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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

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Pediatric Respirology and Critical Care Medicine

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Contents

From CO2 to hemoptysis

This issue of *Pediatric Respirology and Critical Care Medicine* contains several noteworthy discoveries of intriguing articles. Selina Ka-wai *et al.*[1] published an original article "Calibration drift in transcutaneous carbon dioxide (TcCO2) measurement devices." Adequate and high-quality sleep positively impacts children's quality of life, memory, learning, attention, mood, and behavior. Sleep-disordered breathing encompasses a spectrum of conditions, ranging from primary snoring, which does not result in functional impairment, to upper airway resistance syndrome, obstructive hypoventilation, and obstructive sleep apnea syndrome. Continuous monitoring of patients' CO2 levels during sleep is of great significance for assessing disease severity and formulating treatment plans. Selina Ka-wai *et al.*[1] compare the accuracy of two commercially available TcCO2 monitoring devices in nonattended overnight TcCO2 assessment for 9 h in Kwong Wah Hospital, Yau Ma Tei, Hong Kong. They suggested assessing the TcCO2 drift of the machine as an important part of quality control in TcCO2 monitoring.

The following article presents a systematic review and meta-analysis of the effectiveness of telemedicine consultation in improving outcomes of childhood asthma. Ong *et al.*[2] developed a comprehensive set of criteria for evaluating the studies, and after a thorough review, 10 studies were ultimately selected for inclusion in the analysis. They reported that the telemedicine group had more asthma symptom-free days and a higher rate of well-controlled asthma compared with the usual care group. There are several advantages of telemedicine for monitoring asthma in the pediatric population. The implementation of telemedicine consultation has the potential to enhance the accessibility of medical resources, facilitate the provision of timely advice, information, and more frequent monitoring and follow-up for children with asthma, and assist in the development of a more personalized approach to managing the condition. The reduction of medical resources and the alleviation of the disease burden associated with asthma might be the two key benefits. Nevertheless, more research focusing on the effectiveness of telemedicine would be most welcome.

Finally, Freer *et al.*[3] provide a case report of diffuse alveolar hemorrhage (DAH) in children due to post-streptococcal glomerulonephritis in the context of vaping, which also represents a noteworthy contribution to this issue. The etiology of DAH is heterogeneous, with vasculitis and pulmonary hemorrhage representing the most prevalent causes. Additionally, DAH may result from a multitude of underlying conditions, including trauma, infection, cardiovascular disease, tumors, and the use of drugs or toxins. DAH associated with post-streptococcal glomerulonephritis in children is rare and only two cases were reported from the authors' literature search. The majority of patients with this condition experience rapid deterioration, with a high mortality rate. In establishing the diagnosis, it is imperative to seek the causes of DAH actively. This editorial shows the rare etiology and the management of DAH, which enriches our clinical experience.

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Conflicts of interest

There are no conflicts of interest.

Kunling Shen

Department of Respiration, Shenzhen Children's Hospital, Shenzhen, China, Respiratory Department, Beijing Children's Hospital, Capital Medical University, China National Clinical Research Center of Respiratory Diseases, National Center for Children's Health, Beijing, China

Address for correspondence: Prof. Kunling Shen, Department of Respiration, Shenzhen Children's Hospital, No. 7019 Yitian Road, Futian District, Shenzhen 518038, Guangdong, China.
E-mail: kunlingshen1717@163.com

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Comparison of Calibration Drift in Transcutaneous Carbon Dioxide Monitoring Devices for Overnight Level 4 Sleep Study in Hong Kong Children

Selina Ka-wai Ng, Eric Yat-tung Chan, Shuk-yu Leung

Department of Paediatrics and Adolescent Medicine, Kwong Wah Hospital, Hong Kong SAR, China

Abstract

Background: Level 4 sleep study with transcutaneous carbon dioxide ($TcCO_2$) monitoring is a simple, non-invasive method to investigate sleep-related hypoventilation. However, calibration drift in the $TcCO_2$ device weakens its reliability. **Materials and Methods:** We conducted a retrospective study of 61 patients from <1 to 20 years of age in our paediatric unit, who were assigned one of the two models of $TcCO_2$ machines (SenTec Digital Monitoring System and Tina Radiometer Copenhagen TCM4 Transcutaneous Blood Gas Monitor) for performing the Level 4 sleep study, using capillary blood gas carbon dioxide (pCO_2) level at the first and ninth hours as a reference. **Results:** For the 9-h sleep study, there was no change in the attachment site, membrane, or sensor. The $TcCO_2$–pCO_2 difference at the ninth hour in the former model was 0.03 ± 0.61 kPa (0.26 ± 4.59 mm Hg), which was favourable in comparison to the latter (–0.45 ± 1.25 kPa or –3.38 ± 9.38 mm Hg), with $P = 0.014$; the $TcCO_2$–pCO_2 difference between monitors A and B at the ninth hour compared to the first hour did not differ substantially from the former ($P = 0.160$), but a statistically significant difference was noted in the latter model ($P = 0.037$). Both findings indicated calibration drift and hence less accurate $TcCO_2$ readings in the latter model. **Conclusion:** In overnight extended use, calibration drift might affect the diagnosis and management of sleep-related hypoventilation.

Keywords: Calibration drift, level 4 sleep study, sleep-disordered breathing, sleep-related hypoventilation, transcutaneous carbon dioxide

Introduction

Sleep-disordered breathing (SDB) is characterized by a spectrum of conditions, from primary snoring where there is no functional impairment to upper airway resistance syndrome and obstructive hypoventilation and obstructive sleep apnoea syndrome (OSAS), based on their cardinal clinical features and laboratory criteria. While primary snoring can be prevalent—most studies quoting the prevalence between 3% and 15%, with one of them estimating that up to 35% of children under 13 years of age are being involved, this group should be differentiated from OSAS patients who amounting to around 1%–4% of the paediatric population[1,2] and would benefit from tailored management to alleviate symptoms and complications such as hypersomnolence, inattention and hyperactivity, cognitive deficits and academic underperformance, pulmonary and systemic hypertension, and even stunted growth.

Although polysomnography (PSG) is a level 1 sleep test, which offers comprehensive assessment in SDB and is considered the gold standard, it has to be performed in qualified sleep laboratories with dedicated polysomnographic technicians, and cardiorespiratory, electroencephalographic, electrooculographic, and

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Address for correspondence: Dr. Selina Ka-wai Ng, Department of Paediatrics and Adolescent Medicine, Kwong Wah Hospital, 25 Waterloo Road, Hong Kong SAR, China. E-mail: nkw548@ha.org.hk

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electromyographic monitoring is associated with significant costs. In contrast, the level 4 sleep study investigates only two fundamental parameters: oxygen saturation (SpO_2) and carbon dioxide (CO_2) levels. It has the advantages of being simple to conduct and more readily available, rendering it a reasonable first-line screening test.

The interaction of hypercapnia and hypoxia in producing OSA symptoms has not been fully elucidated. Daytime sleepiness, one of the leading features prompting for the sleep study, does not improve with oxygen therapy alone[3,4], despite hypoxia being corrected. A more recent study considered the impact of hypercapnia from the electroencephalographic point of view and showed that decrease in the delta/alpha wave ratio correlated with a lower Epworth Sleepiness Scale score after treatment for hypercapnia by positive airway pressure.[5] This highlights the clinical significance of CO_2 retention, as traditionally, hypoxia is the centre of attention in SDB. The pathophysiological complexity also lies in the fact that hypercapnia cannot be predicted by the type, duration, or frequency of apnoea, and it is possible even in the absence of hypoxia.[6] These intriguing findings have shed light to our study, as we emphasised on how the precise diagnosis of paediatric sleep hypoventilation.

Ideally, arterial blood gas is used for analysis of partial pressure of CO_2 ($PaCO_2$), yet it is hardly justifiable in the context of SDB, especially for children, due to its invasive nature, and only less information can be obtained from a single blood sample. On the other hand, transcutaneous carbon dioxide ($TcCO_2$) monitoring is non-invasive, provides continuous tracing, and can be easily adopted in the general ward settings, making $TcCO_2$ a useful surrogate marker.

A carbon dioxide electrode was first described by Stow and further developed by Severinghaus and Bradley.[7] The electrode measures the pH, which is proportional to CO_2 diffused through a selectively permeable membrane washed in bicarbonate solution. This has established the foundation for $TcCO_2$ measurement. In addition, the surface probe of the $TcCO_2$ monitor contains a heating element that induces vasodilatation of the underlying skin when attached, such that "arterialisation" is achieved.

Under optimal conditions, that is, absence of excessive sweating or movement, a cutaneous site is sufficient for approximately 7 h of $TcCO_2$ log. Though auto-calibration is an inbuilt feature of transcutaneous CO_2 sensors, calibration drift, the process of gradual offset of measurements over a period of time, is not completely preventable; hence, $TcCO_2$ readings can be skewed. Relocation and recalibration of the sensors is time-consuming and labour-intensive. Unlike PSG, patients undergoing the level 4 sleep study are unattended overnight, so a device with negligible $TcCO_2$ drift is preferred.

In this study, we studied the relationship between TcCO2 of the commercially available TcCO2 monitoring devices and Capillary blood gas PCO2, at the start and end of a non-attended overnight 9 h.

Materials and Methods

This retrospective study was performed after the approval of the Institutional Review Board of the Hong Kong Hospital Authority Kowloon Central Cluster Ethics Committee. Paediatric patients investigated for snoring or suspected OSA and who underwent level 4 sleep study including SpO_2 and $TcCO_2$ recording from October 2016 to February 2017 were reviewed. As per the authors' usual practice, $TcCO_2$ was recorded continuously for 12 h for acquiring as much sleep data as possible, preferably at least 6 h for reliability of test results. Data for awake conditions or during other activities (e.g., feeding and bathing) were excluded. Capillary blood gas was taken at the first and ninth hour for verification. Valid informed consents were obtained from subjects' guardians regarding the review and anonymous reporting of the collected data for clinical quality improvement and research purposes.

Monitor A represented the SenTec Digital Monitoring System, and monitor B represented the Tina Radiometer Copenhagen TCM4 Transcutaneous Blood Gas Monitor (specifications in Appendix). Two machines of each were used, and all of them within 3 months since the start of this study. Either monitor A or monitor B was used for each patient, which was allocated in an alternating sequence, that is, patient 1 used monitor A, patient 2 used monitor B, and patient 3 used monitor A. As suggested by Storre *et al*.[8] capillary blood gas was sampled 2 min after the $TcCO_2$ reading stabilised, which is the shortest time interval to allow adequate equilibration. A flat skin surface over the subjects' flank was selected for probe placement for ease of application and reduced chance of dislodgement, with prior cleansing of the site to ensure proper contact. Adhesive rings and contact gels were applied accordingly. Subjects who experienced dislodged transcutaneous transducer or any need for replacement of the probe during the study were excluded.

Topical anaesthetic preparation (EMLA cream 5%) was applied on the subjects' finger pulp 30 min ahead of planned blood sampling time. Blood specimens stored on an ice pack were sent to the hospital's biochemistry laboratory without delay. General medical and nursing care as per standard practices remain unaltered among the two groups.

Statistical analysis

The null hypothesis assumes that monitor A and monitor B performs similarly in terms of accuracy

of $TcCO_2$ measured in kilopascal (kPa). To reject the null hypothesis, a P value of <0.05 is to be achieved. Capillary pCO_2 was defined as the standard reference in this study. The mean difference of $TcCO_2$ against capillary pCO_2 at the first and ninth hours was analysed by Student t test, whereas the standard deviation (SD) of the $TcCO_2$–pCO_2 mean difference between monitor A and monitor B at the first and ninth hours was assessed by Levene's test. The $TcCO_2$–pCO_2 correlations were delineated using Bland–Altman analysis. The numerical differences between $TcCO_2$ and pCO_2 measurements were plotted against their average value. Presuming an effect size of 0.53 kPa (3.98 mm Hg) for the difference between capillary pCO_2 and $TcCO_2$ and 1 SD at 0.60 kPa (4.50 mm Hg), a sample size of 26 patients was required for each $TcCO_2$ machine to achieve α-level of 0.05 and power of 0.8. All data were processed and summarised using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp. Armonk, NY, USA).

