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Contents

Lower Respiratory Tract Infection – An Asian Perspective

Lower respiratory tract infection is one of the common indications for acute hospitalization. In the current issue, original data in this area were reported from Hong Kong and Singapore. Some children with acute lower respiratory tract infection go onto develop persistent bacterial bronchitis and even bronchiectasis. A review article from Chatziparasidis *et al.* updates the readers the pathological progress from acute to chronic lower respiratory tract infection and the recently available methods, that is, lung clearance index and oscillometry, to monitor the progress.

In pneumonia, pediatric clinical practice relies heavily on upper respiratory tract (URT) multiplex polymerase chain reaction (PCR) panels due to its ease of sampling. However, asymptomatic carriage of *Mycoplasma pneumoniae* in healthy children was well documented, reaching prevalence rates up to 56%.[1] This potential high false positive rate of URT multiplex PCR in pediatric pneumonia is addressed by a retrospective analysis of >1000 Hong Kong children, median age of 8 years, with pneumonia diagnosed by chest radiograph and clinical findings.[2] Lam and Lam[2] compared the sputum monoplex PCR with the nasopharyngeal swab (NPS) for multiplex PCR, that is, Biofire RP2.1. They reported that the false positive rate in NPS multiplex PCR for mycoplasma infection was actually very low, that is, 2.5%. The positive predictive value of NPS multiplex, with sputum PCR as the gold standard, was reported to be 97.5%. The accuracy of Biofire RP2.1 for NPS sampels in diagnosing mycoplasma pneumonia was found to be 69%, that is, 788 true positive and true negative over the whole cohort of 1148. The low sensitivity of NPS multiplex, 39.9%, might well be due to the fact that the sample was not sputum.

Macrolide resistant *M. pneumoniae* (MRMP) is common in Asia, >70% in Asian countries and more than 90% in China.[3] Cheung *et al.*[4] identified a much lower rate of macrolide resistance, that is, 11.6%, prevalence rate in Singapore. An important message is that macrolide resistance prolongs fever duration and hospital stay, 5.45 versus 3.59 days. Another important message is the presence of macrolide resistance was not associated with more severe disease. Changing to quinolone did not show evidence of shorter duration of fever although it might be due to the small sample size of six patients in both groups. 71.4% of patients carrying resistant point mutations still responded to macrolide therapy without increased disease severity. MRMP prevalence often triggers immediate clinical escalation to fluoroquinolones or tetracyclines. Cheung *et al.*'s[4] data cautioned against premature antibiotic escalation if patients responded clinically. High clinical response rates to macrolide in patients carrying resistance mutation is likely mediated by the immunomodulatory properties of macrolides.

Chest compression is not a common practice even in pediatric intensive care unit setting and the study by Tai *et al.*[5] was a timely reminder of the importance of simulation training. As baseline testing among pediatric intensive care staff yielded a startling but not surprising zero % of staff were on target with regard to compression rate/depth. The on-target rate rose to 49.2% after reminder and real time visual feedback during compression. This is in line with the literature that real-time visual feedback significantly improves adherence to resuscitation guidelines for chest compression rate, depth, and recoil.[6] It behooves all health care workers to be provided with regular simulation training with real time visual feedback.

On top of circulation, ventilation support is also important. Soong reported his own novel method of providing continuous pharyngeal oxygen paired with intermittent nose-closure and abdominal compression for dynamic airway stenting during bronchoscopy and resuscitation,[7] building on his group's earlier description of the technique.[8] It is named Soong's ventilation, rightly so as a tribute to Prof. Wen-Jeu Soong. This will prove to be life-saving by allowing safer interventional flexible bronchoscopy and beyond, that is, in the arena of resuscitation, as supported by subsequent airway measurement studies.[9] As illustrated by the previous paper on chest compression, simulation with real time feedback would be important. The readers are encouraged to join the annual meeting of Asian Pediatric Pulmonology Society (APPS) and the pre-congress workshop on interventional bronchoscopy as Prof. Soong will lead a hands-on session to impart the skill to attendees.

Chronic cough, that is, more than 4 weeks, is very common in children and wet cough is a common subtype of chronic cough. Persistent bacterial bronchitis (PBB), is a common cause of chronic wet cough and under-treatment of PBB would lead to the other end of the spectrum, that is, bronchiectasis. Hence it would be important to monitor the progress of PBB on top of the symptoms of wet cough. Chatziparasidis and Chang[10] wrote an elegant piece on the pathogenesis of PBB and the method of monitoring PBB by lung clearance index which is an emerging technology

that is commercially available[11] and oscillometry study, a well-established technology.

Finally, I would like to remind readers to come to Hong Kong on 30th October to join the 11th APPS annual congress in Hong Kong, China where you would learn from experts from all over the world with the added bonuses of meeting new friends and enjoying the many beautiful things, for example, great Cantonese food like dim sum, perfect Autumn weather, etc. in Hong Kong.

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There are no conflicts of interest.

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Original Article

Comparing Nasopharyngeal Swab and Sputum in Detecting *Mycoplasma pneumoniae* Pneumonia in Children: A Single-Centre Study in Hong Kong

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Abstract

Background: *Mycoplasma pneumoniae* is an important causative pathogen in childhood pneumonia. Sputum monoplex polymerase chain reaction (PCR) is commonly used for detecting the infection. Recently, the nasopharyngeal swab (NPS) multiplex PCR test has become available. It detects 22 common respiratory tract viruses and bacteria, including *M. pneumoniae*, with a shorter turnover time. This study aimed to compare the NPS multiplex PCR test and the sputum monoplex PCR test in detecting *M. pneumoniae* infection in children with pneumonia. **Methods:** This retrospective study reviewed test results of paediatric patients diagnosed with pneumonia in Tuen Mun Hospital from January 1, 2023, to December 31, 2024, with both the NPS multiplex PCR test and the in-house sputum monoplex PCR test performed. Detection rates were compared. Sensitivity, specificity, likelihood ratios, positive predictive value (PPV), and negative predictive value (NPV) of the NPS test were compared against the sputum test. **Results:** A total of 1148 pneumonia cases with both NPS and sputum tests performed were included in this study. The detection rate of *M. pneumoniae* in sputum was significantly higher (51.3%) than that of NPS (21.0%; $P < 0.001$). The two tests show fair agreement (κ value = 0.38). Although comparing with the sputum test, NPS has a sensitivity of 39.9% and specificity of 98.9% for diagnosing *M. pneumoniae* infection. **Discussion and Conclusions:** Although representativeness is limited by the in-house sputum test used, and results may be affected by NPS collection variability by different nurses, the significantly lower detection rate and sensitivity in the NPS multiplex PCR test reflects it cannot replace the sputum test locally as the major test for detecting *M. pneumoniae* infection.

Keywords: *Mycoplasma*, nasopharyngeal swab, sputum

Introduction

Mycoplasma pneumoniae is a common and important pathogen in community-acquired pneumonia. It is also known as "atypical pneumonia," which does not respond to β-lactam antimicrobial therapy and requires macrolides, tetracyclines, or fluoroquinolones as treatment.[1-3] Each year, it is most prevalent during the winter period and least active during the summer time. Although the infection could be self-limiting, it can also cause complications and severe morbidities. There has been a cyclical high activity of *M. pneumoniae* once every few years in Hong Kong. In 2023, the Centre for Health Protection reported a significant rise in hospital admissions due to *M. pneumoniae* infection.[4,5] There was also a similar surge worldwide, which posed a significant health burden to the healthcare systems.[6,7] Therefore, timely diagnosis is crucial for specific treatment to reduce morbidities, avoid unnecessary antibiotic treatment, and reduce public health burden.

There are multiple means for diagnosing or detecting *M. pneumoniae* infection.[8] As *M. pneumoniae* lacks a cell wall, it cannot be detected by Gram stains like other

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typical respiratory tract bacteria. Microbial culture has a low sensitivity and yield with a long turnover time. Isolation of the pathogen can take up to several weeks and is thus not routinely performed as a diagnostic test. Serological testing through automated enzyme immunoassay is another option as a diagnostic test. It detects acute or recent infection through the detection of immunoglobulin (Ig) M, yet there may be false negatives due to its lack of reactivity in young children. A detection of a significant rise in IgG titre between acute and convalescent samples also confirms the diagnosis, yet treatment can be delayed as the samples should be at least 2 weeks apart.

Thus, nucleic acid amplification test (NAAT) is the most widely used diagnostic method nowadays. Real-time polymerase chain reaction (PCR) is one of the most commonly used NAAT across different clinical laboratories. It extracts DNA from the sample collected and amplifies the targeted gene sequence of the DNA using PCR primers. A fluorogenic probe with reporter dye and quencher dye will be used simultaneously during the amplification. If *Mycoplasma* is present, its DNA polymerase cleaves the probe and generates fluorescent signals. It also enables quantification of the DNA, as the signal generated from the probe is proportional to the copies of DNA present. The turnaround time for PCR tests is much shorter than that of serology and culture. It is considered the new gold standard for testing *Mycoplasma* infection with a high sensitivity and specificity.[8,9]

Locally, sputum samples for monoplex *M. pneumoniae* PCR have been traditionally used for diagnosing *M. pneumoniae* infection. The monoplex PCR test was developed and validated by a local laboratory, and sputum samples are considered the gold standard of specimens used for diagnosing lower respiratory tract infections. However, it is all along a challenge for children to produce sputum for collection and testing. Besides, due to resource availability, the time-to-result for the final reporting may take days. In recent years, the BIOFIRE RP2.1 panel by bioMérieux[10] has become widely available in paediatrics as an investigation for patients with upper and lower respiratory tract infections. It is a multiplex PCR test that uses nasopharyngeal swabs (NPSs) as samples to identify 18 respiratory viruses and 4 respiratory pathogens, including *M. pneumoniae*. Every test has a turnaround time of <2 h. NPS is collected by nurses and is a more reliable means of sampling compared with sputum production by the child alone.

Therefore, this study aimed to compare the detection rates for detecting *M. pneumoniae* infection in paediatric patients with lower respiratory tract infection using the NPS multiplex PCR test and the sputum monoplex PCR test to determine whether the NPS multiplex PCR test could be used to replace the sputum monoplex PCR test.

Materials and Methods

Study design

This is a retrospective observational cross-sectional study conducted at the Department of Paediatrics and Adolescent Medicine of Tuen Mun Hospital, a tertiary public hospital serving a population of over 1.1 million (15% of the total Hong Kong population). Patient lists were retrieved from the Clinical Data Analysis and Reporting System (CDARS), and their medical records were analysed.

All data from this study were anonymised. This study was approved by the Central Institutional Review Board (Ref No.: PAED-2026-010, approved date: March 17, 2026).

Inclusion criteria

Clinical data were retrieved from the CDARS to include all paediatric patients (≤18 years old) in Tuen Mun Hospital admitted in the past 2 years (from January 1, 2023, to December 31, 2024) with a diagnosis of pneumonia.

The diagnosis of pneumonia was made by clinicians with documented clinical history and physical findings of fever, respiratory symptoms such as cough with sputum; auscultatory findings of decreased breath sounds, bronchial breath sounds or crackles; and signs of respiratory distress such as tachypnoea, hypoxaemia, and signs of increased work of breathing (e.g., nasal flaring, grunting, and chest wall retractions). Chest X-rays should be performed and reviewed by clinicians in all included cases to confirm the diagnosis.[11-13] All included cases must have both sputum testing and NPS testing performed.

NPS samples were collected by nurses inserting the swab 1–2 cm inside the nostril parallel to the nasal bridge, or until resistance is felt. The swab is rotated and left in place for 10-15 s before being withdrawn. The swab is then placed into a universal transport medium and sent to the laboratory.

As for sputum samples, the patients were instructed to produce sputum into a sterile container and sent to the laboratory.

NPS samples were analysed by the bioMérieux BIOFIRE Respiratory 2.1 Panels, whereas the sputum samples were analysed by an in-house PCR test for *M. pneumoniae* developed by Tuen Mun Hospital.

Only the first set of paired samples would be included for analysis in the same admission of the patient. The paired NPS and sputum samples should be collected within 24 h.

Exclusion criteria

Cases with either sputum sample data or NPS sample available were excluded from this study. Cases with gastric lavage (GL) for monoplex PCR testing and no sputum testing were also excluded from this study.

Outcome measures and statistical analysis

Basic patients' demographics, including age and gender, would be included in this study. The detection rate (%) of *M. pneumoniae* in both NPS multiplex PCR tests and sputum monoplex PCR tests was analysed and compared through McNemar's Test. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), as well as the likelihood ratios (LRs) of the NPS multiplex PCR test when compared against the sputum monoplex PCR test, will be analysed. Statistically significant difference is defined as a *P* value of <0.05. Statistical analyses were performed using IBM Statistical Package for the Social Sciences Statistics for Windows, Version 28.0.1.1 (IBM Corp, Armonk, NY, USA).[14]

Results

From January 1, 2023, to December 31, 2024, 3363 patients under 18 years old were diagnosed with pneumonia. Of these, 1168 cases had both NPS multiplex PCR and sputum monoplex PCR for *Mycoplasma* performed. About 20 cases were excluded as their sputum and NPS samples were collected more than 24 h apart. A total of 1148 cases with paired samples were included for final analysis. Details were shown in Figure 1.

Among these 1148 cases, 556 (48.4%) were male, and 592 (51.6%) were female. The male-to-female ratio is 1:0.94. The median age at diagnosis was 7.99 years (interquartile range = 4.45)

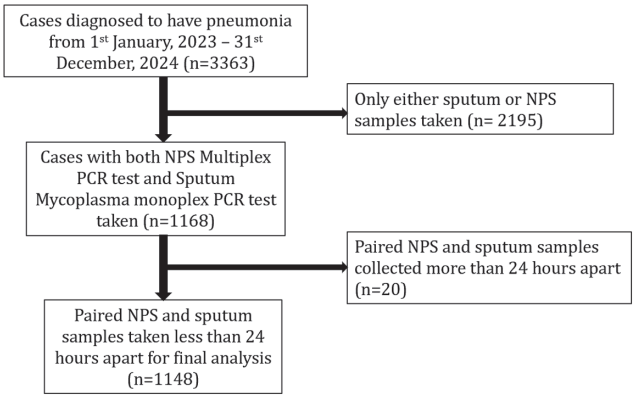

Figure 1: Inclusion and exclusion flowchart for cases recruited in this study

Table 1: Comparison of NPS multiplex PCR test and sputum monoplex PCR test

N (%) of NPS samples	*N* (%) of sputum samples		Total (%)
	Positive	Negative	
Positive	235 (20.4)	6 (0.5)	241 (21.0)
Negative	354 (30.8)	553 (48.2)	907 (79.0)
Total	589 (51.3)	559 (48.7)	1148 (100.0)

NPS = nasopharyngeal swab, PCR = polymerase chain reaction

M. pneumoniae was detected in 595 cases (51.8%). Of these patients, 235 (20.5%) had *Mycoplasma* detected in both NPS and sputum samples, 354 (30.8%) had positive results only in sputum, and 6 (0.5%) had positive results only in NPS samples [Table 1]. Sputum samples had a significantly higher positivity rate (51.3%; 589/1148) than in NPS samples (21.0%; 241/1148; $P < 0.001$).

Compared with sputum PCR, the sensitivity for the NPS multiplex PCR test is 39.9% (95% confidence interval [CI] = 35.9%–44.0%), specificity is 98.9% (95% CI = 97.7%-99.6%); the PPV is 97.5% (95% CI = 94.7%–98.9%) and the NPV is 61.0% (95% CI = 58.9%–62.1%). The positive LR (LR+) is 36.3 (95% CI = 16.67–82.89), whereas the negative LR (LR−) is 0.61 (95% CI = 0.57–0.65).

The overall κ value is 0.38 ($P < 0.001$), which indicates that the two tests demonstrated fair agreement.

Discussion

This study included pneumonia cases over a 2-year period, which recruited over 1000 paediatric patients and covered both the peak season (winter) and non-peak season (summer) of *Mycoplasma*, allowing the results to be more representative for application in this local hospital.

Sputum PCR demonstrated a significantly higher positive rate (51.3%) than that of NPS multiplex PCR (21.0%), with a *P* value of <0.001, indicating sputum PCR is more sensitive in detecting *Mycoplasma* infection in children with pneumonia. It could be due to a higher pathogen load in the lower respiratory tract, where sputum originates, whereas NPS is from the upper respiratory tract. Such results coincide with some overseas findings that lower respiratory tract specimens had a better diagnostic sensitivity.[14–17]

The significantly lower detection rate implies that, despite the turnover time for the NPS multiplex PCR test being shorter than the sputum PCR test, it may not be able to completely substitute the use of the sputum PCR test for diagnosis, and a negative NPS for *Mycoplasma* cannot rule out the infection.

Different published data have shown variable sensitivities for multiplex PCR tests to detect *Mycoplasma*.[15,18] Although this study demonstrated a similar sensitivity with a study conducted in China,[15] it demonstrated a lower detection rate and sensitivity than that of the data from Japan.[18] Such variation and lower sensitivity could be due to the non-standardised NPS collection method. In this retrospective study, NPS were collected by different nurses; whereas only one trained physician was responsible for NPS collection in the Japanese study to ensure the quality and consistency. Age could also be another minor factor, as the median age in this study was slightly younger than that of other studies. Small children tend to struggle

more during sample collection, and affect the final sample yield.

The lower detection rate could also be attributed to the bioMérieux BIOFIRE Respiratory 2.1 Panels used in this study, which are primarily designed for upper respiratory tract infections, whereas children with pneumonia recruited in the study should have more lower respiratory tract manifestations.

However, we often encounter difficulties in daily clinical practice as young children have difficulty producing reliable sputum samples. In view of the higher detection rate, induced sputum should be considered an option to collect sputum samples from young children for PCR testing in the future.[19]

Although the NPS multiplex PCR test may not be used to substitute sputum testing, it can still play a role in the clinical management of pneumonia in children locally, with its quicker turnover time as well as a high specificity and positive LR shown in this study. Clinicians can confidently confirm the diagnosis when NPS detects *M. pneumoniae*. It aids the early commencement of appropriate antibiotics in these cases before sputum PCR test results are available.

There are few limitations and pitfalls of this study as follows:

Firstly, it is a retrospective study, where cases were recruited through diagnosis and clinical findings documented in medical records. The retrieval of the records was based on diagnostic codes. Cases might be missed if the diagnoses and clinical findings were not well stated and coded in the records. Prospective studies should be performed in the future to enable a larger sample with greater generalisability of results.

