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Pediatric Respirology and Critical Care Medicine

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Contents

Advances in Asian Pediatric Respiratory and Neonatal Care

In this issue, there is a total of five insightful articles include the current advances in pediatric respiratory medicine and neonatal intensive care. The pediatric topics range from the diagnostic challenges of rare genetic disorders of diverse populations to the emerging preventive therapies such as respiratory syncytial virus (RSV) prophylaxis. These works provide the importance of precision, timely intervention, and regional needs in enhancing child health outcomes.

A major issue is the detection and management of chronic airway diseases, cystic fibrosis (CF). CF has been considered rare in Asian populations; however, the review by Al-Kindi[1] questions this assumption and suggests that CF may be significantly underdiagnosed across the Asian region. The author points out that Asia's diverse ethnic backgrounds and varying healthcare systems may lead to considerable differences in disease prevalence and genetic patterns. Notably, it has been reported that *CFTR* mutation profiles in Asian populations differ from those who in Western countries, reducing the effectiveness of standard mutation panels and limits access to therapies.[2] This highlights the need for region-specific diagnostic approaches and access to affordable sweat testing to avoid delayed diagnoses for leading to severe malnutrition and early death.

Considerable attention has been given to CF treatment, but managing non-CF bronchiectasis (NCFBE) still presents distinct challenges. In a pilot study in this issue, Dr. Nathan and colleagues explored the use of inhaled antibiotics for treating NCFBE exacerbations in children.[3] While inhaled antibiotics are widely used in CF, this study found that they had limited benefit when used alone for NCFBE exacerbations. In contrast, patients receiving both systemic and inhaled antibiotics showed improvements in cough severity and quality of life. Dr. Nathan's findings suggest that treatment approaches for CF exacerbations cannot simply be applied to NCFBE, especially when systemic therapy is not included.

In clinical practice, a major goal in pediatric respiratory care is to detect lung disease early. However, conventional spirometry is often limited by its low sensitivity and applicability in older children. In this issue, Dr. Welsh highlights another important advance in diagnostic approaches in Multiple Breath Washout and the Lung Clearance Index,[4] which offers a noninvasive alternative that can be used across all age groups, including infants. Dr. Welsh highlights recent advances in the developments of improving the feasibility and accessibility of diagnostic pulmonary function for clinical use of detecting ventilation abnormalities earlier.

The needs of the developing child, particularly in preterm infants, are especially evident in the neonatal intensive care unit. In this issue, Patil *et al*.[5] report an original study evaluating cranial ultrasonography (CUS) in preterm neonates. Preterm infants were found to have a high risk of neurological injury, including germinal matrix hemorrhage, which was seen in 27% of the cohort. The study also observed a clear association between lower birth weight and increased neonatal mortality. However, abnormal findings on CUS were not independently linked to mortality. These results suggest that while CUS is valuable for detecting brain injury, survival in preterm infants is still driven mainly by broader perinatal factors such as birth asphyxia and respiratory distress.

Preventive strategies for RSV, a major cause of infant hospitalizations worldwide, aim to reduce disease burden through timely prophylaxis and early protection in infancy. In this issue, Yip[6] presents a narrative review on the practical use of Nirsevimab, a long-acting monoclonal antibody, with a focus on its application in Hong Kong. Unlike Palivizumab, Nirsevimab can provide protection for the entire RSV season with a single dose. However, in a densely populated setting like Hong Kong, implementation requires a specific approach due to variable RSV seasonality and the structure of the public health system. The author suggests a locally adapted model delivered through Maternal and Child Health Centers, with a phased rollout designed to improve equitable access. This article provides an important reminder that while global medical advances are valuable, they need to be adapted to local epidemiology and healthcare systems to achieve meaningful real-world impact.

Overall, the articles in this issue reflect the wide-ranging scope of modern pediatric care. They range from improving our understanding of genetic disease patterns in Asian populations, to assessing nebulized treatment strategies, introducing more sensitive tools for lung function assessment, and refining approaches to the prophylaxis of neonatal RSV infection. These studies strengthen the evidence base for clinical practice and emphasize that improving child health outcomes requires not only global innovation, but also careful local adaptation and sustained attention to early and accurate diagnosis.

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There are no conflicts of interest.

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Review Article

Cystic Fibrosis in Asia: Epidemiology, Genetics, Challenges, and Future Directions

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Abstract

Cystic fibrosis (CF), a multisystem autosomal recessive disorder caused by pathogenic variants in the CF transmembrane conductance regulator (*CFTR*) gene, has long been considered rare in Asia. However, growing evidence indicates that CF is substantially underrecognized across the region due to limited diagnostic capacity, absence of newborn screening programs, lack of national registries, and low clinical awareness. Asia's marked heterogeneity in ethnicity, consanguinity patterns, and healthcare infrastructure has resulted in a wide variation in disease prevalence, genetic architecture, and clinical outcomes. This narrative review synthesizes current data on CF epidemiology, *CFTR* mutation spectra, clinical presentation, and diagnostic and therapeutic challenges across Asia. A relatively high disease prevalence has been reported in several Middle Eastern countries, driven largely by consanguinity and founder mutations, while South and East Asia likely harbor a significant but underdiagnosed disease burden. Asian *CFTR* mutation profiles differ markedly from those of Western populations, limiting the effectiveness of standard mutation panels and eligibility for currently approved *CFTR* modulator therapies. Delayed diagnosis remains common, contributing to early bronchiectasis, severe malnutrition, recurrent respiratory infections, and increased early mortality in low- and middle-income settings. Addressing these challenges will require region-specific diagnostic strategies, expansion of affordable sweat testing and molecular diagnostics, establishment of national registries, and inclusive development of next-generation *CFTR*-targeted therapies. Strengthening early detection and multidisciplinary pediatric respiratory care is essential to improving outcomes for children with CF across Asia.

Keywords: Asia, *CFTR* mutations, cystic fibrosis, delayed diagnosis, multidisciplinary care, pediatric respiratory disease

Introduction

Cystic fibrosis (CF) is among the most common autosomal recessive genetic disorders, caused by pathogenic variants in the CF transmembrane conductance regulator (*CFTR*) gene. Although historically regarded as a disease predominantly affecting populations of European ancestry, CF is increasingly recognized across Asia. For decades, its burden in Asian countries has been underestimated because of limited diagnostic capacity, low clinical awareness, the absence of newborn screening (NBS) programs, and the lack of national registries.