Results

A total of 61 subjects, aged <1–20 years, were recruited within the study period. Thirty-one subjects were assigned to use monitor A, and 30 subjects were allocated for monitor B. All subjects in the monitor A group were included in the data analysis. Two of those using monitor B were excluded due to a dislodged transducer, and eventually 28 subjects were analysed in this group.

Baseline characteristics of patients in the two groups are listed in Table 1. The mean age was 10.63 years. Approximately 18.6% of patients were <1 year of age (youngest 1 month old; body weight 4.6 kg), eight of them belonged to the group assigned to monitor A, and three of them were in the monitor B group. There were more male than female patients in both groups, with 64.5% males in the monitor A group and 71.4% males in the monitor B group ($P = 0.57$). The body weight and height as well as z-score for body mass index (BMI) calculated using either monitor A and monitor B were similar across all patients, with no statistically significant differences. At the first hour, both $TcCO_2$ and pCO_2 values were also comparable between the two groups.

First-hour $TcCO_2$ readings for monitor A are shown in Figure 1. The $TcCO_2$–pCO_2 mean difference was 0.006 kPa (0.045 mm Hg), ranging from –1.02 to 1.01 kPa (–7.66 to 7.57 mm Hg; 1 SD = 0.52 kPa or 3.89 mm Hg). For monitor B, as represented in Figure 2, the $TcCO_2$–pCO_2 mean difference at the first hour was –0.06 kPa (–0.45 mm Hg), ranging from –1.24 to 1.12 kPa (–9.30 to 8.40 mm Hg), 1 SD = 0.50 kPa (3.75 mm Hg). There were no statistically significant differences in the mean difference ($P = 0.712$) and SD values ($P = 0.307$) while comparing the two groups.

Nevertheless, monitor B demonstrated greater variance in the ninth-hour $TcCO_2$ recordings, as shown in Figure 3. The mean $TcCO_2$–pCO_2 difference was −0.45 kPa (–3.38 mm Hg), ranging from –2.90 to 2.00 kPa (–21.75 to 15.00 mm Hg), with 1 SD of 1.25 kPa (9.38 mm Hg). Monitor A showed a closer correlation of $TcCO_2$–pCO_2 [Figure 4], and the mean difference was 0.034 kPa (0.265 mm Hg), ranging from –1.17 to 1.23 kPa (–8.74 to 9.26 mm Hg), with 1 SD of 0.61 kPa (4.59 mm Hg). The P value was 0.014 for the variance of SD between groups, reaching statistical significance.

To further illustrate the calibration drift for each of the $TcCO_2$ monitors, we compared $TcCO_2$–pCO_2 differences between monitors A and B at the ninth hour against that at the first hour, which is summarised in Table 2. The drift was proven to be statistically significant ($P = 0.037$) in monitor B but not for monitor A ($P = 0.160$).

Discussion

Obstructive hypoventilation is defined by $PaCO_2$ above 50 mm Hg for over 25% of total sleep time for paediatric patients, and in adults by $PaCO_2$ greater than 55–60 mm Hg for more than 10 min, according to the American Academy of Sleep Medicine clinical guidelines.

During sleep, upper airway muscles relax and airway resistance increases. A small physiological increase in end-tidal CO_2 is observed. This change is readily sensed by peripheral and central chemoreceptors. For normal individuals, compensatory mechanisms exist to promote longer inspiratory time and reflex increase in pharyngeal

Table 1: Baseline characteristics

Variables	Monitor A ($n = 31$)	Monitor B ($n = 28$)	P value
Age (year)	10.63 ± 7.62	10.61 ± 7.01	0.909
Male gender, n	20 (64.5%)	20 (71.4%)	0.570
Height (cm)	123.85 ± 39.84	130.14 ± 36.73	0.579
Weight (kg)	35.36 ± 24.44	37.24 ± 24.49	0.786
BMI z-score	0.59 ± 1.23	0.41 ± 1.42	0.612
$TcCO_2$ at the first hour	5.15 ± 0.63 kPa (38.63 ± 4.73 mm Hg)	4.82 ± 0.72 kPa (36.15 ± 5.4 mm Hg)	0.121
pCO_2 at the first hour	5.19 ± 0.82 kPa (38.93 ± 6.15 mm Hg)	4.84 ± 0.49 kPa (36.3 ± 3.68 mm Hg)	0.093
Peak $TcCO_2$	5.43 ± 0.71 kPa (40.73 ± 5.33 mm Hg)	5.62 ± 0.79 kPa (42.15 ± 5.93 mm Hg)	0.222

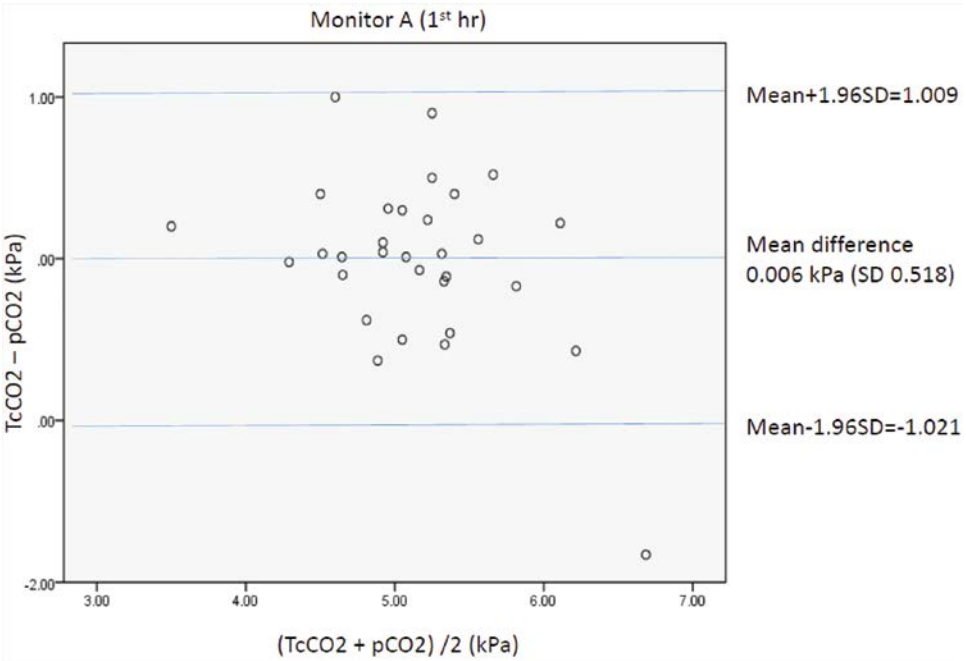

Figure 1: Bland–Altman plot for the $TcCO_2$–pCO_2 correlation of monitor A at the first hour

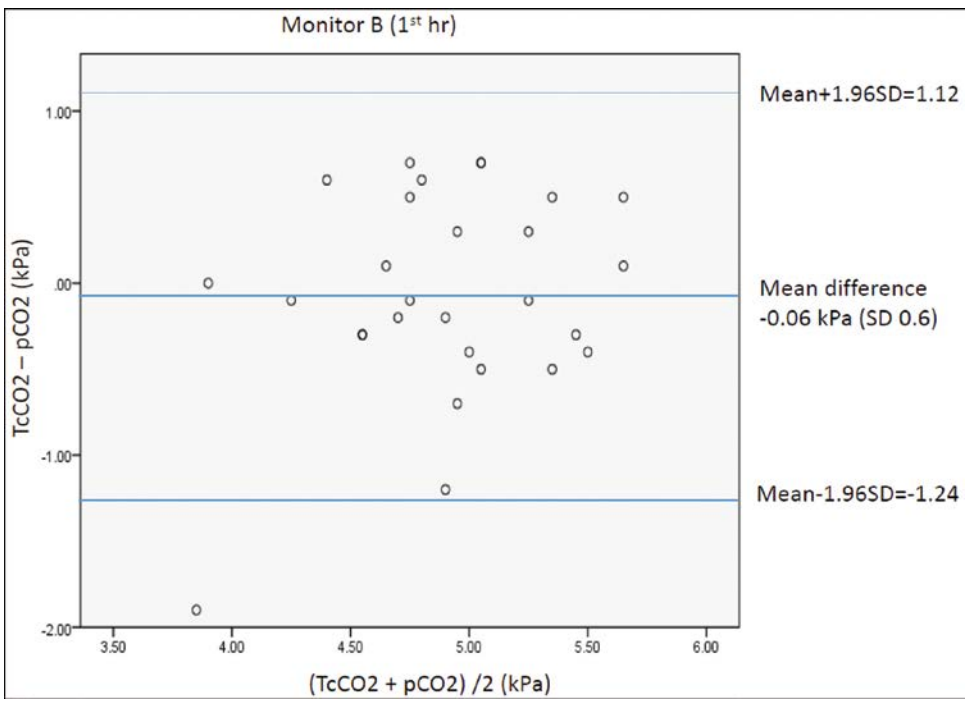

Figure 2: Bland–Altman plot for the $TcCO_2$–pCO_2 correlation of monitor B at the first hour

muscle dilator activity, such that oxygenation can be maintained and sleep remains undisrupted.

However, in OSA patients, the upper airway is often structurally narrowed, with further dynamic collapse during inspiration.[9] Sleep quality is compromised during frequent arousals for forcing open the airway intermittently. This maladaptive process also transiently washes out CO_2 with an overshoot, which is followed by apnoea; a vicious cycle is thus created. With time, the ventilatory response to hypercapnia becomes blunted.[10] The renal system compensates by increasing the bicarbonate buffer. Eventually, hypoventilation in sleep evolves into chronic daytime hypercapnia. Retention of CO_2 contributes to symptoms such as morning headache and daytime sleepiness, which can result in

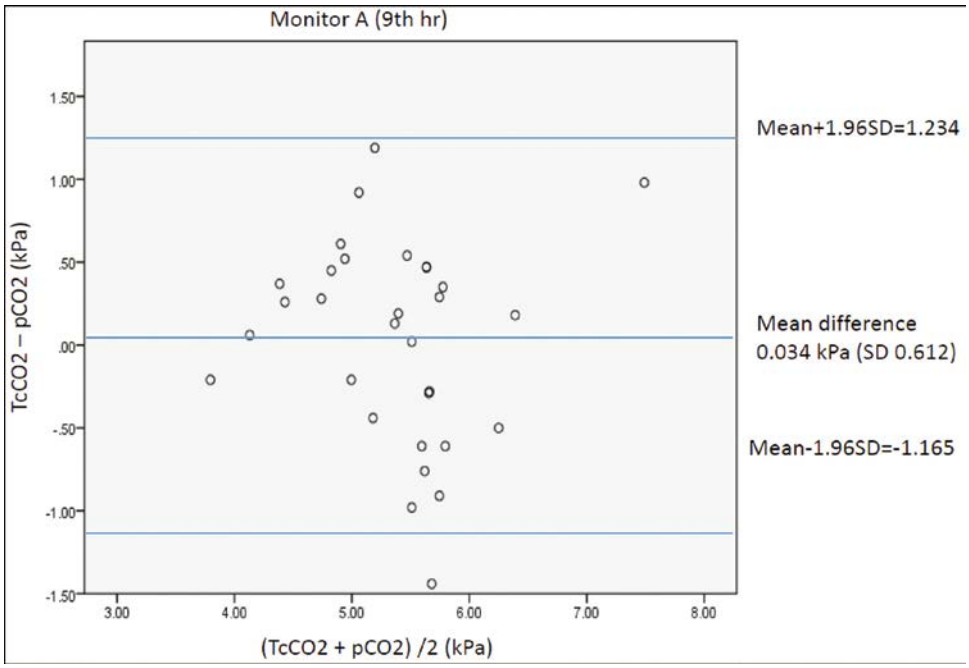

Figure 3: Bland–Altman plot for the $TcCO_2$–pCO_2 correlation of monitor B at the ninth hour