Besides, as limited by the retrospective nature and also resource availability, comparisons could only be made between the bioMérieux BIOFIRE Respiratory 2.1 Panels NPS test and the in-house sputum monoplex PCR test. The differences in detection rates could be due to the sample types or the test kits. Although results could be useful as a local guide for which test is better in detecting *M. pneumoniae* when only these two tests are available, prospective studies using multiplex tests from the same manufacturer for both sputum and NPS samples could allow more representative and unbiased results.[20]

Secondly, only cases with both sputum and NPS taken were included in this study. Infants and toddlers are usually unable to produce samples, and GL aimed for swallowed sputum to be collected for *Mycoplasma* PCR testing instead. These cases were excluded from this study, resulting in data skewed towards an older age group. To further analyse the performance of NPS detection, especially in infants, future studies on the comparison between the detection rates of GL and NPS should be done. Induced sputum for *Mycoplasma* can also be considered as an alternative to GL. Analysis with throat swabs, another upper respiratory tract sample should also be considered, as studies showed combined NPS and throat swabs may increase the overall diagnostic yield of *M. pneumoniae*.

At the same time, since only pneumonia cases with paired samples were included, the overall detection rate for *M. pneumoniae* may not reflect the actual prevalence of *M. pneumoniae* in paediatric pneumonia locally, as a substantial number of cases with only sputum samples taken were excluded from this study. There may also be selection bias, as smaller children were unable to produce sputum for analysis and thus were not included in this study. Prospective studies with paired sampling aid future determination of the true prevalence of *Mycoplasma* in causing pneumonia.

Thirdly, the sputum quality could be highly variable. Sputum samples were not screened by microscopy to assess the quality. There might be contamination from the upper respiratory tract affecting the final results of the detection rate. Future directions should include paired samples with microscopy performed to ensure only quality samples are included for analysis. Similarly, the NPS collection should be performed by a single-trained physician to ensure the quality of samples.

Moreover, this is a single-centred study in which the sputum monoplex PCR test used for *M. pneumoniae* testing was developed and validated by an in-house laboratory. The sensitivity and specificity of the NPS PCR multiplex may be over- or under-estimated. Multi-centred studies and use of internationally validated brands of monoplex PCR tests should be done in the future to increase the accuracy and generalisability of the results.

Conclusion

In conclusion, the detection rate of sputum PCR for *M. pneumoniae* pneumonia is significantly higher in children than that of NPS PCR multiplex. The NPS multiplex PCR test cannot be used to replace the sputum PCR test for detecting and diagnosing *M. pneumoniae* infection in patients with lower respiratory tract infection.

Author contributions

LCYM: Concept, design, literature search, data acquisition, data analysis, statistical analysis, manuscript preparation, editing, and review. SYDL: Concept and review.

Data availability statement

Research data are not shared.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

Prevalence and Treatment of Macrolide-Resistant *Mycoplasma pneumoniae* Infections in Singapore

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Abstract

Background: *Mycoplasma pneumoniae* infection is a common cause of community-acquired pneumonia in children. Defining characteristics of the clinical presentation may improve diagnosis of the disease and allow appropriate treatment to be instituted. Furthermore, there are also increasing reports of macrolide resistance in Asia. We, therefore, aim to characterise the clinical features of *M. pneumoniae* infection in Singapore and review the impact of macrolide resistance. **Methods:** A total of 345 children admitted in 2013 who were positive for *M. pneumoniae* infection identified by real-time polymerase chain reaction were retrospectively reviewed. The domain V region of the 23S rRNA gene was amplified and sequenced to look for the mutations associated with macrolide resistance from throat swab samples. Data on demographic, clinical, laboratory and radiology features, as well as treatment and outcome variables were collected. Statistical comparisons were done between macrolide-resistant and -sensitive groups. **Results:** There were 157 boys (45.5%) and 188 girls (54.5%) with a median age of 6.0 years. The disease spectrum ranged from upper respiratory tract infections to complicated pneumonia with effusion. A total of 21/180 (11.6%) of the isolates had mutations for macrolide resistance. The presence of the mutation was not associated with disease severity but was significantly associated with a longer total duration of fever and hospital stay. The change of antibiotics from macrolides to fluoroquinolones was not associated with a shorter duration of fever. **Conclusion:** *M. pneumoniae* infection affects children of school-going age, manifesting from mild-to-severe disease. The presence of the mutation causing macrolide resistance did not affect disease severity, and the majority will still respond to macrolides.

Keywords: Fluoroquinolones, gene, macrolide, mutation, severity

Introduction

Mycoplasma pneumoniae pneumonia is a leading cause of childhood community-acquired respiratory infection in school-going children,[1] accounting for more than one-quarter of cases of community-acquired pneumonia in Singapore.[2] While *M. pneumoniae* infection causes mild illness in most cases, there can be potentially serious complications such as haemolytic anaemia, encephalitis, Guillain–Barre syndrome, and transverse myelitis, which are life-threatening. Furthermore, there are increasing reports on macrolide-resistant *M. pneumoniae* (MRMP) and its potential impact on the severity of the disease and the efficacy of treatment.[3]

Macrolide–lincosamide–streptogramin B antibiotics inhibit protein synthesis by binding to domains II or V of the 23S rRNA. Thus, any mutations in the domains will result in macrolide resistance. Previous studies have shown that common mutations include an A-to-C transversion or A-to-G transition at position 2063/2064.[4] In recent years, there has also been an increased incidence of MRMP infection worldwide, which was as high as 93% in Japan between 2008 and 2012.[5-7] This high resistance rate is likely associated with antibiotic selective pressure due to high rates of macrolide usage.[8] Previous reports[9] have

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also demonstrated the possibility of developing macrolide resistance after recent treatment with macrolides.

A letter to the Editor published in the Annals Academy of Medicine, Singapore, in 2017 described the prevalence of MRMP detected on laboratory samples from paediatric patients as 13%.[10] A second letter to the Editor published in the same journal in 2022 stated that the prevalence of MRMP detected in hospitalised children was 10%.[11] With this study, we aim to identify the clinical characteristics of MRMP infections so as to optimise treatment options for these patients.

Materials and Methods

This study was approved by the Singhealth Centralised Institutional Review Board (CIRB) on May 20, 2014 (CIRB Ref: 2014/279/E). A retrospective review was conducted on all paediatric patients admitted to a children's hospital in Singapore in 2013, who tested positive for *M. pneumoniae* via real-time polymerase chain reaction testing from throat swab samples. Based on the method described by Winchell *et al.*,[12] this polymerase chain reaction (PCR) assay employs two primers and a dual-labelled probe to target the *M. pneumoniae* community-acquired respiratory distress syndrome toxin gene. For our analysis, we selected *M. pneumoniae*-positive nucleic acid samples that demonstrated a threshold cycle (Ct) below 30 in the diagnostic assay. This specific cut-off was established based on preliminary experiments and provided adequate DNA yields for sequencing. A total of 345 samples were positive for *M. pneumoniae*, and 180 samples had a Ct value of <30. To detect known point mutations associated with macrolide resistance, we amplified a 217 base-pair fragment (positions: 1937–2154) within domain V of the *M. pneumoniae* 23S rRNA gene. This was performed using the Taq Core PCR Kit (Qiagen GmbH, Germany) with primers designed by Wolff *et al.*[13] Following amplification, the DNA was purified via gel extraction (Qiaquick Gel Extraction Kit, Qiagen GmbH) and sent to AITbiotech Pte Ltd. (Singapore) for sequencing. Finally, we conducted multiple sequence alignment on the 180 positive samples, comparing them against the wild-type *M. pneumoniae* M129 23S rRNA reference gene (GenBank accession NC_000912; Gene ID 876745).

Data obtained from medical records included patient demographics, clinical presentation, investigation results including chest X-ray findings, treatment received, and response to treatment. Based on chest X-ray findings and spectrum of disease, the patients were classified as having mild, moderate, or severe infection. The definition of severity of the disease is as follows: mild asthma exacerbation, upper respiratory tract infections, and acute bronchitis were classified as mild disease. Bronchopneumonia and interstitial pneumonitis were classified as moderate disease. Lobar pneumonia and pneumonia with effusion were classified as severe disease.

The data were analysed using IBM Statistical Package for the Social Sciences Statistics for Windows, Version 20.0 (IBM Corp, Armonk, NY, USA). Normality of continuous variables was assessed using the Shapiro–Wilk test. As all continuous variables were non-normally distributed ($P < 0.05$), comparisons across three groups were performed using the Kruskal–Wallis test with Bonferroni-corrected *post hoc* pairwise comparisons, and comparisons between two groups were performed using the Mann–Whitney *U* test. Data are presented as mean ± SD and median (IQR) for continuous variables and frequency (percentage) for categorical variables.

The association between categorical variables was assessed using the chi-square test of independence. Monte Carlo simulation was applied where expected cell counts were below 5, and *post hoc* analysis used adjusted standardised residuals.

Ordinal logistic regression was performed to identify independent predictors of disease severity, with C-reactive protein (CRP) as a continuous covariate and age group as a categorical predictor. A *P* value of <0.05 was considered statistically significant for all analyses.

Results

A total of 345 patients were included in the analysis. Boys accounted for 45.5% of the patients. The race distribution was representative of the racial demographics in Singapore. As shown in Table 1, the median age was 6.0 years, ranging from 5 months to 18 years. The most frequent age group infected was in the school-going age, between 5 and 12 years old. Table 2 demonstrates that the most common symptoms on clinical presentation were cough and fever, which were present in 99.7% and 97.1% of patients, respectively. Other symptoms such as rhinorrhoea, shortness of breath, gastrointestinal symptoms, and rash were less common. On physical

Table 1: Summary of patient characteristics

Total number of patients ($n = 345$)	Number (% or range)
Sex	–
Male	157 (45.5)
Female	188 (54.5)
Race	–
Chinese	232 (67.2)
Malay	44 (12.8)
Indian	40 (11.6)
Eurasian	5 (1.4)
Others	24 (7.0)
Age	–
<5 years	106 (30.7)
5–12 years	226 (65.5)
>12 years	13 (3.8)
Median years	6.00 (0-18)

examination, the most common finding was the presence of crepitations in the lungs in 61.4% of patients. Only 10.7% of patients had wheeze. The disease spectrum ranged widely from upper respiratory tract infections to pneumonia with effusion, with the most common diagnosis being bronchopneumonia. Majority of the cases were classified into the mild and moderate category, at 35.7% and 40.3%, respectively.

Table 3 demonstrates the distribution of disease severity by age group. Univariate analysis using the chi-square test of independence revealed a statistically significant association between age group and the severity of *M. pneumoniae* infection. Monte Carlo simulation confirmed the robustness of this result despite the small expected cell counts. A significant linear trend was also identified, suggesting that disease severity increased systematically with age group. *Post hoc* analysis showed children under 5 years of age had significantly more mild (48.1%, residual = +3.2) and fewer severe cases (11.3%, residual = −3.7) than expected, while the 5–12-year group had fewer mild (29.2%, residual = −3.4) and more severe cases (29.6%, residual = +3.3) than expected. This indicated that younger children under 5 years of age were more likely to present with milder disease, while children in the 5–12-year age group bear a disproportionately higher burden of severe *M. pneumoniae* infection. No significant deviations were observed in the over 12-year age group, which was limited by a small sample size.

Table 4 compared infective markers across disease severity groups. CRP levels differed significantly across severity groups (Kruskal–Wallis, $P = 0.001$). Median CRP increased progressively with disease severity: 23.3 mg/L (IQR 18.2) in mild, 32.4 mg/L (IQR 55.6) in moderate, and 38.1 mg/L (IQR 78.4) in severe cases. *Post hoc* pairwise analysis revealed that CRP was significantly higher in severe compared to mild cases (adjusted $P < 0.001$), while differences between mild and moderate (adjusted $P = 0.128$) and moderate and severe groups (adjusted $P = 0.089$) did not reach statistical significance after Bonferroni correction. Total white blood cell count did not differ significantly across severity groups (Kruskal–Wallis, $P = 0.265$), with median values of 8.54×10^9/L (IQR 3.67), 7.09×10^9/L (IQR 2.71), and 7.84×10^9/L (IQR 4.48) in mild, moderate, and severe cases, respectively, suggesting that total white blood cell count alone is not a reliable marker for differentiating disease severity in *M. pneumoniae* infection.

As age and CRP were both significantly associated with disease severity on univariate analysis, multivariate analysis was performed to identify independent predictors of disease severity. As shown in Supplementary Table 1, ordinal logistic regression identified CRP as the only significant independent predictor of disease severity ($P = 0.001$), with each unit increase in CRP associated with increased odds of higher disease severity. Age group

Table 2: Summary of clinical presentation, diagnosis, and severity of illness

Total number of patients (n = 345)	Number (%)
Clinical presentation	
Cough	344 (99.7)
Fever	335 (97.1)
Vomiting	130 (37.7)
Rhinorrhoea	82 (23.8)
Shortness of breath	74 (21.4)
Diarrhoea	41 (11.9)
Abdominal pain	34 (9.9)
Rash	26 (7.5)
Crepitations	212 (61.4)
Injected pharynx	130 (37.7)
Wheeze	37 (10.7)
Diagnosis	
Asthma exacerbation	3 (0.9)
Upper respiratory tract infection	34 (9.9)
Acute bronchitis	86 (24.9)
Bronchopneumonia	134 (38.8)
Interstitial pneumonitis	5 (1.4)
Lobar pneumonia	65 (18.8)
Pneumonia with effusion	18 (5.2)
Severity	
Mild	123 (35.7)
Moderate	139 (40.3)
Severe	83 (24.1)

Table 3: Distribution of disease severity by age group

	Age (years)			
	<5	5–12	>12	Total
Severity				
Mild, *n* (%)	51 (48.1%)	66 (29.2%)	6 (46.2%)	123
Moderate, *n* (%)	43 (40.6%)	93 (41.2%)	3 (23.1%)	139
Severe, *n* (%)	12 (11.3%)	67 (29.6%)	4 (30.8%)	83
Total	106	226	13	

Pearson's chi-square $P = 0.001$; Monte Carlo $P = 0.001$ (99% CI: 0.000–0.001); Linear-by-linear association $P < 0.001$

Table 4: Comparison of infective markers and severity of illness

	Mild	Moderate	Severe	*P* value
CRP (mg/L), mean ± SD	28.1 ± 23.4	49.3 ± 51.7	71.4 ± 76.0	0.001
CRP (mg/L), median (IQR)	23.3 (18.2)	32.4 (55.6)	38.1 (78.4)	
Total WBC ($\times 10^9$/L), mean ± SD	9.33 ± 5.07	7.95 ± 3.82	8.52 ± 3.32	0.265
Total WBC ($\times 10^9$/L), median (IQR)	8.54 (3.67)	7.09 (2.71)	7.84 (4.48)	

CRP = C-reactive protein, WBC = white blood cell count.

P values derived from Kruskal–Wallis test

Table 5: Comparison of macrolide-resistant and macrolide-sensitive groups treated with macrolides/switched to fluoroquinolones

	Macrolide-sensitive (MSMP)	Macrolide-resistant (MRMP)	*P* value
Macrolide-treated	(*n* = 311)[1]	(*n* = 15)	
Days for fever to resolve after macrolide treatment, mean ± SD	1.28 ± 0.99	2.00 ± 1.46	0.038
Days for fever to resolve after macrolide treatment, median (IQR)	(1.0)	1.0 (2.0)	
Switched to fluoroquinolone	(*n* = 6)	(*n* = 6)	
Days for fever to resolve after switch to fluoroquinolone, mean ± SD	2.80 ± 1.92	2.60 ± 2.30	0.841
Days for fever to resolve after switch to fluoroquinolone, median (IQR)	3.0 (4.0)	3.0 (4.0)	

MSMP = macrolide-sensitive *Mycoplasma pneumoniae*, MRMP = macrolide-resistant *Mycoplasma pneumoniae*.

P values derived from the Mann–Whitney U test. Exact significance reported for the fluoroquinolone-switched subgroup due to the small sample size (*n* = 6 per group).

[1]Seven patients did not require macrolide treatment as clinically improved without antibiotics.

Table 6: Comparison of macrolide-resistant and macrolide-sensitive groups

	Macrolide-sensitive (MSMP; *n* = 324)	Macrolide-resistant (MRMP; *n* = 21)	*P* value
Disease severity			
Mild, *n* (%)	117 (36.1%)	6 (28.6%)	0.817
Moderate, *n* (%)	130 (40.1%)	9 (42.9%)	
Severe, *n* (%)	77 (23.8%)	6 (28.6%)	
Fever duration			
Fever duration at presentation (days), mean ± SD	5.94 ± 2.49	7.82 ± 2.89	0.195
Fever duration at presentation (days), median (IQR)	6.0 (3)	7.0 (3)	
Total fever duration (days), mean ± SD	7.51 ± 3.00	12.09 ± 4.01	0.001
Total fever duration (days), median (IQR)	7.0 (3)	12.0 (7)	
Investigations			
WBC ($\times 10^9$/L), mean ± SD	8.27 ± 3.78	11.23 ± 6.83	0.700
WBC ($\times 10^9$/L), median (IQR)	7.64 (2.83)	8.18 (8.75)	
Neutrophil %, mean ± SD	58.95 ± 14.59	63.55 ± 13.17	0.170
Neutrophil %, median (IQR)	59.0 (19.25)	60.0 (18.00)	
Lymphocyte %, mean ± SD	28.12 ± 12.46	22.82 ± 12.34	0.233
Lymphocyte %, median (IQR)	25.5 (14.25)	23.0 (17.00)	
CRP (mg/L), mean ± SD	47.74 ± 50.64	80.75 ± 116.11	0.607
CRP (mg/L), median (IQR)	29.6 (46.6)	39.1 (104.0)	
Length of admission			
Length of admission (days), mean ± SD	3.59 ± 2.50	5.45 ± 3.05	0.002
Length of admission (days), median (IQR)	3.0 (2)	4.0 (5)	

WBC = white blood cell count, CRP = C-reactive protein, MSMP = macrolide-sensitive *Mycoplasma pneumoniae*, MRMP = macrolide-resistant *Mycoplasma pneumoniae*.

Disease severity *P* value derived from the chi-square test of independence (Monte Carlo); all other *P* values derived from the Mann–Whitney U test

was not independently associated with severity after adjusting for CRP ($P > 0.05$ for all categories).

The median length of stay was 3 days. None of the patients required admission to the intensive care unit. None of the patients developed non-respiratory complications including meningoencephalitis, polyneuropathy, myelitis, vasculitis, arthritis, and haemolytic anaemia.

Almost all patients (98%) were treated with macrolides, with the duration of treatment ranging from 10 to 14 days depending on disease severity. The remaining seven patients were not treated with macrolides as they showed clinical improvement without antibiotic treatment. Out of the patients treated with macrolides, 96.5% responded to macrolides, with resolution of fever within 5 days of starting macrolides, including those with the macrolide-resistant mutation. The remaining 12 patients initially treated with macrolides were converted to fluoroquinolone (ciprofloxacin or levofloxacin) in view of persistent fever and suspected macrolide resistance after initial macrolide

treatment. Of these patients, only six (50%) were retrospectively found to have the macrolide-resistant gene mutation. As demonstrated in Table 5, the presence of the macrolide-resistant mutation was significantly associated with a longer duration to resolution of fever after starting macrolide treatment ($P = 0.038$). No co-pathogens were identified in these patients to account for a longer duration of fever. However, the days to resolution of fever after switching to fluoroquinolone were no different between the macrolide-resistant and macrolide-sensitive groups. ($P = 0.841$)

Twenty-one out of the 180 samples analysed (11.6%) were found to have the macrolide-resistant mutation in the 23S rRNA gene. These were classified as MRMP infection. Those without the mutation were classified as macrolide-sensitive *M. pneumoniae* (MSMP) infection. Fifteen (71.4%) of the patients with MRMP recovered with macrolides alone, while six were switched to fluoroquinolones after failure of macrolide treatment. As demonstrated in Table 6, the presence of this mutation was not significantly associated with disease severity ($P = 0.817$). However, the total duration of fever was significantly longer in the MRMP group compared to the MSMP group ($P = 0.001$). This translated to a significantly longer length of admission in those with MRMP ($P = 0.002$). Total white blood cell, neutrophil (%), lymphocyte (%), and CRP were not useful in predicting the disease caused by the presence of the macrolide-resistant gene mutation.

