ISSN: 2543-0343 Volume 5 Issue 3 July-September 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

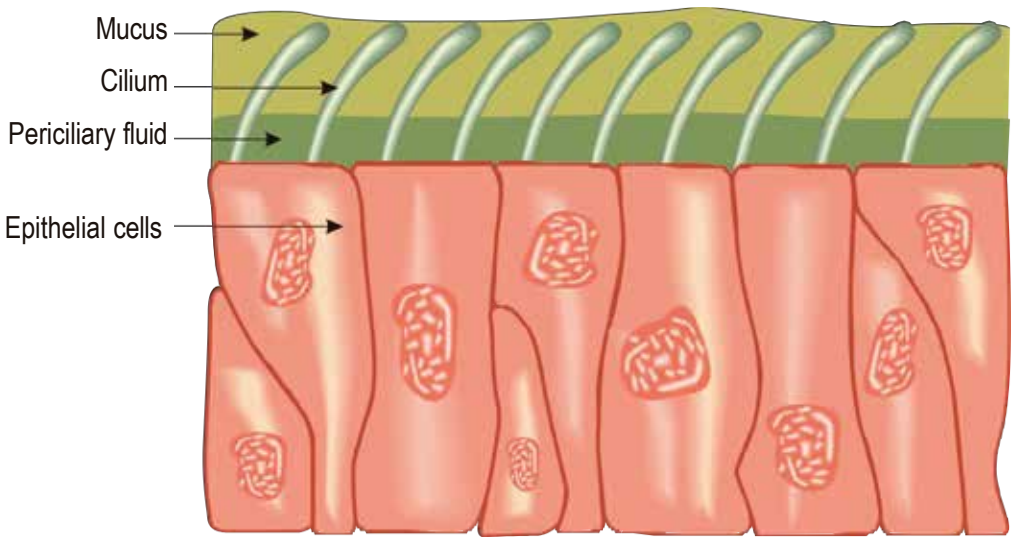
Nasal tissue.
What it is all about

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 3 ¦ July-September 2021

Contents

The Last Mile of COVID-19?

While the COVID-19 pandemic appears to be entering its final phase, there are still many regions of concern, including Southeast Asia. As the BA.4 and BA.5 sub-variants of Omicron have gradually become the dominant strains in Europe and America, people cannot think that the pandemic will end soon.

There are three excellent articles in this issue. The first article is a review article about spontaneous pneumomediastinum (SPM) in children by Dr. Nong *et al*. Besides reminding us that SPM will improve uneventfully in most children, the authors emphasize that some situations may require aggressive treatment, and that the prognosis can be poor if SPM is complicated with certain underlying diseases or complications.

The second article is an original study on obstructive sleep apnea (OSA) in children. In the article, Ms. Fung *et al.* investigated the relationship between the percentage of total sleep time with mouth breathing (SMBP) and post-adenotonsillectomy apnea-hypopnea index in non-obese children. They found that the children with SMBP >10.5% after surgery had a higher risk of residual OSA. This is the first report to demonstrate that SMBP is a significant risk factor for persistent OSA after adenotonsillectomy in non-obese children.

The third article is an invited commentary about diagnostic testing for COVID-19. Accurate and timely diagnostic testing is important to allow for the optimal treatment of patients and evaluate the trend of COVID-19. In this issue, Dr. Rina Triasih brings us an excellent review regarding the diagnostic tests for COVID-19 and when to use them. Molecular tests to identify the RNA of the virus and serological tests to detect the immunoglobulins to SARS-CoV-2 are also discussed in detail.

Hopefully COVID-19 will enter the final stage in the near future, and that we can return to normal life and meet each other again soon!

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Yu-Tsun Su

Department of Pediatrics, E-Da Hospital/I-Shou University, Kaohsiung, Taiwan

Address for correspondence: Dr. Yu-Tsun Su, Department of Pediatrics, E-Da Hospital, School of Medicine for International Students, I-Shou University, Kaohsiung City, Taiwan.
E-mail: suyutsun@gmail.com

Submitted: 23-06-2022 **Revised:** 24-06-2022
Accepted: 24-06-2022 **Published:** 01-08-2022

Access this article online

Quick Response Code:

Website: www.prccm.org

DOI: 10.4103/prcm.prcm_9_22

How to cite this article: Su Y-T. The last mile of COVID-19? Pediatr Respirol Crit Care Med 2021:5:41.

Review Article

Spontaneous Pneumomediastinum in Children

Yen-Jhih Liao[1], Yung-Feng Huang[2,3], Bao-Ren Nong[3,4]

[1]Department of Pediatrics, Kaohsiung Veterans General Hospital, Kaohsiung City, [2]Fu Jen Catholic University Hospital, Taipei, [3]Department of Pediatrics, National Defense Medical Center, Tri-Service General Hospital, Taipei, [4]Division of Pediatric Allergy, Immunology and Rheumatology/Pulmonology, Department of Pediatrics, Kaohsiung Veterans General Hospital, Kaohsiung City, Taiwan ROC

Abstract

Scarce studies about spontaneous pneumomediastinum (SPM) in pediatric patients are published because of lower incidence in a child than an adult. This article is a literature review of pediatric SPM, discussing about aspects of incidence rate, epidemiology, pathophysiology, diagnosis, management, and prognosis about pediatric SPM. In conclusion, SPM is usually a benign disease and treatable with only supportive care. However, poorer prognosis is noted; if it is complicated with other underlying diseases or complications, then aggressive treatment might be needed.

Keywords: Children, pneumomediastinum, primary spontaneous pneumomediastinum, recurrence

Key Messages: Spontaneous pneumomediastinum (SPM) is a rare and usually self-limited disease in pediatric population. However, it might need aggressive treatment and have a poorer prognosis if complicated. Therefore, the evaluation of predisposing factor and caution on complications is important.

Introduction

Pneumomediastinum is defined as the circumstance that air accumulated in the mediastinum. Pneumomediastinum can be categorized into two types: spontaneous and traumatic. Traumatic type is related to blunt or penetrating trauma to the chest or iatrogenic trauma such as mechanical ventilation. SPM can be further classified into primary and secondary types, based on whether there is preexisting lung disease or not.

Compared with adults, it is an uncommon disease in children under 18 years old. Therefore, there were scarce researches of primary pneumomediastinum. This article is a literature review on pneumomediastinum in pediatric patients, mainly about epidemiology, diagnosis, management, and prognosis.

Epidemiology

It is an uncommon disease in the pediatric population. Hauri-Hohl *et al.* reported that it happened commonly in neonatal period, with an estimated incidence of one per 1000, and one-third of the cases received respiratory support prior to diagnosis.[1] There was a peak incidence rate between 6 months old and 3 years old, ranging from one in 800 to one in 42,000 patients presenting at hospital emergency units, which might be related to increased frequency of respiratory tract infection.[2-8] The incidence rate is higher among children with underlying asthma, which is between 0.3% and 5%.[5] In adolescence, thin, tall males were disproportionately affected and seem likely related with predisposing anatomic factors.[9]

Pathogenesis

Most cases of SPM are due to air leakage through ruptures of pulmonary alveoli to the surrounding broncho-vascular sheath.[10] Some result from air leak secondary from the upper respiratory tract, intrathoracic

Access this article online

Quick Response Code:

Website: www.prccm.org

DOI: 10.4103/prcm.prcm_13_21

Address for correspondence: Dr. Bao-Ren Nong, Division of Pediatric Allergy, Immunology and Rheumatology/Pulmonology, Department of Pediatrics, Kaohsiung Veterans General Hospital, No. 386, Dajhong 1st Road, Zuoying District, Kaohsiung City 81362, Taiwan ROC.
E-mail: brnong@gmail.com

Submitted: 10-07-2021 **Revised:** 16-03-2022
Accepted: 08-05-2022 **Published:** 01-08-2022

How to cite this article: Liao Y-J, Huang Y-F, Nong B-R. Spontaneous pneumomediastinum in children. Pediatr Respirol Crit Care Med 2021;5:42-7.

airways, or gastrointestinal tract. The air then moves centripetally along the sheath and dissects to the hilum, eventually spreads into the mediastinum space, or further dissects the loose mediastinal fascia to the subcutaneous area of thorax, upper limbs, neck, peritoneum, spine, and retroperitoneum.[2,11-20]

In some circumstances, air spreads into the pericardial space and causes pneumopericardium. The air may accumulate in the mediastinal space and progress to tension pneumomediastinum or tension pneumopericardium because of rise in mediastinal pressure and compression of intrathoracic structure. Both tension pneumomediastinum and tension pericardium were reported to be the most common happening in patients under mechanical ventilation.[2,21-25]

The predisposing factors or triggers can be found in most cases of SPM [Table 1].[2,8,26,27] Acute asthma attack is the most common trigger, which accounts for 20%–30% of cases.[6,28] Other frequent trigger includes lower respiratory tract infection, vomiting,[29] and Valsalva maneuver (e.g., coughing, sport-related).[17,30]

Coronavirus illness 2019, abbreviated as COVID-19, is a novel disease, which is highly infectious and was declared a universal pandemic in March 2020. Cases of SPM in adult patients with COVID-19 were reported, incidence rate ranging from 0.64% to 13.6%.[51-55] The incidence of pneumomediastinum in COVID-19-related acute respiratory distress syndrome (ARDS) increases compared with ARDS from other causes; larger studies to establish the association are required.[54] In pediatric population, COVID-19 infection complicated with pneumomediastinum was also reported.[55-59] Pneumomediastinum might be considered as a complication of COVID-19 infection because of increased lung frailty and destruction on lung parenchyma, even in infants or children. Early detection and close monitoring are important because it might be a potential indicator of worsening disease and higher mortality rate.[60-62]

Table 1: Causes of SPM in children

Medical conditions
Asthma[2,6-8,31-34]
Respiratory tract infections, including laryngitis, bronchiolitis, measles infection, pertussis, etc.[2,8,33]
Cystic fibrosis[33]
Convulsion, seizure
Gastroesophageal reflux disease
Retropharyngeal abscess[2]
Iatrogenic conditions
Lung function testing[35]
Dental procedures[12,18,36]
Heimlich maneuver[37]
Surgical condition
Foreign body aspiration[38-40]
Rupture of esophagus, gastrointestinal tract[41,42]
Respiratory and Valsalva maneuvers
Cough, crying, screaming[8,36]
Vomiting, especially malnutrition condition (under chemical therapy, anorexia, etc.)[14-16,32,35,43]
Hyperpnea, especially ketoacidosis[44]
High-intensity strength or competitive exercise[5,8,36,45,46]
Valsalva maneuver, including balloon blowing, lifting objects, defecation[17,47]
Inhalation of illegal drug, helium[20,27,44,48-50]
Irritant gases exposure[8,36]
Scuba diving, flying