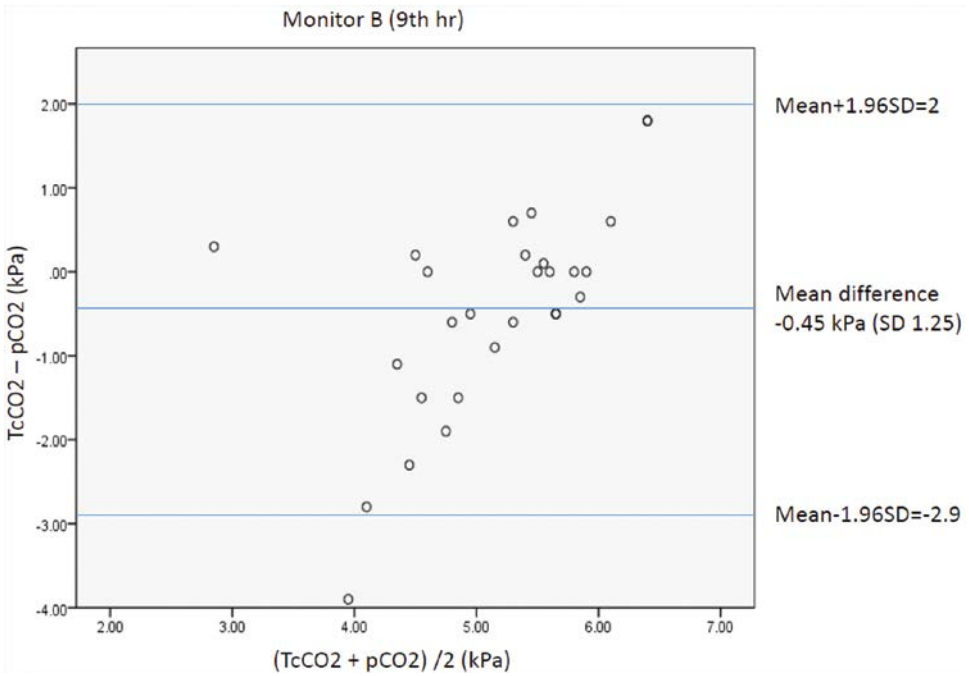

Figure 4: Bland–Altman plot for the $TcCO_2$–pCO_2 correlation of monitor A at the ninth hour

Table 2: $TcCO_2$–pCO_2 difference at the first and ninth hours

Monitors	$TcCO_2$–pCO_2 difference		*P* value
	1st hour	9th hour	
Monitor A	0.01 ± 0.52 kPa (0.08 ± 3.90 mm Hg)	0.03 ± 0.61 kPa (0.23 ± 4.58 mm Hg)	0.160
Monitor B	–0.06 ± 0.50 kPa (–0.45 ± 3.75 mm Hg)	–0.45 ± 1.25 kPa (–3.38 ± 9.38 mm Hg)	0.037

dysfunctions in daily activities and neurobehavioural disorders.[11] It is therefore important to identify sleep-related hypoventilation in its early stage. The level 4 sleep study, though not structured to evaluate all components of sleep architecture, has its strength in serving such a purpose.

Various ways to ascertain the partial pressure of CO_2 during sleep have been sought. Previous studies have compared the use of transcutaneous CO_2 monitoring against capnography,[12] which detects exhaled CO_2, both being non-invasive means of approximating arterial CO_2 levels and showed agreeable findings in general between the two methods. Nonetheless, for the moderate- or severe-disease group with the apnoea–hypopnoea index of greater than or equal to 10 events per hour, capnography is less accurate, as end-tidal CO_2 signaling is grossly limited by restriction of nasal airflow. From the authors' own experience, another limitation of capnography is that the fitting of the nasal cannula can be bothersome, especially to young children, triggering restlessness that can hinder data collection and its quality. Furthermore, use of a nasal cannula as a consumable increases the expense related to the test. Overall, transcutaneous CO_2 monitoring is comparatively reliable across OSA patients with varying severities, causes less discomfort to patients, and is a more economical choice.

The noteworthy setback of $TcCO_2$ monitoring is calibration drift, which is subjected to device wear-and-tear, inappropriate use, or with extended time of monitoring. Our study explored this issue by evaluating the performance of two commonly employed models of $TcCO_2$ monitors. At the end of a 9-hour level 4 sleep study, $TcCO_2$ readings of monitor B differed remarkably from the actual capillary pCO_2, with maximal underestimation by 2.9 kPa (21.8 mm Hg) to overestimation by 2.0 kPa (15.0 mm Hg). On the other hand, monitor A performed more steadily, with a narrower range of the $TcCO_2$–pCO_2 difference (–1.2 to 1.2 kPa; –8.7 to 9.3 mm Hg) at the ninth hour. This is possibly explained by differences in the calibration systems featured in the two monitors. Both of them automatically calibrate upon operation, yet monitor A has an additional re-calibration process at termination before being switched off.

Most studies addressed that $TcCO_2$ tends to be higher than pCO_2 due to the underlying biochemical mechanism, and the calibration drift is expected to broaden the gap further. Our study adds that considerable underestimation could also happen, as evidenced by the negative values of mean $TcCO_2$–pCO_2 differences for monitor B. As such, hypoventilation could be overlooked, which delays appropriate management for SDB.

We have recruited subjects with a wide age range in this study. In particular, those in their infancy have more delicate skin, are less likely to cooperate compared to older children and adolescents, and they may easily pull off the $TcCO_2$ sensors, or unintended displacement can occur due to the frequent need for attendance like feeding, changing nappies, and consolation. However, no subjects in the monitor A group experienced such problems necessitating probe replacement, though there were more patients under the age of 1 year in this group than in monitor B group. No burns or skin irritation were noted.

Limitations

Capillary blood gas was used instead of arterial blood gas for pCO_2, a less invasive method but with reduced precision.[13] Pairing of pCO_2 with $TcCO_2$ periodically throughout the entire Level 4 sleep study could have better reflected the calibration drift, but it is practically challenging as multiple capillary pricks would be required, interrupting the intrinsic sleep cycle. Potential error also arises from blood taking techniques, as well as hyperventilation from crying due to pain. Though blood taking skills could not be adjusted for, we attempted to minimise pain as possible with application of local anaesthetics.

The study design can be further improved if both models of $TcCO_2$ machines were applied simultaneously in each subject for direct comparison. This was not implemented in our study due to the substantial expenditure involved, contrasting to our limited budget—monitor A costed HK$223 per night and monitor B costed HK$201 per night in the year of 2016.

Conclusion

In our level 4 sleep study series with no re-site or recalibration of the $TcCO_2$ sensor, monitor A produced more agreeable $TcCO_2$–pCO_2 measurements than monitor B toward the end of the sleep duration. In the study involving non-attended patients overnight, we suggested to assess the $TcCO_2$ drift of the machine before putting it into service.

Financial support and sponsorship

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Nil.

Conflict of interest

There are no conflicts of interest.

Author contributions

Concept, design, definition of intellectual content – Eric YT Chan, Selina KW Ng. Literature search, clinical studies – Selina KW Ng. Data acquisition, data analysis, statistical analysis – SY Leung, Selina KW Ng. Manuscript preparation, manuscript editing – Selina KW Ng, Eric YT Chan. Manuscript review – Selina KW Ng.

Data availability

To protect privacy of participants, data of this study is not shared openly.

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Appendix: Specifications of transcutaneous CO_2 monitors

Variables	Monitor A	Monitor B
CO_2 range	0–200 mm Hg (0–26.7 kPa)	5–100 mm Hg (0.7–13.4 kPa)
Accuracy	± 3 mm Hg (0.4 kPa)	± 5 mm Hg (0.7 kPa)
Drift	< 0.5%/h	±10% over calibration interval
Calibration interval (h)	Up to 12	4

Review Article

The Effectiveness of Telemedicine Consultation in Improving Outcomes of Asthma in the Paediatric Population: A Systematic Review and Meta-Analysis

Leong Tung Ong, Audrey Joe Chii Loh, Nicholas Ming Zher Chee
Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia

Abstract

Telemedicine facilitates clinicians in providing virtual consultations and assessments to paediatric patients, offering a more convenient and efficient healthcare delivery. The aim of this study was to assess the efficacy of telemedicine compared with usual care in paediatric asthma. A systematic literature search was conducted in PubMed, Scopus, Embase, and Ovid SP. Risk ratios (RRs) were used for dichotomous outcomes, and standardised mean differences (SMDs) were used for continuous outcomes with 95% confidence intervals (CIs). A total of 10 studies were included in the meta-analysis. The telemedicine group had more asthma symptom-free days compared with the usual care group with an SMD of 0.18 (95% CI = 0.04–0.32). The telemedicine group had a higher rate of well-controlled asthma in telemedicine compared with the usual care group with an RR of 1.27 (95% CI = 1.14–1.42). The present findings suggest that telemedicine may be an effective alternative to in-person visits for improving asthma control.

Keywords: Asthma, outcome, paediatric, telemedicine

Introduction

Asthma is the leading cause of chronic illnesses in childhood, and it remains a significant cause of childhood disability and morbidity.[1] The global incidence rate of asthma in the paediatric population is 876.0 per 100,000 with a mortality rate of 0.5 per 100,000.[2] Appropriate medication, proper patient education, and compliance with prescribed therapy are important measures of good asthma control.[3] Good asthma control is crucial to lower the risk of asthma exacerbations and frequency of hospitalisation as asthma is a chronic illness that requires frequent monitoring.[4] The Global Initiative for Asthma provides the latest evidence-based guidelines for the diagnosis and management of asthma and aims to improve asthma outcomes, awareness, and its health consequences.[5] Despite the emergence of several adherence interventions and management guidelines, asthma remains a predominant healthcare burden and healthcare utilisation due to frequent exacerbations.[6] Several risk factors contribute to recurrent exacerbations of asthma, including inadequate preventive therapy, limited resources, poor adherence, and lack of appropriate follow-up care, particularly in rural areas.[7-9]

The implementation and widespread use of telemedicine has become prevalent since the onset of the coronavirus disease 2019 pandemic.[10] Telemedicine is a healthcare service that utilises communication technologies to exchange information between a remote physician and a patient.[11] Telemedicine facilitates clinicians in providing virtual consultations and assessments to paediatric patients, eliminating the need for in-person visits to their doctors' offices, and offering a more convenient and efficient

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Address for correspondence: Dr. Leong Tung Ong, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Wilayah Persekutuan Kuala Lumpur, Malaysia.
E-mail: leotungong@gmail.com

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healthcare delivery.[12] Some studies in adults have shown that telemedicine may lead to a reduction in the frequency of acute asthma exacerbations, hospital admissions, and visits to the emergency department.[13] However, few Cochrane reviews showed that there was no strong evidence that telemedicine can improve the outcomes of asthma as there are no significant differences in exacerbations, asthma control, or quality of life remote and face-to-face checkups for asthma.[14,15] Furthermore, there is limited information regarding the efficacy of telemedicine for asthma control in the paediatric population. Hence, this systematic review is conducted to assess the efficacy of telemedicine consultation compared with usual care for asthma control in the paediatric population.

Materials and Methods

Search strategies

We searched the electronic databases, including PubMed, Scopus, Embase, and Ovid SP, up until September 2023 to identify the relevant studies. The following search strategy was used: (telemedicine OR telehealth OR telecommunication OR telepharmacy OR remote OR virtual OR distance OR telephone OR videoconference) AND (asthma) AND (pediatric OR paediatric OR children OR adolescent). Furthermore, we also screened through the references of the included publications to retrieve additional studies. The search strategy was restricted to studies published in peer-reviewed journals and English language. Abstracts and case reports were excluded from the literature search.