Discussion

Consistent with previous reports from other countries, the majority of patients diagnosed with *M. pneumoniae* infection in our study were of school-going age. It is important to consider *M. pneumoniae* as a cause of a respiratory tract infection with persistent fever in this age group. The most common presenting complaints of fever and cough are generally not helpful in distinguishing *M. pneumoniae* infection from infections caused by other viral and bacterial organisms. The decreased severity in younger patients may be due to increased vigilance and investigation in this age group, resulting in earlier diagnosis of *M. pneumoniae* infection and earlier treatment before more severe disease occurs.

Studies from Taiwan[14] have shown macrolide resistance rates of 23.6% from 2010 to 2017, while Fukuoka prefecture in Japan[5] reported resistance rates of up to 80%–90% in 2011. Compared to these countries, the macrolide resistance rate in our study was significantly lower at only 11.6%. A possible explanation for this could be the low rate of macrolide use in the primary care setting. In our study cohort, only 55.9% of patients received antibiotics prior to hospital admission, and the majority had received a beta-lactam antibiotic, with only 13.4% being treated with a macrolide. Another reason for the low resistance rate is that not all samples were tested for the macrolide resistance mutation. In the worst-case scenario, the prevalence will be 53.9% assuming all remaining samples were positive, but this is unlikely given that all untested patients in this group recovered with macrolide treatment alone.

The low rate of macrolide use could also account for the high number of community-acquired pneumonia hospitalisation rates that were caused by *M. pneumoniae*. Early administration of macrolides had previously been shown to decrease the duration of symptoms.[15] The study in Taiwan[14] demonstrated an association between delayed macrolide treatment with a more severe disease course. This emphasises the importance of early diagnosis of *M. pneumoniae* infection to allow for early administration of effective macrolide treatment.

The first-line antibiotic for treating *M. pneumonia* infection is a macrolide. From our study, this recommendation still holds true as the majority (71.4%) of the patients with the macrolide resistance mutation still responded to macrolides. A study by Kawai in Japan reported a response to macrolides within 48 h in six out of 21 (28.5%) of their patients who had the macrolide-resistant gene mutation.[16] Other studies also reported that macrolides are effective in up to 30% of patients with MRMP infections.[17–19] The response to macrolide despite the presence of the mutation has been postulated to be related to the immunomodulatory effect of macrolides.[20] In our study, the MRMP strains all had mutations in the 2063 position in the 23S rRNA gene.[10] Although a mutation at position 2063 has been reported to be associated with high-level macrolide resistance and high azithromycin/clarithromycin minimum inhibitory concentrations,[21] this did not significantly affect the response to macrolide in our study.

Our review also showed that the presence of the macrolide-resistant mutation was not associated with increased disease severity but was associated with a longer duration of fever, which translated to a longer hospital stay. This is consistent with the results of most previous studies which reported that patients with MRMP have a longer duration of fever but no difference in the clinical outcome.[16–19,22] However, there are also reports[23–25] of severe cases of pneumonia associated with the macrolide-resistant mutation that were treated with macrolides. A study done in Hangzhou, China, reported more extrapulmonary complications and severe radiological findings in patients with the macrolide-resistant mutation.[26]

Of the children who received fluoroquinolone for persistent fever and suspected macrolide resistance, there was no significant difference in the number of days to resolution of fever between the macrolide-resistant and macrolide-sensitive groups. This lack of difference can likely be attributed to the immunomodulatory effect of the initial macrolides administered. The study by Kawai *et al.*[27]

reported that the *M. pneumoniae* DNA copy numbers in the macrolide-resistant patients decreased promptly after the administration of tosufloxacin. However, there was no significant difference in the duration of fever in patients treated with tosufloxacin compared to macrolides. As fluoroquinolones can be associated with musculoskeletal adverse effects,[28] the overall benefit of starting the antibiotic may not outweigh the risks when taking into consideration the limited benefit in our study.

The main limitation of our study was that our study population comprised only hospitalised cases of *M. pneumoniae* infection, and the testing was done retrospectively on the stored throat swab samples. Hence, the resistance rate reported may not completely reflect what is happening in the community, and also the degradation of the samples may make detection of the gene mutation inaccurate. The testing was done on only half the samples, which may under-report the true prevalence. The study reviewed patients over a 1-year period, resulting in a small sample size. A larger prospective study may address some of these limitations.

In conclusion, this retrospective review over a 1-year period showed that *M. pneumoniae* infection occurred more commonly in the school-going children, with younger children having milder disease compared to the older children. MRMP incidence is low in Singapore at 11.6%, and the majority of those with the macrolide-resistant gene mutation still responded to macrolides. Macrolides, therefore, should remain the first-line antibiotic of choice in treating *M. pneumoniae* infection.

Author contributions

KHSC: design, literature search, data acquisition, data analysis, and manuscript preparation. LHL: data acquisition. NWST: data acquisition. AENG: concept, design, literature search, data analysis, and manuscript editing and review.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Conflicts of interest

There are no conflicts of interest.

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Supplementary Table 1: Independent Predictors of Disease Severity

	Estimate	*P* value	OR	95% CI
CRP[1]	0.010	0.001	1.010	0.004–0.016
Age group < 5 years	− 0.097	0.902	-	-
Age group 5–12 years	0.895	0.236	-	-
Age group > 12 years (reference)	-	-	-	-

[1]*CRP: C-Reactive Protein. Model: $\chi^2(3) = 28.167$, $p = <.001$; Nagelkerke $R^2 = .162$. Statistical method: Ordinal Logistic Regression*

Original Article

Real-Time Feedback Improves Quality of Chest Compression in Pediatric Cardiopulmonary Resuscitation Training Course

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Abstract

Background: High-quality cardiopulmonary resuscitation (CPR) is vital for pediatric survival, yet maintaining precision remains difficult even for specialists. This study evaluated the impact of real-time audiovisual feedback on pediatric CPR and identified independent factors influencing performance. **Methods:** This prospective study recruited 110 pediatric intensive care unit providers. Performance data were collected using an infant manikin and a defibrillator system with dual anterior–posterior sensors to eliminate mattress deflection artifacts. "On-target" quality was defined as the simultaneous achievement of American Heart Association-recommended rate (100–120/min) and depth (≥4.0 cm or one-third anterior-posterior diameter). Participants performed two 1-min sessions of compression-only CPR: A baseline session and a subsequent session with real-time visual feedback. Data were analyzed using nonparametric tests and multivariable logistic regression. **Results:** At baseline, performance was suboptimal (0% on-target), with female participants compressing too fast and certified providers performing significantly shallower compressions. With real-time feedback, the median rate was corrected to 110/min, and the median depth increased from 2.2 to 4.0 cm ($P < 0.001$), raising the on-target rate to 49.2%. Feedback usage was the strongest independent predictor of rate adherence (adjusted odds ratios = 27.23). Notably, feedback enabled certified providers to reverse baseline trends and achieve greater depths than noncertified counterparts. Furthermore, participants with at least six real-world experiences achieved the highest on-target scores (median = 0.60). **Conclusions:** Real-time feedback effectively standardizes CPR quality by eliminating gender and training recency gaps. While it ensures a critical performance baseline, extensive clinical experience remains essential for achieving peak resuscitation quality.

Keywords: Chest compression quality, pediatric resuscitation, real-time audiovisual feedback

Introduction

Pediatric in-hospital cardiac arrest affects approximately 1%–3% of children admitted to pediatric intensive care units (PICUs), with the incidence climbing to 6% among patients suffering from congenital heart conditions.[1] Although historical survival outcomes were poor, the rate of survival to hospital discharge has experienced a substantial upward trajectory over the past quarter-century, rising from 9% to roughly 35%. Concurrently, favorable neurological recovery is now documented in 78.1% of these survivors.[2,3] This therapeutic progress is primarily driven by enhanced clinical vigilance, the execution of high-quality chest compressions (CC), rapid deployment of extracorporeal membrane oxygenation (ECMO) for refractory cases, and sophisticated postarrest management.[4]

Despite these substantial gains in survival, cardiopulmonary resuscitation (CPR) quality remains largely unmeasured in clinical practice. High-quality CPR is succinctly captured by the American Heart Association (AHA) mantra, "Push hard and push fast".[5] Specifically,

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the AHA has established benchmarks for variables defining high-quality CPR, including CC depth, rate, fraction (the proportion of time spent performing CCs during an arrest event), and "CC in-target"—defined as compressions simultaneously meeting both rate and depth metrics. Other critical variables include minimizing preshock and postshock pauses. However, healthcare providers frequently struggle to maintain guideline-compliant CPR, even though such adherence is directly linked to improved patient survival.[6]

Embracing the robust link between resuscitation proficiency and patient survival, the 2015 and 2020 Pediatric Advanced Life Support (PALS) guidelines underscored the necessity of systematic monitoring and quality improvement (QI) programs.[7] Even though life support training remains a mandatory institutional requirement, conventional basic life support (BLS) courses seldom focus on objective competency metrics. Consequently, certified clinicians frequently demonstrate a sharp decline in CPR quality shortly after course completion, with substantial skill degradation typically surfacing within 3–6 months.[8] Given that standard recertification operates on a biennial cycle, the lack of regular, deliberate manikin practice remains a major barrier to long-term skill retention.[9] Furthermore, providers are often unaware of their actual performance quality during training.

A growing body of literature supports the use of real-time audiovisual feedback (RTAVF) devices to display quantitative CPR metrics and improve CC quality during both training and actual cardiac arrests.[10-15] In this study, we hypothesize that RTAVF provides an objective measurement of CPR quality and significantly improves adherence to AHA guidelines during training at our children's hospital, regardless of the rescuer's career experience, training level, or the time elapsed since their last BLS certification.

Materials and Methods

Hospital setting and participants

This study was conducted at an academic, free-standing tertiary pediatric referral center. The facility features a 32-bed PICU specializing in the management of critically ill patients, including those requiring postcardiac surgery care, shock resuscitation, and ECMO support.

Institutional policy mandates that all hospital employees maintain BLS certification. Furthermore, PALS certification is required for all PICU staff, including registered nurses, residents, respiratory therapists, and attending physicians. Both BLS and PALS certifications require completion of in-person training every 2 years. Participants for this study were recruited directly from the PICU healthcare staff.

Ethics and study design

This study was designed as a prospective, single-center QI initiative. As the program was implemented as part of an institutional effort to enhance resuscitation standards, it was categorized as a QI program and was determined to be exempt from review by the National Taiwan University Hospital Institutional Review Board; the requirement for individual informed consent was waived.

Equipment and cardiopulmonary resuscitation quality

According to the literature, CPR quality is more difficult to achieve when facing small infants than in adult-sized children, possibly due to fear of internal damage such as rib fracture and cardiac contusion.[16] We chose an infant-sized manikin (Resusci Anne, Laerdal Medical, Stavanger, Norway) in this study, from which performance data were collected.

CC metrics were measured and recorded during CPR training with a commercial monitor and defibrillatory system (R-series, Zoll Medical, Chelmsford, MA, USA). Dual sensors were placed anterior–posterior over the chest to record actual CC rate and depth and eliminate artifact due to mattress deflection. Any event that deployed anterior apical placement of electrode pads was excluded from analysis. Application of "pediatric" electrode pads (for children 0–8 years or <25 kg) enables display of compression rate and depth measurements on the defibrillator screen. Corrective voice attempts and visual indication of CC performance are not possible with use of the pediatric electrodes in this study, due to the guidelines not recommending a specific depth for the 0- to 8-year-old age range. Target CPR goals in this study were compression depth at least 4 cm or one-third the anterior-posterior diameter, and compression rate 100–120/min. Compression on-target is defined when providers achieve both a depth of at least 4 cm and a compression rate of 100–120/min as well. Data were recorded on an internal hard drive and then transferred to a computer for analysis of compression rate and depth with Zoll RescueNet Code Review Software Version 5.90 (Zoll Medical Cooperation, Chelmsford, MA, USA).

Study protocol

This study was performed in a quiet, isolated, designated room to avoid synchronization or external influence. After a short video coach of BLS to emphasize CC quality, rescuers knelt beside the infant manikin and applied compressions using the encircling two-thumb method for two sessions. To focus the efficiency of CC, they were informed that this was a compression-only resuscitation simulation, requiring no airway management, and that the researchers would prompt each phase using "start" and "stop" voice cues. In the first session, participants performed compression-only CPR without visual feedback for 1 min. CPR quality was recorded as baseline data. There was a short break of about 2 min. During this break, participants were reminded of the AHA guidelines and advised to offload fully. Thereafter, in the second session, rescuers performed compression-only CPR for 1 min again

and were allowed to view their overall performance results on CC rate and depth. The primary outcome measure was the improvement of CPR quality, measured as CC metrics, with audiovisual feedback. We also sought the factors associated with individual CPR performances.

Statistical analysis

Statistical computations were executed utilizing Statistical Package for the Social Sciences (version 22, IBM Corp., Armonk, NY, USA). Patient demographics and baseline characteristics were summarized as frequencies and percentages for categorical data. Continuous metrics were summarized using medians accompanied by interquartile ranges (IQRs) due to their non-Gaussian distribution. To evaluate differences in CC parameters between the baseline and experimental sessions, the Wilcoxon signed-rank test was applied. Intergroup variations (e.g., gender differences, clinical experience, and certification status) were evaluated via the Mann–Whitney *U* test. Factors linked to optimal CC rate adherence were identified using univariate and multivariable logistic regression models. Variables yielding a *P* value of <0.05 in the univariate screening were integrated into the multivariable regression to determine adjusted odds ratios (aORs) along with 95% confidence intervals (CIs). Statistical significance across all tests was established at a two-tailed *P* value of <0.05.

Results

Study population characteristics

A total of 110 participants were recruited for this study, consisting of 50 males (45.5%) and 60 females (54.5%). The professional composition of the cohort was diverse: registered nurses represented the largest group (n = 41, 37.3%), followed by pediatric residents (n = 36, 32.7%), medical students (n = 28, 25.5%), and attending physicians (n = 5, 4.6%). The average length of professional experience was 4.9 ± 3.2 years (range: 0–23 years), with 49 participants (44.5%) having a career history of 5 years or more. Regarding advanced life support qualifications, 89 participants (80.9%) held current PALS or ACLS certification, of whom 31 (28.2%) had been certified within the 6 months before the study. Assessment of real-world clinical experience revealed that while 25 participants (22.7%) had never performed CC on an actual pediatric patient, 57 (51.8%) had participated in one to five resuscitation events, and 28 (25.5%) reported at least six actual clinical experiences within the past 2 years. Detailed demographic data are summarized in Table 1.

Impact of real-time feedback on chest compression quality

As shown in Table 2, the implementation of RTAVF resulted in a significant improvement across all CC quality metrics. In the absence of feedback, only 35 (31.8%) participants adhered to the AHA guideline for compression rate (100–120/min), with a median rate of 126/min (IQR = 114–137). Upon application of the feedback device, rate adherence increased to 91.8% (n = 101), and the median rate was precisely corrected to 110/min (IQR = 106–114, $P < 0.001$). Regarding compression depth, baseline performance without feedback was insufficient, with a median depth of 2.2 cm (IQR = 1.8–2.4). Notably, no participants reached the AHA target of ≥4.0 cm, nor the clinical threshold of ≥3.7 cm (representing one-third of the chest anteroposterior

Table 1: Baseline characteristics of the study participants

Characteristics	*N* = 110	%
Gender		
Male	50	45.5
Mean career years (range)	4.9 years (0–23 years)	
Career years ≥5 years	49	44.5
Career types		
Registered nurse	41	37.2
Pediatric resident	36	32.7
Medical student	28	25.5
Attending physician	5	4.6
PALS/ACLS qualification	89	80.9
<6 months after certification	31	28.2
Chest compression on actual pediatric patients within 2 years		
Never	25	22.7
1–5 times	57	51.8
>6 times	28	25.5

PALS = pediatric advanced life support, ACLS = advanced cardiovascular life support.

Data are presented as n (%) or mean (range). Real-world experience refers to chest compressions performed on actual pediatric patients within the past 2 years

Table 2: Comparison of chest compression quality with and without real-time audiovisual feedback

All participant	Without feedback	With feedback	*P* value
Chest compression depth (>4 cm or one-third anteroposterior diameter of chest wall)			
≥4 cm	0 (0%)	72 (65.4%)	<0.001
≥3.7 cm	0 (0%)	96 (87.2%)	<0.001
Median depth, cm (IQR)	2.2 (1.8~2.4)	4.0 (3.9–4.2)	<0.001
Chest compression rate (goal 100–120/min)			
Guideline adherence (%)	35 (31.8%)	101 (91.8%)	<0.001
Median rate, /min (IQR)	126 (114–137)	110 (106–114)	<0.001
Chest compression on-target (%)	0 (0%)	54 (49.2%)	<0.001

IQR = interquartile range.

Data are presented as n (%) or median (IQR). *P* values were calculated using the Wilcoxon signed-rank test for continuous variables and McNemar's test for categorical variables. Compression on-target defines the percentage of time during which both compression depth and rate were within guideline-recommended ranges simultaneously

diameter). With real-time feedback, the median compression depth significantly improved to 4.0 cm (IQR = 3.9–4.2, $P < 0.001$). Under device guidance, 72 (65.4%) participants achieved the target of ≥4.0 cm, and 96 (87.2%) reached the threshold of ≥3.7 cm. Furthermore, "on-target" quality—defined as the simultaneous achievement of both guideline-recommended rate and depth—was not achieved by any participant (0%) during the nonfeedback phase. Following the application of the real-time feedback device, nearly half of the participants (49.2%, $n = 54$) maintained "on-target" CC quality throughout the resuscitation cycle ($P < 0.001$).

