEN CHILD GROWTH FORMULA WITH MOST PRIVATE PEDIATRICIANS' RECOMMENDATION#

Chocolate flavor available

*Refers to 100% Partially-Hydrolysed Whey Protein formula can help reduce the risk of cow's milk protein intolerance, 98% Lactose Free formula can help reduce the risk of lactose intolerance, 0% Palm Olein Oil formula can help reduce the risk of dry and hard stools, and the prebiotics can help soften the stools. + HMO : Human Milk Oligosaccharide 2′-FL (20 mg / 100ml), not from human milk. ^ NTs: Nucleotides (Stage 1 - 5.8 mg/ 100 ml , stage 2 - 2.3mg / 100ml) ††Partially hydrolyzed whey protein formulas have been shown to reduce the incidence of eczema during the first 3 years in infants at risk of allergy. ^Uplifting lactation power refers to help lactating mothers to sustain exclusive breastfeeding for 6 months. According to the medical research article published in February 2019 or before, Abbott Similac® Mom is the only maternal milk formula in Hong Kong with clinical study evidence to support mothers having double chances to sustain exclusive breastfeeding for 6 months (Zhang Z, et al. PLoS ONE 2018, 13(7):e0200519; coordinate with the breastfeeding support plan: includes a 1-off prenatal breastfeeding education, 3 times of postpartum breastfeeding consultation and 2 servings of Similac Mom® per day). Abbott Similac® Mom contains most of the nutrients mentioned in National Institutes of Health (NIH) on the important maternal nutrients during lactation, including protein, DHA (12.5mg/100ml), folic acid, and 18 vitamins and minerals. Suggest to have 2 servings per day with a balanced diet, while staying active and relaxed to support breastfeeding. ‡Compared to the previous formula, Abbott Similac (contains one HMO, 2′-FL), upgraded formula contains 5 HMOs to support immunity. §HMOs: Human Milk Oligosaccharides (2′-FL, 3-FL, 3′-SL, 6′-SL, LNT; Stage 1 & 2: 250mg/100ml; Stage 3 & 4: 180mg/100ml), not from human milk. ¶BB-12® is a registered trademark of Chr. Hansen and the world's most documented Bifidobacterium. Jungersen, Mikkel et al. "The Science behind the Probiotic Strain Bifidobacterium animalissubsp. lactis BB-12®." Microorganisms vol. 2,2 92-110. 28 Mar. 2014. Stage 2-4 contains BB-12® while Stage 1 powder and RTF do not. #PediaSure - The most recommended Child Nutrition Supplement by private pediatricians. Abbott Laboratories Ltd's claim conducted by Nielsen in 2018 among private pediatricians in Hong Kong. Sample size is 57 (Copyright © 2019, The Nielsen Company)

REFERENCES: 1. Southgate DA. Am J Clin Nutr. 1995;62(1 Suppl):203S-211S. 2. von Berg A, et al. J Allergy Clin Immunol. 2008;121(6):1442-1447. 3. Goehring KC, et al. J Nutr. 2016;146(12):2559-2566. 4. Buck RH, et al. Pediatr Res. 2004;56(6):891-900. 5. Reverri EJ, et al. Nutrients. 2018;10(10):1346.

IMPORTANT NOTICE: Breastfeeding is the best source of infant nutrition. Good maternal nutrition is important for the preparation and maintenance of breastfeeding. When infant formulas is to be used, a mother should be aware of the negative effect on breastfeeding along with the financial and social implications of formula feeding, the difficulty of reversing the decision not to breastfeed, and the care that must be taken to prevent partial formula feeding from interfering with lactation. A healthcare professional should be consulted before initiating formula feeding.

商品圖片只供參考。

FOR HEALTHCARE PROFESSIONALS' REFERENCE ONLY

PZZ-COMM-40316

Abbott
雅培