Eligibility criteria

The inclusion criteria for the meta-analysis include the following: (i) randomised controlled trials (RCTs), prospective cohort studies, retrospective cohort studies, cross-sectional studies, or case-control studies; (ii) diagnosis of asthma; (iii) paediatric population; (iv) telemedicine consultation, which involves communication with the professionals either through videoconferencing or telephone; and (v) report the outcomes of asthma comparing between the telemedicine group and the usual care group. The exclusion criteria for the meta-analysis include the following: (i) reviews, systematic reviews, case reports, or case series; (ii) adult population or combined adult and paediatric population; (iii) noninteractive telemedicine such as web-based resources, education resources, or asthma monitoring diary; and (iv) do not report outcomes of asthma comparing both groups.

Studies selection and data extraction

The titles and abstracts of the articles were screened independently by two authors based on the eligibility criteria. Full-text articles were assessed for eligibility if the screening based on titles and abstracts was inconclusive. Both authors then read the full text of all relevant articles separately to determine the eligibility to be included in the meta-analysis. Any disagreements or discrepancies regarding the eligibility criteria were resolved through discussion and consensus with a third author. Two authors extracted the relevant data of the included studies independently into a predesigned standardised electronic form created in Excel. The extracted data from the studies included the following: first author name, year of study, country, study design, sample size, gender, mean or median age, intervention type, intervention duration, follow-up duration, emergency department visits, hospitalisation, symptom-free days, number of patients with well-controlled asthma, number of patients with poorly controlled asthma, Asthma Control Test (ACT) scores, childhood-ACT (c-ACT) scores, and caregiver Paediatric Asthma Quality of Life Questionnaire (PAQLQ) scores.

Quality assessment

The methodological quality of the RCT was assessed using the Cochrane risk-of-bias tool for randomised trials (RoB 2) according to six domains (bias arising from the randomisation process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, bias in selection of the reported result, and overall risk) as low risk, some concerns, or high risk.[16] The Risk of Bias Assessment Tool for Nonrandomised Studies was used for non-RCTs,[17] and Newcastle–Ottawa Scale (NOS) was used for the observation study.[18] The qualities of each of the original articles were evaluated independently by two authors, and discrepancies were resolved through discussion by a third author.

Data analysis

For continuous variables, standardised mean difference (SMD) with a corresponding 95% confidence interval (CI) was expressed. For dichotomous variables, risk ratios (RRs) with corresponding 95% CI were expressed. A random-effects model was used to calculate the pooled estimate. Heterogeneity between studies was determined using the chi-square test, with the degree of heterogeneity quantified by I^2. I^2 values of >25%, >50%, and > 75% correspond to low, moderate, and high degree of heterogeneity effects, respectively. Visual inspection of the funnel plot and Egger's regression test were used to evaluate the presence of publication bias. A P value of <0.05 was considered statistically significant. Statistical analysis was performed using the Cochrane Review Manager v5.4 (The Cochrane Collaboration) and R programming (A language and environment for statistical computing, R Core Team). The findings of this meta-analysis were reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

Results

Study selection

The electronic database search yielded a total of 1904 records and 2 additional records identified through

other sources. A total of 551 records remained after duplicates were removed and were subsequently screened. Overall, 536 records were excluded based on title and abstract review, and subsequently, 15 records were full-text screened, leading to the rejection of five papers due to reasons such as not reporting intended outcomes, involving noninteractive web-based monitoring, and including adult patients. In the end, 10 studies were included in this meta-analysis. The study flow diagram is shown in Figure 1.

Study characteristics

Ten studies involving 3756 patients (1846 in the telemedicine group and 1910 in the usual care group) were included in this meta-analysis.[7,11,19-26] The majority of the studies were conducted in the United States with seven studies with the rest being in the Netherlands, Jordan, and Thailand. Most studies demonstrated predominantly male participants with the percentage ranging from 53.3% to 67.3% in the telemedicine group and 48.9%–71.1% in the usual care group. The age of the participants ranged from 6.6 to 11.3 in the telemedicine group and 7.1 to11.3 in the usual care group. The intervention used in this study includes telephone consultation or videoconferencing with pharmacists, nurses, doctors, and peer trainers. The follow-up duration ranged from 3 to 24 months. The study characteristics are provided in Table 1.

Study quality assessment

Seven randomised control trials included in this study were assessed using the RoB 2 [Figure 2]. None of the included RCTs employed a double-blind design, and the impossibility of blinding patients and caregivers due to the intervention may introduce the potential for bias. Two studies had blinded the outcome assessors. Two non-randomised trials were assessed using the risk of bias in

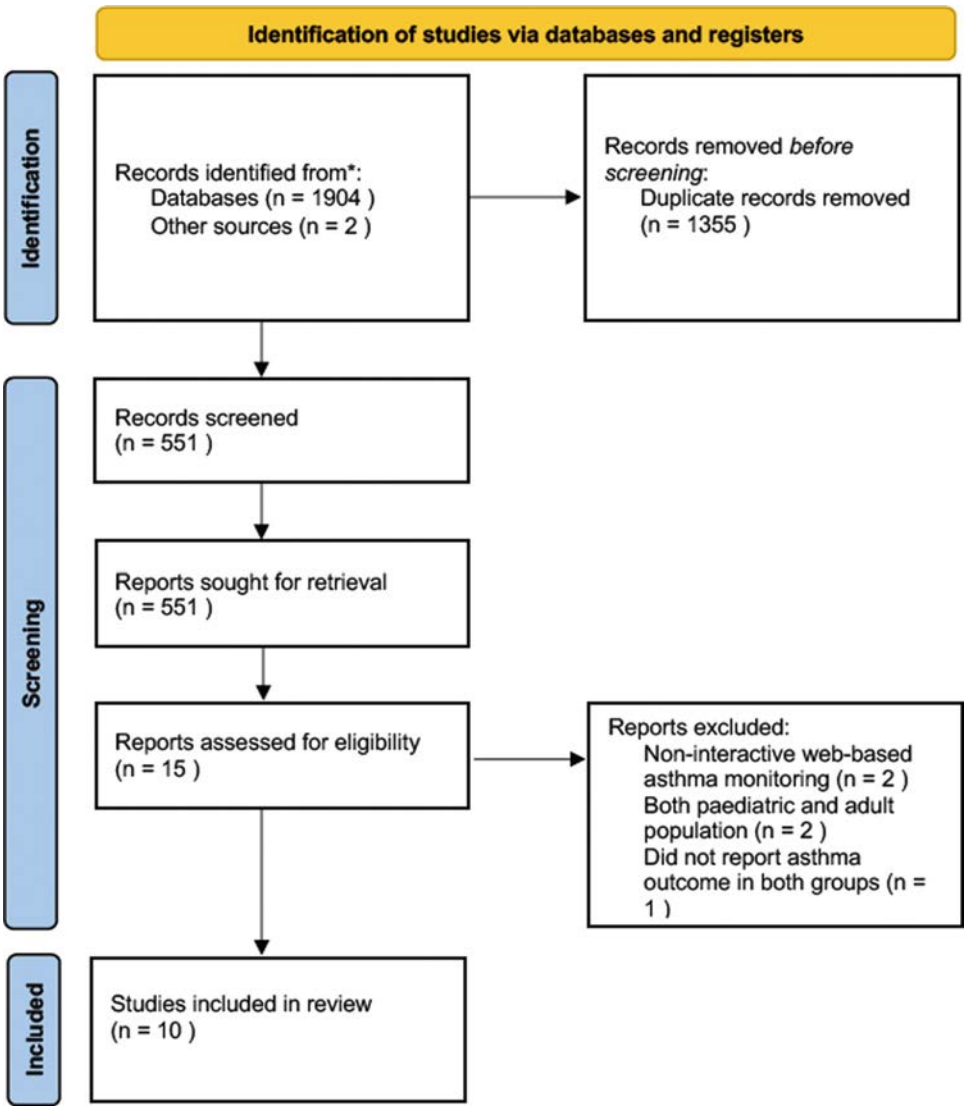

Figure 1: Study flow diagram

Table 1: Study characteristics

References	Country	Study design	Study setting	Sample size	Male (%)	Age	Intervention type	Intervention duration	No of sessions	Follow-up duration (months)
Chan *et al.*[19]	The United States	RCT	Military dependent children	Intervention: 60 Control: 60	61.7 63.3	10.2 (3.1) 9.0 (3.0)	Internet-based home monitoring and education with nurse or pediatric clinical pharmacist	NR	3	12
Garbutt *et al.*[20]	The United States	RCT	Community	Intervention: 190 Control: 172	63.2 60.5	8 (5-13) 7.5 (5-13)	Asthma management training via telephone by pediatric nurses	10 min	NR	12
Bender *et al.*[21]	The United States	RCT	Hospital	Intervention: 452 Control: 447	67.3 61.1	8.2 (0.13) 8.1 (0.13)	Speech recognition intervention with support from asthma nurse and pharmacy staff	NR	NR	24
Garbutt *et al.*[22]	The United States	RCT	Community	Intervention: 462 Control: 486	63.9 61.5	6.6 (2.6) 7.1 (2.8)	Asthma management training via telephone by peer trainers	Total: 3.8 h	18	12
Portnoy *et al.*[23]	The United States	Controlled trial	Hospital	Intervention: 69 Control: 100	55.1 71.0	NR	Asthma consultation by registered nurse or respiratory therapist	NR	NR	6
van den Wijngaart *et al.*[24]	The Netherlands	Prospective, controlled trial	Hospital	Intervention: 105 Control: 105	61.0 58.1	11.3 (2.9) 11.3 (2.7)	Asthma management using the virtual asthma clinic	NR	NR	16
Halterman *et al.*[7]	The United States	RCT	School-based	Intervention: 200 Control: 200	61.5 62.0	7.7 (1.7) 7.9 (1.7)	Asthma consultation by telemedicine clinician	NR	3	12
Perry *et al.*[25]	The United States	RCT	Rural school	Intervention: 180 Control: 183	54.4 58.5	9.6 (8.6-11.6) 9.6 (8.1-11.4)	Asthma education and consultation by a board-certified allergist for the patients, caregivers, and nurses	30-45 min	5	3
Shdaifat *et al.*[26]	Jordan	RCT	Hospital	Intervention: 45 Control: 45	53.3 48.9	7.2 (1.8) 7.8 (2.21)	Proper inhaler use counselling by pharmacist	10 min	NR	3
Sitthikarnkha *et al.*[11]	Thailand	Retrospective cohort	Hospital	Intervention: 83 In-person: 112	66.3 64.3	8.1 (4.1) 8.0 (4.0)	Asthma consultation by clinician	NR	NR	3

NR = not reported, RCT = randomized control trials

non-randomised studies - of interventions-1 score and demonstrated a low risk of bias. The NOS score for the retrospective cohort study was 8 out of 9, which is of good quality.