Subgroup analysis of factors influencing cardiopulmonary resuscitation performance with and without real-time feedback

Subgroup analysis revealed that several individual factors significantly influenced baseline CPR performance in the absence of feedback [Figure 1]. Regarding compression

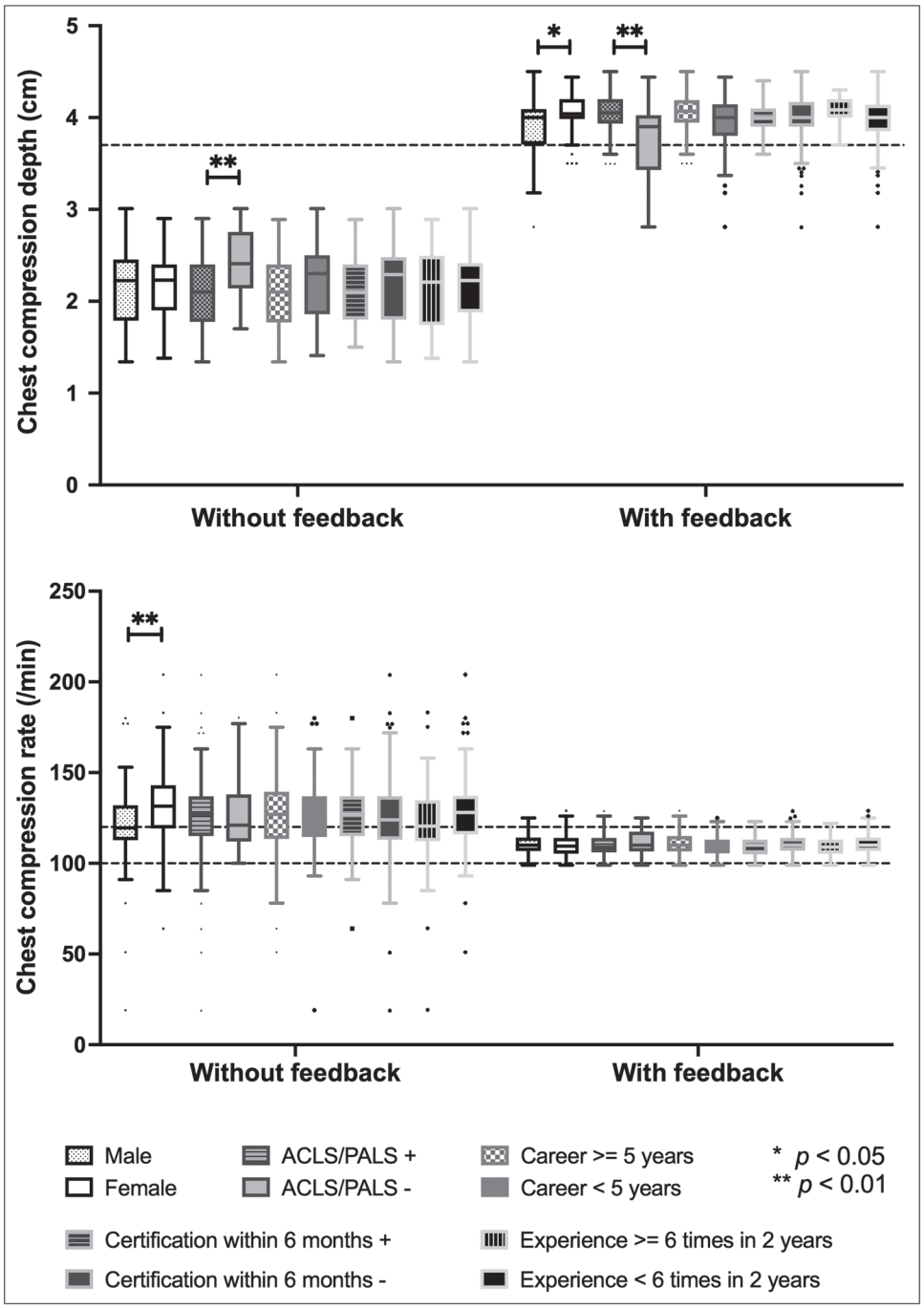

Figure 1: Impact of real-time audiovisual feedback on standardizing chest compression depth and rate across subgroups. Box-and-whisker plots illustrating the comparison of compression depth and rate between the nonfeedback and feedback phases among 110 participants. Dashed lines indicate the clinical targets (depth ≥3.7 cm and rate 100–120/min). The dashed lines indicate depth = 3.7 cm and rate between 100 and 120/min. *P* value was calculated by using the Mann–Whitney *U* test for subgroup comparisons

Table 3: Factors associated with compression rate adherence: univariate and multivariate logistic regression analyses

	Rate adherence (100-120/min)	OR (95% CI)	*P* value	aOR (95% CI)	*P* value
Feedback vs. no	91.8% vs. 31.8%	24.05 (10.90–53.05)	<0.001	27.23 (11.97–61.97)	<0.001
Male vs. Female	69.0% vs. 55.8%	1.76 (1.01–3.07)	0.046	2.53 (1.22–5.23)	0.012
Career >5 years vs. no	58.2% vs. 64.8%	0.76 (0.44–1.31)	0.318		
PALS/ACLS certification vs. no	60.7% vs. 66.7%	0.77 (0.38–1.57)	0.473		
Certification within 6 months vs. no	61.3% vs. 62.0%	0.97 (0.53–1.77)	0.920		
CC experiences >6 vs. no	64.3% vs. 61.0%	1.15 (0.61–2.16)	0.660		

CI = confidence interval, OR = odds ratio, aOR = adjusted odds ratio, PALS = pediatric advanced life support, ACLS = advanced cardiovascular life support.

Multivariable logistic regression models were constructed using factors that reached statistical significance ($P < 0.05$) in the univariate analysis

Table 4: Subgroup analysis of chest compression quality during the use of real-time audiovisual feedback

	Depth adherence (≥3.7 cm)	OR (95% CI)	*P* value	aOR (95% CI)	*P* value
Male vs. Female	78.0% vs. 93.3%	0.25 (0.08–0.85)	0.027	0.77 (0.16–3.69)	0.012
Career >5 years vs. no	90.0% vs. 84.3%	1.68 (0.50–5.67)	0.405		
PALS/ACLS certification vs. no	93.3% vs. 57.1%	10.38 (3.13–34.35)	<0.001	8.86 (2.00–39.37)	0.004
Certification within 6 months vs. no	93.5% vs. 83.5%	2.86 (0.61–13.48)	0.185		
CC experiences >6 vs. no	100% vs. 81.7%	NA	0.015		

CI = confidence interval, OR = odds ratio, aOR = adjusted odds ratio, PALS = pediatric advanced life support, ACLS = advanced cardiovascular life support.

Multivariable logistic regression models were constructed using factors that reached statistical significance ($P < 0.05$) in the univariate analysis

rate, a significant gender disparity was observed, with female participants performing compressions at a much higher rate than males (median = 132/min vs. 120/min, $P < 0.01$). For compression depth, participants with PALS/ACLS certification performed shallower compressions than those without (median = 2.1 cm vs. 2.4 cm, $P < 0.01$). The implementation of RTAVF effectively acted as a "performance equalizer," standardizing quality across all subgroups. In terms of rate, the baseline gender difference was eliminated, with all groups successfully converging to the target of 110/min [Figure 1]. Most notably, the feedback mechanism reversed the baseline trends for depth; under device guidance, participants with professional certification—who exhibited inadequate depth at baseline—achieved significantly greater compression depths than their noncertified counterparts (median = 4.1 cm vs. 3.9 cm, $P < 0.01$).

Independent predictors of chest compression performance

To identify independent predictors of CC rate adherence (100–120/min), we performed a logistic regression analysis [Table 3]. Univariate analysis indicated that real-time feedback usage (OR = 24.05, 95% CI: 10.90–53.05, $P < 0.001$) and male gender (OR = 1.76, 95% CI: 1.01–3.07, $P = 0.046$) were significantly associated with rate adherence. After adjusting for these factors in a multivariable model, real-time feedback usage remained the most powerful independent predictor of achieving the target rate, with an aOR of 27.23 (95% CI: 11.97–61.97, $P < 0.001$). Additionally, male gender was confirmed as an independent predictor of rate adherence (aOR = 2.58, 95% CI: 1.10–6.05, $P = 0.029$). Regarding compression depth [Table 4], while feedback significantly improved performance across all subgroups, female gender, professional certification (PALS/ACLS), and clinical experience remained key factors influencing final depth outcomes. Furthermore, when evaluating "on-target" quality (simultaneous adherence to both rate and depth), participants with at least six real-world clinical experiences demonstrated the highest level of performance (median on-target = 0.60, $P = 0.044$) [Figure 2]. These findings suggest that while real-time feedback serves as a critical tool for standardizing CPR quality across diverse demographics, baseline professional qualifications and practical experience remain essential for reaching peak resuscitation performance.

Discussion

This study demonstrates that high-quality CPR remains inherently challenging for pediatric healthcare providers. Without real-time guidance, baseline performance was poor: only 31.8% achieved the target rate, and none met the recommended depth, resulting in a 0% "on-target" quality rate. Notable insufficiencies included female participants compressing too fast and certified providers performing shallower compressions. The implementation of real-time feedback precisely corrected these deficits. The median rates were standardized to 110/min, and a median depth nearly doubled from 2.2 to 4.0 cm, increasing the "on-target" rate to 49.2%. Most significantly, feedback enabled certified providers to reverse their baseline trends

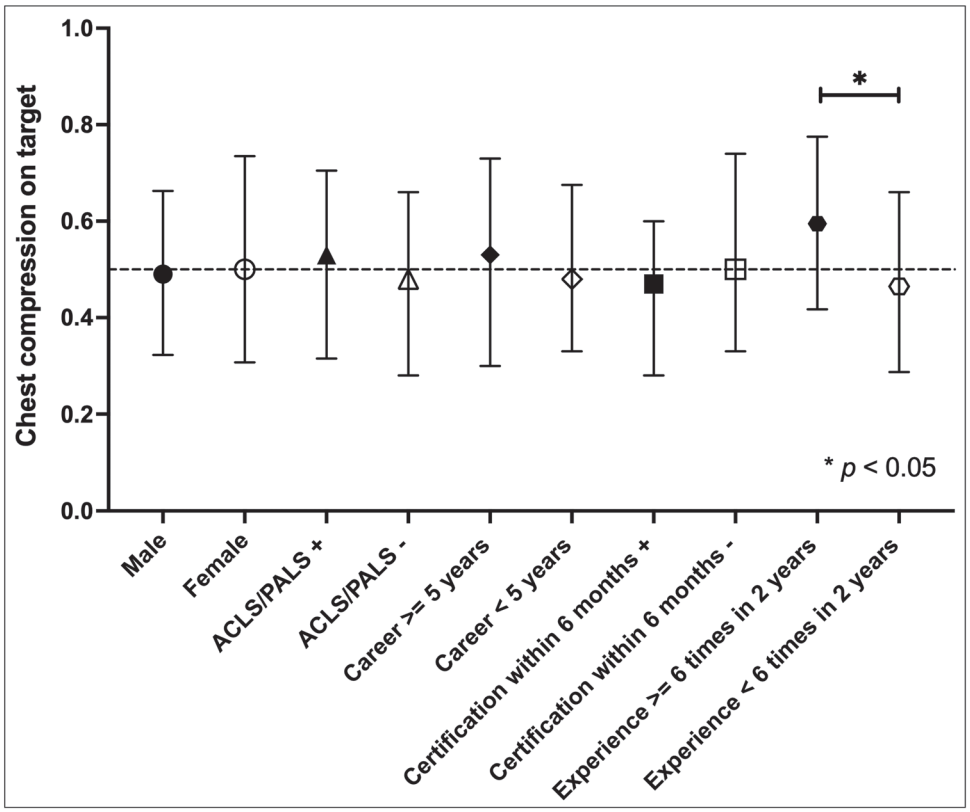

Figure 2: Subgroup analysis of overall chest compression quality adherence with real-time feedback. Subgroup comparisons of overall compression on-target, which is presented as the percentage of time during which both compression depth and rate were simultaneously within the guideline-recommended ranges. The *P* value was calculated by using the Mann–Whitney *U* test for subgroup comparisons

and achieve greater depths than their counterparts. Furthermore, real-world experience remained a key determinant of peak quality; under device guidance, participants with at least six resuscitation experiences achieved the highest on-target performance (median = 0.60). These results suggest that while feedback bridges baseline gaps, professional experience remains essential to optimize resuscitation quality.

Following the 2010 AHA guideline restructuring, which reordered the life support sequence from A–B–C to C–A–B, immediate and high-quality CC became the cornerstone of resuscitation. Nevertheless, our baseline data exposed a concerning deficit in technical proficiency, with no participant concurrently achieving target velocity and depth goals. Delivering standard CC demands rigorous physical exertion; hence, performance stability is easily compromised by rescuer fatigue or individual physical traits such as sex and body weight.[17-20] The introduction of RTAVF engineered a profound shift in performance, driving rate adherence from 31.8% to 91.8% and depth accuracy up to 87.2%. These observations parallel earlier documentation indicating that feedback systems can boost rate and depth compliance by over 40% and 15%, respectively.[15,21,22] Our findings also align with studies showing that the two-thumb technique, when guided by RTAVF, can achieve near-perfect compliance (up to 90%) in infant simulations.[13,23,24] Recognizing these benefits, the AHA mandated in 2019 that all adult CPR courses utilize RTAVF devices to measure critical metrics such as rate, depth, recoil, and ventilation. While various feedback modalities exist—ranging from sensor-integrated manikins to handheld devices—we utilized a defibrillator-based system capable of seamless transition from training to clinical practice. Our data, specifically summarized in Table 2 and Figure 1, suggest that CPR training programs should place a heightened focus on achieving adequate compression depth, as this was the most significant baseline deficit in our cohort. Collectively, our evidence reinforces the growing consensus that RTAVF-assisted CPR, like a CPR coach, is vastly superior to conventional manual CPR in ensuring guideline adherence.

A notable finding in this study was the prevalence of excessive compression rates during the baseline phase. While previous literature has frequently reported that rescuers tend to perform compressions too slowly,[25] our cohort demonstrated an opposite trend, with a median baseline rate of 126/min. Excessive compression rates are clinically concerning as they often result in insufficient compression depth and inadequate chest recoil, ultimately compromising overall perfusion quality.[22] Furthermore, we observed a paradoxical relationship between professional certification and baseline performance: Participants

with PALS/ACLS certification performed significantly shallower compressions than their noncertified counterparts. This finding underscores the rapid nature of "skill decay" following standardized training. However, the introduction of real-time feedback effectively reversed this trend, enabling certified providers to not only correct their depth but also outperform noncertified rescuers. This suggests that while manual skills erode over time, the underlying knowledge from prior training allows certified providers to achieve superior results when guided by objective feedback.

The difficulty of maintaining CPR quality is further amplified in pediatric scenarios. Compared with adult resuscitation, pediatric cardiac arrest management is associated with significantly higher cognitive load and lower performance quality among healthcare providers, despite similar levels of theoretical knowledge. Previous simulations have shown that up to 58% of pediatric cases involve inadequate compression depth and 27% involve excessive rates exceeding 120/min.[26] These disparities highlight the unique challenges of infant CPR, where the smaller thoracic dimensions and the fear of causing internal injury often lead to hesitant or imprecise maneuvers. Our results emphasize that due to the higher complexity and cognitive demands of pediatric resuscitation, the implementation of RTAVF is even more critical in the pediatric setting than in adult care to bridge the gap between clinical knowledge and technical execution.

This study further highlights that baseline professional training is insufficient without regular practical reinforcement. We found that participants with at least six real-world clinical experiences within the past 2 years achieved superior "on-target" performance (median score = 0.60) when guided by real-time feedback. This frequency translates to approximately one clinical resuscitation every 4 months, aligning with the "Low-Dose, High-Frequency" training model advocated by Professor Vinay.[27] Their research demonstrated that CPR skill retention improves significantly with frequency, with providers being 2.3 and 2.9 times more likely to retain skills after two and three training sessions, respectively. However, it is noteworthy that while RTAVF is a powerful corrective tool for immediate performance, feedback alone—without concurrent instructor guidance—may result in lower long-term retention rates (OR = 0.41, $P = 0.043$) compared to structured, instructor-led training. This suggests that the optimal strategy for maintaining peak resuscitation quality is not merely the presence of a feedback device during an arrest, but the integration of RTAVF into high-frequency, instructor-led simulation training. By increasing the frequency of brief, feedback-guided sessions, institutions can bridge the critical gap between biennial certification and actual clinical events. Therefore, to ensure maximum efficacy in every pediatric CPR event, healthcare organizations should implement mandatory, frequent simulation drills that combine real-time feedback with professional oversight to reinforce muscle memory and combat the inevitable decay of manual skills.

This study has several limitations. First, as a simulation-based study using infant manikins, it cannot fully replicate the physiological complexity, tactile resistance, or psychological stress of real-life pediatric cardiac arrests. Thus, the observed improvements in "on-target" quality may be more pronounced than in clinical settings. Second, as a single-center study in a specialized PICU, these findings may not be fully generalizable to prehospital or general pediatric providers with different training backgrounds. Furthermore, we focused on immediate performance gains and did not assess long-term skill retention. Given the rapid nature of skill decay, further longitudinal research and crossover studies are needed to determine if real-time feedback leads to sustained manual proficiency or if performance reverts once the device is removed.

Conclusion

In conclusion, high-quality pediatric CPR remains a significant challenge for healthcare providers. This study demonstrates that RTAVF serves as a critical corrective tool, effectively standardizing compression rates and significantly improving depth adherence regardless of gender or certification status. While RTAVF acts as a powerful "equalizer" to bridge skill decay, extensive clinical experience remains essential for achieving peak resuscitation quality. To optimize patient outcomes, healthcare institutions should integrate RTAVF into high-frequency simulation training, combining objective guidance with deliberate practice to reinforce muscle memory in pediatric intensive care.

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Author contributions

JHT: Study design, data acquisition, data analysis, statistical analysis, and manuscript preparation. CCW: Data analysis and statistical analysis. FLL: Literature search, concept, and study design. ETW: Study design, manuscript preparation, manuscript editing, and manuscript review.

Data availability statement

The data generated and analyzed during the current study are not publicly available due to institutional

privacy and ethical restrictions, but are available from the corresponding author on reasonable request.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Review Article

A Novel Technique of Noninvasive Ventilation (Soong's Ventilation): Pharyngeal Oxygen with Nose–Closure and Abdominal–Compression

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Abstract

Soong's ventilation (SV) is a simple, novel, and noninvasive ventilation technique. It could provide patients with effective oxygenation, ventilation, and partial circulation. SV comprises three main components: continuous pharyngeal oxygen insufflation, with optional and intermittent maneuvers of nose–closure, and/or abdominal–compression, which could generate controllable positive airway pressure, improve oxygenation, and facilitate both inspiration and expiration. Particularly, SV could achieve sufficient airway pressures to overcome airway resistance and expand the lumen, even in cases of airway narrowing or apneic status, while minimizing the need for more complicated and invasive respiratory supporting strategies. This SV technique enables simultaneous maintenance of cardiorespiratory stability as well as preservation of a clear vision of flexible bronchoscopy, thereby enhancing both diagnostic and therapeutic interventions. Its simplicity, effectiveness, and adaptability may make it a valuable adjunct and alternative in pediatric cardiopulmonary support, airway management, and resuscitation settings. Overall, SV could offer an effective respiratory support that promotes patient safety and clinical procedural success.