Evaluation and Diagnosis

Most of the patients are symptomatic when SPM occurs; thus, it is suspected when typical symptoms or signs were noted. The most relevant signs of SPM are chest pain, neck pain, and sore throat.[63] Other common clinical manifestations were dyspnea, cough, odynophagia, and dysphagia.[2,64] Pain is typically retrosternal, exacerbates during inspiration or posture change, and radiates to upper limbs, neck, or back.[2,8,26,65,66] Dyspnea may be caused by chest pain or predisposing lung disease or related to complications such as pneumothorax. Other common symptoms include neck swelling, weakness, torticollis, dysphagia, dysphonia, abdominal pain, or back pain.[2,26,31,45,47,66-72] Some experience low-grade fever (body temperature below 38.5°C) a few hours after other symptoms occur.[20,73,74]

In addition to diagnosis, evaluation should also include reviewing a patient's history to clarify predisposing or trigger factors, excluding other causes of the presenting symptoms, and evaluating complications. The history-taking focuses on predisposing and trigger factors, such as asthma, underlying lung disease, vomiting, choking, drug history, and trauma. The physical examination is normal in up to 30% of patients with pneumomediastinum without complications.[5,75] The most common characteristic presentation is subcutaneous emphysema, ranging from 30% to 90% of patients with pneumomediastinum,[6,63,76] which is usually noted over neck or precordial area. Hamman sign, found in 12%–50% of patients with pneumomediastinum, is a systolic crepitation over precordium, sometimes associated with muffling of heart sounds.[75,77]

The severity and complications must be evaluated. The accumulation of large amount of air could cause compression of airway and reduction in venous return. It is contraindicated to measure peak expiratory flow rate because it may exacerbate the pneumomediastinum.[2] We could use pulse oximetry to evaluate oxygen saturation condition in dyspneic patients. Some symptoms suggested complications other than pneumomediastinum. Marked dyspnea or respiratory distress is related with underlying lung disease, pneumothorax, pneumonia, aspiration of foreign body, or compression of airway caused by

tension pneumomediastinum. Decreased breathing sound in unilateral lung area suggests association with pneumomediastinum, pneumonia, or aspiration. Distended neck veins can be seen with associated tension pneumomediastinum with compromised venous return. Esophageal perforation is a rare but relatively severe predisposing factor and should be searched for.[2]

The confirmed diagnosis is based on characteristic findings on frontal and lateral chest radiographs, including the cervical region.[78] Signs are listed in Table 2. Diagnosis by chest CT, neck imaging was also reported.[79] In addition to classic findings of pneumomediastinum, signs of pneumothorax, pneumopericardium, retropneumoperitoneum, and pneumoperitoneum should be looked for if patients present with related features or worsened symptoms. Subcutaneous emphysema can be evaluated with radiograph of the cervical region. Pleural effusion, usually left-sided, might be seen if associated with esophageal perforation.[80,81] Hyperinflation may be linked with redisposing asthma attack.

Differential Diagnosis

Pneumomediastinum might be combined with pneumothorax or esophageal rupture, and symptoms are easily confused with pericarditis. Pneumothorax can be distinguished by clinical manifestation and chest radiograph.

The esophageal rupture, also called Boerhaave syndrome, is rare in children and should be noted because of serious morbidity.[87] The patient usually presents with similar symptoms as pneumomediastinum. Clinical diagnosis is based on clinical presentation of vomiting, intense chest pain, and subcutaneous emphysema, also known as Mackler's triad.[81] The severity of clinical presentation depends on the location of perforation and leakage degree. It often happens after vomiting, foreign body aspiration, or trauma.[41,88,89] The chest radiograph sometimes reveals accompanied presence of a pleural effusion, which might develop after injury. Confirmed diagnosis can be made with water-soluble contrast esophagram or combined with computed tomography (CT). Because of the high risk of mediastinitis and high morbidity, all suspected patients require close monitoring and further intensive care if needed.[32]

Pericarditis presents with symptoms similar to pneumomediastinum such as chest pain. Physical examination findings such as reduced heart sound, abnormal cardiac auscultation, and electrocardiogram change can differentiate pericarditis from pneumomediastinum.[33,38]

Management

SPM is generally a self-limited disease, which resolves without further complications within 3–18 days.[2,26,90] Most patients are hospitalized, and in some series, there can be up to 25.8% of patients requiring intensive care.[61] The management is based on its complication. The management of uncomplicated SPM is conservative and includes pain control, rest, avoiding pulmonary pressure increase, which included the measurement of peak expiratory flow, forced expiration, physical activity, and Valsalva maneuver.[91,92] Therapy with high-concentration oxygen was suggested for patients with progressed or severe symptoms of dyspnea, chest pain, etc. It enhanced nitrogen washout and accelerated absorption of air accumulation.[93-95] Some suggested that further studies including repeat chest X rays, chest CT, esophagram, and diagnostic laryngoscopy did not yield additional diagnostic information in a clinically well-appearing patient after initial diagnosis.[79] Despite the lack of standardized clinical guidelines of management, stable-condition pediatric patients with SPM can be only observed for short period and discharged with resting and no further imaging follow-up according to the current evidence.[91]

The therapy of complicated SPM depends on complications. The management of SPM complicated with pneumothorax is similar to isolated pneumothorax, and needle aspiration and thoracostomy tube insertion are indicated if tension pneumothorax was diagnosed. In some case reports, severe tension pneumomediastinum mediastinal compression was treated by double mediastinotomy under local anesthesia or surgical decompression via video-assisted thoracic surgery.[11,21,37,96] Some published cases reported SPM complicated with pneumopericardium that resolved spontaneously with no treatment,[7,18,39,44,65,97-99] but we should always pay attention to the possibility of cardiac tamponade.

Table 2: Signs of pneumomediastinum in chest radiograph

Lucent streak due to gas accumulation outlines mediastinum structure, including the left side of the heart and aortic arch on the frontal view, often extend into chest wall or the neck to cause emphysema. Lucent streak outlines ascending aorta and aortic arch, retrosternal, precardiac, periaortic, and peritracheal area on the lateral view.[80]
V sign of naclerio: Outline of the left lateral margin of descending aorta, extending laterally between parietal pleura and the left hemidiaphragm, causing dual linear V-shaped radiolucency.[78,82]
Continuous diaphragm sign: Gas accumulation outlines the superior part of diaphragm and pericardium, separated diaphragm from heart.[83]
Ring around the artery sign: Radiolucency caused by gas surrounding the right pulmonary artery on lateral view.[84,85]
Spinnaker sign: Infants' thymic lobes deviate upwardly and outwardly.[86]
Extrapleural air sign: Linear radiolucency noted between pleura and diaphragm.

Prognosis

SPM is usually a benign disease that spontaneously resolves with no complication and progression in 2–15 days.[2,5,26] No need of a follow-up image study was recommended because of sufficient information provided by physical examination.[6,27] The recurrence of SPM is rare, which is less than 5% of reported cases.[2,9,26,100] It is suspected that recurrence might be related with predisposing factors, so we might suggest patients to avoid certain activities or conditions that might cause increased pressure or barotrauma, such as Valsalva maneuvers, scuba diving, etc. Pneumomediastinum had worse prognosis if complicated with an underlying lung disease, pneumothorax, or measles.[65,101]