Emergency department visits, hospitalisations, and symptom-free days

Patients in the telemedicine consultations group did not show an increased risk of emergency department visits due to asthma exacerbation compared with patients in the usual care group with an RR of 0.84 (95% CI = 0.60–1.19) [Figure 3]. In terms of hospitalisations due to asthma exacerbation, there was also no significant difference between telemedicine consultations compared with patients in the usual care group (RR = 0.73, 95% CI= 0.46–1.15) [Figure 3]. Subgroup analysis of RCT also demonstrated that there were no significant differences in terms of emergency department visits

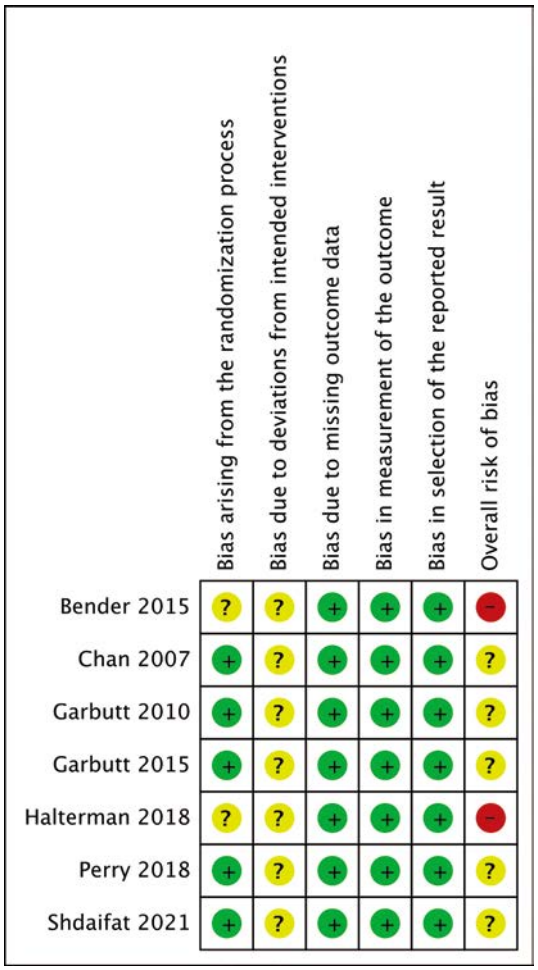

Figure 2: Study methodological quality according to the Cochrane risk-of-bias tool

(RR = 0.84, 95% CI = 0.59–1.21) and hospitalisations (RR = 0.74, 95% CI = 0.46–1.18) due to asthma exacerbation. However, the meta-analysis proved that patients in the telemedicine group had more symptom-free days compared with those in the usual care group with an SMD of 0.18 (95% CI = 0.04–0.32) [Figure 3]. Similarly, subgroup analysis of RCT also demonstrated that the telemedicine group had more symptom-free days compared with the usual care group (SMD = 0.14, 95% CI = 0.01–0.26).

Well-controlled asthma and poorly controlled asthma

The result showed that patients in the telemedicine group had a higher rate of well-controlled asthma in telemedicine compared with the usual care group with an RR of 1.27 (95% CI = 1.14–1.42) [Figure 4]. However, subgroup analysis of RCT demonstrated that there was no significant difference in the rate of well-controlled asthma between the two groups (RR = 1.40, 95% CI = 0.99–1.98). In addition, there was no significant difference in the risk of poorly controlled asthma between the two groups (RR = 0.81, 95% CI = 0.6–1.1) [Figure 4]. Similarly, subgroup analysis of RCT also demonstrated no significant difference (RR = 0.78, 95% CI = 0.55–1.13).

Asthma outcome scores

The result demonstrated that there were no significant differences in the ACT score and c-ACT score of patients between the telemedicine group and the usual care group with an SMD of -0.44 (95% CI = -3.07 to 2.19) and 2.17 (95% CI = -0.28 to 4.62), respectively [Figure 5]. However, subgroup analysis of RCT for c-ACT score demonstrated that the telemedicine group had a higher c-ACT score compared with the usual care group with an SMD of 5.11 (95% CI = 4.21–6.01). However, the meta-analysis demonstrated a significant increase in the PAQLQ score in the telemedicine group with an SMD of 3.07 (95% CI = 0.19–5.95) compared with the usual care group [Figure 5].

Publication bias

The funnel plot for the RR of emergency department visits and hospitalisations and SMD of symptom-free days demonstrated symmetrical distributions [Figure 6]. Furthermore, Egger's regression test for the RR of emergency department visits and hospitalisations and SMD of symptom-free days also demonstrated no significant publication with the *P* value of 0.5078, 0.2885, and 0.6998, respectively.

Discussion

The aim of this meta-analysis was to assess the efficacy of virtual consultation and education on asthma with professionals to improve the outcome of asthma in the paediatric populations. Our meta-analysis has reported several clinical outcomes and demonstrated the improvement of asthma control in the telemedicine intervention group.

Our meta-analysis demonstrated no statistically significant difference in the emergency department visits and hospitalisation for asthma exacerbation between the telemedicine and control groups. There are several reasons that may contribute to this statistically insignificant RR. Bender *et al.*[21] reported a lower asthma exacerbation rate in the population, as evidenced by 0.09% of the study population having emergency department visits and 0.03% experiencing hospitalisation before recruitment into the study. Furthermore, hospital urgent care events for asthma exacerbation were infrequent and the primary care physicians might not record all the visits completely.[27] Garbutt *et al.*[20] suggested that the study intervention may not have been comprehensive or intensive enough to influence asthma outcomes significantly, and any observed improvements might be attributed to study participation rather than the specific intervention's impact on risk outcomes. Effective ambulatory treatment should reduce

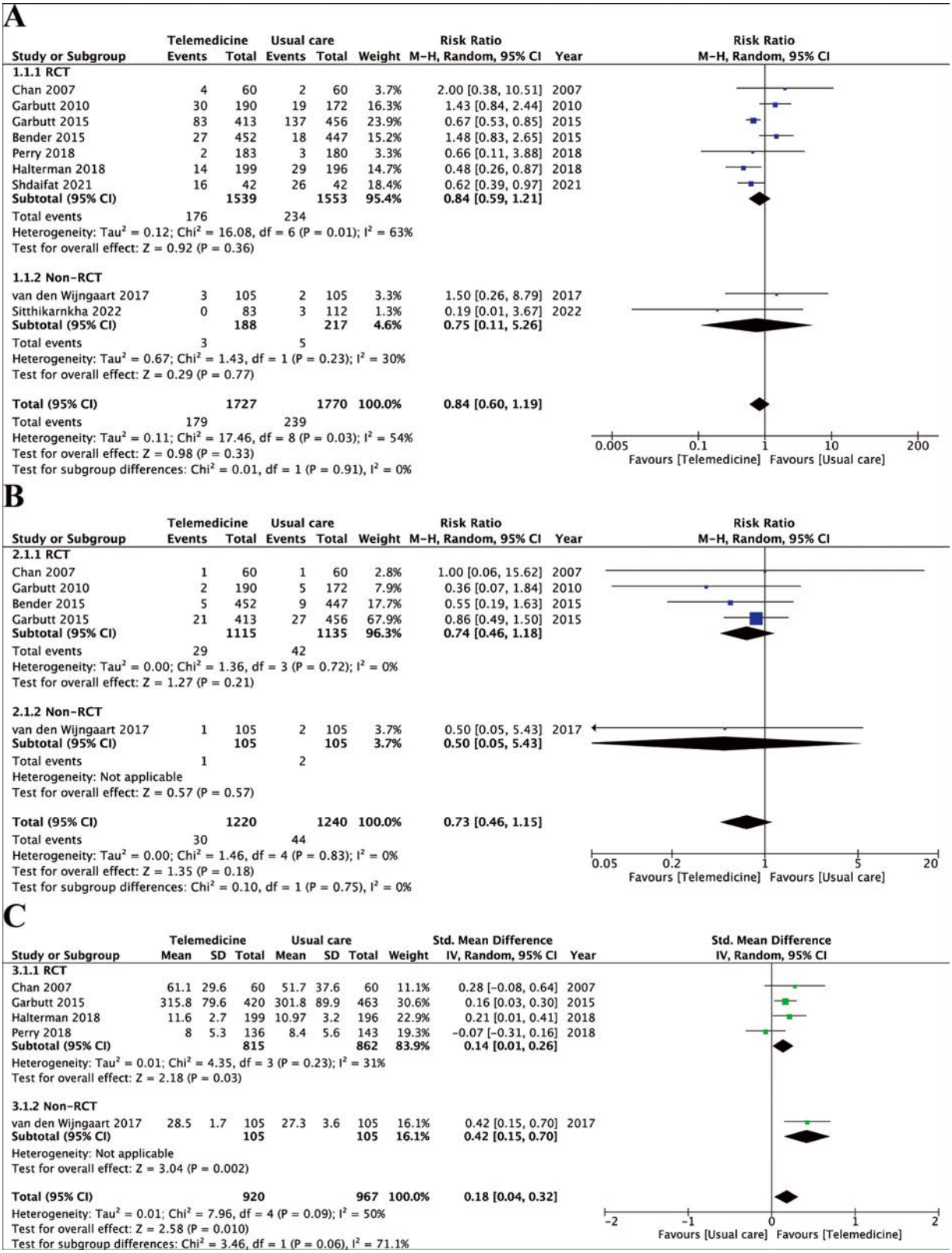

Figure 3: Forest plot for (A) risk ratio for emergency department visits, (B) risk ratio for hospitalization, and (C) standardized mean difference for symptom-free days

hospitalisations and ambulatory emergency department visits as asthma-related hospitalisation signifies unsuccessful outpatient management in most children.[19] Therefore, there is limited potential for improvement in hospitalisation or emergency department visits in the studied population.[21]

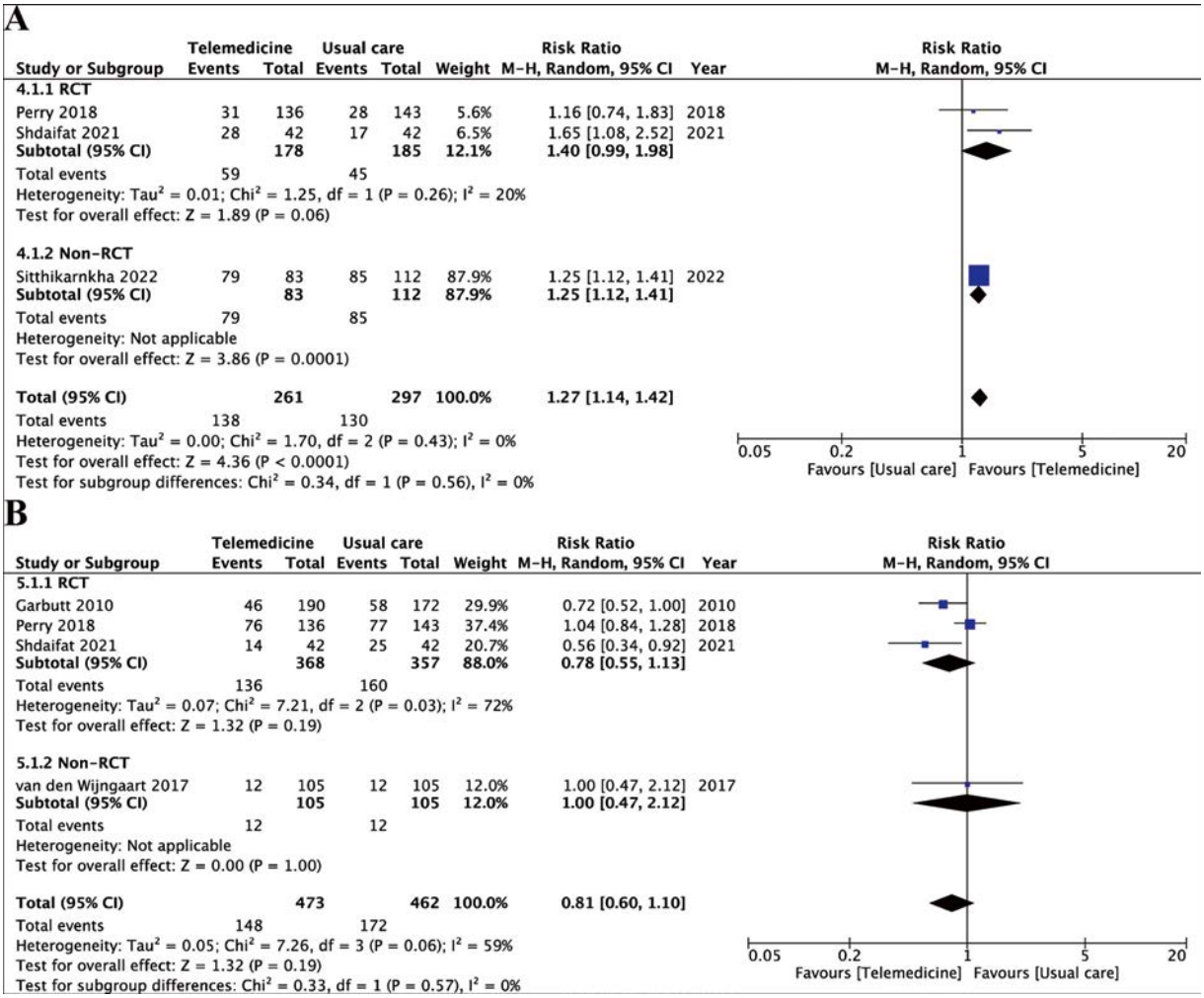

Figure 4: Forrest plot for (A) risk ratio of well-controlled asthma and (B) risk ratio of poorly controlled asthma