Keywords: Flexible bronchoscopy, noninvasive ventilation, pediatric bronchoscopy, resuscitation, Soong's ventilation

Introduction

Traditional cardiopulmonary resuscitation (CPR), especially for providing resuscitative ventilation (RV), may involve the use of airway and ventilation devices such as bag–valve–mask (BVM), Ambu bag, laryngeal mask airway, endotracheal tube (ETT), and/or even a mechanical ventilator. However, in an emergency of sudden apnea, hypoxia, or in a source-limited area, these life-saving tools, techniques, and skilled providers may not be appropriately and immediately available. Particularly in pediatric patients with wide variations in airway size and body weight, from less than 1 kg to more than 60 kg, airway management can be challenging. In addition, for doing flexible bronchoscopy (FB) interventions, patients under sedation or anesthesia, these artificial airway devices themselves may block and limit bronchoscope insertion and performance, especially in high-risk patients with compromised cardiopulmonary function or difficult airway. Here, we introduce a simple, safe, and effective oxygenation and ventilation supporting technique that has been clinically applied, even in critical and high-risk patients, for more than three decades.

Soong's ventilation (SV), known as pharyngeal oxygen with nose–closure and abdominal–compression (PhO_2–NC–AC), is an innovative noninvasive ventilation (NIV) technique and has been shown to be effective in clinical practice.[1,2] It is specifically designed for respiratory support in the neonatal, pediatric, and even adult also useful. This method utilizes a soft catheter to

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deliver a continuous oxygen flow into the pharynx (PhO_2), then optionally and intermittently performs NC and AC to create positive pressure ventilation (PPV). Different from traditional assisted ventilation systems, SV provides dynamic pneumatic stenting of both upper and lower airway lumens, preventing lumen collapse, improving oxygenation and gas exchange, and supporting circulation without any airway or ventilation devices. In the past three decades, it has been proven particularly transformative during various FB procedures and CPR in risky patients.[3-18] It enhances healthcare professionals' competence and confidence in maintaining patients' safety during clinical practice.

Scenario Case 1

An 8-month-old female infant weighing 6 kg was transferred from an overseas medical center because of failed weaning from the ventilation settings. She had multiple cardiopulmonary anomalies, including right lung hypoplasia without blood perfusion, bilateral main bronchi narrowing, pulmonary hypertension, and scoliosis. After admission to our pediatric intensive care unit, fever and worsening respiratory status developed. The chest radiograph showed dextroposition of the heart with bilateral (right dominant) lung haziness and pneumonia. Therefore, she was tracheal intubated and supported with high ventilation settings: FiO_2 100%, peak inspiratory pressure (PIP)/positive end expiratory pressure (PEEP) 25/20 cm H_2O, rate 20/min, and inspiration time 1.2 s. Arterial blood gas analysis revealed pH 7.22, pCO_2 72 mmHg, and pO_2 57 mmHg. On the second day, because her breathing showed progressive deterioration, she was arranged to do a FB examination. After titrated intravenous sedation with midazolam 5 mg and ketamine 40 mg, both ETT and the ventilator were removed and replaced with SV support. The FB (OD: 3.0 mm) revealed right main bronchus stenosis (<2.5 mm) and severe left mainstem bronchomalacia (near total collapse). Therefore, stent insertion was recommended. After getting the parent's permission, a balloon-expandable metallic stent, 8 mm × 17 mm, was implanted over the left main bronchus. Throughout the whole FB course of 20 min, the patient's vital signs were maintained within normal limits: heart rate around 120/min, blood pressure 90/60 mm Hg, and SpO_2 > 90%. After completing the FB procedure, the patient was not intubated, and respiratory support was shifted to nasal prongs NIV. This support was gradually weaned off in 4 days, and she was discharged on the 10th day of admission. Since then, she had never received tracheal intubation again, even during the stent follow-up management with balloon dilatation of the stent and laser ablation of the granuloma in the following 5 years. Finally, the implanted stent was retrieved 6 years later.

Scenario Case 2

A 7-month-old male infant weighing 3.5 kg had a history of postsurgical correction of congenital heart disease of dextro-tranposition of the great arteries, atrial septal defect, patent ductus arteriosus, hydrocephalus with V-P shunt, and moderate encephalopathy. He was referred to our hospital because of difficulty weaning the PPV support after operations. He was receiving nasal prongs bilevel positive airway pressure (BiPAP) with settings of FiO_2 100%, rate 25/min, and PIP/PEEP 25/8 cm H_2O. The patient still showed severe dyspnea, stridor, retractions, and bradycardia (<100/min). The arterial blood gas analysis revealed pH 7.1, pCO_2 90, and pO_2 40. A FB examination was recommended to detect the airway problems. After IV sedation with midazolam 2.0 mg and ketamine 15 mg, the BiPAP was removed and replaced with SV support. FB successfully confirmed that there were multiple lesions of laryngomalacia, severe subglottic stenosis (<2.5 mm), mid-tracheal stenosis (<3 mm), and distal tracheomalacia (80% collapse). After got parent's permission, these lesions were gradually managed with therapeutic FB procedures of laser-plasty, balloon dilatation, and stent implantation during the following 3 months. Throughout the whole course of FB procedures, the patient's vital signs of heart beat, blood pressure, and SpO_2 (>90%) could all be maintained within normal limits. Finally, the patient was discharged without any respiratory support.

Both cases were in severe cardiopulmonary failure and life-threatening situations. Throughout the whole course of their various FB interventions, the only respiratory support used was the SV. The traditional respiratory support settings could not capably maintain the stability and in time proceed with both diagnostic and therapeutic FB interventions to preserve their life. Even under heavy or procedural sedation, with neuromuscular blocking agents, the SV support could keep the patient in a stable condition and further allow the device-free and unlimited FB performances in their complicated airway lumens.

Soong's Ventilation

SV requires only two basic and essential medical supplies, making it simple and readily applicable in a wide range of clinical settings.

(1) An oxygen flow, which usually comes from an oxygen tank or wall source, is delivered as a continuous, warm, and humidified flow at a rate of 0.5–1.0 L/kg/min (maximum: 15.0 L/min), even in patients weighing more than 40 kg. In an oxygen-limited setting, an airflow source can be substituted.
(2) A soft and flexible catheter acts as a nasopharyngeal catheter (NPC) to deliver oxygen flow. Usually, a bedside suction catheter is suitable. The choice of catheter size depends on the patient's body weight: 6–8 F for patients weighing less than 5 kg, 8–10 F for those weighing between 5 and 15 kg, 12 F for those weighing between 15–30 kg, and 14 F for those weighing more than 30 kg.

The insertion length of NPC is the distance measured from the one side nasal ala to the ipsilateral earlobe.

The ideal location of the NPC tip should be free in the oropharyngeal space, the best site is between the uvula and larynx. In infants, which can be touched and checked with the operator's index finger from the mouth. During insertion, care should be taken not to kink or block the catheter in a blind pouch, especially around hypertrophic adenoids or tonsillar regions in school-age children. The external portion of NPC should be firmly secured to the patient's face with adhesive tape and then connected to the oxygen flow.

There are three main components of SV: PhO_2, NC, and AC.

Soong's Ventilation Maneuver

Pharyngeal oxygen

PhO_2, the NPC delivering oxygen can fill the pharyngolaryngeal space. Continuous PhO_2 insufflation alone is similar to and better than the setting of a "high-flow nasal cannula (HFNC)." The tip of the NPC is closer to the laryngeal inlet than the nasal prongs, flushes the upper airway, and has less ventilation dead space, thereby providing inspiratory volume and a high fraction of oxygen. Physiologically, the PhO_2 itself has integrated effects of "apneic oxygenation."[19,20] Multiple randomized controlled trials have proven that only this simple PhO_2 management could significantly prolong the period of safe oxygen saturation and reduce the risk of unintended hypoxemia in patients with sedation, muscle paralysis, or even during difficult airway management.[21,22]

A comparative clinical study,[23] titled "Comparison of oxygenation among different supplemental O_2 methods [*nasal cannula, nasal prongs-CPAP & pharyngeal catheter (PhO$_2$)*] during flexible bronchoscopy in infants," conducted by our group demonstrated that the "PhO_2" method achieved the most convenient and highest SpO_2 levels while the tip of the bronchoscope was located in pharyngeal airway lumen ($P < 0.05$) and carina ($P < 0.01$). Another infant study by Frey *et al.*[24] also revealed that, in nine infants, PhO_2 at flow rates of 0.5, 1.0, and 2.0 L/min alone could generate positive pressure levels of 1.6 ± 1.4, 2.8 ± 2.7, and 4.0 ± 2.9 cm H_2O, respectively, in the pharyngeal space. Another two similar studies[25,26] have also demonstrated that an isolated PhO_2 flow of 1.0 L/kg/min (maximum: 10.0 L/min) alone, without doing NC and AC maneuvers, can create positive pressure of 4–5 cm H_2O and improve oxygenation and safety during FB in children.

Nose–closure

After the initiation of PhO_2, when the patient needs PPV support, the operator can simply perform the NC maneuver. This is performed by intermittently closing both patient's nostrils with the operator's right-hand thumb and middle finger while simultaneously blocking the mouth by hooking the patient's mandible with operator's index finger [Figure 1]. During the NC, a positive pressure oxygen will be created in this closed upper airway (pharyngolaryngeal) space. This pressurized oxygen can transmit (through the larynx inlet) to the lower airway (tracheobronchial) lumens and therefore facilitate oxygen PPV (O_2–PPV) of the lungs. Simultaneously, the operator may perform cricoid depression to block the esophageal inlet to enhance more effective lung ventilation. The duration of NC can be optionally sustained from 0 to 5 s, depending on the operator's demand. In a fixed PhO_2 flow, a tighter and longer durations of NC will create higher pressure levels in both the pharyngeal space and mid-tracheal lumen with a linear positive correlation, up to 50 cm H_2O by 5 s of NC.[25,26] This optional NC maneuver can actively create dynamic changes of positive pressure, which allows sustainable and controllable expansion of both upper and lower airway lumens, which benefits delicate, difficult, and complicated FB interventions.[4-7,13-18] The combination of PhO_2–NC may also promote O_2–PPV through a patent airway into distal bronchioles and lungs.

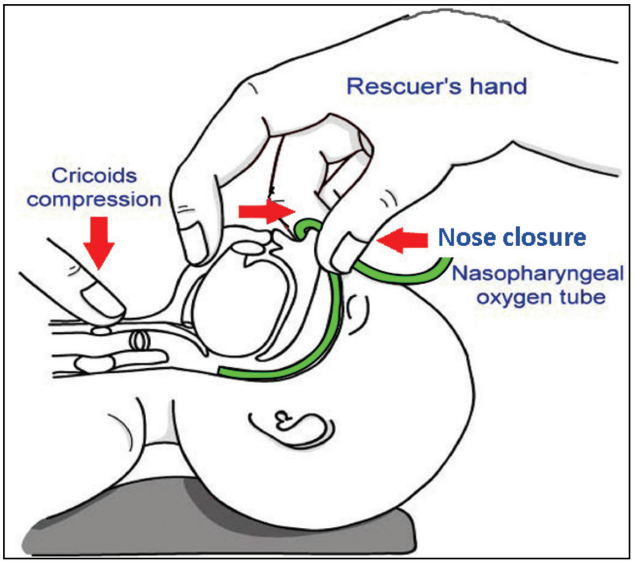

Figure 1: Soong's ventilation of one-person maneuver. Nasopharyngeal oxygen with nose–closure and optional cricoid compression

Some factors may affect the pressure levels of this NC-created PPV, such as the airway anatomical variations, flow rate of PhO_2, tightness and duration of NC, patient's clinical condition or cooperation, and blockage of the esophageal inlet. However, the PPV pressure levels are easily controllable by the operator's willingness.

Abdominal–compression

AC maneuver is used as an adjunct to improve breathing mechanics, especially in situations while patient's spontaneous ventilation or expiration is limited. It is performed with the operator's (or assistant's) fingers

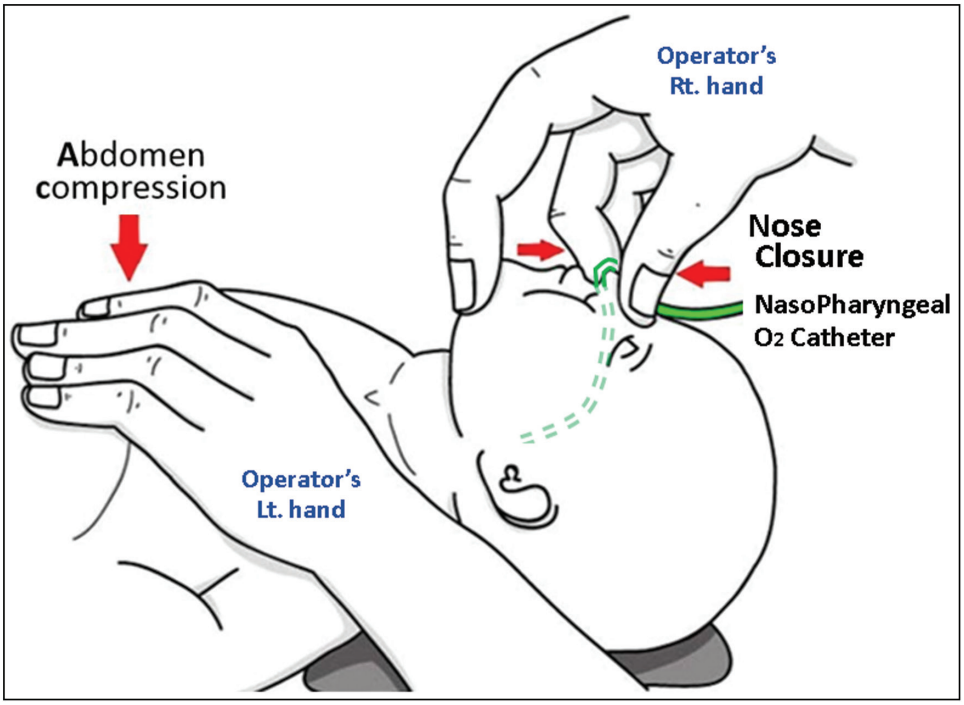

Figure 2: Soong's ventilation of one person maneuver. Three steps of nasopharyngeal oxygen with nose–closure and abdominal compression

softly pressing at the patient's umbilical region [Figure 2]. Which promotes: (1) *Active expiration*: Compressing the abdomen pushes the diaphragm upward, forces trapped gas out from the bottom of the lungs, improves expiratory flow, and removes carbon dioxide more effectively.[27] (2) *Enhances subsequent inspiration*: After release of the AC, the diaphragm passively moves downward, which creates an intrathoracic negative pressure and allows better O_2–PPV entry from the upper airway into the lungs (passive inspiration), resulting in a larger tidal volume of the following breath. (3) *Assists weak respiration*: Particularly in patients with respiratory muscle weakness, paralysis, and shallow breathing effort, it acts as a manual aid to ventilation, synchronizing with the above NC cycles. (4) *Promotes secretion clearance*: The increased gas flow during forced expiration can mobilize secretions and benefit airway clearance, like the "Heimlich maneuver." AC in SV essentially acts like a manual "expiration assist," improving both ventilation efficiency and gas exchange. (5) *Improve circulation*: Mechanistically, AC acts through an "abdominal pump" effect, promoting cardiac venous return from the splanchnic circulation, increasing subsequent cardiac output, augmenting aortic diastolic pressure, and improving coronary and systemic perfusion.[28-30]

Clinical Application of Soong's Ventilation

SV can be performed with one or two persons [Figure 3]. Small-sized patients are easier to manage with one provider. The conceptual mechanism of SV includes (1) continuous PhO_2, with (2) optional NC maneuver (0–5 s) creating intermittent PPV, and (3) optional AC facilitating bidirectional breathing flow (inspiration and expiration). This upper airway-driven O_2–PPV can effectively transmit to the lower airway lumen[26] and may achieve lung ventilation. Supplementary Table S1 shows the comparison of SV with other respiratory support systems. SV can optionally and intentionally generate high dynamic peak airway pressure (50 cm H_2O) without a sealed interface, enabling ventilation in apnea without intubation. In addition, SV, as a hybrid ventilation mode, combines features of continuous oxygen flow of HFNC,[31] baseline positive pressure of continuous positive airway pressure (CPAP), intermittent high positive inspiratory pressure of BVM, without requiring airway devices, no intubation, and no need for a mechanical ventilator.

SV extends beyond a simple oxygen delivery technique and functions as a dynamic PPV strategy. Its ability to provide O_2–PPV without requiring a sealed interface uniquely positions it for many clinical applications, as shown in Table 1, including respiratory support, RV, an alternate positive pressure source, and assistance during airway and esophageal endoscopy. SV functionality fills the gap between HFNC, CPAP, and BVM, particularly in nonintubated patients. However, in critical scenarios such as "cannot intubate, cannot oxygenate/ventilate (CICO)" situations, it should be used more cautiously and with appropriately monitored settings.

As a resuscitation technique

SV can generate effective O_2–PPV (PhO_2–NC) and enhance expiration (AC) with simple settings and easy maneuvers.