Asia encompasses more than half of the world's population and is characterized by profound heterogeneity in ethnicity, consanguinity patterns, healthcare infrastructure, and genetic backgrounds. These factors collectively shape a CF landscape that differs substantially from that observed in Western countries. Consequently, the true incidence, prevalence, and natural history of CF in Asia remain incompletely defined.

This review synthesizes available evidence on CF in Asia, with a focus on regional epidemiology, *CFTR* mutation

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spectra, clinical presentation, diagnostic and management challenges, and healthcare system constraints. Key knowledge gaps are highlighted, and future directions are proposed to improve diagnosis, care, and outcomes for people with CF across the region.

Epidemiology of Cystic Fibrosis in Asia

Once considered exceedingly rare in Asia, CF is now increasingly recognized across multiple regions, although the reported incidence and prevalence remain highly variable because of the heterogeneous diagnostic capacity, NBS coverage, registry availability, and clinical awareness.

A region-wide perspective was provided by a survey conducted under the auspices of the Asian Pediatric Pulmonology Society, which assessed CF prevalence and diagnostic capacity across 15 member countries. While three reported no documented cases, the remaining 12 reported variable numbers, with widespread disparities in diagnostic infrastructure, registry coverage, and access to advanced therapies, reinforcing the likelihood of substantial underdiagnosis.[1] Available data suggest three broad epidemiologic patterns: (1) high-prevalence regions driven largely by consanguinity and founder effects, (2) regions with a substantial but underrecognized disease burden, and (3) regions where CF remains genuinely rare [Table 1].

High-Prevalence Regions in the Middle East

Jordan

Jordan represents one of the highest-incidence settings for CF in Asia. A prospective neonatal screening study reported an incidence of 39 per 100,000 live births (approximately 1 in 2,560).[2,3] This observation was supported by subsequent national clinical reviews, confirming that CF is relatively common in Jordanian children.[4,5] The establishment of the first national electronic CF registry in 2025 represents an important milestone for regional CF surveillance. Analysis of registry data identified 385 confirmed patients, of whom approximately 63.6% were less than 20 years of age. These findings place Jordan among the Asian countries with the highest reported CF incidence.[6,7]

Saudi Arabia

Saudi Arabia also carries a substantial disease burden. A systematic review estimated an incidence of 23.7 per 100,000 live births (approximately 1 in 4,243), among the highest reported in the Arab world.[8,9] This elevated burden is attributed primarily to high rates of consanguineous marriage and strong regional founder effects for specific *CFTR* mutations.[10-14]

Oman

In Oman, the epidemiology and genetic landscape of CF are comparatively well characterized. Early Gulf region studies identified key regional mutations, including c.2988+1G>A and p.Ser549Arg.[15] Carrier-frequency modeling predicted a high *CFTR* carrier rate of approximately 1 in 29, suggesting a substantial national disease burden.[16] Subsequent molecular studies described novel Omani *CFTR* mutations.[17] A national multicenter study identified 227 affected children, reported a prevalence of 10.3 per 100,000 population, and confirmed the marked predominance of the p.Ser549Arg mutation, accounting for approximately 52% of alleles.[18] Together, these data establish Oman as a country with moderate-to-high CF prevalence among Arab nations.

Iran

Although precise national incidence or prevalence data for Iran are unavailable, genetic studies suggest a considerable disease burden. Estimated *CFTR* carrier frequencies of 1 in 40 to 1 in 50 correspond to a

Table 1: Reported incidence and prevalence of cystic fibrosis in selected Asian countries

Country/region	Reported incidence (per 100,000 live births)	Estimated prevalence (per 100,000)	Data source/notes
Jordan	~39 (1 in 2,560)	Not established	Neonatal screening study; early national data
Saudi Arabia	~23.7 (1 in 4,243)	Not established	Systematic review; high consanguinity
Oman	Not established	~10.3	National multicenter registry-based study
Bahrain	~17.2 (1 in 5,800)	~3	Retrospective hospital-based data
UAE	~6.3 (1 in 15,876)	Not established	Pilot genetic study
Iran	10–15.6 (estimated)	Not established	Carrier-frequency extrapolation
India	2.5–10 (estimated)	~1–2.3	Underdiagnosed; no national registry
Pakistan	2.5–10 (estimated)	Not established	Severe underdiagnosis
China	~0.8 (1 in 128,000)	Likely underestimated	Exome-based estimates; expert consensus
Japan	~0.3 (1 in 350,000)	Very low	National reviews
Southeast Asia	<1	Very low	Case reports only

Incidence and prevalence values reflect heterogeneous methodologies and should be interpreted cautiously.

theoretical disease incidence of approximately 1 in 6,400 to 1 in 10,000 live births (10–15.6 per 100,000).[19,20] High consanguinity rates and expanding diagnostic capacity in major referral centers have contributed to increasing case detection.

Bahrain

A retrospective 20-year study from Bahrain reported an incidence of approximately 1 in 5,800 live births (17.2 per 100,000) and a point prevalence of 3 per 100,000 population, based on clinical assessment and sweat testing.[21,22]

United Arab Emirates

In the United Arab Emirates, a pilot genetic screening study identified 20 CF patients among approximately 300,000 nationals, suggesting an incidence of 1 in 15,876 (6.3 per 100,000).[23-25] This study was among the earliest to demonstrate that CF is more prevalent in the Gulf region than previously assumed.

Significant but Underdiagnosed Burden in South Asia

India

India lacks reliable national incidence or prevalence data because of the absence of universal NBS and a national CF registry.[26] Historically considered rare, CF is now recognized as substantially underdiagnosed. Estimates derived from hospital-based series and diaspora studies suggest an incidence ranging from 1 in 10,000 to 1 in 40,000 live births (2.5–10 per 100,000).[27] Reported prevalence estimates range from approximately 1 in 43,000 to 1 in 100,000. Increasing reports from major pediatric and respiratory centers support the existence of a significant but previously overlooked disease burden.[28] Recent studies from South India have further highlighted the genetic heterogeneity of CF in Asian populations. In a cohort of 120 individuals with CF, 55 *CFTR* variants were identified. In addition to classical *CFTR* mutations, several region-specific variants have been reported, including six novel variants, including c.1802T>C (p.Ile601Thr), which has been associated with severe clinical phenotypes in affected children.[29]

Pakistan

Pakistan faces similar challenges, including high birth rates, widespread consanguinity, and limited access to sweat chloride testing and molecular diagnostics. Based on genetic carrier frequencies and regional extrapolations, the estimated incidence is also 1 in 10,000–40,000 live births.[31,32] Profound underdiagnosis persists, with many patients presenting late and with advanced disease.