This study has shown that telemedicine had improved the asthma symptom-free day compared with the usual care group and had a higher rate of well-controlled asthma. This difference may be attributed to a higher adherence to inhaled corticosteroids in the telemedicine group, which was 44.5%, compared with the usual care group with a demonstrated adherence of 35.5%, as reported by Bender *et al*.[21] Furthermore, Chan *et al*.[19] reported that children in the telemedicine group have a better technique in metered-dose inhalers with valve holding chambers compared with those in the usual care group due to more frequent monitoring. Good inhaler technique has been shown to increase asthma control and reduce asthma exacerbations.[28] Patients in the telemedicine group have a higher rate of well-controlled asthma, which may be attributed to an increase in disease awareness resulting from study participation, potentially leading to improved medication adherence and, consequently, better asthma control.[24] Telemedicine has demonstrated greater efficacy in providing counseling compared with traditional clinic-based counseling and better education to the patients.[26,28]

Our meta-analysis demonstrated that there are not significant changes in the ACT and c-ACT. Shdaifat *et al*. and van den Wijngaart *et al*. demonstrated statistically significant improvement in the ACT and c-ACT scores.[24,26] However, ACT or c-ACT scores could potentially be influenced by several factors, including viral respiratory infections, comorbidities, or exposure to the potential triggers, which may affect the asthma control status.[23] Furthermore, the meta-analysis results may be influenced by the limited of studies reporting ACT or c-ACT scores. Another explanation is that patients with well-controlled asthma had minimal potential for improvements during the follow-up period and only children with uncontrolled asthma demonstrated significant improvement of the ACT scores.[24] Portnoy *et al*.[23] demonstrated that the telemedicine group is not inferior to the usual care group based on the minimal important difference of the adjusted asthma scores comprising Test for Respiratory and Asthma Control in Kids, ACT, and c-ACT. Furthermore, our meta-analysis demonstrated a significant improvement in the caregiver PAQLQ score in the telemedicine group compared with the usual care group. The improvement

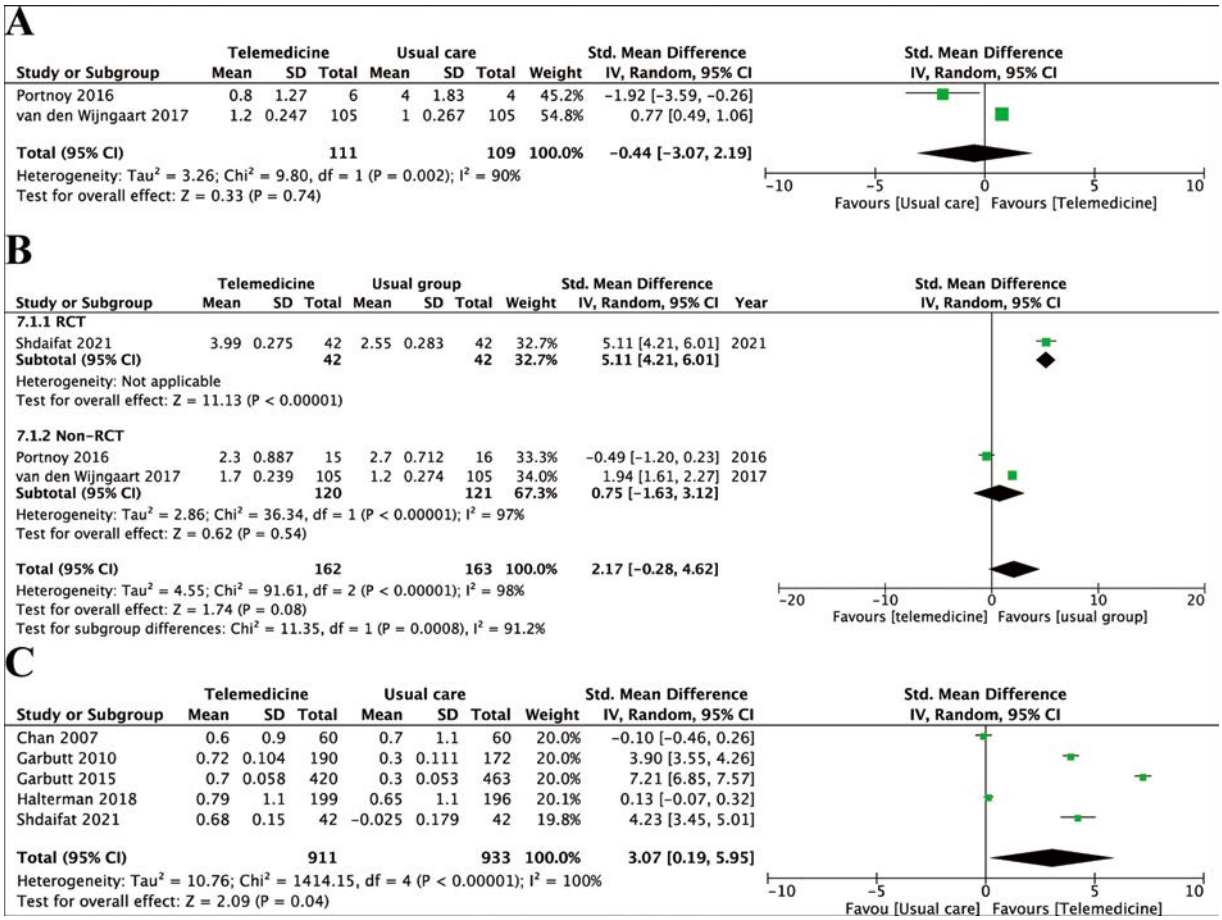

Figure 5: Forest plot for standardized mean difference for asthma outcome scores, (A) Asthma Control Test, (B) childhood-Asthma Control Test, and (C) Paediatric Asthma Quality of Life Questionnaire

in quality of life in the parents may be explained by a perceived improvement in asthma control, better understanding of asthma, and enhanced access to care.[19] Furthermore, telemedicine has been shown to improve self-management of asthma-related behaviors, potentially leading to increased health and greater freedom for both the child and the family.[29]

There are several advantages of telemedicine for monitoring compared with usual care. Internet-based telemedicine serves as an effective adjunct for home monitoring in paediatric asthma, with the increasing availability of affordable technology and better Internet access likely enhancing ambulatory management tools.[19] Furthermore, the telemedicine model improves access to medical services for traditionally underserved children and families facing geographic barriers to specialty care.[30] Telemedicine facilitates virtual communication between patients and healthcare providers, offering timely advice, information, and more frequent monitoring and follow-up.[31] Additionally, telemedicine proves beneficial in nonemergency situations or routine follow-ups, minimising resource use, and reducing infection transmission.[32] Telemedicine enables efficient virtual examinations, real-time monitoring of asthma symptoms and triggers in the patient's environment, and the development of personaliaed care plans for patients with asthma.[33] However, there are concerns about the lack of physical examinations, privacy issues, and potential digital exclusion despite positive outcomes and user satisfaction with telemedicine.[34]

There are several limitations of this study. The broad definition of telemedicine includes diverse technologies and interventions, contributing to high heterogeneity that complicates the comparison and synthesis of results across various studies. Moreover, the variability in reported outcomes across different studies may affect the results of this meta-analysis. There are a limited number of studies that used validated and standardised scores as outcome measures.

Conclusion

In conclusion, the results of the meta-analysis looking at the efficacy of telemedicine compared with the usual care group in paediatric asthma follow-ups suggest that telemedicine may be an effective alternative to

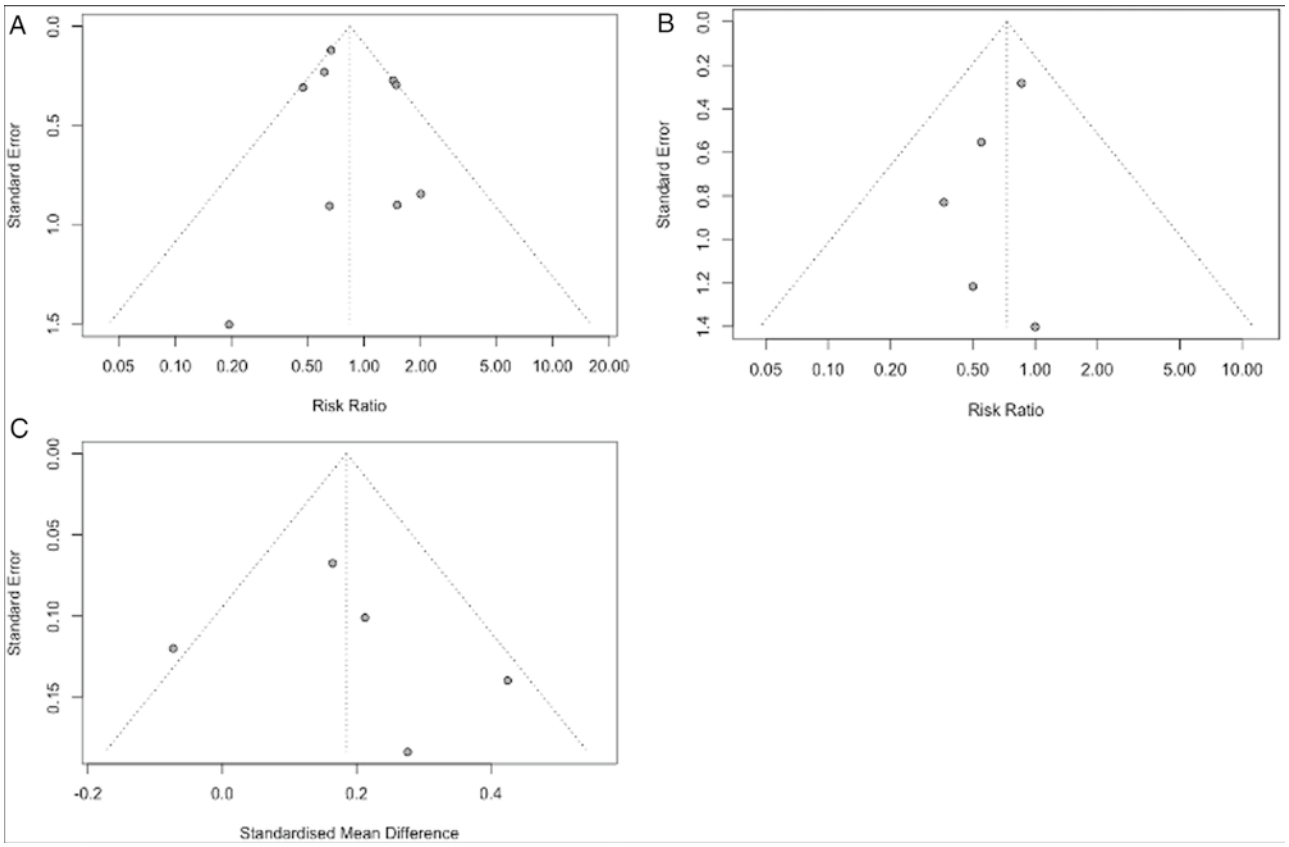

Figure 6: Funnel plots for the primary outcomes, (A) emergency department visits, (B) hospitalizations, and (C) symptom-free days

in-person visits for paediatric asthma follow-ups in improving asthma control. This could be attributed to better compliance with medication, increased parental confidence in administering quick-relief medications, and increased expectations for asthma control. However, studies concentrating on the efficacy of telemedicine remain limited. Hence, this warrants future research looking at the long-term outcomes of the effectiveness of telemedicine in managing paediatric asthma. These studies are important to reduce the burden of clinicians and resources while simultaneously improving asthma control among paediatric population.