Conclusion

SPM is an uncommon disease in children, which is diagnosed by physical examination and radiography. It is usually benign and needs only pain control and rest if it is uncomplicated. On the other hand, SPM complicated with pneumothorax, esophageal perforation, or other underlying lung disease had poor prognosis and might need aggressive treatment. SPM is also a complication of COVID-19 and might worsen disease condition. Therefore, we should evaluate possible predisposing factors and take caution on complications.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Hauri-Hohl A, Baenziger O, Frey B. Pneumomediastinum in the neonatal and paediatric intensive care unit. Eur J Pediatr 2008;167:415-8.
2. Chalumeau M, Le Clainche L, Sayeg N, Sannier N, Michel JL, Marianowski R, *et al*. Spontaneous pneumomediastinum in children. Pediatr Pulmonol 2001;31:67-75.
3. Bodey GP. Medical mediastinal emphysema. Ann Intern Med 1961;54:46-56.
4. Versteegh FG, Broeders IA. Spontaneous pneumomediastinum in children. Eur J Pediatr 1991;150:304-7.
5. Yellin A. Spontaneous pneumomediastinum. Chest 1992;101:1742-3.
6. Stack AM, Caputo GL. Pneumomediastinum in childhood asthma. Pediatr Emerg Care 1996;12:98-101.
7. Bierman CW. Pneumomediastinum and pneumothorax complicating asthma in children. Am J Dis Child 1967;114:42-50.
8. Abolnik I, Lossos IS, Breuer R. Spontaneous pneumomediastinum. A report of 25 cases. Chest 1991;100:93-5.
9. Jougon JB, Ballester M, Delcambre F, Mac Bride T, Dromer CE, Velly JF. Assessment of spontaneous pneumomediastinum: Experience with 12 patients. Ann Thorac Surg 2003;75:1711-4.
10. Macklin CC. Transport of air along sheaths of pulmonic blood vessels from alveoli to mediastinum: Clinical implications. Arch Intern Med 1939;64:913.
11. Beg MH, Reyazuddin, Ansari MM. Traumatic tension pneumomediastinum mimicking cardiac tamponade. Thorax 1988;43:576-7.
12. Shackelford D, Casani JA. Diffuse subcutaneous emphysema, pneumomediastinum, and pneumothorax after dental extraction. Ann Emerg Med 1993;22:248-50.
13. Schulman A, Fataar S, Van der Spuy JW, Morton PC, Crosier JH. Air in unusual places: Some causes and ramifications of pneumomediastinum. Clin Radiol 1982;33:301-6.
14. Wolowodiuk OJ, McMicken DB, O'Brien P. Pneumomediastinum and retropneumoperitoneum: An unusual complication of syrup-of-ipecac-induced emesis. Ann Emerg Med 1984;13:1148-51.
15. Zegel HG, Miller WT. Subcutaneous emphysema in a young man. JAMA 1979;241:1273-4.
16. Woodruff WW 3rd, Merten DF, Kirks DR. Pneumomediastinum: An unusual complication of acute gastrointestinal disease. Pediatr Radiol 1985;15:196-8.
17. Mumford AD, Ashkan K, Elborn S. Clinically significant pulmonary barotrauma after inflation of party balloons. Br Med J [Clin Res] 1996;313:1619.
18. Sandler CM, Libshitz HI, Marks G. Pneumoperitoneum, pneumomediastinum and pneumopericardium following dental extraction. Radiology 1975;115:539-40.
19. Donahoe PK, Stewart DR, Osmond JD 3rd, Hendren WH 3rd. Pneumoperitoneum secondary to pulmonary air leak. J Pediatr 1972;81:797-800.
20. Uva JL. Spontaneous pneumothoraces, pneumomediastinum, and pneumoperitoneum: Consequences of smoking crack cocaine. Pediatr Emerg Care 1997;13:24-6.
21. Herlan DB, Landreneau RJ, Ferson PF. Massive spontaneous subcutaneous emphysema. Acute management with infraclavicular "blow holes." Chest 1992;102:503-5.
22. Mohamed IS, Lee YH, Yamout SZ, Fakir S, Reynolds AM. Ultrasound guided percutaneous relief of tension pneumomediastinum in a 1-day-old newborn. Arch Dis Child Fetal Neonatal Ed 2007;92:F458.
23. Rao KL, Imamuddin S, Kumar AP. Isolated tension pneumopericardium in a case of acute lymphoblastic leukemia. Indian Heart J 2013;65:705-6.
24. Cummings RG, Wesly RL, Adams DH, Lowe JE. Pneumopericardium resulting in cardiac tamponade. Ann Thorac Surg 1984;37:511-8.
25. el Gamel A, Barrett P, Kopff G. Pneumopericardium: A rare cause of cardiac tamponade in an infant on a positive pressure ventilation. Acta Paediatr 1994;83:1220-1.
26. Dekel B, Paret G, Szeinberg A, Vardi A, Barzilay Z. Spontaneous pneumomediastinum in children: Clinical and natural history. Eur J Pediatr 1996;155:695-7.
27. Panacek EA, Singer AJ, Sherman BW, Prescott A, Rutherford WF. Spontaneous pneumomediastinum: Clinical and natural history. Ann Emerg Med 1992;21:1222-7.
28. Wong KS, Wu HM, Lai SH, Chiu CY. Spontaneous pneumomediastinum: Analysis of 87 pediatric patients. Pediatr Emerg Care 2013;29:988-91.
29. Forshaw MJ, Khan AZ, Strauss DC, Botha AJ, Mason RC. Vomiting-induced pneumomediastinum and subcutaneous emphysema does not always indicate Boerhaave's syndrome: Report of six cases. Surg Today 2007;37:888-92.
30. Grossman A, Romem A, Azaria B, Goldstein L, Barenboim E. Pneumomediastinum in student aviators: 10 cases with return to flying duty. Aviat Space Environ Med 2005;76:63-5.
31. Harley EH. Spontaneous cervical and mediastinal emphysema in asthma. Arch Otolaryngol Head Neck Surg 1987;113:1111-2.
32. Søreide JA, Viste A. Esophageal perforation: Diagnostic work-up and clinical decision-making in the first 24 hours. Scand J Trauma Resusc Emerg Med 2011;19:66.
33. McSweeney WJ, Stempel DA. Non-iatrogenic pneumomediastinum in infancy and childhood. Pediatr Radiol 1973;1:139-44.
34. Covantev S, Mazuruc N, Uzdenov R, Corlateanu A. Spontaneous pneumomediastinum—A rare asthma complication. Folia Med (Plovdiv) 2019;61:472-7.
35. Varkey B, Kory RC. Mediastinal and subcutaneous emphysema following pulmonary function tests. Am Rev Respir Dis 1973;108:1393-6.

36. Yellin A, Gapany-Gapanavicius M, Lieberman Y. Spontaneous pneumomediastinum: Is it a rare cause of chest pain? Thorax 1983;38:383-5.
37. Fink JA, Klein RL. Complications of the Heimlich maneuver. J Pediatr Surg 1989;24:486-7.
38. Dattwyler RJ, Goldman MA, Bloch KJ. Pneumomediastinum as a complication of asthma in teenage and young adult patients. J Allergy Clin Immunol 1979;63:412-6.
39. Frascone RJ, Cicero JJ, Sturm JT. Pneumopericardium occurring during a high-speed motorcycle ride. J Trauma 1983;23:163-4.
40. Burton EM, Riggs W Jr, Kaufman RA, Houston CS. Pneumomediastinum caused by foreign body aspiration in children. Pediatr Radiol 1989;20:45-7.
41. Engum SA, Grosfeld JL, West KW, Rescorla FJ, Scherer LR, Vaughan WG. Improved survival in children with esophageal perforation. Arch Surg 1996;131:604-10; discussion 611.
42. Channer KS, Roberts CJ, Jeyasingham K. Recurrent idiopathic pneumomediastinum. Postgrad Med J 1985;61:1073-5.
43. Bullimore DW, Cooke D. Cyclical vomiting with pneumomediastinum. Acta Paediatr Scand 1982;71:675-6.
44. Haines JD Jr, Chop WM Jr, Swyden SN. Spontaneous pneumothorax, pneumomediastinum, and pneumopericardium in a 16-year-old drug-abusing motorcyclist surrounded by a pack of coyotes. Postgrad Med 1989;86:79-80.
45. Grant T. Primary (spontaneous) pneumomediastinum presenting as abdominal pain after swimming. Ann Emerg Med 1988;17:1368-9.
46. Feldtman RW, Oram-Smith JC, Manning LG, Buckley CJ. Spontaneous mediastinal emphysema. J Pediatr Surg 1980;15:648-50.
47. Ralph-Edwards AC, Pearson FG. Atypical presentation of spontaneous pneumomediastinum. Ann Thorac Surg 1994;58:1758-60.
48. Adrouny A, Magnusson P. Pneumopericardium from cocaine inhalation. N Engl J Med 1985;313:48-9.
49. Shesser R, Davis C, Edelstein S. Pneumomediastinum and pneumothorax after inhaling alkaloidal cocaine. Ann Emerg Med 1981;10:213-5.
50. Luque MA, Cavallaro DL, Torres M, Emmanual P, Hillman JV. Pneumomediastinum, pneumothorax, and subcutaneous emphysema after cocaine inhalation and marijuana smoking. Pediatr Emerg Care 1987;3:107-9.
51. Yassin Z, Ebrahimian M, Motamedi O, Afshar H, Aloosh O, Sayyahfar S, *et al*. Spontaneous pneumothorax and pneumomediastinum in patients with COVID-19: A case series from Iran. Clin Case Rep 2022;10:e05355.
52. Diaz A, Patel D, Sayedy N, Anjum F. COVID-19 and spontaneous pneumomediastinum: A case series. Heart Lung 2021;50:202-5.
53. Pokhrel B, Adhikari G, Pangeni R, Regmi PR, Baniya A. Pneumomediastinum in COVID-19 patients with acute respiratory distress syndrome. J Nepal Health Res Counc 2021;19:460-6.
54. Lemmers D, Hilal M, Bnà C, Prezioso C, Cavallo E, Nencini N, *et al*. Pneumomediastinum and subcutaneous emphysema in COVID-19: Barotrauma or lung frailty? ERJ Open Res 2020;6:00385-2020.
55. Zhou C, Gao C, Xie Y, Xu M. COVID-19 with spontaneous pneumomediastinum. Lancet Infect Dis 2020;20:510.
56. Sinclair V, Sharieff I, Gaskell B, McKechnie A. COVID-19 presenting with spontaneous massive pneumomediastinum in a three-month-old child. Anaesth Rep 2021;9:e12126.
57. Dixit A, Uvaise M, Canet-Tarres A, Lillie J. Spontaneous massive pneumomediastinum in a previously well infant with COVID-19. Pediatrics 2021;148:2021051904.
58. Carroll AG, Quinn N, Byrne C, Kassab G, Whelan S, Colleran GC. Pneumomediastinum in a child with severe COVID-19. Br J Radiol 2021;7:20200062.
59. Buonsenso D, Gatto A, Graglia B, Rivetti S, Ferretti S, Paradiso FV, *et al*. Early spontaneous pneumothorax, pneumomediastinum and pneumorrhachis in an adolescent with SARS-CoV-2 infection. Eur Rev Med Pharmacol Sci 2021;25:4413-7.
60. Chowdhary A, Nirwan L, Abi-Ghanem AS, Arif U, Lahori S, Kassab MB, *et al*. Spontaneous pneumomediastinum in patients diagnosed with COVID-19: A case series with review of literature. Acad Radiol 2021;28:1586-98.
61. Quincho-Lopez A, Quincho-Lopez DL, Hurtado-Medina FD. Case report: Pneumothorax and pneumomediastinum as uncommon complications of COVID-19 pneumonia—Literature review. Am J Trop Med Hyg 2020;103:1170-6.
62. Belletti A, Palumbo D, Zangrillo A, Fominskiy EV, Franchini S, Dell'Acqua A, *et al*.; COVID-BioB Study Group. Predictors of pneumothorax/pneumomediastinum in mechanically ventilated COVID-19 patients. J Cardiothorac Vasc Anesth 2021;35:3642-51.
63. Gasser CR, Pellaton R, Rochat CP. Pediatric spontaneous pneumomediastinum: Narrative literature review. Pediatr Emerg Care 2017;33:370-4.
64. Zachariah S, Gharahbaghian L, Perera P, Joshi N. Spontaneous pneumomediastinum on bedside ultrasound: Case report and review of the literature. West J Emerg Med 2015;16:321-4.
65. Legrand M, Dassonneville JC, Lesorbre R. Le pneumomédiastin spontané. Semin Hop Paris 1975;51:2087-94.
66. Werne C, Ulreich S. An unusual presentation of spontaneous pneumomediastinum. Ann Emerg Med 1985;14:1010-3.
67. Roe PF, Kulkarni BN. Pneumomediastinum in children with cough. Br J Dis Chest 1967;61:147-50.
68. Dekel B, Paret G, Vardi A, Katz M, Barzilay Z. Torticollis: An unusual presentation of spontaneous pneumomediastinum. Pediatr Emerg Care 1996;12:352-3.
69. Shuster MJ. Pneumomediastinum as a cause of dysphagia and pseudodysphagia. Ann Emerg Med 1981;10:648-51.
70. Rose WD, Veach JS, Tehranzdeh J. Spontaneous pneumomediastinum as a cause of neck pain, dysphagia, and chest pain. Arch Intern Med 1984;144:392-3.
71. Walsh-Kelly C, Kelly KJ. Dysphonia: An unusual presentation of spontaneous pneumomediastinum. Pediatr Emerg Care 1986;2:26-7.
72. Bratton SL, O'Rourke PP. Spontaneous pneumomediastinum. J Emerg Med 1993;11:525-9.
73. Munsell WP. Pneumomediastinum. A report of 28 cases and review of the literature. JAMA 1967;202:689-93.
74. Cooley JC, Gillepsie JB. Mediastinal emphysema: Pathogenesis and management. Chest 1966;49:104-8.
75. Pène P, Bourgeade A, Serres JJ, Lesquerre C. L'emphysème médiastinal, complication fréquente de la rougeole en milieu tropical. A propos de 46 cas. Semin Hop Paris 1970;46:989-99.
76. Sahni S, Verma S, Grullon J, Esquire A, Patel P, Talwar A. Spontaneous pneumomediastinum: Time for consensus. N Am J Med Sci 2013;5:460-4.
77. Hamman L. Spontaneous mediastinal emphysema. Bull Johns Hopkins Hosp 1939;64:1.
78. Bejvan SM, Godwin JD. Pneumomediastinum: Old signs and new signs. Ajr Am J Roentgenol 1996;166:1041-8.
79. Noorbakhsh KA, Williams AE, Langham JJW, Wu L, Krafty RT, Furtado AD, *et al*. Management and outcomes of spontaneous pneumomediastinum in children. Pediatr Emerg Care 2021;37:e1051-6.
80. Dodds WJ, Stewart ET, Vlymen WJ. Appropriate contrast media for evaluation of esophageal disruption. Radiology 1982;144:439-41.
81. Parkin GJS. The radiology of the perforated oesophagus. Clin Radiol 1973;24:324-32.
82. Naclerio EA. The V sign in the diagnosis of spontaneous rupture of the esophagus (an early roentgen clue). Am J Surg 1957;93:291-8.
83. Levin B. The continuous diaphragm sign. A newly-recognized sign of pneumomediastinum. Clin Radiol 1973;24:337-8.
84. Hammond DI. The "ring-around-the-artery" sign in pneumomediastinum. J Can Assoc Radiol 1984;35:88-9.
85. Agarwal PP. The ring-around-the-artery sign. Radiology 2006;241:943-4.
86. Lawal TA, Glüer S, Reismann M, Dördelmann M, Schirg E, Ure B. Spontaneous neonatal pneumomediastinum: The "spinnaker sail" sign. Eur J Pediatr Surg 2009;19:50-2.
87. Mackler SA. Spontaneous rupture of the esophagus; an experimental and clinical study. Surg Gynecol Obstet 1952;95:345-56.
88. Reilly J, Thompson J, MacArthur C, Pransky S, Beste D, Smith M, *et al*. Pediatric aerodigestive foreign body injuries are