Emerging Recognition in East Asia

China

China formally listed CF as a rare disease in 2018.[30] Exome-based genetic analyses estimate a prevalence of approximately 1 in 128,000.[33] The 2023 Chinese Experts Consensus Statement projected that more than 20,000 individuals in China may have CF, despite only a few hundred genetically confirmed cases reported to date.[34] Limited access to sweat chloride testing and the absence of a national registry strongly suggest that the true burden is substantially underestimated.[30,34]

Japan

The incidence of CF is exceptionally rare in Japan. An early national review estimated an incidence of approximately 1 in 350,000 live births.[35] Although improved awareness may have modestly increased detection rates, the prevalence remains extremely low, reflecting a distinct *CFTR* mutation spectrum.

Extreme Rarity in Southeast Asia

Across Southeast Asia, the incidence of CF remains very rare, with only isolated case reports from Thailand, Malaysia, Indonesia, Vietnam, and the Philippines. Recent case reports have documented the first genetically confirmed native Vietnamese patients,[36,37] whereas NBS programs have recently identified the first Filipino infant diagnosed with CF through neonatal screening.[38] The estimated incidence is generally below 1 in 100,000 to 1 in 200,000 live births. Diagnostic barriers are substantial, and when cases are identified, diagnosis is often delayed until adolescence or adulthood, frequently with atypical presentations such as isolated bronchiectasis or congenital bilateral absence of the vas deferens.[36–40]

Genetic Spectrum of *CFTR* Mutations in Asia

The *CFTR* mutation landscape in Asia is highly heterogeneous and markedly different from that of Western populations, where p.Phe508del predominates [Table 2]. This diversity poses major challenges for diagnosis, screening, genetic counseling, and equitable access to *CFTR* modulator therapies.[38,42]

Implications

The marked genetic heterogeneity across Asia underscores two critical issues: (1) Western-centric mutation panels are insufficient for diagnosis, necessitating population-specific or sequencing-based approaches; and (2) many Asian patients are ineligible for currently available *CFTR* modulators, highlighting the need for inclusive drug development and precision medicine strategies.

Table 2: Predominant cystic fibrosis transmembrane conductance regulator mutations by region in Asia

Region/ country	Most common mutations	Approximate frequency/notes
India	p.Phe508del; 3849 + 10kbC>T; c.1029delC; c.2052dup	p.Phe508del: 19%–34%; highly heterogeneous
Hong Kong	p.I1023R	Very rare (four reported patients)[41]
China	p.Gly970Asp; c.1766 + 5G>T; p.Arg553X; p.Asn1303Lys	>40% private/unique variants
Iran	p.Phe508del; c.2183_2184delAAinsG; p.Ser466X	Mixed global and local spectrum
Saudi Arabia	p.Gly473GlufsX54; p.Ile1234Val; p.Phe508del; p.Ser549Arg	Strong regional clustering
Oman	p.Ser549Arg; p.Phe508del; c.2988 + 1G>A	p.Ser549Arg ~52%
UAE	p.Ser549Arg; p.Phe508del	Founder effects evident
Southeast Asia	p.Trp202X; p.Phe508del; p.Arg1066Cys	Sparse data; country-specific

Table 3: Clinical feature of cystic fibrosis in Asia

Feature	Asian populations	Western populations
Age at symptom onset	Early (often <6 months)	Early, often detected via NBS
Age at diagnosis	Delayed (months to years)	Neonatal or early infancy
Meconium ileus	Uncommon (except Oman)	15%–20%
Pseudomonas aeruginosa colonization	Early and frequent	Later, with structured surveillance
Nutritional status at diagnosis	Severe malnutrition common	Variable, often preserved
Mortality	Higher early mortality	Improved long-term survival

Clinical Presentation and Diagnosis

Clinical features: Asia versus Western populations

Across Asian cohorts, CF typically presents with severe respiratory and nutritional manifestations, including chronic cough, recurrent pneumonia, bronchiectasis, failure to thrive, and steatorrhea.[1,2,6,10] Compared with Western populations, several distinguishing features are notable [Table 3].

Diagnostic challenges

Key challenges include delayed diagnosis, low disease awareness, frequent misdiagnosis as tuberculosis (TB) or asthma, limited access to sweat chloride testing and molecular diagnostics, high consanguinity rates, and significant resource constraints. The median age at diagnosis ranges from early infancy in Oman to late childhood in South Asia.[16,29,33] These gaps underscore the critical importance of early clinical recognition of CF, particularly in settings without NBS.

Diagnostic pitfalls: Tuberculosis mimicry and pseudo-Bartter syndrome

In many Asian countries where TB is endemic, CF is frequently misdiagnosed as pulmonary TB. Chronic cough, recurrent pulmonary infections, weight loss, and radiographic abnormalities may overlap with TB, leading to empiric antituberculous therapy before alternative diagnoses are considered. However, clinicians should reconsider CF in children with chronic respiratory symptoms who show poor clinical or radiological response to anti-TB therapy, particularly when microbiological confirmation of TB is lacking. Additional features that should prompt evaluation for CF include failure to thrive, recurrent pneumonia, persistent productive cough, nasal polyposis, early bronchiectasis, or a family history suggestive of autosomal recessive disease.[43,44] In such scenarios, timely sweat chloride testing and, where available, *CFTR* genetic analysis are essential to avoid prolonged diagnostic delay.