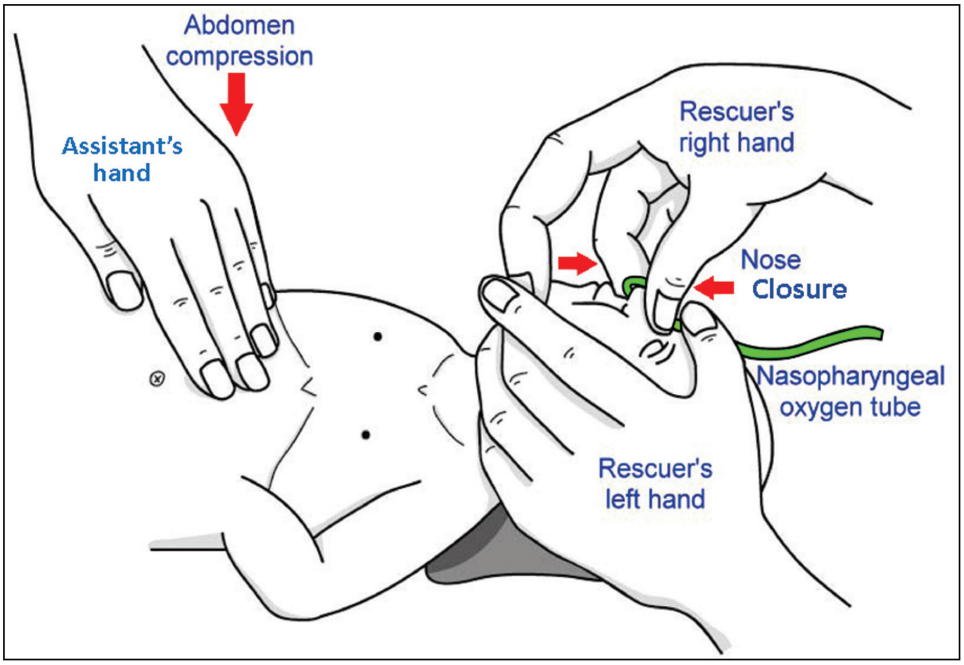

Figure 3: Soong's ventilation of two-person maneuver. Three steps of nasopharyngeal oxygen with nose–closure and abdominal–compression

Table 1: Clinical indications of using Soong's ventilation

Indications
Respiratory support
During sedation, hypoventilation, apnea
Difficult airway, OSAS
Limited respiratory devices available
Resuscitative ventilation
Difficult BVM ventilation
Airway block (partial)
Cannot intubate, cannot oxygenate/ventilate
Alternative to positive pressure devices
BVM, CPAP, HFNC, MV
Manual control ventilation
Flexible endoscopy
Airway, esophagus, stomach
Diagnostic, therapeutic

OSAS = obstructive sleep apnea syndrome, BVM = bag–valve–mask, CPAP = continuous positive airway pressure, HFNC = high-flow nasal cannula, MV= mechanical ventilation

Our animal (piglet) study[2] involved using the SV during CPR in a severe asphyxia condition and was published in 2012. All pulmonary parameters of blood gas analysis and intratracheal PEEP/PIP showed positive responses. This demonstrated that SV of "NPO_2–NC–AC is an effective CPR technique for severe acute cardiopulmonary asphyxia in piglets." In the other clinical studies,[25,26] SV is capable of creating peak airway pressures up to 50 cm H_2O in both the pharynx and mid-tracheal lumen, thereby facilitating O_2–PPV in the absence of classical CPR devices such as BVM, laryngeal mask airway, ETT, or mechanical ventilator and even in the presence of a tracheal endoscope. This is particularly beneficial in the pediatric population with hypoxia, poor ventilation, or limited medical resources. In addition, the generated pressure changes of NC and AC may contribute to a "thoraco-abdominal pump" effect, offering circulatory support. Clinical studies have validated these physiological benefits. Investigations by Sack *et al.*[27,28] included randomized trials published in Circulation and JAMA, respectively. Both demonstrated that the AC maneuver significantly improved coronary perfusion pressure, return of spontaneous circulation, and survival outcomes in patients with cardiac arrest. Similarly, Ward *et al.*[29] showed increased end-tidal CO_2 levels during AC, serving as a surrogate marker of enhanced cardiac output. Across both experimental and clinical studies,[27-30] the evidence consistently indicates that the AC maneuver can increase effective cardiac output and perfusion, particularly when used as an adjunct to standard CPR.

However, despite these benefits, SV should not be considered as a replacement for standard CPR as recommended by the American Heart Association, since AC could not reliably provide sufficient cardiac output compared with traditional chest compression. Instead, it may be regarded as an adjunctive or bridging technique for providing oxygenation, ventilation, and partial circulation during situations of apnea, "CICO," or cardiac arrest with appropriate monitoring, especially in skill-restricted or resource-limited settings.

Benefits of Flexible Bronchoscopy

SV is a simple technique that can effectively support and enhance the performance of pediatric FB in both

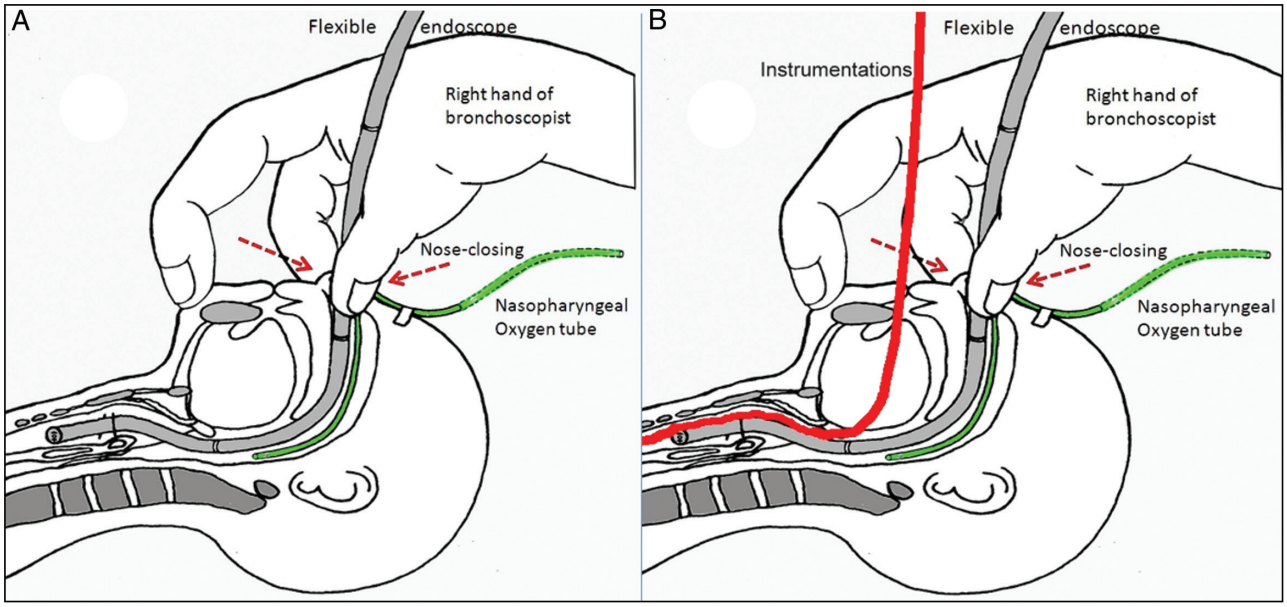

Figure 4: Flexible bronchoscopy with Soong's ventilation support: (A) simple procedure and (B) an instrument can advance parallel and coexist with the bronchoscope into the tracheobronchial lumen

diagnostic and therapeutic interventions, even in severely compromised airways or critical illness, as the above two presented cases were managed successfully and published papers.[13-19] SV can be used in conjunction with FB to improve airway patency, enable dynamic and precisely controllable expansion of airway lumens, and facilitate accurate diagnostic assessment. SV without interference from other airways or ventilation support systems thereby provides more facial space, central airway lumens, and smoother instrument manipulation [Figure 4]. In addition, SV also enables safer cardiopulmonary stability during various and complicated therapeutic interventions, such as laser ablation, balloon dilation, cryotherapy, stent implantation and repair in both upper and lower airway lumens.[4] Both the NC and the AC maneuvers can be optionally performed at a rate of 0–20 cycles/min as needed before, during, and following the FB. In the past three decades, our team has accomplished more than 12,000 FB procedures, about one-third related to therapeutic procedures in neonates, children, and even adults with this SV–FB modality. There are no age (preterm neonates to adults) or body weight (500 g to 110 kg) limitations. SV helps optimize the success of FB. Overall, SV serves as a safe, practical, and efficient adjunct that provides synergistic respiratory support while allowing synchronized coordination with both diagnostic and therapeutic FB.

Advantages of Soong's Ventilation

The continuous PhO_2 coupling with optional NC and/or AC comprises this SV skill, which can offer a synergistic, safe, and more effective O_2–PPV. For patients with compromised or high-risk airways, apnea, and respiratory failure, this NIV skill may be used as an alternative RV to maintain breathing, reduce hypoxia, be life-saving, and buy time for more advanced management.

SV offers several clinical advantages. First, it can be easily prepared. SV is simple, feasible, cost-effective, easy to perform, and valuable in resource-limited scenarios. Second, SV has less ventilation dead space compared with other devices such as facemasks or nasal prongs. Its O_2–PPV interface is near the larynx inlet. Third, FB coupling SV has more manipulation space. In SV, only a small NPC is used in the upper airway, which is less invasive, causes less distortion and visual obstruction, allows easy passage and manipulation of FB, and permits unhindered and dynamic inspection of both upper and lower airways while still capable of providing O_2–PPV. Therefore, it can yield accurate diagnosis and effective therapy[32-37] that may be incapable with other supporting systems. Finally, SV may also benefit other clinical procedures requiring patient sedation or respiratory support, as well as in adult populations.

Contraindications

Some restrictions should be considered when using SV. Among the three components of SV, NPO_2 is continuously delivered; both NC and AC can be performed optionally and independently. Table 2 lists some relative and absolute contraindications of these three components, respectively.

Severe intranasal, facial, pharyngeal, or basal skull trauma, which may result leak out of NPO_2 or pressurized

Table 2: Contraindications in application of three components of Soong's ventilation[1]

Nasopharyngeal catheter oxygen	Nose–closure[2]	Abdominal–compression[2]
Peri-nasal injury	Nasal trauma	Periumbilical trauma
Peri-mouth injury	Pharyngeal laceration, trauma	Intra-abdominal surgery or trauma (recent)[3]
Nasal tract fracture[3]	Basal skull fracture[3]	Diaphragm hernia
Nasal tract atresia, bilateral[3]	Diaphragm hernia[3]	Gastric distension
Pharyngeal laceration	Gastric distension	
Basal skull fracture[3]		

[1]Includes "nasopharyngeal catheter oxygen + nose–closure + abdominal–compression"

[2]Can optionally perform

[3]Absolute contraindications

oxygen flow into the surrounding tissue, prevents the use of NPC insertion, NPO_2, and NC maneuver. Nasal tract stenosis or unilateral atresia may still allow the insertion of a nasal PhO_2 catheter. In bilateral nasal atresia, the PhO_2 catheter may be inserted from the mouth. Recent severe periumbilical or intra-abdominal surgery may not allow doing the "AC," but may be acceptable in doing the "PhO_2 and NC." In patients with diaphragmatic hernia are not appropriately using NC, the O_2–PPV gas flow may inflate the stomach, increase intra-abdominal pressure, and limit lung ventilation. Gastric gas, fluid, or food should be frequently suctioned out to prevent distension and aspiration risk before and during the SV.

Cautions and limitations

Some cautions and limitations in using SV should be considered. As the majority of cited references originate from a single research group and lack independent external studies, the possibility of bias should be considered, which may limit the generalizability of the SV. Although SV can create PPV in both pharyngeal and tracheal lumens, it may not demonstrate and result in effective and adequate minute ventilation. However, this SV may serve as adjunctive O_2–PPV and partial circulatory support; rather than replacing standard CPR modalities, and it should be closely monitored. In the SV, the tip of the NPC should be free, not embedded, in the pharyngeal space. The NPC should not be deeply inserted into the esophagus; otherwise, oxygen flow may inflate the esophagus and stomach instead of the trachea and lungs. SV is a highly operator-dependent skill, and the presence of PPV inconsistency remains a weakness, which cannot be precisely measured as it is with ETT and mechanical ventilation. Limited standardization of SV maneuvers exists in current practice. Proficiency in performing these maneuvers might vary among operators. Appropriate training programs and increased practical experience are necessary to improve operators' skills in using SV and coupling it with FB before widespread application.

Conclusion

SV is a simple, safe, and effective NIV technique that can provide airway patency, maintain oxygenation, facilitate ventilation, and partially support circulation. Particularly, it may be useful in patients doing FB under sedation, with muscle paralysis, apnea, and difficult airway scenarios. It may serve as a versatile technique capable of generating significant positive airway pressures, O_2–PPV, and enabling bidirectional ventilation flow, thereby supporting both diagnostic and therapeutic airway interventions and acting as a potential RV.

Author contribution

WJS: originator and developer of SV, manuscript preparation, manuscript editing, and writing.

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Conflicts of interest

There are no conflicts of interest.

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Supplementary Table S1: Comparison of Soong's ventilation with other respiratory support systems

Parameter	Soong's Ventilation (SV)	High—Flow Nasal Cannula (HFNC)	Continuous Positive Airway Pressure (CPAP)	Bag—Valve—Mask (BVM)	ETT[1] + Mechanical Ventilation (MV)
Interface site	Pharynx	Intra-nose	Face/ intra-nose	Face	Intra-trachea
Airway Invasiveness	Minimal	✕	✕	✕	✓
Create Positive Pressure (max.)	Operator-controlled (~50 cmH_2O)	Continuous,~5 cmH_2O	Continuous, ~8 cmH_2O	Operator-controlled	Machine-set
Ventilation Capability	✓, both in/out	✕ Limited	✕ Limited	✓; active in, passive out	✓; active in, passive out
Apneic Support	✓	✕	✕	✓	✓
Use During Bronchoscopy	✓, Ideal	✓, Adjunct	✕, Difficult	✕, Difficult	✕, limited
Complicated Setup	Very low	Moderate	Moderate	Low	High
Devices Required	Flow source + catheter	HFNC system	CPAP system	BVM devices	ETT + MV system
Gastric Insufflation	Low–Moderate	Low	Moderate	High	Low
Operator Dependency	High (manual)	Low	Low	High	Low
Barotrauma risk	Low	Low	Low	Moderate	High
Use in Resource-Limited Settings	✓, Ideal	✕	✕	Moderate	✕
Indications	Apnea, bronchoscopy, CICO,[2] resuscitation	O_2 + Low pressure support	O_2 + Low pressure support	Short-term resp. support	Long-term resp. support

[1]endotracheal tube, [2]cannot intubate, cannot oxygenate/ventilate

Review Article

Small Airway Dysfunction and Ventilation Inhomogeneity in Pediatric Bronchiectasis: Toward Earlier Physiological Detection

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Abstract

Pediatric bronchiectasis unrelated to cystic fibrosis is increasingly being recognized as a potentially preventable and, in some children, radiographically reversible chronic airway disease, particularly when identified and treated early in its course. Traditionally, the diagnosis has been made using high-resolution computed tomography (HRCT) to demonstrate bronchial dilatation. Nonetheless, emerging evidence suggests that mucus hyperconcentration, neutrophilic inflammation, ventilation inhomogeneity, and small airway dysfunction may occur prior to established structural damage. These observations support the potential value of combining anatomical assessment with physiological evaluation of small airway dysfunction. Emerging evidence suggests that impaired mucociliary clearance, airway surface dehydration, mucus retention, and muco-inflammatory injury may contribute to the pathogenesis and progression of pediatric bronchiectasis. In this context, oscillometry and the Lung Clearance Index (LCI) may provide sensitive evaluations of small airway dysfunction, often undetected by classical spirometry. LCI evaluates the ventilation inhomogeneity due to airway obstruction and mucus plugging, while oscillometry evaluates the respiratory impedance and small airway mechanics during tidal breathing. It is important to note that changes in these physiological indices may be detectable even in children with normal spirometric parameters and relatively mild HRCT abnormalities, suggesting that functional impairment may precede or occur in the absence of established irreversible structural remodeling, though this temporal relationship has not yet been confirmed through large prospective longitudinal studies. This narrative review examines the evolving role of small airway physiology, ventilation inhomogeneity, and oscillometry in the early identification and ongoing assessment of pediatric bronchiectasis.

Keywords: Bronchiectasis, LCI, oscillometry, pediatric, small airways

Introduction

Pediatric bronchiectasis unrelated to cystic fibrosis (CF) (hereafter referred to as "pediatric bronchiectasis") is a chronic suppurative lung disease marked by enduring endobronchial infection, compromised mucociliary clearance, neutrophilic inflammation, and progressive airway destruction, evidenced by an abnormal broncho-arterial ratio greater than 0.8 on a high-resolution computed tomography (HRCT) scan.[1] Pediatric bronchiectasis, often considered an irreversible chronic airway disease, is now increasingly being recognized as a condition where early diagnosis and proactive care can significantly improve long-term respiratory outcomes.[2-4]

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The classical "vicious cycle" hypothesis describes a self-perpetuating sequence in which impaired mucociliary clearance leads to chronic bacterial colonization, which in turn causes neutrophilic inflammation and airway

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damage, further impairing mucus clearance and causing structural airway injury. More recently, this linear model has been complemented by the concept of the "vicious vortex," which is fundamentally different in stressing the importance of multidirectional and individualized interactions between the multiple simultaneous drivers of disease (mucus dysfunction, chronic infection, neutrophilic inflammation, airway remodeling, host-defense impairment, microbial colonization, exacerbation susceptibility, and immune dysregulation). In contrast to the linear vicious cycle, the vicious vortex model recognizes the simultaneous interaction of these elements rather than their sequential interaction and hence favors personalized evaluation and therapeutic strategies.[1,5,6] Importantly, recent studies suggest that these pathogenic processes may commence in small airways long before irreversible bronchial dilatation is apparent on the HRCT scan. Within this model, distal airway mucus plugging, ventilation inhomogeneity, and airway wall inflammation may represent early manifestations of disease activity and progression.[7,8]

Standard spirometry may underestimate small airway involvement, particularly in early disease, when forced expiratory indices may remain within normal reference limits.[7-10] As a result, there has been a growing emphasis on sensitive physiological instruments that can identify early small airway dysfunction prior to the onset of significant structural remodeling. The Lung Clearance Index (LCI), obtained using multiple-breath washout (MBW), and oscillometry techniques such as the forced oscillation technique (FOT) have emerged as potential noninvasive methods for assessing small airway physiology in pediatric bronchiectasis.[11]

This narrative review proposes a conceptual framework based on the emerging evidence linking small airway dysfunction, ventilation inhomogeneity, mucus hyperconcentration, and early structural airway changes in pediatric bronchiectasis. It is not intended to provide validated diagnostic or management pathways. Rather, it aims to offer a hypothetical framework that, if prospectively validated, could facilitate earlier detection and management of bronchiectasis and help define priorities for future clinical research.