complications related to timeliness of diagnosis. Laryngoscope 1997;107:17-20.
89. Flynn AE, Verrier ED, Way LW, Thomas AN, Pellegrini CA. Esophageal perforation. Arch Surg 1989;124:1211-4; discussion 1214-5.
90. Sturtz GS. Spontaneous mediastinal emphysema. Pediatrics 1984;74:431-2.
91. Macia I, Moya J, Ramos R, Morera R, Escobar I, Saumench J, *et al*. Spontaneous pneumomediastinum: 41 cases. Eur J Cardiothorac Surg 2007;31:1110-4.
92. Fitzwater JW, Silva NN, Knight CG, Malvezzi L, Ramos-Irizarry C, Burnweit CA. Management of spontaneous pneumomediastinum in children. J Pediatr Surg 2015;50:983-6.
93. Markarian MK, MacIntyre DA, Cousins BJ, Fildes JJ, Malone A. Adolescent pneumopericardium and pneumomediastinum after motor vehicle crash and ejection. Am J Emerg Med 2008;26:515.e1-2.
94. Patel A, Kesler B, Wise RA. Persistent pneumomediastinum in interstitial fibrosis associated with rheumatoid arthritis: Treatment with high-concentration oxygen. Chest 2000;117:1809-13.
95. Mcnicholl B. Pneumomediastinum and subcutaneous emphysema in status asthmaticus, requiring surgical decompression. Arch Dis Child 1960;35:389-92.
96. Tutor JD, Montgomery VL, Eid NS. A case of influenza virus bronchiolitis complicated by pneumomediastinum and subcutaneous emphysema. Pediatr Pulmonol 1995;19:393-5.
97. Toomey FB, Chinnock RF. Subcutaneous emphysema, pneumomediastinum, and pneumothorax in diabetic ketoacidosis. Radiology 1975;116:543-5.
98. Leitman BS. Pneumomediastinum and pneumopericardium after cocaine abuse. Am J Roentgenol 1988;151:614.
99. Perna V, Vilà E, Guelbenzu JJ, Amat I. Pneumomediastinum: Is this really a benign entity? When it can be considered as spontaneous? Our experience in 47 adult patients. Eur J Cardiothorac Surg 2010;37:573-5.
100. Alemu BN, Yeheyis ET, Tiruneh AG. Spontaneous primary pneumomediastinum: Is it always benign? J Med Case Rep 2021;15:157.
101. Swar MO, Srikrishna BV, Abusin A, Khogali FM. Post-measles pneumomediastinum and subcutaneous emphysema in malnourished children. Afr J Med Med Sci 2002;31:259-61.

Mouth Breathing during Sleep and Persistence of OSA after Adeno-tonsillectomy in Non-obese Children

Brigitte Kim-yook Fung, Mei-yee Lau[1], Shuk-yu Leung[1], Rebecca Suk-yin Wong, Ka-li Kwok[1], Daniel Kwok-keung Ng[1,2]

Physiotherapy Department, Kwong Wah Hospital, [1]Department of Paediatrics and Adolescent Medicine, Kwong Wah Hospital, [2]Department of Paediatrics, Hong Kong Sanatorium & Hospital, Hong Kong SAR, China

Abstract

Objective: To evaluate the relationship between the percentage of total sleep time with mouth breathing (SMBP) and post-adeno-tonsillectomy apnea-hypopnea index (AHI) in non-obese children. **Materials and Methods:** Non-obese obstructive sleep apnea (OSA) children with pre- and post- TandA PSG done between August 2011 and February 2019 were reviewed and mouth breathing during sleep was manually scored. Percentage of total sleep time with mouth breathing (SMBP) was calculated. Its correlation with post-operative AHI >1.5/h was studied. **Results:** Fifty-nine children were included in the analysis and 47 of the study group (79.7%) were male. The mean age at pre-operative PSG was 9.2+/-3.1 years. The mean AHI dropped from 8.3+/-19.8 to 4.1+/-11.6 ($P < 0.001$). Thirty-one (50.8%) were cured of OSA defined as AHI<=1.5/h. There was a statistically significant positive correlation between post-operative log-transformed AHI and log-transformed SMBP (r=0.265, $P = 0.044$). The optimal SMBP for detecting residual OSA was 10.5%. The sensitivity, specificity, positive predictive value, negative predictive value and Youden Index were 0.86, 0.37, 0.57, 0.73 and 0.23, respectively. Post-operative children with SMBP >10.5% had higher risk for residual OSA (OR 4.2, 95%CI: 1.2–15.0, $P = 0.029$). **Conclusion:** Obstructive sleep apnea children with mouth breathing for more than 10.5% of total sleep time are more likely to have residual OSA after TandA.

Keywords: Adenoidectomy, child, mouth breathing, obstructive sleep apnea, tonsillectomy

Introduction

Mouth breathing (MB) is a respiratory dysfunction with prevalence ranging from 12–55% in children[1-4] and it is often the consequence of increased nasal resistance usually due to allergic rhinitis and/or adeno-tonsillar hyperplasia.[5] Healthy subjects usually breathe through the nose and spend an average of 96% of total sleep time (TST) with nasal breathing.[6] Increase in MB is associated with a backward and downward displacement of the mandible and tongue leading to an increased tendency of upper airway collapse during sleep, i.e. obstructive sleep apnea (OSA).[7] Tonsillectomy and adenoidectomy (TandA) improves obstructive sleep apnea syndrome (OSAS) but does not completely eliminate it.[8,9] Persistent MB might be one of the reasons for the persistence of OSA after TandA. Furthermore, persistent MB pattern would have an abnormal impact on the upper airway growth and the neuromuscular responsiveness to inspiration, an essential feature to prevent collapse of the pharynx during inspiration..[10] To date, the report of MB was based on questionnaire, otorhinolaryngological examination or polysomnography (PSG).[1-4,11] Three studies were published in evaluating the normal values of MB during sleep. The largest study done involved 90 children and the upper limit of normal was suggested to be 15% of TST.[6] Another study of 10 children suggested the upper limit of normal to be 35% of TST.[12] A study of 10 normal adults found MB occurred in 4% of TST.[13] The purpose of this study was to evaluate the relationship between MB during sleep and post TandA apnea -hypopnea index (AHI).

Access this article online

Quick Response Code:

Website: www.prccm.org

DOI: 10.4103/prcm.prcm_17_21

Address for correspondence: Ms. Brigitte Kim-yook Fung, Department of Physiotherapy, Kwong Wah Hospital, 25 Waterloo Road, Hong Kong SAR, China.
E-mail: fungky3@ha.org.hk

Submitted: 13-09-2021 **Revised:** 20-04-2022
Accepted: 08-05-2022 **Published:** 01-08-2022

How to cite this article: Fung BK, Lau MY, Leung SY, Wong RS, Kwok Kl, Ng DK. Mouth breathing during sleep and persistence of OSA after adeno-tonsillectomy in non-obese children. Pediatr Respirol Crit Care Med 2021;5:48-52.