Another important but often underrecognized diagnostic indicator in Asia is pseudo-Bartter syndrome (PBS). Hot climates, high perspiration rates, and recurrent salt loss predispose infants and young children with CF to the risk of developing metabolic alkalosis with hypochloremia and hypokalemia. In several Asian cohorts, PBS has been reported as a presenting manifestation of CF rather than merely a complication.[45,46] Children presenting to emergency departments with unexplained metabolic alkalosis, dehydration, recurrent vomiting, or electrolyte disturbances—particularly in the absence of gastrointestinal losses—should prompt the consideration of CF, especially when accompanied by poor weight gain or respiratory symptoms. Increased awareness of PBS as an early diagnostic indicator may help reduce missed or delayed CF diagnoses in resource-limited settings.

Newborn Screening for Cystic Fibrosis in Asia

NBS for CF has significantly improved early diagnosis and long-term outcomes in many high-income countries by enabling timely nutritional support, early initiation of airway clearance therapy, and prevention of irreversible lung damage. In Asia, however, CF NBS programs remain limited or absent in most countries.[47] From a public health perspective, implementing NBS could reduce diagnostic delays, facilitate early referral to specialized care, and improve epidemiological surveillance through better case identification and registry development. Nevertheless, several challenges must be considered by policymakers, including the relatively low reported prevalence of CF in some populations, variability in regional *CFTR* mutation spectra that may reduce the sensitivity of standard

mutation panels, and the need for infrastructure to perform confirmatory testing such as sweat chloride analysis. In this context, targeted or pilot screening programs in higher-prevalence settings—particularly in parts of the Middle East—may represent a pragmatic initial strategy to evaluate the feasibility and cost-effectiveness before broader implementation.[48]

Pediatric Intensive Care and Critical Illness in Cystic Fibrosis

Although most children with CF are managed in outpatient settings, some develop life-threatening complications requiring admission to the pediatric intensive care unit (PICU), most commonly due to acute respiratory failure during severe pulmonary exacerbations. Despite advances in CF management, outcomes after PICU admission remain guarded, with studies reporting substantial mortality and persistent risk during long-term follow-up.

Several factors have been associated with poorer outcomes in critically ill CF patients, including female sex, severe hypercapnia at admission, electrolyte disturbances, and infection with opportunistic pathogens such as *Stenotrophomonas maltophilia*. Older age at admission (particularly >5 years) has also been linked to higher mortality, likely reflecting more advanced lung disease.[49,50]

Management typically includes intensive antimicrobial therapy, airway clearance, nutritional support, and respiratory assistance, often using noninvasive ventilation. In severe cases, extracorporeal membrane oxygenation may be used as a bridge to recovery or lung transplantation. However, access to advanced critical care remains limited in many Asian low- and middle-income settings, highlighting the importance of early diagnosis and specialized multidisciplinary care.

Nutritional Status and Regional Risk Factors

Malnutrition remains a major challenge in children with CF across many Asian and Middle Eastern countries and contributes significantly to poor pulmonary outcomes and increased morbidity. A recent 14-year retrospective study from Saudi Arabia[51] reported that 60.4% of children with CF were malnourished, highlighting the substantial nutritional burden in this population. Independent risk factors identified in this cohort included poor or fair appetite and inadequate dietary intake, delayed diagnosis, and uncontrolled fat malabsorption. These findings underscore the critical importance of early nutritional assessment and aggressive management of pancreatic insufficiency in children with CF.

Outcomes and Complications

Many patients present with advanced disease, including established bronchiectasis, early *Pseudomonas aeruginosa* colonization, electrolyte disturbances such as PBS, and deficiencies of fat-soluble vitamins. Early mortality remains high in several low-resource settings, largely driven by delayed diagnosis and inadequate access to multidisciplinary care.[26,31,33] Improving outcomes will therefore depend on earlier diagnosis and the development of coordinated multidisciplinary teams capable of delivering comprehensive respiratory, nutritional, and psychosocial care for children with CF.

CFTR Modulator Therapy: A Limited Reality in Asia

Although *CFTR* modulator therapies, including ivacaftor and the triple combination elexacaftor–tezacaftor–ivacaftor, have transformed the management of CF in many high-income countries, their impact across Asia remains limited.[44,45] This therapeutic gap partly reflects differences in the region's genetic landscape. In contrast to Western populations, where the p.Phe508del mutation predominates, many Asian patients carry rare or population-specific *CFTR* variants, rendering a substantial proportion of the population genetically ineligible for currently approved modulators.

Even among eligible patients, access to these therapies remains constrained by high medication costs, limited regulatory approvals, and the absence of reimbursement pathways in many low- and middle-income countries (LMICs). Addressing this disparity will require multiple parallel strategies. Continued development of next-generation modulators, mRNA-based therapies, and gene-editing approaches targeting a broader range of *CFTR* mutations may expand the therapeutic eligibility for Asian patients. In addition, strengthening access to molecular diagnostics, establishing population-specific mutation databases, and promoting the inclusion of Asian patients in international clinical trials will be essential for advancing precision medicine in the region.

Policy mechanisms may also play an important role in improving therapeutic equity across Asia. Voluntary licensing agreements, similar to those used for antiretroviral and hepatitis C therapies, could facilitate the legal production of lower-cost generics in selected countries while maintaining intellectual property protections. Modeling studies suggest that generic versions of triple therapy manufactured in countries such as India or China could potentially be produced for approximately US$5000–6000 per patient per year—substantially lower than the current list prices in high-income markets. In parallel, the development of national rare-disease frameworks and the inclusion of CF within public health insurance programs may help reduce financial barriers to treatment. Strengthening regional registries and genetic databases will also be important to better define the proportion of Asian patients who may benefit from currently available *CFTR* modulators.[52–54]

Future directions and recommendations

Improving CF outcomes in Asia requires coordinated, region-specific strategies:

- Enhance awareness among healthcare professionals and policymakers.
- Expand access to affordable sweat testing and molecular diagnostics.
- Develop population-specific *CFTR* mutation panels or sequencing-based diagnostics.
- Pilot cost-effective NBS programs.
- Establish national and regional CF registries.
- Promote research into region-prevalent mutations and inclusive *CFTR* modulator development.