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Nil.

Author contributions
L.T.O. designed the study. L.T.O and N.M.Z.C. performed literature search, data extraction, and statistical analysis. L.T.O, A.J.C.L., and N.M.Z.C. wrote, edited, and reviewed the manuscript. All authors approved the final version of manuscript.

Data availability
The data underlying this article will be shared on reasonable request to the corresponding author.

Conflicts of interest
There are no conflicts of interest.

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An Unusual Cause of Diffuse Alveolar Haemorrhage: Post-Streptococcal Glomerulonephritis or Vaping Associated Lung Injury

Geraud J. Freer, Nagaraj Pandharikar, Geshani Jayasuriya
John Hunter Hospital, Lookout Road, New Lambton Heights, New South Wales, Australia

Abstract

Diffuse alveolar haemorrhage (DAH) is associated with various clinical entities. Its connection with post-streptococcal glomerulonephritis (PSGN) is uncommon, especially in children, with only two previously reported cases. With the increased prevalence of vaping, DAH has also been described in the context of e-cigarette or vaping-associated lung injury. We present a case of DAH associated with PSGN and vaping exposure in a 14-year-old male. Two weeks after receiving penicillin for pharyngitis, he presented with acute respiratory distress and acute kidney injury, necessitating non-invasive ventilation. High-dose methylprednisolone therapy (30 mg/kg/day) was administered, considering the available evidence from uncontrolled case studies in paediatric and adult populations suggesting benefit in patients with DAH due to PSGN requiring respiratory support. He subsequently experienced rapid improvement in his respiratory and renal function. We believe DAH was due to PSGN, and that smoking cigarettes and vaping may have increased the risk of pulmonary haemorrhage in this context. We hypothesize that early steroid therapy may have been beneficial and should be considered in such patients.

Keywords: Diffuse alveolar hemorrhage, post-streptococcal glomerulonephritis, vaping

Key Messages: Post-streptococcal glomerulonephritis can present as diffuse alveolar haemorrhage in children, and intravenous steroid therapy may provide therapeutic benefit in these cases.

Introduction

Diffuse alveolar haemorrhage (DAH) is a clinical syndrome that can manifest acutely with catastrophic respiratory failure. Differentiating between its many potential causes can pose a diagnostic challenge to clinicians. Its association with post-streptococcal glomerulonephritis (PSGN) is rare, particularly in children, with only two known cases reported.[1,2] It is also increasingly reported in association with the use of vaping.[3] We present an adolescent with PSGN and a history of vaping presenting with DAH. He demonstrated significant and rapid improvement with supportive therapy and a pulse dose of intravenous corticosteroids.

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Case History

A 14-year-old boy presented with a 2-day history of dyspnoea, haemoptysis, and haematuria. At presentation, he exhibited respiratory distress with a respiratory rate of 64 breaths per minute and the use of accessory muscles. His oxygen saturation was 88% on room air and 93% on high-flow oxygen, with FiO2 50%. He had a heart rate of 130/min, blood pressure of 134/84 mm Hg,

Address for correspondence: Dr. Geraud J. Freer, John Hunter Hospital, Lookout Road, New Lambton Heights, New South Wales 2305, Australia.
E-mail: Geraud.freer@gmail.com

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and temperature of 38.8°C. He had bilateral crackles on auscultation. He had periorbital oedema and mild pitting ankle oedema, but did not have raised jugular venous pressure, cardiomegaly, hepatomegaly, or gallop rhythm. There was no rash or lymphadenopathy.

He had a history of cough, sore throat, and fever three weeks prior and received a course of oral penicillin for tonsillitis from his primary care provider. He had a history of vaping for eight months, approximately 300 inhalations per day, and was smoking three cigarettes per week. He had no other significant medical or travel history. His immunization was up to date.

Initial investigations showed a high white blood cell count (17.8×10^9/L), low haemoglobin (100 g/L), and average platelet count (365×10^9/L). His urea (14.6 mmol/L) and creatinine (162 µmol/L) were elevated. He had an elevated C-reactive protein (57 mg/L), low sodium (133 mmol/L), high potassium (5.7 mmol/L) and low bicarbonate (16 mmol/L). His coagulation parameters were normal. His initial venous blood gas showed metabolic acidosis with complete respiratory compensation. His urinalysis revealed albuminuria (694 mg/L) and an albumin/creatinine ratio of 137 mg/mmol. His urine microscopy demonstrated high leukocytes (WBC $>100 \times 10^6$/L) and blood (RBC $>100 \times 10^6$) and occasional broad casts.

His chest X-ray demonstrated bilateral airspace opacification with varying degrees of confluence, more prominent on the right [Figure 1]. Computed tomography (CT) of the chest showed bilateral patchy airspace infiltrates consistent with DAH, as well as bilateral pleural effusions [Figure 2]. He had a normal echocardiogram. He received antibiotics for community-acquired pneumonia while undergoing diagnostic evaluation. He received a dose of intravenous hydrocortisone (4 mg/kg) because of his history of vaping and a possible diagnosis of e-cigarette or vaping product-associated lung injury (EVALI) while awaiting retrieval to the paediatric intensive care unit (PICU).

Upon admission to the PICU at our hospital, he was commenced on non-invasive ventilation for respiratory distress. He had acute kidney injury (AKI), fluid overload, and hyperkalaemia, which were managed medically with fluid restriction, regular furosemide, low potassium intake, and resonium. Continuous renal replacement therapy (CRRT) was considered for the management of AKI but was not required. He also had hypertension, which was treated with amlodipine. High-dose methylprednisolone therapy (30 mg/kg/day) was administered for 5 days for the provisional diagnosis of DAH secondary to PSGN and the proposed benefit observed in previous cases.[1,2,4,5] The primary differential diagnosis was thought to be DAH secondary to EVALI, and intravenous corticosteroids may also be beneficial in this condition.[6,7] Other potential differential diagnoses included Goodpasture's syndrome and systemic vasculitis with pulmonary involvement.

Further investigations revealed elevated antistreptolysin O antibodies (802 IU/ml), low C3 (0.13 g/L), and standard C4 (0.18g/L), consistent with a diagnosis of PSGN. Anti-neutrophil cytoplasmic antibodies (ANCA-i), anti-myeloperoxidase, anti-proteinase 3, anti-glomerular basement membrane (anti-GBM), anti-CCP, and rheumatoid factor antibodies were all negative. Blood and urine cultures were negative. Urinary streptococcal antigen and legionella antigen testing were negative. Throat cultures were negative for beta-haemolytic *Streptococcus*. Respiratory viral polymerase chain reaction (PCR) was positive for picornavirus and

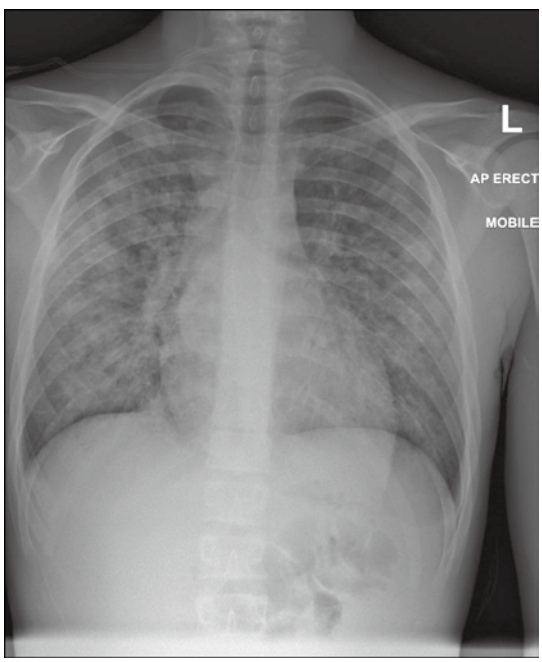

Figure 1: Chest radiograph on the day of admission

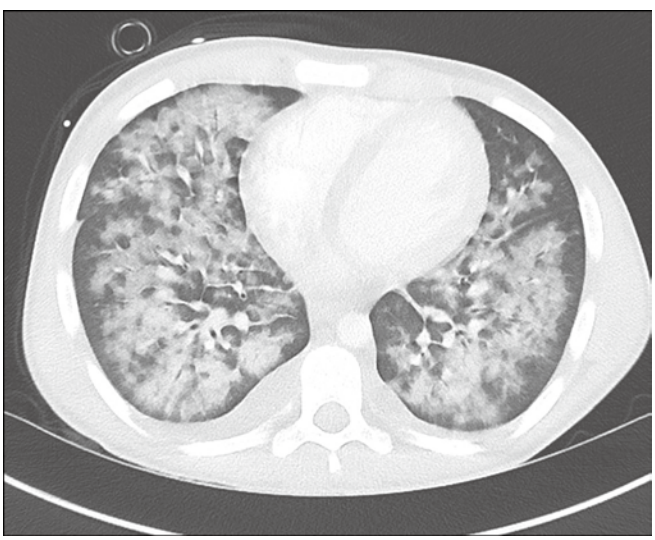

Figure 2: CT chest at presentation demonstrating findings consistent with diffuse alveolar haemorrhage

negative for severe-acute-respiratory-syndrome-related coronavirus-2, respiratory syncytial virus, influenza, adenovirus, and parainfluenza virus. Bacterial PCR was negative for *Bordetella pertussis* and *Mycoplasma pneumoniae*. Mycoplasma IgM and IgG antibodies were non-reactive. Abdominal ultrasound demonstrated no structural renal tract abnormality, as well as moderate volume ascites. Renal biopsy was considered but ultimately not conducted due to rapid clinical improvement and consistency of investigations with PSGN. Bronchoalveolar lavage and lung biopsy were considered but not performed. The patient demonstrated significant improvement by day 3 in the hospital, and resolution was evident on his chest X-ray[Figure 3]. He was successfully weaned off respiratory support and experienced no further episodes of haemoptysis.

He was discharged from the hospital after 6 days and continued amlodipine for hypertension. At 7 months follow-up, he had returned to his baseline activity status, and his pulmonary function test results, including spirometry, lung plethysmography, and diffusing capacity of the lungs for carbon monoxide, were normal.