Materials and Methods

Subject selection

This was a retrospective study of a group of non-obese children (body mass index, BMI-z score <1.645) who had TandA. Children were included if they had pre-operative and post-operative PSG conducted between August 2011 and February 2019 in the sleep laboratory. Exclusion criteria included children with (1) pre-operative PSG AHI<1.5/h; (2) older than 18 years of age at the time of first PSG; (3) children who previously had a TandA before the study period; (4) significant medical illnesses like cardiac, respiratory or renal insufficient or dysmorphic syndrome; (5) poor quality of PSG, e.g. inadequate sleep duration, poor signals making reading impossible. This study was approved by the research ethics committee of the Kowloon Central/Kowloon East Clusters of the Hospital Authority in Hong Kong (KC/KE-18–0151/ER-4).

Polysomnography

PSG were performed by qualified sleep technologists in the Paediatric Sleep Laboratory in Kwong Wah Hospital in Hong Kong. Standardized PSG was recorded with electroencephalogram (C3-A2,C4-A1, O1-A2, O2-A1, F3-A2, F4-A1), right and left electro-oculogram (EOG), chin submental electromyogram, electrocardiograhy (ECG), nasal flow through a nasal pressure transducer to detect nasal breathing, pulse oximetry (SpO2), oximeter plethysmography waveform, thoracic and abdominal respiratory inductance belt, digital synchronized infrared video and sound monitoring, and transcutaneous carbon dioxide pressure (TCM 4, Radiometer, Copenhagen, Denmark), position sensor, snoring microphone, anterior tibialis electromyogram, intercostal respiratory electromyogram and diaphragmatic respiratory electromyogram. The recording was carried out using a digital polysomnography system (Profusion Sleep 3, Compumedics, Australia). For detection of MB, oral thermistor (Protech, WA, USA) was used afterward.

Apnea and hypopnea were scored according to AASM.[14] In the current study, MB was defined as an increase by >=50% of amplitude from baseline as obtained by the oral thermal sensor associated with thoracic-abdominal movement and the presence of flow limitation in nasal cannula lasting more than 2 consecutive breaths during sleep. During bio-calibration, patient was instructed to close the mouth and breathe through the nose and the baseline signal from the oral thermal sensor was adjusted to zero. This has helped to minimize the artifact in MB signal created by nasal breathing. The duration of MB was scored manually and the time of MB was reported as percentage of time during sleep spent in mouth breathing (SMBP).[6] In the current study, we used AHI >1.5/h to define OSA..[15-17]

Sleep questionnaire

Data of the Chinese version of modified Epworth Sleepiness Scale (mESS),[18] OSAS quality of life survey (OSA-18) score,[19] and Sleep-Related Breathing Disorder (SRBD) scale of the Paediatric Sleep Questionnaire (PSQ)[20] during pre-operative and post-operative PSG were reviewed. PSQ is a validated tool to assess sleep disorders by Chervin *et al.*[21] In the current study, the validated Taiwan version of PSQ was used[20] to provide a Chinese version of SRBD.

Statistics

Pre-operative and post-operative demographic data, including age, gender, weight, height, PSG parameters, mESS score, OSA-18 score and SRBD scare were collected. BMI (kg/m^2) was calculated and converted into BMI z-score by using normal value published for Hong Kong Chinese children[22] by using the Cole's LMS method.[23] Non-Obese was defined as the BMI z-score<=1.645 (<=95th percentile). The normality of data was assessed by Shapiro-Wilk test. Continuous variables were presented as the mean+/- standard deviation (SD). Paired t-test was used for comparing continuous variables such as age, weight, height, BMI z-score, PSG parameters, mESS score, OSA-18 score and SRBD score before and after operation. McNemar test was used for comparing paired categorical variable. As some of parameters, i.e. AHI, DI, PaCO2>50mmHg, mouth breathing % of TST and mESS score were skewed, they were transformed by natural log. For the value of zero, the value of 0.1 was added to allow it to be transformed by natural log. Pearson's correlation coefficient analysis was used for assessing the association between AHI and the percentage of total mouth breathing during sleep time. Youden index (sensitivity +specificity – 1)[24] was used for determining the optimal cut-off value of the percentage of total sleep time spent mouth breathing. A p- value <0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp. in Armonk, NY, USA).

Results

A total of 66 non-obese children underwent TandA and had pre-operative and post-operative PSG during the studied period. Seven children were excluded because of following reasons: one pre-operative PSG AHI<1.5/h, two with Down syndrome, four without oral thermistor in pre-operative PSG. Therefore, 59 children were included in the analysis with 47 boys (79.7%). The mean age at pre-operative PSG was 9.2+/-3.1 years. The mean age at operation was 10.5 +/- 3.1 years. The mean length of time between TandA and post-operative PSG was 0.9+/-0.6 years. The mean AHI dropped from 8.3+/-19.8 to 4.1+/-11.6 ($P < 0.001$). Thirty-one (50.8%) children were

Table 1: Demographic, anthropometric, PSG parameters and questionnaire data at the time of pre-operative and post-operative PSG, n=59

	Pre-operative Mean (SD)	Post-operative Mean (SD)	P-value
Male gender, n(%)	47 (79.7%)	47 (79.7%)	-
Age, year	9.2 (3.1)	11.4 (3.2)	<0.001
Weight, kg	31.8+/-14.1	40.4+/-16.1	<0.001
Height, cm	132.8+/-20.0	144.8+/-19.1	<0.001
BMI, kg/m^2	17.1+/-3.1	18.4+/-3.3	<0.001
BMI z score	0.2+/-1.0	0.4+/-1.0	0.040
Sleep effectively, %	88.6+/-6.9	88.6+/-7.3	0.995
TST, min	476.7+/-60.5	458.1+/-66.5	0.082
AHI, /h	8.3 +/- 19.8	4.1 +/- 11.6	<0.001†
AHI>1.5/h, n(%)	59 (100%)	29 (49.2%)	<0.001
DI,/h	3.8+/-10.6	1.7+/-3.9	<0.001†
SpO2 nadir, %	88.2+/-7.9	91.6+/-3.9	<0.001
PaCO2>50mmHg, min (n=56)	11.9+/-25.5	10.1+/-26.4	0.498†
Mouth breathing, % of TST	27.6 +/- 15.2	17.9+/-12.9	<0.001†
SRBD scale (n=23)	8.7+/-4.5	4.7+/-3.0	<0.001
OSA18 score (n=45)	59.2+/-20.7	48.8+/-14.7	0.001
mESS score (n=41)	6.2+/-5.4	5.7+/-3.9	0.883†

Data are presented as mean+/-standard deviation (SD) or number (%)

BMI = body mass index ; AHI = apnea-hypopnea index; sAHI =Stanford apnea-hypopnea index; TST = total sleep time; DI = desaturation index

†Based in log transformed values

Paired t-test, McNemar test

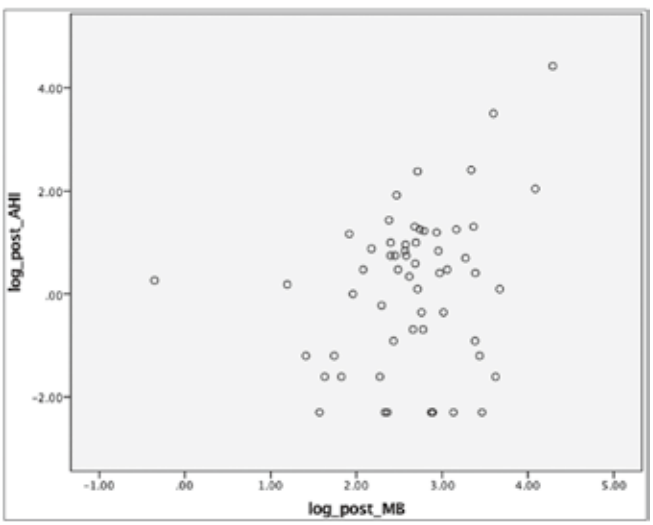


Figure 1: Correlation between post-operative log-transformed AHI and the percentage of total mouth breathing during sleep time

There was a statistically significant positive correlation between post-operative log-transformed AHI and log-transformed total mouth breathing during sleep time, Pearson correlation = 0.265, p = 0.044

cured of OSA (AHI<=1.5) after the operation. The mean SpO2 nadir increased from 88.2+/-7.9% to 91.6+/-3.9% (P < 0.001). The mean SMBP dropped from 27.6+/-15.2% to 17.9+/-12.9% (P < 0.001). The mean SRBD scales and mean OSA-18 scores dropped from 8.7+/-4.5 to 4.7+/-3.0 (P < 0.001) and from 59.2+/-20.7 to 48.8+/-14.7 (P = 0.001), respectively. [Table 1]

After operation, the AHI values had a significant correlation with them SMBP (r=0.265, P = 0.044) [Figure 1]. SMBP >10.5% yielded the best Youden index of 0.23. The sensitivity, specificity, positive predictive value, negative predictive value for the SMBP >10.5% were 0.86, 0.37, 0.57, 0.73 respectively [Table 2]. In the current study, the odds of post-operative children with SMBP >10.5% having residual OSA was 4.2 times that of those withy SMBP <=10.5% of %TST-MB (95%CI: 1.2–15.0, P = 0.029) [Table 3].

Discussion

Kim and Guilleminault[12] suggested MB during sleep could be measured by recording obtained from the modified cannula with oral scoop. In Kim and Guilleminault study, the 30 seconds epoch would be defined as MB if more than 50% of the epoch showed oral air flow by using this definition, the cut off point for MB was defined as a minimum of 35% of TST based on that study with 10 children. In another study,[25] it was suggested that the normal "nasal breathing" children had an average of around 4% of TST MB and the maximum duration of MB was 10% asleep in asymptomatic children with normal PSG. Upper limit of normal for MB during sleep was suggested to be 15% of TST.[25] The current study was the first report that demonstrated MB during sleep as a significant risk factor for persistent OSAS after TandA. This corroborated previous study that suggested 15% of TST MB to be abnormal.