Conclusion

Evidence across the region demonstrates that CF commonly presents early in life with severe respiratory and nutritional compromise, yet diagnosis is frequently delayed because of limited awareness, lack of NBS programs, and restricted access to diagnostic testing. Delayed diagnosis contributes to early bronchiectasis, recurrent severe lower respiratory tract infections, electrolyte disturbances such as PBS, and preventable early mortality. Strengthening early detection, improving access to multidisciplinary pediatric respiratory care, and ensuring adequate nutritional support are, therefore, central to improving outcomes.

At a systems level, incorporation of CF into national rare-disease frameworks, development of registries, and investment in affordable diagnostics are critical priorities for LMICs. Addressing these gaps will help reduce inequities in survival and quality of life for children with CF across Asia, and it aligns directly with the clinical and public health mission of pediatric respiratory and critical care medicine.

A greater regional collaboration among pediatric pulmonology networks in Asia (Asian Paediatric Pulmonology Society) will be essential to advance research, improve diagnostic capacity, and ensure equitable access to emerging CF therapies.

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Review Article

Multiple Breath Washout and Lung Clearance Index in Paediatric Lung Disease

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Abstract

Multiple breath washout (MBW) is a non-invasive tidal breathing test that quantifies ventilation inhomogeneity by measuring how efficiently the lungs are able to clear an inert tracer gas such as nitrogen (N_2) or sulphur hexafluoride (SF_6), and holds the key advantage of being applicable to all age groups. Though first described over 60 years ago, MBW has only garnered increased interest in the past 20 years. This has primarily been driven by the development and availability of commercial equipment, which has seen momentous advances in rapid gas analysers, highly sensitive flow systems, and user-friendly software enhancements. The principal MBW outcome, Lung Clearance Index (LCI), reflects global gas mixing efficiency and is regarded as a more sensitive method to identify the subtle changes seen in early lung disease when compared to traditional lung function measures such as spirometry. These properties have seen MBW begin to transition from paediatric respiratory research in specialised laboratories towards becoming a routine clinical assessment. Although nitrogen-based systems are currently more common, the tracer gas selected can introduce important methodological differences, and SF_6-based MBW remains the preferred method in infants. This review examines the physiological principles underpinning MBW, outlines key methodological aspects of testing, and discusses the interpretation and application of LCI in paediatric clinical practice.

Keywords: Children, infants, Lung Clearance Index, multiple breath washout, sulphur hexafluoride

Introduction

Multiple breath washout (MBW) was first described by Dr Margaret Becklake in 1952;[1] however, the technique has only become routinely available over the past two decades due to improvements in fast-response gas analysers, precise flow measurement systems, advanced signal processing algorithms, and the development of robust commercial devices.[2-4]

The early stages of many paediatric obstructive pulmonary diseases are characterised by subtle, "patchy" abnormalities in peripheral airways that are often asymptomatic and remain undetected by conventional lung function tests such as spirometry.[5] While indispensable in clinical practice, spirometry primarily reflects large airway flow and is reliant upon effort-dependent manoeuvres that may be inaccurate or unattainable in younger children. As a result, the opportunity to detect initial small-airway damage and provide early intervention may be missed.

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MBW addresses this gap and provides the ability to detect peripheral airway pathology by assessing gas mixing throughout the lungs during "normal" tidal breathing, a process that involves all airways. Indeed, MBW quantifies ventilation inhomogeneity by measuring how efficiently the lungs are able to clear an inert tracer gas such as nitrogen (N_2) or sulphur hexafluoride (SF_6). This efficiency is represented by the Lung Clearance Index (LCI), which reflects the number of lung turnovers required to clear the tracer gas and has repeatedly demonstrated high sensitivity for detecting early lung disease across paediatric

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populations.[6-8] Importantly, the higher the LCI, the greater the ventilation inhomogeneity present and the less efficient the lungs are at gas mixing.

This review examines the physiological principles of MBW, describes the testing methodology, and discusses the clinical application of LCI in paediatric practice.

Physiological Principles of Ventilation Inhomogeneity in MBW

Ventilation, even within healthy lungs, is not perfectly uniform. Instead, inspired gas distributes unevenly across the large number of parallel lung units that make up the bronchial tree and acinar structures. This uneven distribution, termed "ventilation inhomogeneity," arises from differences in airway geometry, the effects of gravity, regional lung compliance, and airway resistance.[9,10]

Gas transport within the lungs occurs through a combination of convection and diffusion. In the conducting airways (i.e., trachea to terminal bronchioles), gas movement is dominated by convection, where bulk flow distributes gas to progressively smaller airway branches. Beyond the terminal bronchioles, in the acinar region, the primary mode of gas transport changes to molecular diffusion due to extremely small-airway dimensions and low flow velocities.[11,12] The transition between these two modes of gas transport occurs at the "quasi-stationary" diffusion–convection front, which is typically located near the entrance to the acinus in healthy lungs. The location of this front determines the regions in which the various mechanisms of ventilation inhomogeneity take place.[13]

Specifically, there are three principal physiological mechanisms that contribute to ventilation inhomogeneity. The first is convection-dependent inhomogeneity (CDI), which occurs in the conducting airway zone proximal to the terminal bronchioles. CDI arises when lung units that share airway branch points receive different levels of ventilation due to variations in airway resistance or regional lung mechanics. When this occurs, these lung units exhibit different time constants, causing asynchronous filling and emptying rather than simultaneous ventilation. This asynchronous ventilation produces differences in tracer gas concentration between adjacent lung regions and contributes to a delayed clearance of the tracer gas during MBW.[14-16]

The second mechanism involves diffusion–convection interaction-dependent inhomogeneity (DCDI), which occurs in the transitional region around the diffusion–convection front at the acinar entrance. In this region, gas transport is influenced by both bulk flow and diffusion. Structural asymmetry at airway branch points, such as differences in airway diameter or the volume of lung tissue subtended by each branch, can disrupt normal gas mixing. Consequently, the tracer gas may be unevenly distributed within the acinar structures, producing delayed equilibration and prolonged washout (i.e., a longer emptying time constant). In healthy lungs, DCDI is thought to represent the dominant physiological contributor to ventilation inhomogeneity detected by washout techniques.[17]

A third, less common mechanism involves diffusion-limited inhomogeneity within pathologically enlarged acinar structures. In conditions that significantly enlarge distal air spaces (e.g., alveolar simplification in bronchopulmonary dysplasia),[18,19] diffusion distances are increased and gas mixing becomes less efficient, further contributing to uneven ventilation distribution.