Discussion

DAH associated with PSGN in children is rare, and to our knowledge, only two cases have been reported.[1,2] PSGN is the most common cause of acute nephritis in children. It typically occurs between 1 and 3 weeks following group A beta hemolytic streptococcus pharyngitis. Most children are asymptomatic, but haematuria, hypertension, oedema, and acute renal failure can develop. The proposed mechanism for kidney injury is inflammation and complement activation resulting from immune complex formation by streptococcal antigens within the glomerulus.[8]

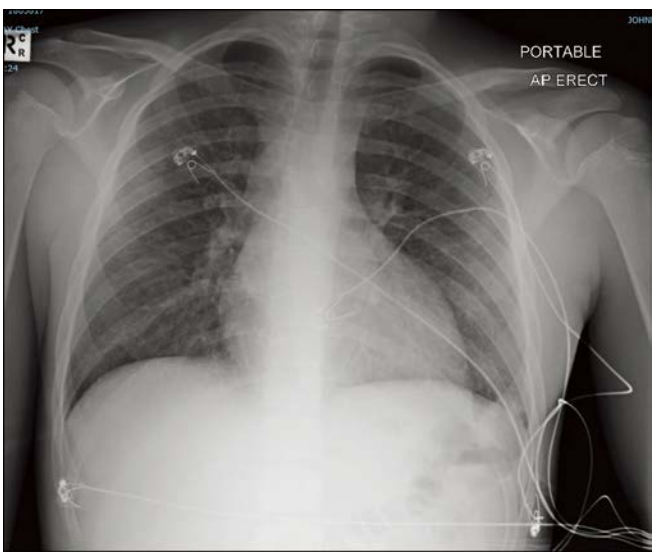

Figure 3: Chest radiograph on day 3 of admission

DAH is a rare and potentially fatal complication of various disease entities. It is most commonly reported with Goodpasture's syndrome and other systemic vasculitis syndromes.[9] The occurrence of pulmonary capillaritis and glomerulonephritis in Goodpasture syndrome is attributed to circulating antibodies directed against the glomerular and alveolar basement membranes. Our patient was evaluated for Goodpasture's and other vasculitis, but his antibody levels were negative. When clinical and laboratory features are non-diagnostic, lung biopsy can provide histopathological evidence of the underlying cause of DAH,[9] but it was not indicated in our case due to rapid improvement.

The pathophysiological mechanisms linking PSGN and DAH remain uncertain. One proposed mechanism for simultaneous renal and respiratory involvement is the similar cellular morphology of the vessels, which may exhibit similar responses to immunological disorders. A previous case report of DAH with nephritis suggested immune complex deposition played a role in both pulmonary and renal lesions.[2]

EVALI is an umbrella term that refers to acute respiratory illness secondary to vaping.[6] The diagnosis is based on a history of using e-cigarettes or related products, lung opacities on chest radiograph/CT, and exclusion of alternative diagnoses. There are increasing reports that DAH can occur as a consequence of vaping.[3,6,7] Currently, there are no randomized data for the treatment of EVALI. However, typically supportive oxygenation, empirical antibiotics, and steroid therapy are employed.[6,7] The lung injury in EVALI is characterized by non-specific patterns, including bronchiolocentric organizing pneumonia, fibrinous pneumonitis, foamy macrophages, and diffuse alveolar damage patterns, as described in the literature.[6] In one case report, DAH secondary to vaping presented with bland pulmonary haemorrhage without diffuse alveolar damage.[7] Individuals with Goodpasture's syndrome and a history of smoking cigarettes and inhalation of illicit drugs have a higher likelihood of pulmonary haemorrhage.[10] In our case, it is biologically plausible that smoking cigarettes and vaping may have contributed to lung injury and precipitated the rare manifestation of DAH in the context of PSGN.

The management of patients with DAH and PSGN is primarily supportive. Two previously reported cases were treated in intensive care, receiving intravenous corticosteroids, and showed good outcomes.[1,2] The most recent case describes a 4-year-old girl who deteriorated with haemoptysis and renal failure. She was treated with intravenous steroids, CRRT, and invasive ventilation.[1] The other case involved a 12-year-old girl who received 1 g/day of methylprednisolone for 3 days after deterioration with respiratory distress and reduced mental status. Both cases experienced rapid recovery with treatment. Previous

case reports in adults have shown significant improvement in pulmonary haemorrhage with high-dose steroid therapy.[4,5,11] Treatment for vaping-associated lung injury is primarily supportive, with consideration for steroids, especially in patients with significant respiratory distress and/or hypoxemia.[6] Based on this evidence, we decided to administer steroids early in our patient's treatment, which may have contributed to the rapid clinical improvement and discharge from the intensive care unit without renal replacement therapy, in contrast to a previous case report.[1]

Conclusion

We present a pediatric case of DAH in a patient with PSGN and a significant history of vaping. This presentation is very rare in children and adolescents and is described only in two other pediatric case reports. We believe that the history of smoking and vaping might have increased the risk of pulmonary hemorrhage in our patient. Based on previous case reports and considering the possibility of EVALI in the differential diagnosis, we opted for high-dose pulse intravenous methylprednisolone therapy. Our patient showed rapid clinical improvement, suggesting that intravenous steroids may have been beneficial in the treatment of DAH. However, controlled studies are lacking to provide evidence in this regard.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Authors Contributions

Concepts, design, definition of intellectual content, manuscript preparation, manuscript editing, manuscript review – Freer GJ, Pandharikar N, Jayasuriya G. Literature search – Freer GJ, Pandharikar N. Guarantor – Freer GJ.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Data availability

As it is a case study, there is no data or statistics, and any external sources are already referenced.

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Presentation: Budesonide/Formoterol Turbuhaler. **Indications:** In adults and adolescents (12 years and older), for the treatment of asthma, to achieve overall asthma control, including the relief of symptoms and the reduction of the risk of exacerbations. Symptomatic treatment of moderate to severe COPD in adults. **Dosage: Asthma *1) Symbicort anti-inflammatory reliever therapy (patients with mild disease) 160/4.5 mcg Turbuhaler*** *Adult & Adolescent ≥ 12yr:* 1 inhalations as needed in response to symptoms. If symptoms persist after a few minutes, 1 additional inhalation should be taken. No more than 6 inhalations should be taken on any single occasion. A total daily dose of more than 8 inhalations is normally not needed, however a total daily dose of up to 12 inhalations can be used temporarily. ***2) Symbicort maintenance and reliever therapy*** *Adult & Adolescent ≥ 12yr:* Patients should take 1 inhalation of Symbicort Turbuhaler 160/4.5 mcg as needed in response to symptoms to control asthma. If symptoms persist after a few minutes, 1 additional inhalation should be taken. No more than 6 inhalations should be taken on any single occasion. Recommend maintenance dose is 1 inhalation b.d. and some may need 2 inhalations b.d.. A total daily dose of more than 8 inhalations is normally not needed, however a total daily dose of up to 12 inhalations can be used temporarily. ***3) Symbicort maintenance therapy 160/4.5 mcg Turbuhaler*** *Adult & Adolescent ≥ 12yr:* 1-2 inhalations b.d.. Max daily dose is 4 inhalations. **COPD *160/4.5 mcg Turbuhaler*** *Adult:* 2 inhalations b.d.. Max daily dose is 4 inhalations. **Contraindications:** Hypersensitivity to budesonide, formoterol or lactose. **Precautions:** Should be used for the shortest duration of time required to achieve control of asthma symptoms. Should only be used long-term in patients whose asthma cannot be adequately controlled on asthma controller medications. Not be used to initiate treatment with inhaled steroids in patients being transferred from oral steroids. It is recommended that the maintenance dose be tapered when long-term treatment is discontinued. Potential systemic effects of ICS, HPA axis suppression and adrenal insufficiency, bone density, growth, visual disturbance, infections/tuberculosis, sensitivity to sympathomimetic amines, cardiovascular disorders, hypokalaemia, diabetes, pneumonia, lactose, pregnancy & lactation. Not recommended for children below 12 years of age. Incidence of candidiasis can be minimized by having patients rinse their mouth out with water after inhaling their maintenance dose. **Interactions:** CYP3A4 inhibitors, beta-receptor blocking agents, other sympathomimetic agents, Xanthine derivatives, mineralocorticosteroids and diuretics, Monoamine oxidase inhibitors, tricyclic antidepressants, quinidine, disopyramide, procainamide, phenothiazines and antihistamines. **Undesirable effects:** Palpitations, Candida infections in the oropharynx, headache, tremor, mild irritation in the throat, coughing, hoarseness. **Full local prescribing information is available upon request.** API.HK.SYM.0721

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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 received add-on subcutaneous DUPIXENT at a dose of 200 or 300 mg every 2 weeks or mated 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 (FEV1) before bronchodilator use in the overall trial population. Secondary endpoints included the exacerbation rate and FEV, 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, every 2 weeks; SOC, standard of care.

References: 1. DUPIXENT Hong Kong prescribing information. **2.** Rabe KF, et al. N Engl J Med. 2018 Jun 28;378(26):2475-2485. **3.** Castro M, et al. 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; severe atopic dermatitis in children 6 months to 11 years old 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. In children 6 to 11 years old 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 medium to high dose ICS plus another medicinal product for maintenance treatment. For 300 mg only – Chronic rhinosinusitis with nasal polyposis (CRSwNP): As an add-on therapy with intranasal corticosteroids for the treatment of adults with severe CRSwNP for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control. Prurigo Nodularis (PN): Moderate-to-severe PN in adults who are candidates for systemic therapy. Eosinophilic esophagitis (EoE): In adults and adolescents ≥12 years, weighing ≥40 kg, who are inadequately controlled by, are intolerant to, or who are not candidates for conventional medicinal therapy. **Dosage & Administration:** Subcutaneous injection. AD adults: Initial dose of 600 mg (two 300 mg injections), followed by 300 mg Q2W. AD adolescents (12-17y/o): Body weight <60 kg- initial dose of 400 mg (two 200 mg injections), followed by 200 mg Q2W. Body weight ≥60 kg- same dosage as adults. AD children (6-11y/o): Body weight 15kg~<60 kg- initial dose of 300 mg on Day 1 follow by 300 mg on Day 15, then 300mg Q4W. Body weight ≥60 kg- same dosage as adults. * The dose may be increased to 200 mg Q2W in patients with body weight of 15 kg~< 60 kg based on physician's assessment. AD children (6 months-5y/o): Body weight 5kg~<15 kg- initial dose of 200 mg, then 200 mg Q4W. Body weight 15kg~<30 kg- initial dose of 300 mg, then 300 mg Q4W. 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 adults and adolescents: Initial dose of 400 mg, followed by 200 mg Q2W. For patients with severe asthma and on oral corticosteroids or with severe asthma and co-morbid moderate-to-severe AD or adults with co-morbid severe CRSwNP- initial dose of 600 mg, followed by 300 mg Q2W. Asthma children (6-11y/o): Body weight 15kg~<30 kg- 300 mg Q4W. Body weight 30kg~<60 kg- 200 mg Q2W; or 300 mg Q4W. Body weight ≥60 kg- 200 mg Q2W. For paediatric patients (6-11y/o) with asthma and co-morbid severe atopic dermatitis, as per approved indication, the recommended dose should follow AD children (6-11y/o). 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. CRSwNP: Initial dose of 300 mg, followed by 300 mg Q2W. Consider discontinuing treatment in patients who have shown no response after 24 weeks. PN: Initial dose of 600 mg (two 300 mg injections), followed by 300 mg Q2W. Dupilumab can be used with or without topical corticosteroids. Consider discontinuing treatment in patients who have shown no response after 24 weeks. EoE: 300 mg QW. Dupilumab 300 mg QW has not been studied in patients with EoE weighing <40 kg. Dosing beyond 52 weeks has not been studied. For Missed dose instructions, please refer to the full prescribing information. **Contraindications:** Hypersensitivity to dupilumab or any of the excipients. **Precautions:** Not 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. Cases of enterobiasis were reported in children 6 to 11 years old in the paediatric asthma development program. Advise patients to promptly report new onset or worsening eye symptoms. Patients who develop conjunctivitis, dry eye and keratitis that does not resolve following standard treatment should undergo ophthalmological examination. Sudden changes in vision or significant eye pain that does not settle warrant urgent review. Patients with comorbid asthma should not adjust or stop asthma treatments without consultation with physicians. Carefully monitor patients after discontinuation of dupilumab. Avoid using 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:** Most common adverse reactions reported- injection site reactions, conjunctivitis, conjunctivitis allergic, arthralgia, oral herpes, eosinophilia and injection site bruising. Safety profile observed in adolescents and children 6 months to 11 years old consistent with that seen in adults. 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-23.10

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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