Table 2: Receiver operating characteristic (ROC) curve analysis of post-operative percentage of total mouth breathing during sleep time for detecting residual OSA (AHI>1.5/hr)

Cut-off point, mouth breathing, % of TST	Sensitivity	Specificity	PPV	NPV	Youden Index
>9.5	0.86	0.27	0.53	0.67	0.129
>10.0	0.86	0.33	0.56	0.71	0.195
>10.5	**0.86**	**0.37**	**0.57**	**0.73**	**0.229**
>11.0	0.83	0.40	0.57	0.71	0.228
>11.5	0.76	0.43	0.56	0.65	0.192

PPV = positive predictive value; NPV= negative predictive value; Youden Index = sensitivity +specificity – 1

Table 3: Post-operative percentage of total mouth breathing during sleep time and residual OSA, n=59

	Post-operative AHI>1.5 (n=29)	Post-operative AHI<=1.5 (n=30)	P-value
Mouth breathing, % of TST:			
>10.5%	25 (86.2%)	18 (60%)	0.024*
<=10.5%	4 (13.8%)	12 (40%)	

*Chi Square test

*p<0.05

The main difference between the current study and the previous two studies were (1) previous studies used a modified cannula with oral scoop[12,25] and (2) the method of counting MB. The oral scoops are not commonly available whereas the oral thermistor used in the present study was readily available. Method used in counting MB as the exact duration in seconds in the current study was more labor intensive and probably more accurate compared with the method of counting MB as epoch in the previous two studies. This difference probably accounted for the difference in the result.

Cure rate of TandA was 50.8% in the current study and this was similar to the 55% reported in a previous meta-analysis.[8] This center reported in 2010[9] that 45% of 44 children were cured of OSA after TandA. Lee *et al*[6] also suggested that 26 children out of the 64 children who had the TandA done persisted to have the OSA symptoms and 55% of these patients had the problem of MB.

Chronic MB leads to structural change of the airway as it was identified in a study that the mandible was more retruded in MB children[26] with a greater inclination of the mandibular and occlusal plane than the nasal breathing group. Matheus *et al*[27] reported that both airway volume, area and minimum axial area were significantly reduced in the MB group. Chronic MB also had high arch palate.[28] MB during growth periods in children led to clockwise rotation of the mandible, with a disproportionate increase in anterior lower vertical face height and decreased posterior facial height,[29] resulting in the adenoid face. Furthermore, MB led to increased surface tension of the fluid lining the pharyngeal mucosa while nasal breathing reduced surface tension.[30] Surface tension is important in the genesis of OSA as reducing surface tension with surfactant in patients with OSA reduced the number of folds in the upper airway,[31] improved upper airway collapsibility and reduced OSA severity.[32]

Treatment of chronic MB would be an important part of management of childhood OSAS and this includes intensive treatment of allergic rhinitis after TandA. Myofunctional therapy was reported to be effective as an adjunct treatment for childhood OSA.[8,33-35] Myofunctional therapy comprises of orofacial exercises, breathing re-education and body work.[6] However, all these studies did not demonstrate the direct impact of myofunctional therapy on MB. Further intervention studies are required to assess the impact of myofunctional therapy on MB and the impact of treatment of MB on AHI.

The main limitation of the current paper was the rather small sample size of 59 children who had OSAS. Future study with a larger population looking at the impact of treating mouth breathing on the AHI is warranted.

Conclusion

Obstructive sleep apnea children with mouth breathing for more than 10.5% of total sleep time are more likely to have residual OSA after TandA.

Contributors' statements

BK Fung and DK Ng, designed the study, supervised all aspects of the research, supervised analyses, interpreted the results, wrote sections of the initial draft, and reviewed and approved the final version.

M Lau, S Leung, RS Wong and K Kwok conducted and interpreted analyses, wrote sections of the initial draft, and reviewed and approved the final version.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Financial support and sponsorship

This work was supported by the Tung Wah Group of Hospitals Research Fund 2018/2019.

Conflicts of interest

The authors have no conflicts of interest to this article to disclose.

References

1. Abreu RR, Rocha RL, Lamounier JA, Guerra AF. Prevalence of mouth breathing among children. J Pediatr (Rio J) 2008;84:467-70.
2. Leal RB, Gomes MC, Granville-Garcia AF, Goes PS, de Menezes VA. Impact of breathing patterns on the quality of life of 9- to 10-year-old schoolchildren. Am J Rhinol Allergy 2016;30:147-52.
3. Tachibana M, Kato T, Kato-Nishimura K, Matsuzawa S, Mohri I, Taniike M. Associations of sleep bruxism with age, sleep apnea, and daytime problematic behaviors in children. Oral Dis 2016;22:557-65.
4. Bonuck KA, Chervin RD, Cole TJ, Emond A, Henderson J, Xu L, *et al*. Prevalence and persistence of sleep disordered breathing symptoms in young children: A 6-year population-based cohort study. Sleep 2011;34:875-84.
5. Sateia MJ, Thorpy MJ. Classification of sleep disorders; Avidan AY. Non-rapid eye movement parasomnias: Clinical spectrum, diagnostic features, and management. In: Kryger M, Roth T, Dement WC, editors. Principles and Practices of Sleep Medicine. 6th ed. Philadelphia, PA: Elsevier; 2017. p. 618-26;981-92.
6. Lee SY, Guilleminault C, Chiu HY, Sullivan SS. Mouth breathing, "nasal disuse," and pediatric sleep-disordered breathing. Sleep Breath 2015;19:1257-64.
7. Lee SH, Choi JH, Shin C, Lee HM, Kwon SY, Lee SH. How does open-mouth breathing influence upper airway anatomy? Laryngoscope 2007;117:1102-6.
8. Ng DK, Huang YS, Teoh OH, Preutthipan A, Xu ZF, Sugiyama T, *et al*. The Asian Paediatric Pulmonology Society (APPS) position statement on childhood obstructive sleep apnea syndrome. Pediatr Respirol Crit Care Med 2017;1:26-38.
9. Ng DK, Wong JC, Chan CH, Leung LC, Leung SY. Ambulatory blood pressure before and after adenotonsillectomy in children with obstructive sleep apnea. Sleep Med 2010;11:721-5.
10. Guilleminault C, Sullivan SS. Towards restoration of continuous nasal breathing as the ultimate treatment goal in pediatric obstructive sleep apnea. Pediatr Neonatal Biol 2014;1:1-5.
11. Yi LC, Jardim JR, Inoue DP, Pignatari SS. The relationship between excursion of the diaphragm and curvatures of the spinal column in mouth breathing children. J Pediatr (Rio J) 2008;84:171-7.
12. Kim JH, Guilleminault C. The nasomaxillary complex, the mandible, and sleep-disordered breathing. Sleep Breath 2011;15:185-93.
13. Fitzpatrick MF, Driver HS, Chatha N, Voduc N, Girard AM. Partitioning of inhaled ventilation between the nasal and oral routes during sleep in normal subjects. J Appl Physiol (1985) 2003;94:883-90.
14. Iber C, Ancoli-Israel S, Chesson A, Quan SF. The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications. Westchester, IL: American Academy of Sleep Medicine; 2007.
15. Uliel S, Tauman R, Greenfeld M, Sivan Y. Normal polysomnographic respiratory values in children and adolescents. Chest 2004;125:872-8.
16. Traeger N, Schultz B, Pollock AN, Mason T, Marcus CL, Arens R. Polysomnographic values in children 2-9 years old: Additional data and review of the literature. Pediatr Pulmonol 2005;40:22-30.
17. Witmans MB, Keens TG, Davidson Ward SL, Marcus CL. Obstructive hypopneas in children and adolescents: Normal values. Am J Respir Crit Care Med 2003;168:1540.
18. Chan EY, Ng DK, Chan CH, Kwok KL, Chow PY, Cheung JM, *et al*. Modified epworth sleepiness scale in chinese children with obstructive sleep apnea: A retrospective study. Sleep Breath 2009;13:59-63.
19. Franco RA Jr, Rosenfeld RM, Rao M. First place–resident clinical science award 1999. Quality of life for children with obstructive sleep apnea. Otolaryngol Head Neck Surg 2000;123:9-16.
20. Huang YS, Wang CH, Guilleminault C. An epidemiologic study of sleep problems among adolescents in north taiwan. Sleep Med 2010;11:1035-42.
21. Chervin RD, Hedger K, Dillon JE, Pituch KJ. Pediatric sleep questionnaire (Psq): Validity and reliability of scales for sleep-disordered breathing, snoring, sleepiness, and behavioral problems. Sleep Med 2000;1:21-32.
22. Leung SS, Cole TJ, Tse LY, Lau JT. Body mass index reference curves for chinese children. Ann Hum Biol 1998;25:169-74.
23. Cole TJ. The Lms method for constructing normalized growth standards. Eur J Clin Nutr 1990;44:45-60.
24. Youden WJ. Index for rating diagnostic tests. Cancer 1950;3:32-5.
25. Valera FC, Trawitzki LV, Anselmo-Lima WT. Myofunctional evaluation after surgery for tonsils hypertrophy and its correlation to breathing pattern: A 2-year-follow up. Int J Pediatr Otorhinolaryngol 2006;70:221-5.
26. Chung Leng Muñoz I, Beltri Orta P. Comparison of cephalometric patterns in mouth breathing and nose breathing children. Int J Pediatr Otorhinolaryngol 2014;78:1167-72.
27. Alves M Jr, Baratieri C, Nojima LI, Nojima MC, Ruellas AC. Three-dimensional assessment of pharyngeal airway in nasal-and mouth-breathing children. Int J Pediatr Otorhinolaryngol 2011;75:1195-9.
28. Grippaudo C, Paolantonio EG, Antonini G, Saulle R, La Torre G, Deli R. Association between oral habits, mouth breathing and malocclusion. Acta Otorhinolaryngol Ital 2016;36:386-94.
29. Harari D, Redlich M, Miri S, Hamud T, Gross M. The effect of mouth breathing versus nasal breathing on dentofacial and craniofacial development in orthodontic patients. Laryngoscope 2010;120:2089-93.
30. Kirkness JP, Madronio M, Stavrinou R, Wheatley JR, Amis TC. Surface tension of upper airway mucosal lining liquid in obstructive sleep apnea/hypopnea syndrome. Sleep 2005;28:457-63.
31. Kairaitis K, Foster S, Amatoury J, Verma M, Wheatley JR, Amis TC. Pharyngeal mucosal wall folds in subjects with obstructive sleep apnea. J Appl Physiol (1985) 2015;118:707-15.
32. Jokic R, Klimaszewski A, Mink J, Fitzpatrick MF. Surface tension forces in sleep apnea: The role of a soft tissue lubricant: A randomized double-blind, placebo-controlled trial. Am J Respir Crit Care Med 1998;157:1522-5.
33. Guilleminault C, Huang YS. Pediatric obstructive sleep apnea: A short review of clinical aspects. Pediatr Respirol Crit Care Med 2017;1:39-45.
34. Huang YS, Guilleminault C. A review of treatment options in paediatric sleep-disordered breathing. Pediatr Respirol Crit Care Med 2017;1:54-58.
35. Villa MP, Brasili L, Ferretti A, Vitelli O, Rabasco J, Mazzotta AR, *et al*. Oropharyngeal exercises to reduce symptoms of Osa after At. Sleep Breath 2015;19:281-9.