Taken together, these three mechanisms collectively influence the clearance kinetics of the tracer gas measured throughout the MBW test. When ventilation is relatively homogeneous, tracer gas concentrations decline rapidly, and to a certain degree, uniformly with each successive breath. However, when ventilation inhomogeneity is present, poorly ventilated regions empty more slowly than better-ventilated regions, resulting in a prolonged washout phase.[20] This delayed clearance is primarily reflected by the LCI, which quantifies the number of lung volume turnovers required to reduce the tracer gas concentration to a pre-specified fraction of its initial value (i.e., 1/40th of the initial starting concentration). As mentioned above, an increased LCI reflects greater ventilation inhomogeneity and indicates that the lungs are less efficient at gas mixing.

MBW Procedure

MBW is measured during relaxed tidal breathing at functional residual capacity (FRC), and can either be performed using an exogenous tracer gas such as 4.0% SF_6 or endogenous "resident" N_2 which is washed out with 100% oxygen (O_2). For either tracer gas, the subject breathes through a sealed interface which is connected to a flow sensor and gas analyser that continuously measures respiratory flow and tracer gas concentration [Figure 1].

For infants, a sealed facemask which covers the nose and mouth is required for testing. For pre-school-aged children, either a mouthpiece and nose-clip assembly or a facemask that covers the nose and mouth are appropriate interface options.[21] Importantly, dead space volume adjustments must be made according to the interface selected. School-aged children are required to use the mouthpiece and nose-clip assembly.

Throughout testing, infants should be in the supine position with their head in midline and in the sniffing position to optimise upper airway patency. For pre-school-aged children and above, testing should be performed while in a seated position with their head in midline.

High-quality MBW measurements depend on maintaining stable tidal breathing around FRC throughout the test.

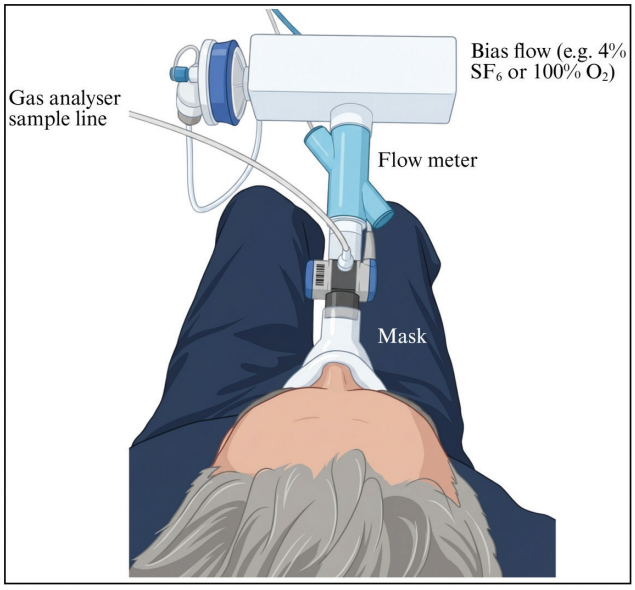

Figure 1: Illustration of inert gas washout system

The measured FRC reflects the lung volume at which the washout commences (i.e., the end-expiratory lung volume) and is therefore critical to the quality of the measurement. Large visible sighs in infants can alter FRC and should prompt test exclusion. Similarly, for older children, large inspiratory breaths can mobilise trapped gas and alter the FRC. The breathing pattern should remain regular, without large sighs or deep breaths, and the subject should avoid swallowing, coughing, or breath-holding. Likewise, leaks around the interface or entrainment of room air must be prevented, as these artefacts can distort tracer gas concentration signals and invalidate the washout profile. Continuous observation of the flow and gas signals is therefore essential to ensure adequate signal stability and appropriate breathing pattern throughout the measurement.

When SF_6 is used, the tracer gas is first washed into the lungs. During the wash-in phase, the subject continues to breathe SF_6 until the end-tidal tracer gas concentration stabilises, indicating that equilibrium between inspired and alveolar SF_6 concentration has been achieved. Following equilibration, the washout phase is initiated by switching the inspired gas to room air. During this phase, the subject continues to breathe normally at FRC while the concentration of SF_6 in the expired gas is measured continuously. With each breath, SF_6 is progressively cleared from the lungs and the washout continues until the end-tidal tracer gas concentration falls to 1/40th (2.5%) of the starting concentration [Figure 2]. LCI can then be calculated as the cumulative expired volume required to reach that end point (i.e., 1/40th of the initial concentration), divided by the FRC, thereby expressing the number of lung volume turnovers (i.e., FRCs) required to clear the tracer gas.

$$LCI = \frac{\text{Cumulative expired volume}}{\text{Functional residual capacity}}$$

When N_2 is used as the tracer gas, MBW is performed by washing out the resident N_2 within the lungs rather than introducing an exogenous tracer gas. Following a period of stable tidal breathing at FRC, the washout phase is initiated by switching the inspired gas from medical air (21% O_2 and 79% N_2) to 100% O_2, which contains no nitrogen. As the subject continues to breathe quietly, alveolar N_2 is progressively diluted and eliminated with each breath. The concentration of N_2 in expired gas is measured continuously until the end-tidal N_2 concentration falls to 1/40th (2.5%) of the starting concentration. The LCI can then be calculated in the same fashion as described above.