Small-Airway-First Hypothesis in Pediatric Bronchiectasis

Small airways are defined as non-cartilaginous airways having an internal diameter of less than 2 mm (terminal and respiratory bronchioles, alveolar ducts).[11] Notably, small airways have traditionally been referred to as the "silent zone" due to the potential of significant pathological abnormalities arising prior to any alterations in conventional spirometry results.[12,13]

Small airways are especially susceptible to inflammatory and muco-obstructive damage due to many morphological and physiological characteristics. Their narrow airway diameter, lack of cartilaginous support, limited collateral ventilation, and increased vulnerability to airway closure contribute to the development of localized airflow obstruction and ventilation inhomogeneity. Furthermore, small airways are particularly vulnerable to changes in airway surface hydration and mucus transport.[14,15]

New mechanistic models suggest that pediatric bronchiectasis may originate in small airways because of progressive mucus dehydration, impaired mucociliary clearance, and the accumulation of inflammatory secretions. Small airway obstruction by mucus and ventilation inhomogeneity may be present prior to irreversible bronchial dilatation and established bronchiectatic remodeling.[7,16]

This hypothesis is supported by studies showing significant physiological derangements in children with mild HRCT changes. Oscillometric indices and LCI are both able to detect ongoing changes in lung physiology prior to the emergence of spirometric impairment, indicating that dysfunction of small airways might be an early stage in disease progression.[17,18]

Hyperconcentrated Mucus and Muco-Inflammatory Dysfunction

Hyperconcentrated mucus has emerged as a primary pathophysiological mechanism in chronic suppurative airway disorders. The concentration of mucus indicates the equilibrium between mucin secretion and the hydration of the airway surface. Loss of airway surface liquid results in a higher concentration of mucus solids and the formation of very viscous secretions that are poorly transported.[16,19]

Several mechanisms can lead to mucus hyperconcentration, including increased epithelial sodium absorption, decreased chloride and bicarbonate secretion, increased mucin production, ciliary dysfunction, and protease-mediated epithelial injury. These anomalies lead to the collapse of the periciliary layer, impaired ciliary motion, and progressive mucus accumulation in the distal airways.[20,21]

Neutrophilic inflammation seems to play a particularly important role in this process. Neutrophil elastase, a key neutrophil-derived serine protease, not only serves as a biomarker of airway inflammation but also directly contributes to epithelial injury, excessive mucus production, and impairment of mucociliary transport. Persistent activity of neutrophil elastase and other proteases may further worsen airway surface dehydration and mucus obstruction, forming a self-sustaining muco-inflammatory feedback loop.[7,22]

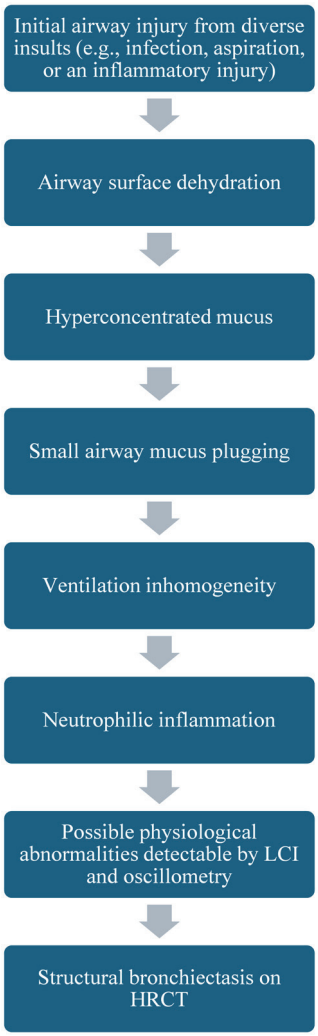

Figure 1: Proposed small-airway-first model of pediatric bronchiectasis progression. The proposed model illustrates a hypothetical progression from an initial airway injury and mucus dehydration to small airway plugging, ventilation inhomogeneity, neutrophilic inflammation, physiological abnormalities detectable by LCI and oscillometry, and eventual structural bronchiectatic remodeling visible on HRCT. The sequence is conceptual and requires prospective validation in pediatric bronchiectasis. LCI = Lung Clearance Index, HRCT = high-resolution computed tomography

This mechanistic paradigm also provides a scientific explanation for the appearance of physiological abnormalities before the onset of permanent anatomical change. Small airway mucus obstruction and ventilation inhomogeneity may therefore represent early detectable manifestations of disease activity, although their temporal relationship with subsequent structural remodeling remains to be established [Figure 1].

Contemporary Diagnostic Work-Up in Pediatric Bronchiectasis

A thorough diagnostic evaluation is crucial in pediatric bronchiectasis, as it can identify underlying etiologies in a significant number of cases. Current international guidelines recommend systematic investigation for inborn errors of immunity (including primary immunodeficiency), CF, primary ciliary dyskinesia (PCD), aspiration syndromes, and other causes of chronic suppurative airway disease.[1]

Diagnostic assessment typically includes quantitative immunoglobulins, functional antibody responses, sweat chloride testing, microbiological evaluation, and screening for PCD using nasal nitric oxide, ciliary beating analysis, and genetics when indicated. Bronchoalveolar lavage may additionally provide information regarding airway microbiology and inflammatory activity.[23]

Importantly, modern diagnostic algorithms increasingly aim not only to establish etiology but also to characterize disease activity, physiological impairment, and risk of progression. In this context, physiological assessment of small airway dysfunction has become increasingly relevant.[24]

Lung Clearance Index and Ventilation Inhomogeneity

MBW testing and LCI provide highly sensitive assessment of ventilation distribution and small airway function. LCI is the number of lung turnovers needed to wash out an inert tracer gas from the lungs during tidal breathing. High values reflect an inhomogeneous distribution of ventilation due to airflow obstruction, mucus plugging, and air trapping.[25,26]

Ventilation inhomogeneity is increasingly being appreciated as a hallmark of early small airway disease. Peripheral mucus plugging, airway wall thickening, and inflammatory narrowing produce abnormalities in gas mixing long before spirometric impairment becomes detectable.[27]

Several studies suggest that LCI may be more sensitive than spirometry for detecting early lung disease in children with chronic suppurative airway disorders. A pilot study by Alkoussa *et al.*[28] reported abnormal LCI values in children with pediatric bronchiectasis despite normal forced expiratory volume in 1 s, suggesting that LCI may detect physiological abnormalities not identified by conventional spirometry.

In PCD, studies have demonstrated strong correlations between increased LCI and structural abnormalities on HRCT, further supporting the importance of ventilation inhomogeneity as an early marker of progressive airway disease.[29] These results suggest that LCI may be a marker of small airway dysfunction at an early stage and may help identify children needing closer longitudinal assessment. It must be recognized that there is limited direct longitudinal evidence that abnormal LCI predicts or leads to subsequent irreversible bronchiectatic remodeling in

pediatric bronchiectasis, and these associations must be interpreted with appropriate caution.

Despite its increasing clinical significance, LCI has important limitations that currently preclude its widespread application in pediatric bronchiectasis. A significant difficulty is the absence of comprehensive international standards in MBW systems, tracer gases, software algorithms, and washout methods. There is considerable diversity across commercially available MBW systems employing sulfur hexafluoride (SF_6) or nitrogen washout techniques, and measurements from different systems are not always readily interchangeable. As a result, establishing widely agreed diagnostic thresholds and longitudinal cutoff values is challenging across many centers and studies.[30,31] Moreover, because pediatric bronchiectasis may be localized to a single lobe, LCI may remain within the normal range, whereas it is more likely to be abnormal in diseases characterized by diffuse airway involvement, such as CF or PCD.

Age, respiratory patterns, sedation level, device dead space, and fundamental ventilation dynamics, especially in younger children, may affect the interpretation of LCI results. Even though LCI is highly sensitive for detecting ventilation inhomogeneity, its specificity for bronchiectasis progression is less well established, as abnormal values may also occur in asthma, bronchiolitis obliterans, and other small airway disorders.[32]

Another important limitation concerns the definition of the upper limit of normal (ULN) for LCI. The reported ULN values vary widely across studies, owing to differences in equipment, tracer gas methodologies, population demographics, and reference equations. In pediatric populations, an LCI value of ~7.0–7.5 is often considered the ULN for nitrogen washout systems; however, this cutoff is not universally applicable to all MBW platforms.[31,33] Therefore, the interpretation of borderline variations should be made with caution, particularly for comparisons of data across institutions or longitudinal studies using different instruments or software versions.

Additionally, MBW testing is still relatively time-consuming, technically challenging, and less widely available than spirometry. The quality of measurement is significantly contingent upon the operator and necessitates considerable patient cooperation, meticulous leak prevention, and rigorous quality-control protocols. These technical requirements may constrain feasibility in younger children and diminish reproducibility in standard clinical practice.[34,35]

Nevertheless, despite these limitations, LCI remains one of the most sensitive currently available physiological markers of small airway dysfunction and ventilation inhomogeneity. When interpreted longitudinally within the same patient and using consistent methodology, LCI may provide clinically valuable information regarding early small airway pathology and disease progression in pediatric suppurative lung disorders.

Oscillometry and Small Airway Mechanics

Oscillometry, including the FOT, provides effort-independent assessment of respiratory impedance during tidal breathing. Unlike spirometry, oscillometry is particularly sensitive to abnormalities involving small airways and therefore represents an attractive tool for pediatric respiratory assessment.[36]

Oscillometric parameters reflect both airway resistance and the elastic properties of the respiratory system. Increased frequency dependence of resistance ($R_{5–20}$) indicates inhomogeneous airflow obstruction involving small airways, whereas abnormalities in reactance parameters, particularly X_5 and the Area of Reactance (AX), reflect impaired small airway compliance, airway closure, and ventilation inhomogeneity.[37,38] Therefore, in the absence of advanced structural destruction, the pre-bronchiectatic lung may have increased small airway resistance and abnormal reactance.

Current data highlight the increasing role of oscillometry in pediatric bronchiectasis and suggest that oscillometric abnormalities are associated with early HRCT findings such as bronchial wall thickening and small airway involvement. It should be noted that oscillometric abnormalities are not specific for bronchiectasis and can be observed in other diseases of small airways such as asthma and bronchiolitis obliterans.[39,40] Importantly, increased AX is associated with distal mucus plugging, airway narrowing, and inflammatory infiltration, which may reflect the mechanical consequences of these processes on small airway compliance. Oscillometry assesses respiratory mechanics during tidal breathing and thus may detect subtle peripheral abnormalities that forced expiratory maneuvers may miss.[41]

A major limitation of oscillometry in clinical practice and research is the lack of global consensus about international standards for instruments, reference equations, signal processing methods, and measurement techniques. Despite oscillometry's high sensitivity for detecting peripheral airway dysfunction, there remains substantial inter-device variability between commercially available systems, with differences in oscillation frequencies, waveform generation, calibration methods, impedance filtering algorithms, and output interpretation. As a result, absolute values derived from various devices may not be directly interchangeable, hindering the generation of widely accepted cutoff values for the severity of pediatric bronchiectasis and for longitudinal surveillance. Moreover, existing reference equations differ based on demographic characteristics, ethnicity, age distribution, and device-specific techniques,

hence confounding cross-study comparisons and broader clinical use. Technical issues such as upper airway shunting, cheek support, respiratory abnormalities, and respiratory rate variability can also influence repeatability of measurements, especially in younger children. In spite of the impressive achievements in methodological harmonization, set by the recent international technical standards issued by the European Respiratory Society, oscillometry has not yet achieved comparable levels of international standardization and clinical acceptance as spirometry. Nonetheless, despite these constraints, oscillometry continues to be one of the most promising methods for the noninvasive evaluation of small airway physiology in pediatric respiratory conditions, especially when analyzed longitudinally within the same patient and utilizing device-specific reference standards.[42-44]

Functional–Structural Mismatch: Physiology Before Anatomy

An important emerging concept in pediatric bronchiectasis is the presence of a functional–structural mismatch. Children with relatively mild HRCT abnormalities may show significant physiological impairment on LCI or oscillometry, while structural imaging alone may fail to accurately assess active small airway pathology.[32]

This apparent discordance should not be regarded as inconsistency; rather, it may suggest that physiological dysfunction can occur before, or in the absence of, established irreversible anatomical remodeling. Ventilation inhomogeneity, small airway obstruction, mucus plugging, and airway closure may represent early signs of disease activity or progression before the radiological appearance of significant bronchial dilatation.[32,45]

These data underscore the necessity of including sensitive physiological instruments into longitudinal disease surveillance and endorse the notion of a "pre-bronchiectatic" phase primarily defined by functional rather than structural anomalies. For the purpose of this review, the proposed pre-bronchiectatic phase refers to a conceptual clinical state characterized by persistent respiratory symptoms, such as a chronic wet cough, or recurrent bouts of protracted bacterial bronchitis, normal or near-normal spirometry, abnormal LCI and/or oscillometry results, and absent or mild HRCT abnormalities not fulfilling the established radiological criteria for the diagnosis of bronchiectasis. This framework is provisional and requires further validation.

Hyperconcentrated Mucus as a Treatable Trait

The concept of "treatable traits" has become increasingly important in precision respiratory medicine. This method focuses on specific biochemical and physiologic derangements that cause disease progression, rather than relying solely on diagnostic labels.[46,47]

Hyperconcentrated mucus may represent a potentially relevant treatable trait in pediatric bronchiectasis, linking dehydration of airway surface liquid to impaired mucociliary clearance, chronic infection, and neutrophilic inflammation. Therapeutic strategies aimed at increasing airway hydration, improving mucus clearance, reducing protease-mediated injury to the airway, controlling chronic bacterial infections, and preventing distal mucus plugging may potentially modify the muco-inflammatory cascade, although their ability to prevent irreversible airway remodeling has not yet been established.[4,48]

In this setting, LCI and oscillometry may function as objective physiological indicators for assessing treatment response and disease progression. They are especially helpful for longitudinal monitoring and individualized therapeutic assessment because of the detection of subtle small airway abnormalities.

Prognostic Implications and Longitudinal Monitoring

Persistent abnormalities in LCI and oscillometric parameters such as AX, X_5, and $R_{5–20}$ are associated with structural lung disease, ventilation inhomogeneity, and disease severity in pediatric suppurative airway diseases and are indicative of ongoing small airway dysfunction.[18]

These physiological abnormalities may more accurately indicate small airway dysfunction and ventilation inhomogeneity than spirometry alone. The longitudinal integration of physiological testing with imaging and clinical evaluation may thus enable earlier identification of illness development and more tailored therapeutic approaches.[17,25]

Complementary Roles of LCI and Oscillometry and a Proposed Physiology-Driven Framework

Both LCI and oscillometry provide valuable information on small airway function but, although methodologically different, are clinically complementary rather than interchangeable. LCI reflects a global inhomogeneity of ventilation (overall inhomogeneous distribution of airflow across all lung regions) and is therefore especially sensitive to diffuse airway disease, mucus plugging, and air trapping.[25,26] In contrast, oscillometry allows for immediate breath-by-breath measurement of small airway resistance ($R_{5–20}$, frequency dependence) and peripheral airway compliance (X_5, AX), reflecting the mechanical consequences of mucus obstruction and airway occlusion during tidal breathing.[36-38] When used alone, each modality measures different

pathophysiological aspects, but when used together, they may provide a more comprehensive physiological characterization of early airway disease than either assessment alone.

A conceptual assessment framework incorporating LCI as a measure of global ventilation inhomogeneity and oscillometry as an assessment of small airway mechanics might provide the basis for future evaluation of children with, or at risk of, bronchiectasis. Children with higher LCI and increased AX or frequency-dependent resistance ($R_{5–20}$) may be a subgroup with more severe distal airway dysfunction who may warrant closer clinical assessment and longitudinal monitoring.[18] Further validation in well-defined pediatric groups is needed to determine if this combined physiological profile can function as a clinically useful early screening tool. Given the current limitations of device variability and the lack of universal diagnostic standards, the definition of strict absolute cutoffs for clinical application would be premature.[30,31,42-44] However, clinically relevant and physiology-based clinical decision pathways, tailored to individual patient trajectories, may be feasible.

In practice, the following physiology-based indicators may be considered when managing children with or at risk of bronchiectasis:

i. Progressive decline in LCI:

A reproducible increase in LCI over successive assessments, interpreted relative to the patient's baseline, may prompt clinical reassessment of symptoms, adherence to airway clearance therapy, airway microbiology, and the possible need for further investigation.[31]

Table 1: Comparison of physiological and structural assessment modalities in pediatric bronchiectasis

Feature	Spirometry	LCI/MBW	Oscillometry (FOT/IOS)	HRCT
Domain assessed	Global expiratory airway flow and airway obstruction (FEV_1, FVC, FEV_1/FVC)	Ventilation inhomogeneity	Respiratory impedance, small airway resistance and compliance	Airway structure
Sensitivity to small airway disease	Low (limited sensitivity to early small airway dysfunction)	High (may detect abnormality before spirometry changes)	High (sensitive to small airway resistance and reactance changes)	Moderate (early structural changes may be subtle or absent)
Specificity for bronchiectasis	Not disease-specific	Not disease-specific (abnormal values occur in asthma, BO, CF, PCD)	Not disease-specific (reflects any small airway pathology)	Specific (provides direct structural evidence of bronchial dilatation but needs interpretation within the appropriate clinical context)
Effort dependence	Requires maximal forced expiratory maneuvers	Effort-independent, requires only tidal breathing	Effort-independent, requires only tidal breathing	None
Feasibility in young children (<6 years)	Limited feasibility, achievable in some preschool children with appropriate coaching	Feasible from ~3 years with training	Feasible from ~3 years	Feasible but radiation exposure is a concern
Patient cooperation	High, requires understanding and reproducible maximal effort	Needs tidal breathing for 3–5 min	Needs tidal breathing with cheek support	Requires still positioning, may need sedation in infants
Equipment availability*	Widely available in most centers	Less widely available	Increasingly available but not yet universal and often restricted to specialized centers	Widely available: restricted availability in low-resource settings
Technical standardization	Well standardized (ATS/ERS)	Lack of global standardization, inter-device variability	Inter-device variability, ERS standards published in 2020	Requires radiological expertise
Role in longitudinal monitoring	Limited sensitivity for tracking early small airway changes	May detect subclinical small airway changes longitudinally	May detect subclinical small airway changes longitudinally	Useful when clinically indicated, but unsuitable for frequent monitoring because of cumulative radiation exposure
Clinical applications in bronchiectasis	Baseline assessment, monitoring gross obstruction, treatment response	Early detection of ventilation inhomogeneity, monitoring disease progression, treatment response when spirometry is normal	Assessment of small airway mechanics, complementary to LCI when spirometry is normal or borderline	Diagnosis confirmation, etiology assessment, severity staging, structural progression

LCI = Lung Clearance Index, MBW = multiple-breath washout, HRCT = high-resolution computed tomography, FEV_1 = forced expiratory volume in 1 s, BO = bronchiolitis obliterans, CF = cystic fibrosis, PCD = primary ciliary dyskinesia, ATS = American Thoracic Society, ERS = European Respiratory Society, FOT = forced oscillation technique, IOS = impulse oscillometry, FVC = forced vital capacity

ii. Deterioration in oscillometric parameters:

Increases in AX and $R_{5–20}$ or a fall in X_5 from a patient's baseline may reflect the development or worsening of small airway dysfunction.[18,37,38] In such cases, clinicians may consider reassessing symptoms, treatment adherence, airway clearance technique, microbiology, and the need for additional physiological or imaging evaluation. These changes should not, in isolation, be regarded as validated indications for initiating a new treatment, such as hypertonic saline or prolonged antibiotics.

iii. Discrepancy between spirometry and physiological parameters:

Clinicians should not be falsely reassured that "spirometry is stable" if LCI or oscillometric parameters are deteriorating.[32,45] Such discrepancy may suggest progression of small airway dysfunction, which may warrant clinical assessment, microbiological reassessment, and possibly imaging evaluation.

These proposed pathways reflect the authors' interpretation of the currently available evidence and their clinical experience. They are hypothesis-generating and should not be adopted as clinical management algorithms without validation in large-scale, well-designed prospective studies.

Table 1 summarizes a comprehensive comparison of spirometry, LCI/MBW, oscillometry, and HRCT in different domains.