Diagnostic Tests for COVID-19

Rina Triasih

Department of Pediatric, Faculty of Medicine Universitas Gadjah Mada/Dr. Sardjito Hospital, Jl. Kesehatan 1 Yogyakarta, Indonesia

In general, the diagnosis of COVID-19 in children is the same as that in adults, which is based on the clinical and epidemiological history of the patient. Clinicians should have a suspicion of COVID-19 when a child shows one or more clinical manifestations of COVID-19 and, within 14 days before the onset of the disease, had at least one of the risks of COVID-19, that is, living or history of traveling in areas with the local transmission of SARS-CoV-2 or history of close contact with a confirmed case of COVID-19. The diagnosis is supported by a chest X-ray or CT scan, and diagnostic tests to identify the virus or immune response to the virus. Because of the high morbidity and transmission rates of COVID-19, accurate and timely diagnostic tests are important to control the outbreak of the disease and to help the clinician in deciding on diagnosis and management. Currently, the diagnostic tests for COVID-19 mainly consist of molecular tests to identify the RNA of the virus and serological tests that detect the immunoglobulins against SARS-CoV-2.

Real-time Reverse Transcriptase Polymerase Chain Reaction

The gold standard of COVID-19 is the detection of the virus, SARS-CoV-2, on a variety of specimens, including naso/oropharyngeal swabs, sputum, bronchoalveolar lavage fluid, bronchoscope brush biopsies, or feces through nucleic acids amplification test using real-time reverse transcriptase polymerase chain reaction (rRT-PCR).[1] This test can detect the RNA at the early stage of infection when the viral load is low and antibodies have not been formed, as shown in Figure 1.[2]

If done properly, the diagnostic values of rRT-PCR are good. The high specificity of rRT-PCR indicates a low probability of false-positive. Nevertheless, the false-negative of this test was reported as high as 41%.[3-5] Several studies have identified that the false-negative can occur if the amount of virus in the specimen is too low to be amplified and detected, which relates to sampling operation, specimen source, sampling timing (before or after symptoms onset), and the performance of detection kit.[2] A study from China reported that within 14 days of the onset of the disease, sputum samples had the highest yield of the virus (85% and 78%), followed by nasal swabs (73% and 63%) in severe and mild cases, respectively.[6] Further studies are needed to determine the most appropriate specimens and timing for peak viral load during SARS-CoV-2 infection.

In a clinical setting, the decision to treat or not to treat a patient as COVID-19 should not rely on the result of rRT-PCR only because a negative result does not completely rule out the possibility of COVID-19.[7] Re-testing should be considered in a patient with high suspicion of COVID-19.

Serological Tests

Serological tests for COVID-19 measure antibodies in the blood when the body is infected with SARS-CoV-2. There are two assay methods of serological tests available: automated tests (enzyme-linked immunosorbent assays [ELISA] or chemiluminescence enzyme immunoassays [CLIA]) and rapid detection test (lateral flow immunoassays [LFIA]).

The antibodies remain in the blood for several weeks to months after symptom onset; therefore, the test can identify recent or previous exposure to the virus, depending on the type of the immunoglobulin detected.

Access this article online

Quick Response Code:

Website: www.prccm.org

DOI: 10.4103/prcm.prcm_16_21

Address for correspondence: Dr. Rina Triasih, Department of Pediatric, Faculty of Medicine Universitas Gadjah Mada/ Dr. Sardjito Hospital, Jl. Kesehatan 1 Yogyakarta, Indonesia.
E-mail: rina_triasih@yahoo.com

Submitted: 16-07-2021 **Revised:** 31-05-2022
Accepted: 18-07-2021 **Published:** 01-08-2022

How to cite this article: Triasih R. Diagnostic tests for COVID-19. Pediatr Respirol Crit Care Med 2021;5:53-4.

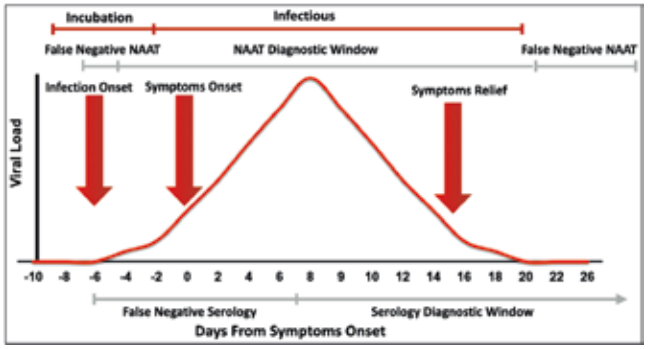


Figure 1: Viral load and the clinical course during SARS-CoV-2 infection (taken from reference[2])

IgM antibodies against SARS-CoV-2 are detectable in the blood a few days after initial infection, but the presence of IgM throughout infection has not been well characterized. IgG is detectable as early as three days from the onset of the symptom or 7–10 days after the initial infection.[8]

Although the serology tests are easier, faster, and cheaper to perform at the point of care than rRT-PCR, the diagnostic accuracies of these tests are also problematic. A recent systematic review of 40 studies documented that the pooled sensitivity of ELISA for IgG and IgM was 84.3% (95% confidence interval: 75.6%–90.9%), of LFIA was 66.0% (49.3%–79.3%), and of CLIA was 97.8% (46.2%–100%).[9] The pooled specificity ranged from 96.6% to 99.7%. This test will falsely identify 44% to 87% of persons as not having COVID-19 when the test was done within one week of symptom onset. In the later stage of the disease, the false-negative of IgG serology tests was also of concern. These results imply that the utility of the serological test in clinical decision-making, both establishing the diagnosis and initiation of the treatment, is very limited. The serological tests are beneficial for large-scale use to assess the seroprevalence in a population, not for establishing the diagnosis.

How to Diagnose COVID-19 When Diagnostic Tests Not Readily Available

Despite the limitation of the accuracy of the diagnostic tests for COVID-19, clinicians should perform rRT-PCR on all symptomatic children to confirm COVID-19. In fact, this test is not always available or cannot be accessed in some settings, so that a presumptive or probable diagnosis should be made. A simple algorithm or a scoring system consists of clinical findings, and simple laboratory investigations will be very valuable to help clinicians in this situation. Nevertheless, no studies or recommended guidelines have been published.

High probability of COVID-19 is more likely in a symptomatic child with no other apparent causes of the symptoms. Moreover, if the child is from an area with a high prevalence of local transmission rate COVID-19, in this situation, it is reasonable to make a presumptive diagnosis of COVID-19. The decision of treatment will depend on the severity of the clinical manifestations, the presence of comorbid, and the balance between the risk and benefit of the treatment.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References

1. Wang W, Xu Y, Gao R, Lu R, Han K, Wu G, *et al*. Detection of SARS-CoV-2 in different types of clinical specimens. JAMA 2020;323:1843-4.
2. Younes N, Al-Sadeq DW, Al-Jighefee H, Younes S, Al-Jamal O, Daas HI, *et al*. Challenges in laboratory diagnosis of the novel coronavirus SARS-CoV-2. Viruses 2020;12:582.
3. Xie X, Zhong Z, Zhao W, Zheng C, Wang F, Liu J. Chest CT for typical coronavirus disease 2019 (COVID-19) pneumonia: Relationship to negative RT-PCR testing. Radiology 2020;296:E41-5.
4. Ai T, Yang Z, Hou H, Zhan C, Chen C, Lv W, *et al*. Correlation of chest CT and RT-PCR testing for coronavirus disease 2019 (COVID-19) in China: A report of 1014 cases. Radiology 2020;296:E32-40.
5. Fang Y, Zhang H, Xie J, Lin M, Ying L, Pang P, *et al*. Sensitivity of chest CT for COVID-19: Comparison to RT-PCR. Radiology 2020;296:E115-7.
6. Yang Y, Yang M, Shen C, Wang F, Yuan J, Li J, *et al*. Evaluating the accuracy of different respiratory specimens in the laboratory diagnosis and monitoring the viral shedding of 2019-nCoV infections. medRxiv 2020. doi: 10.1101/2020.02.11.20021493
7. Food and Drug Administration. New York SARS-CoV-2 Real-time RT-PCR Diagnostic Panel. Rockville, MD: Food and Drug Administration; 2020.
8. Lauer SA, Grantz KH, Bi Q, Jones FK, Zheng Q, Meredith HR, *et al*. The incubation period of coronavirus disease 2019 (COVID-19) from publicly reported confirmed cases: Estimation and application. Ann Intern Med 2020;172:577-82.
9. Lisboa Bastos M, Tavaziva G, Abidi SK, Campbell JR, Haraoui LP, Johnston JC, *et al*. Diagnostic accuracy of serological tests for covid-19: Systematic review and meta-analysis. BMJ 2020;370:m2516.

讓呼吸再序

Dymista® 鼻舒達®

有效舒緩鼻敏感症狀：

流鼻水、鼻塞、鼻痕、打噴嚏、眼部不適

Dymista®
Azelastine hydrochloride and Fluticasone propionate

2合1
鼻敏噴劑[2]

5分鐘
起效[1]

參考資料：1. Bousquet J, et al. Onset of Action of the Fixed Combination Intranasal Azelastine-Fluticasone Propionate in an Allergen Exposure Chamber. *J Allergy Clin Immunol Pract*. 2018;6(5):1726-1732.e6.
2. Dymista (azelastine hydrochloride/fluticasone propionate) Prescribing Information. Viatris Healthcare Hong Kong Limited: Version August 2020.