With regard to acceptability criteria, a minimum of three technically acceptable MBW trials should be performed. Technically acceptable trials should include a stable tidal volume and end-expiratory lung volume for at least 30 s during the wash-in phase for SF_6 measurements or during the pre-washout phase for N_2 MBW. The trials should include a washout phase which demonstrates regular stable breathing; is free of cough or breath-holding; and has no evidence of leak, no evidence of significant trapped gas release, and no evidence of entrainment of room air. There should also be sufficient intervals between trials when using resident inert gases to allow the inert gas concentration to return to baseline values. Earlier guidelines proposed a within-session FRC repeatability threshold of ≤10%; however, this criterion is no longer strictly recommended in paediatric testing due to limited feasibility. Consistent with current recommendations, repeatability should therefore be interpreted in the context of overall test quality, with measurements demonstrating substantial variability reviewed for potential technical issues. Trials where the FRC differs by >25% from the median FRC across the three tests should be automatically rejected.[22]

Considerations for Inert Gas Choice

Although both SF_6-based and N_2-based approaches can quantify ventilation distribution, measure FRC, and generate LCI, it is important to highlight that the physiological properties of the tracer gases introduce important methodological differences. While SF_6 has negligible solubility in blood or tissue, N_2 is not physiologically inert, as it is partially soluble in blood and body tissues. During N_2 MBW, the high inspired O_2 fraction markedly lowers alveolar N_2 partial pressure which can promote diffusion of N_2 from blood and tissues into the alveolar space. As endogenous N_2 enters the lungs, particularly in the latter stages of the test when alveolar N_2 concentrations are low, additional N_2 appears

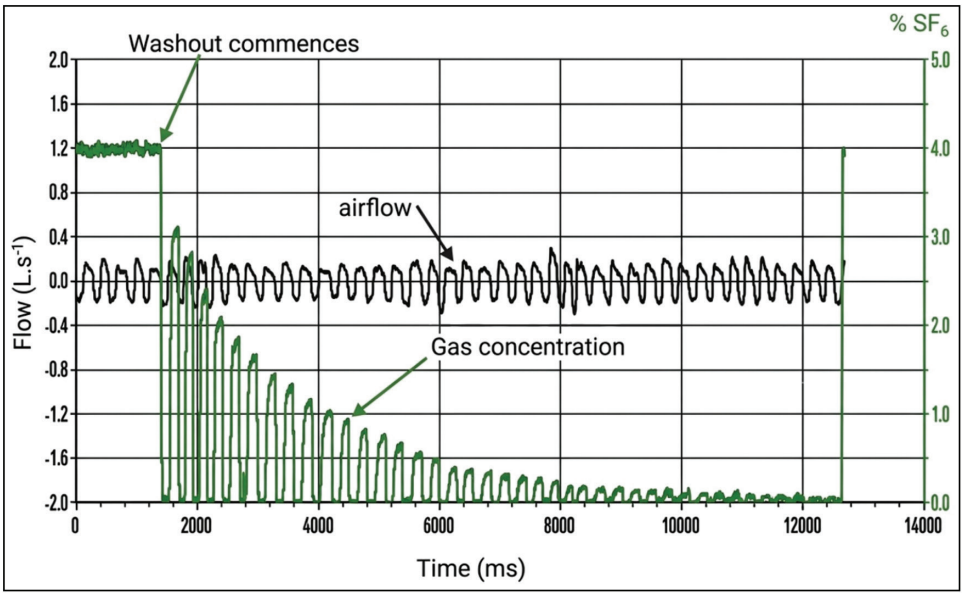

Figure 2: Time-based trace of airflow and inert gas concentration during SF_6 washout

in exhaled gas. This process may prolong the washout and result in a small overestimation of FRC.[22,23]

Whereas either tracer gas appears to be suitable for testing pre-school and school-age children, N_2-based MBW is not recommended in infants.[24] Exposure to breathing 100% O_2 has been shown to reduce tidal volume by around 30%, which can significantly alter FRC and LCI measurements.[25,26]

Despite this, N_2-based MBW offers several practical advantages. The technique uses widely available and inexpensive 100% O_2 and avoids the need for an initial wash-in phase, thereby removing repeated connections to the breathing circuit between trials. Moreover, because N_2 is present within all lung units, including very slowly ventilated compartments, N_2 washout may enhance sensitivity for detecting abnormalities compared to other inert gases, which may not fully equilibrate within these regions during wash-in.[22]

Table 1 highlights the key differences between SF_6-based and N_2-based MBW.

Table 1: Comparison of SF_6 and N_2 MBW methodologies

Feature	SF_6	N_2
Tracer gas source	Exogenous tracer gas (introduced during wash-in)	Endogenous nitrogen washed out with 100% O_2
Wash-in phase required	Yes (to achieve equilibrium)	No
Washout gas	Room air	100% O_2
Physiological impact during test	Minimal; maintains near-normal breathing conditions	Potential alteration in breathing pattern due to high O_2, particularly in infants
Tissue gas exchange effects	Minimal (low tissue solubility, negligible back-diffusion)	Potential for nitrogen back-diffusion from tissues, particularly during late washout
Test duration	Potentially longer due to wash-in phase	Often shorter overall due to no wash-in, however may be longer in severe disease
Suitability in infants	Well suited; avoids high O_2 exposure and preserves breathing stability	More uncertain effects of 100% O_2 on breathing pattern and lung physiology in infants
Suitability in pre-school children	High feasibility	High feasibility, widely used
Physiological interpretation	Direct tracer washout; less confounded by tissue gas exchange	Influenced by tissue N_2 excretion and oxygen exposure
Clinical comparability	Not directly interchangeable with N_2 values	Not directly interchangeable with SF_6 values

MBW = multiple breath washout, N_2 = nitrogen, O_2 = oxygen, SF_6 = sulphur hexafluoride.

Clinical Applications

The LCI measured via MBW provides a sensitive physiological marker of ventilation inhomogeneity and is becoming a more commonly used clinical assessment. Emerging studies that utilise MBW to assess and monitor diseases that cause obstructive lung defects include cystic fibrosis,[27] bronchiectasis,[2] bronchiolitis obliterans syndrome (BOS),[28] and prematurity-associated lung disease (PLD).[29,30] Moreover, recently published normative reference equations from the Global Lung Initiative (GLI) now enable more robust comparisons of individual patient measures with population-level

Table 2: Clinical utility of LCI across paediatric respiratory disease

Disease	Key MBW findings	Clinical utility of LCI	Evidence
Cystic fibrosis	LCI elevated in early life, before FEV_1 decline	Early disease detection, monitor progression/ clinical response, clinical trial endpoint	Abnormal LCI in infants and children with normal spirometry[4,6,7]
Bronchiectasis	Increased LCI reflecting uneven ventilation distribution	Assessment of disease burden; potential marker of progression	MBW feasible and sensitive in bronchiectasis cohorts[2]
Asthma	LCI may be elevated despite normal spirometry	Identifies small-airway phenotype; explains symptom–spirometry discordance	Persistent ventilation inhomogeneity in wheezing disorders[32]
BOS	Elevated LCI often preceding spirometric changes	Early detection and surveillance of BOS post-HSCT	Higher LCI in BOS vs non-BOS patients[28]
Bronchopulmonary dysplasia	Persistent ventilation inhomogeneity into childhood	Long-term monitoring; phenotyping of prematurity-associated lung disease	Elevated LCI in preterm cohorts and longitudinal studies[29,30]
Recurrent wheeze	Elevated LCI post-exacerbation; persistent abnormalities	Tracking early disease trajectory and recovery	LCI worsens after exacerbations in pre-school children[32]