Clinical Application of Lung Clearance Index and Oscillometry

LCI and oscillometry, besides their value as research tools, have several potential roles in the clinical management of children with bronchiectasis or at risk of developing it.[41] These modalities may be considered for the following clinical contexts:

i. Baseline physiological assessment:

LCI and oscillometry may be considered as complementary assessments at the time of diagnosis to characterize small airway physiological impairment that may not be detected by spirometry.[7-10]

ii. Serial monitoring of disease progression:

Serial LCI or oscillometric assessments, using consistent methodologies and the same equipment, may detect longitudinal changes in ventilation inhomogeneity or small airway function before clinical deterioration or spirometry changes are evident.[17,25,31]

iii. Assessment of treatment response:

Changes in LCI or oscillometric parameters following interventions such as airway clearance therapy, inhaled antibiotics, or mucoactive agents may indicate physiological improvement in small airways even in the presence of stable spirometry.[4,48]

iv. Assessment of children with chronic respiratory symptoms and normal spirometry:

Children with persistent symptoms but normal spirometry may have abnormalities in LCI or oscillometry, suggesting involvement of small airways, which may support further clinical assessment while recognizing that these abnormalities are not specific to bronchiectasis.[7-10,32]

v. Complementary assessment in case of mild or inconclusive imaging findings:

In cases where HRCT findings are equivocal or do not fulfill the diagnostic criteria for bronchiectasis, physiological indices such as ventilation inhomogeneity or increased small airway resistance may provide supplementary physiological information but should not be used to establish or exclude the diagnosis of bronchiectasis in the absence of appropriate clinical and radiological assessment.[32,45]

Conclusion

The diagnostic and pathophysiological understanding of pediatric bronchiectasis continues to evolve. Emerging evidence supports an association between small airway dysfunction, ventilation inhomogeneity, mucus hyperconcentration, neutrophilic inflammation, and early disease manifestations; however, their temporal and causal relationships with subsequent structural progression remain incompletely defined and require prospective longitudinal validation.

The complementary use of LCI and oscillometry may improve the physiological characterization of early or clinically inconspicuous small airway dysfunction. These physiological tools are associated with the identification of small airway impairment that may precede the permanent bronchiectatic changes observable on HRCT, though prospective longitudinal data in pediatric bronchiectasis remain limited. Their complementary nature supports further investigation of their combined use for early physiological assessment and longitudinal monitoring of children with, or at risk of, bronchiectasis.

This emerging framework may contribute to a more individualized approach to pediatric bronchiectasis by encouraging the evaluation of physiological abnormalities alongside clinical and structural findings. Prospective longitudinal studies are required to determine whether such an approach can reliably identify a therapeutically relevant window before irreversible structural lung damage develops.

Author contributions

GC contributed to the conceptualization, literature review, data interpretation, writing, review, and editing and AC to

the revision of the manuscript, writing, and final approval of the submitted version.

Ethical policy and Institutional Review Board statement

Ethical approval was not required for this narrative review.

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Conflicts of interest

There are no conflicts of interest.

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Case Report

Pulmonary Paragonimiasis: A Case Report of a Rare Cause of Pleural Effusion in Children

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Abstract

Paragonimiasis is a parasitic infection caused by the genus *Paragonimus.* It is a food-borne parasite that is isolated in the freshwater snails, crabs, and crayfish, as they are the hosts for the spread to humans who consume uncooked/raw or undercooked crustaceans. Pulmonary paragonimiasis mimics pulmonary tuberculosis. We report a case of a 5-year-old boy, resident of the northeastern state, who initially presented with persistent cough, hemoptysis, chest pain, and pleural effusion. Epidemiological features, along with history, examination, and investigations, particularly radiological imaging, led to the diagnosis of pulmonary paragonimiasis. Parasitic lung infections are rare in the pediatric population, especially in northern India, but should be considered as a differential diagnosis in cases from Northeast India presenting with persistent cough and pleural effusion.

Keywords: Hemoptysis, lung fluke, parasitic lung infection, pleural effusion, pulmonary paragonimiasis

Introduction

Pulmonary paragonimiasis is caused by lung flukes of the genus *Paragonimus*. The causative agent in most of the cases is *Paragonimus westermani*. Most of the reported cases of pulmonary paragonimiasis are from Southeast Asia, but it is also reported from Central Africa and South America.[1] In India, endemic foci are seen in the northeastern states, where *Paragonimus heterotremus* is the most common cause of paragonimiasis.[2-4] Freshwater crab or crayfish are the intermediate hosts, which may infect an individual if raw or undercooked food is consumed. Here, we present a case of pleural effusion due to a rare cause of parasitic infection.

Case Report

A 5-year-old boy, resident of Aizawl, Mizoram, presented in the pediatric pulmonology clinic of Sir Ganga Ram Hospital, New Delhi, with the chief complaint of cough for 6 months. The cough was wet, nonspasmodic, with no diurnal or postural variation. Sputum was whitish in color, and there were three episodes of blood streaking of sputum. There was associated chest pain on the right side. There was no history of prolonged fever, weight loss, or Koch's contact. The child had no other comorbidities. He received antibiotics and nebulization before arriving at our hospital. At presentation, he was thin-built with a weight of 13.4 kg (<5th centile for age), height of 102 cm (between 3rd and 50th centile for age), and weight-for-height was between 3rd and 50th centile for age. On systemic examination, the thorax was symmetrical with equal movement bilaterally. The percussion note was stony dull on the right side in mammary, infra-mammary, and infrascapular areas, and air entry was also decreased in the same regions with no adventitious sounds. Investigations revealed hemoglobin of 12.5 g/dL, total leucocyte count 16,300/mm^3 with neutrophils 17%, lymphocytes 24%, eosinophils 55%, and monocytes 4%,

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whereas platelets were adequate (5.26 lakhs/mm^3). Total serum immunoglobulin (Ig) E was high at 738.65 IU/mL (lab reference value for age group 4–6 years: <60 IU/mL). Chest radiograph postero-anterior view in erect posture showed some infiltrates on the right side with right-sided pleural effusion [Figure 1a]. Contrast-enhanced computerized tomography of the chest was suggestive of curvilinear band-like opacities in the anterior segment of the right upper lobe at the pleuro-pulmonary interface associated with adjacent ground-glassing, and similar tubular cystic channels were also seen at the pleuro-pulmonary interface in the left upper lobe, involving the apico-posterior and the anterior segments with subtle thickening of the adjacent sub-segmental bronchi. There were prominent vascular channels with focal sub-pleural linear opacities. These channels likely represented tunnels/burrows of parasitic infestation. The computed tomography (CT) also revealed bilateral effusion (right >

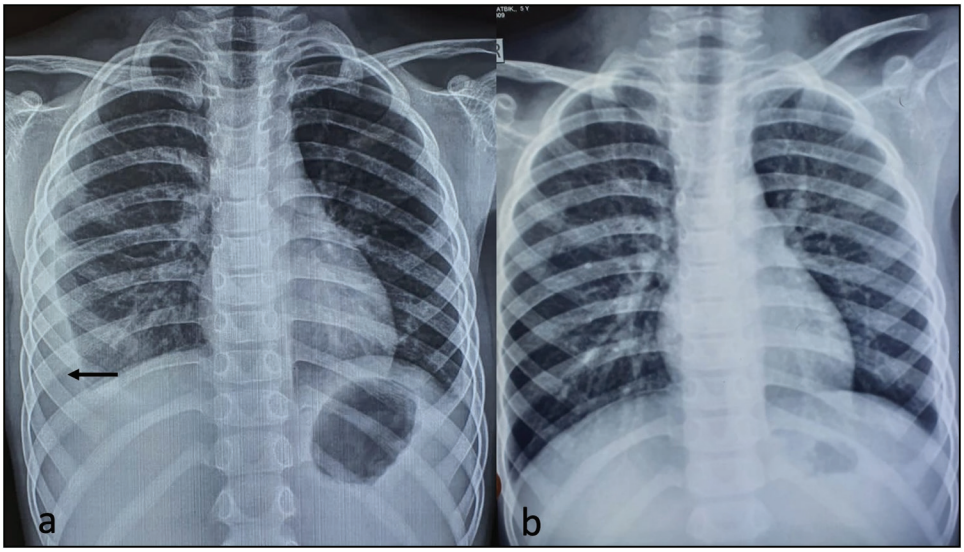

Figure 1: (a) Chest radiograph shows mild right pleural effusion obliterating the right costophrenic angle (arrow), and (b) completely resolved in follow-up radiograph after treatment

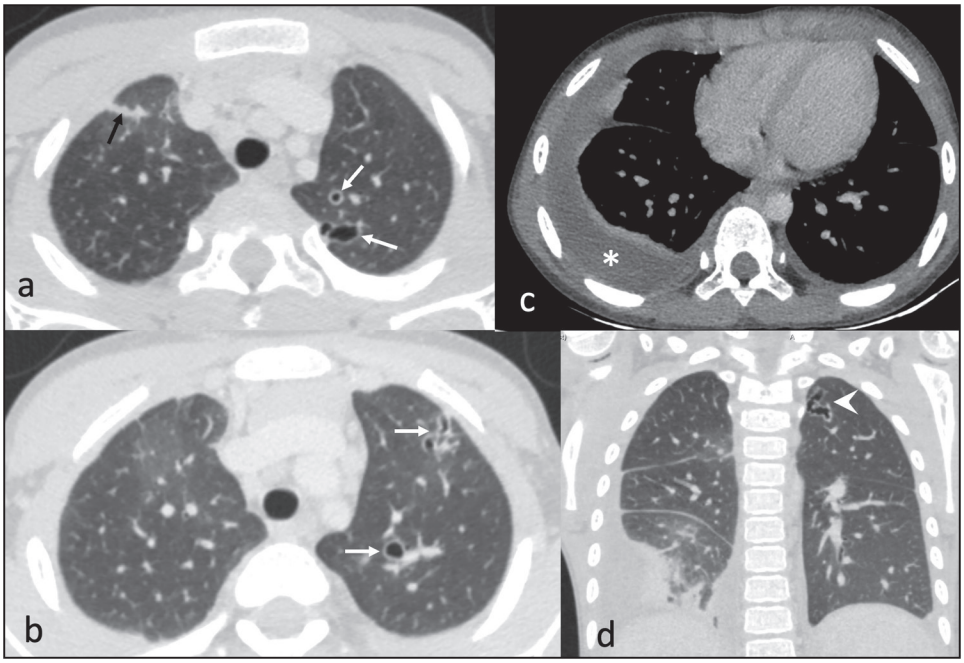

Figure 2: Axial computed tomography of the chest in lung window setting shows linear sub-pleural opacity (black arrow in a) and sub-pleural serpiginous air-filled tunnels (white arrow in a and b) likely representing "worm tracts" formed by worms migrating into the lung parenchyma through the pleura. Some ground glass opacity is also noted in the right lung. Right pleural effusion with basal atelectatic changes seen in the axial mediastinal window setting (Asterisk in c). A "worm tract" better seen on the coronal lung window setting in the left apical region (arrowhead in d)

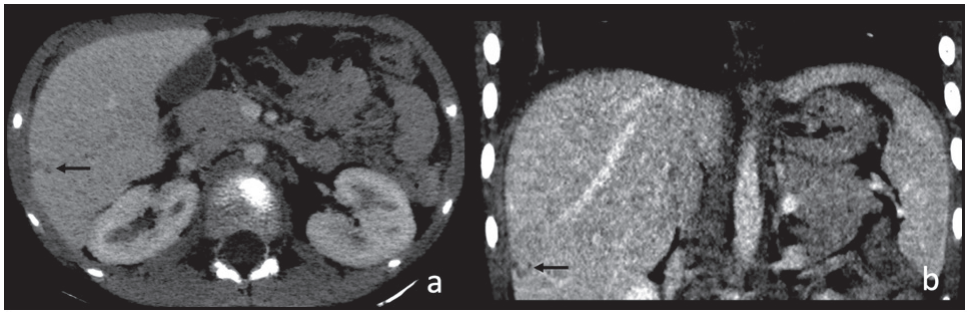

Figure 3: Axial and coronal post-contrast image in abdominal setting shows a subcapsular curvilinear hypodense tract (arrow in a and b)

left) with right pleural fluid showing loculation at places with atelectatic bands in the underlying lung parenchyma and few variable-sized nonnecrotic mediastinal lymph nodes, pre-/para-tracheal, aorto-pulmonary window, and sub-carinal lymph nodes [Figures 2 and 3]. Bronchoalveolar lavage (BAL) obtained by fiberoptic flexible bronchoscopy revealed 471 cells/μL, with 30% neutrophils, 64% lymphocytes, and 6% eosinophils. BAL culture was sterile, and detailed investigations for tuberculosis were also negative. Stool sample showed no ova or cysts on three occasions. The blood sample was sent to the Regional Medical Research Center, Indian Council of Medical Research (ICMR) Laboratory, Dibrugarh, Assam, and was reported positive for IgM and IgG paragonimiasis by the enzyme-linked immunosorbent assay (ELISA) method. The child was prescribed the tablet praziquantel at 25 mg/kg, three doses for 3 days. The child tolerated treatment and had no adverse effects. On follow-up, after 2 months, the child had improved with no cough and chest pain along with resolution of pleural effusion on chest radiograph [Figure 1b].

Discussion

Paragonimiasis is a neglected food-borne parasitic zoonosis in India. It is caused by *Paragonimus*; about 50 *Paragonimus* species have been described in the literature. In India, the first case of the disease was described by Singh *et al*.[5] in the year 1981, the patient was from Manipur. Another case of pulmonary paragonimiasis was seen in 1984 in Maharashtra.[6] Singh *et al.* reported 39 cases of pulmonary paragonimiasis with a prevalence of 6.7% in endemic areas of Manipur.[7] Although the incidence of paragonimiasis is high in the northeastern states, reliable data on its annual incidence in India is lacking.

The infection results after eating raw, partially cooked, or pickled crabs/crayfish, which contain the metacercarial stage, which is the infective stage for paragonimiasis. After ingestion, the larva penetrates through the intestinal wall and migrates to the lung parenchyma, leading to pulmonary paragonimiasis. The incubation period of paragonimiasis is long, and it ranges from 1 to 2 months. The child was nonvegetarian, and he even ate live crayfish and crab after catching them from a local pond.

Pulmonary paragonimiasis is clinically classified into three forms: pulmonary, extra-pulmonary, and pleuro-pulmonary forms. Pulmonary is the most common form, occurring in 76%–90% of cases.[6-8] In pulmonary form, the patient presents with cough, chest tightness or pain, hemoptysis, pleural effusion, and pneumonia. They may also have associated fever, anemia, weakness, and weight loss. This presentation mimics pulmonary tuberculosis, particularly in the Indian subcontinent. Often, anti-tubercular treatment is started even in the absence of microbiological evidence of disease.[9] There is significant overlap of clinical presentation and radiological findings of pulmonary paragonimiasis and tuberculosis. Clinicians should take a detailed history of dietary habits and family history of contact with the Koch patient and *Paragonimus* infection. Diagnostic tests of sputum or BAL and immunological tests are required to reach a definitive diagnosis. Clinicians should have a high index of suspicion, especially in endemic areas.

The presence of eosinophilic pleural effusion and peripheral blood eosinophilia are laboratory pointers of parasitic infection. CT findings may show pulmonary nodules or masses, infiltrates, cavitation, fibrosis, effusion, or pleural thickening. Frank pleural effusion is seen in 20% cases of pulmonary paragonimiasis.[2,10]

Im *et al*.[11] reported a study on 71 patients of pleuro-pulmonary paragonimiasis. The most common CT finding was air-space consolidation in 82%, followed by nodules in 41% and linear opacities extending from the pleura to the lung in 41%. Other findings were bronchiectasis in 35% cases. On chest radiograph, 83% had pulmonary consolidation, cysts, nodules, and linear opacities, whereas 61% of patients had pleural lesions like pleural effusion, hydropneumothorax, and pleural thickening.[11]

The disease is confirmed by demonstrating characteristic golden brown, ellipsoidal or oval operculated *Paragonimus* ova under microscopy and is considered the gold standard test. Various specimens that can be used are sputum, BAL,

aspirated fluids, feces, excised tissue, or cyst or pleural aspirate. The preferred sputum sample is a morning sample to visualize *Paragonimus* ova and Charcot–Leyden crystals in pleuro-pulmonary paragonimiasis.[1] The eosinophilic counts are high and are usually elevated in pleural and BAL fluids as well, in cases of pulmonary paragonimiasis. The literature suggests that *Paragonimus* ova can be isolated from sputum in 55.6% to 72% cases of pulmonary paragonimiasis.[1]

When ova are not seen in the stool or in respiratory and body fluid secretions, serological tests are needed to prove the diagnosis. The various immunological tests that have been evaluated are the intradermal test, complement fixation test, immunodiffusion, indirect hemagglutination test, ELISA, dot-ELISA, and Western blot. A specific IgG and IgM antibody to *Paragonimus* is helpful in making the diagnosis.[12] In our case, we could not isolate the organism from either the BAL or stool sample; therefore, serology testing was done at a regional ICMR laboratory to confirm the diagnosis.

Three anti-helminthic drugs, praziquantel, bithionol, and triclabendazole, are available for the treatment of paragonimiasis. Praziquantel is the drug of choice for both pulmonary and extrapulmonary paragonimiasis. The recommended dose is 25 mg/kg body weight administered orally three times a day after meals for 3 days. Earlier, bithionol was used to treat paragonimiasis at doses of 40 mg/kg body weight in two equally divided doses on alternate days for a course of 10–20 doses. Recently, triclabendazole has been used in humans as a single dose of 10 mg/kg, and a good response has been observed.[13] Though both praziquantel and triclabendazole are effective against paragonimiasis, neither drug is clearly superior to the other. However, some studies have shown that patients treated with praziquantel may require multiple courses or subsequent treatment with triclabendazole, whereas very few patients who were treated with triclabendazole needed retreatment with praziquantel.[14,15]

Case reports have their own inherent limitations, and results are not applicable in general. Our case report highlights a rare and important cause of hemoptysis and pleural effusion in children. Though pulmonary tuberculosis is far more common as a cause of pulmonary effusion and hemoptysis in our country, parasitic lung infections should be considered in endemic areas. It is important to obtain the dietary habits of patients. Pulmonary paragonimiasis may not be considered as one of the differential diagnoses in the vegetarian population residing in North India, although it can happen in vegetarians as well who consume contaminated water from natural sources like rivers, lakes, or ponds.[16]

Control measures include conducting epidemiological surveys and educating the public about the disease and its transmission in areas where the prevalence of diseases is high. People in the areas should be advised to avoid consuming raw or undercooked crabs and crayfish. Also, proper hygiene practices—such as proper hand washing, thoroughly cleaning utensils, cutting boards, strainers, and knives after handling fresh crabs and crayfish—should be emphasized.[17]

This case highlights the importance of a detailed history, including habits of eating crab/crayfish and imaging studies, particularly CT scan and serological tests, in patients with suspicion of paragonimiasis and to differentiate from tuberculosis.

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.

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Author contributions

DK: Data collection and preparation of initial draft. AS: Conceptualization, clinical data interpretation, and manuscript preparation and editing. SS: Preparation and interpretation of radiological images and manuscript preparation. MK: Contributed clinical data, preparation, and critical review of manuscript.

Ethical policy and Institutional Review Board statement

This case report contains de-identified data only; neither patient consent nor ethics approval was required, as determined by the Institutional Review Board (IRB)/Ethics Committee per institutional policy on nonidentifiable single case reports.

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Conflicts of interest

There are no conflicts of interest.

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