DYMISTA NASAL SPRAY SUMMARY OF PRODUCT INFORMATION: 1. TRADE NAME: DYMISTA NASAL SPRAY **2. PRESENTATION:** Each Dymista nasal spray bottle contains 23 g suspension in 25 ml bottles. One actuation (0.14 g) delivers 137 micrograms azelastine hydrochloride (= 125 mcg azelastine) and 50 mcg fluticasone propionate. **3. INDICATIONS:** Relief of symptoms of moderate to severe seasonal and perennial allergic rhinitis if monotherapy with either intranasal antihistamine or glucocorticoid is not considered sufficient. **4. DOSAGE:** For nasal use only. Adult and adolescents (12 years and older): one actuation in each nostril twice daily (morning and evening). Children below 12 years: not recommended for use in children below 12 years. Elderly population: no dose adjustment required. No data in patients with renal and hepatic impairment. **5. CONTRAINDICATIONS:** Hypersensitivity to the active substances or to any of the excipients. **6. WARNINGS & PRECAUTIONS:** Systemic effects may occur, particularly at high doses for prolonged periods. Potential systemic effect may include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, cataract, glaucoma and more rarely, a range of psychological or behavioral effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children). Caution is advised in patients with severe liver disease given the extensive first-pass metabolism of Dymista Nasal Spray and thus higher systemic exposure of intranasal fluticasone propionate. Reduce intranasal fluticasone formulation to the lowest dose at which effective control of symptoms is maintained. Weigh the possible benefit against risk in patients with tuberculosis, any type of untreated infection, or have had a recent surgical operation or injury to the nose or mouth. Care must be taken in patient transferring from systemic steroid treatment to Dymista Nasal Spray with impaired adrenal function. Visual disturbance may be reported with systemic and topical corticosteroid use. Closely monitor patients with a change in vision or with a history of increased ocular pressure, glaucoma and/or cataracts. Growth retardation has been reported in children. Regularly monitor the growth of adolescents receiving prolonged treatment with nasal corticosteroids. Dymista contains benzalkonium chloride, which may cause irritation of the nasal mucosa and bronchospasm. **7. INTERACTIONS:** Avoid concomitant use with ritonavir and other CYP3A4 inhibitors including cobicistat-containing products unless the benefit outweighs the increased risk of systemic corticosteroid side-effects. Care is advised in concomitant use with potent CYP3A4 inhibitors (e.g. ketoconazole), sedative and central nervous medication. **8. PREGNANCY AND LACTATION:** No or limited data in pregnant woman. Unknown if the ingredients/metabolites are excreted in human breast milk. Used only if the potential benefit justifies the potential risk. **9. SIDE EFFECTS:** Epistaxis. Headache, dysgeusia, unpleasant smell. Reference: HK PI (Aug 2020) Date of preparation: OCT2021 Identifier number: DYMI1021
FULL PRESCRIBING INFORMATION IS AVAILABLE UPON REQUEST.

Mylan Pharmaceutical Hong Kong Ltd., a Viatris company
Suites 2401-07 & 12, 24/F., One Island East, 18 Westlands Road, Quarry Bay, Hong Kong T 2290 7100 F 2673 0008 W www.viatris.com

VIATRIS 暉致

The **FIRST AND ONLY** asthma biologic to inhibit IL-4 and IL-13 signaling

AN ADD-ON MAINTENANCE TREATMENT FOR PATIENTS (12+ YEARS) WITH **INADEQUATELY CONTROLLED SEVERE ASTHMA** WITH TYPE 2 INFLAMMATION[1]

A CLEAR PATH TO ASTHMA CONTROL

NOW AVAILABLE

UP TO 72% REDUCTION
SIGNIFICANT EXACERBATION REDUCTION
in annualized severe exacerbations at Week 24 with DUPIXENT 200 mg Q2W + SOC vs placebo + SOC (*P*=0.0003)[1]

86% OF PATIENTS
REDUCED OR NO INCREASE IN THEIR OCS DOSE
by Week 24 with DUPIXENT 300 mg Q2W + SOC vs 68% with placebo + SOC (P<0.001)[2]

200 mL IMPROVEMENT
RAPID AND SUSTAINED IMPROVEMENT IN LUNG FUNCTION
at Week 52 with DUPIXENT 200 mg Q2W + SOC vs placebo + SOC (*P*<0.001)[3]

UP TO 75% OF PATIENTS
HIGH RESPONDER RATE
in Asthma Control Questionnaire measures of **sleep, activity limitations, and breathing**[1]

SELF-INJECTABLE
Convenient subcutaneous injection[1]

LIBERTY ASTHMA VENTURE Study Design[2]: 210 patients were randomly assigned with oral glucocorticoid-treated asthma to receive add-on DUPIXENT (at a dose of 300 mg) or placebo every 2 weeks for 24 weeks. After a glucocorticoid dose-adjustment period before randomization, glucocorticoid doses were adjusted in a downward trend from week 4 to week 20 and then maintained at a stable dose for 4 weeks. The primary end point was the percentage reduction in the glucocorticoid dose at week 24. Key secondary end points were the proportion of patients at week 24 with a reduction of at least 50% in the glucocorticoid dose and the proportion of patients with a reduction to a glucocorticoid dose of less than 5 mg per day. Severe exacerbation rates and the forced expiratory volume in 1 second (FEV_1) before bronchodilator use were also assessed.

LIBERTY ASTHMA QUEST Study Design[3]: 1902 patients who were 12 years of age or older with uncontrolled asthma were randomly assigned in a 2:2:1:1 ratio to receive add-on subcutaneous DUPIXENT at a dose of 200 or 300 mg every 2 weeks or matched-volume placebos for 52 weeks. The primary end points were the annualized rate of severe asthma exacerbations and the absolute change from baseline to week 12 in the forced expiratory volume in 1 second (FEV_1) before bronchodilator use in the overall trial population. Secondary end points included the exacerbation rate and FEV_1 in patients with a blood eosinophil count of 300 or more per cubic millimetre. Asthma control and DUPIXENT safety were also assessed.

EOS, eosinophils; FeNO, fractional exhaled nitric oxide; ICS, inhaled corticosteroid ; OCS, oral corticosteroid; Q2W, once every 2 weeks; SOC, standard of care.

References: 1. DUPIXENT Summary of Product Characteristics. May 2020. **2.** Rabe KF, Nair P, Brusselle G, et al. Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. N Engl J Med. 2018;378(26):2475-2485. **3.** Castro M, Corren J, Pavord ID, et al. Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma. N Engl J Med. 2018;378(26):2486-2496.

Presentation: Dupilumab solution for injection in a pre-filled syringe with needle shield. **Indications:** Atopic Dermatitis (AD): Moderate-to-severe AD in adults and adolescents ≥12 years who are candidates for systemic therapy. Asthma: In adults and adolescents ≥12 years as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised FeNO, who are inadequately controlled with high dose ICS plus another medicinal product for maintenance treatment. **Dosage & Administration:** Subcutaneous injection. AD adults: Initial dose of 600 mg (two 300 mg injections), followed by 300 mg every other week. AD adolescents: Body weight <60 kg- initial dose of 400 mg (two 200mg injections), followed by 200 mg every other week. Body weight ≥60 kg- same dosage as adults. Dupilumab can be used with or without topical corticosteroids. Topical calcineurin inhibitors may be used, but should be reserved for problem areas only, e.g. face, neck, intertriginous and genital areas. Consider discontinuing treatment in patients who have shown no response after 16 weeks. Asthma: Initial dose of 400 mg, followed by 200 mg every other week. For patients with severe asthma and on oral corticosteroids or with severe asthma and co-morbid moderate-to-severe AD- initial dose of 600 mg, followed by 300 mg every other week. Patients receiving concomitant oral corticosteroids may reduce steroid dose gradually once clinical improvement with dupilumab has occurred. The need for continued dupilumab therapy should be considered at least annually as determined by a physician. If a dose is missed, administer it asap and thereafter, resume dosing at the regular scheduled time. **Contraindications:** Hypersensitivity to dupilumab or any of the excipients. **Precautions:** Safety and efficacy in children <12 years not been established. Not to be used to treat acute asthma symptoms, acute exacerbations, acute bronchospasm or status asthmaticus. Do not discontinue corticosteroids abruptly upon start of dupilumab. Reduction should be gradual and performed under supervision of a physician; it may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy. Biomarkers of type 2 inflammation may be suppressed by systemic corticosteroid use. If systemic hypersensitivity reaction occurs, discontinue dupilumab and initiate appropriate therapy. Be alert to vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in patients with eosinophilia. Treat pre-existing helminth infections before initiating dupilumab. If patients become infected while receiving dupilumab and do not respond to anti-helminth treatment, discontinue dupilumab until infection resolves. Patients who develop conjunctivitis that does not resolve following standard treatment should undergo ophthalmological examination. AD patients with comorbid asthma should not adjust or stop asthma treatments without consultation with physicians. Carefully monitor patients after discontinuation of dupilumab. Do not give live and live attenuated vaccines concurrently with dupilumab. Patients should be brought up to date with immunisations before starting dupilumab. **Drug Interactions:** Immune responses to TdaP vaccine and meningococcal polysaccharide vaccine were assessed. Patients receiving dupilumab may receive concurrent inactivated or non-live vaccinations. **Pregnancy and lactation:** Should be used during pregnancy only if potential benefit justifies potential risk to foetus. Unknown whether dupilumab is excreted in human milk or absorbed systemically after ingestion. Decision must be made whether to discontinue breast-feeding or dupilumab taking into account benefit of breast feeding for the child and benefit of therapy for the woman. **Undesirable effects:** AD: Most common adverse reactions reported- injection site reactions, conjunctivitis, blepharitis and oral herpes. Safety profile observed in adolescents consistent with that seen in adults. Asthma: Most common adverse reaction reported- injection site erythema. For other undesirable effects, please refer to the full prescribing information. Preparation: 2 x 300mg/2ml in pre-filled syringe with needle shield, 2 x 200mg/1.14ml in pre-filled syringe with needle shield. **Legal Classification:** Part 1, First & Third Schedules Poison **Full prescribing information is available upon request.** API-HK-DUP-20.05

MAT-HK-2000267-1.0-08/2020 4IC_1408

sanofi

Sanofi Hong Kong Limited
1/F & SECTION 212 on 2/F, AXA SOUTHSIDE, 38 WONG CHUK HANG ROAD,
WONG CHUK HANG, HONG KONG
Tel: (852) 2506 8333 Fax: (852) 2506 2537

DUPIXENT® (dupilumab) Injection
200mg · 300mg