BOS = bronchiolitis obliterans syndrome, FEV_1 = forced expiratory volume in 1 s, HSCT = haematopoietic stem cell transplant, LCI = Lung Clearance Index, MBW = multiple breath washout

references.[31] In infants, children, and adolescents, LCI can detect early signs of lung disease, monitor disease progression, and identify clinically meaningful changes in lung function.

As early as 3 months of age, LCI was demonstrated to be significantly higher in infants with cystic fibrosis when compared with age-matched controls,[6] while a study of pre-schoolers with recurrent wheezing showed a persistent worsening of LCI post-exacerbation.[32] Among children who received a haemopoietic stem cell transplant, LCI was significantly elevated in patients who developed BOS when compared to patients who did not develop BOS,[28] while a recent birth cohort study showed pre-schoolers who demonstrated aeroallergen sensitisation at 1 year of age had higher LCI values by 4 years of age compared with those with no early-life aeroallergen sensitisation.[33] Taken together, LCI represents a sensitive marker of lung disease across a range of paediatric respiratory conditions from infancy through to adolescence. Clinical utility is summarised in Table 2.

Clinical Interpretation and Integration of LCI

Defining normal and abnormal values

Recently published GLI reference equations for MBW provide a single standardised framework for defining normal and abnormal values.[31] To support clinical interpretation, age-specific predicted values and upper limit of normal (ULN) thresholds (defined by *z*-score limits) are summarised in Table 3. Importantly, a *z* score of 1.65 corresponds to the 95th percentile, meaning that only 5% of healthy individuals would be expected to exceed this threshold, while a *z* score of 1.96 corresponds to the 97.5th percentile, where only 2.5% of healthy individuals would be expected to exceed the ULN.

In clinical practice, values exceeding the ULN indicate abnormal ventilation inhomogeneity. Notably, the relatively narrow range of predicted LCI values across age underscores the stability of ventilation efficiency in health across the lifespan. Consequently, even small absolute increases above the ULN may represent clinically meaningful abnormalities, particularly in early or mild disease. Importantly, a 15% increase in absolute LCI between visits denotes a clinically significant change.

Table 3: Predicted LCI and ULN for LCI

Age (years)	Predicted LCI	ULN (1.64 *z* scores)	ULN (1.96 *z* scores)
2	6.5	7.7	8.0
5	6.4	7.5	7.8
7	6.4	7.4	7.6
10	6.3	7.2	7.3
15	6.2	6.9	7.1
20	6.1	6.9	7.0
25	6.1	6.9	7.0
30	6.1	6.9	7.1
40	6.3	7.2	7.4
50	6.5	7.5	7.7
60	6.9	8.0	8.2

LCI = Lung Clearance Index, ULN = upper limit of normal

Clinical interpretation across disease trajectories

LCI is most informative when interpreted within the context of the individual and their disease trajectory. In early lung disease, an elevated LCI in the presence of normal spirometry suggests peripheral airway dysfunction and impaired gas mixing: a pattern consistently demonstrated in cystic fibrosis.[6,34] Interpretation, however, should reflect either pre-test probability of a specific disease or a pre-existing diagnosis. For example, in conditions where there is structurally remodelled distal airways and alveolar simplification (such as individuals with PLD), elevated LCI may more likely reflect abnormal acinar function as opposed to conducting airway pathology. For disease monitoring, serial measurements allow individuals to act as

Table 4: Scenario interpretation

Scenario	Spirometry	LCI	Interpretation
Normal FEV_1 and normal LCI	Normal	Normal	Likely normal lung function. Lung disease is unlikely
Normal FEV_1 with elevated LCI	Normal	Abnormal	Suggestive of early peripheral lung disease
Reduced FEV_1 and elevated LCI	Abnormal	Abnormal	Consistent with established lung disease

FEV_1 = forced expiratory volume in 1 s, LCI = Lung Clearance Index

their own control, with changes in LCI relative to baseline, and movement across clinically relevant thresholds, providing insight into temporal disease progression. In the context of treatment response, interpretation should recognise that LCI reflects ventilation distribution rather than airway calibre and is therefore unlikely to change acutely with interventions that primarily target bronchomotor tone in the conducting airways, particularly where structural disease predominates.[20,35]

Integration with spirometry and complementary assessments

Where possible, MBW should be integrated within a broader framework of lung function assessments. Spirometry provides information on airflow limitation, whereas MBW reflects ventilation distribution; these measures offer complementary insight into pulmonary physiology. For example, a normal FEV_1 with elevated LCI suggests early or peripheral airway disease, whereas concurrent abnormalities in both indices indicate more advanced or widespread dysfunction (see Table 4 for a guide on scenario interpretation). Integration with oscillometry may further enhance interpretation by linking ventilation inhomogeneity to airway resistance and reactance, providing a more complete picture of peripheral airway function.

Future Directions

Despite growing clinical adoption, further work is required before MBW can be fully integrated into routine practice, with standardisation across devices, protocols, and tracer gases remaining a central priority. The recent development of GLI reference equations for MBW[31] represents an important step towards this goal; however, current datasets remain geographically and demographically limited, with most contributing sites derived from high-income countries and predominantly Caucasian populations. Importantly, the final prediction models demonstrated residual variability in LCI and FRC between sites, and it remains unclear whether this reflects variations in equipment and testing protocols or true population-level differences in lung health—a distinction with direct implications for how reference thresholds are applied across diverse clinical settings.

From a clinical perspective, additional research is required to better define the interpretation of LCI and its relationship to structural lung disease, symptom burden, and long-term outcomes. Secondary parameters, such as Scond and Sacin, which partition ventilation inhomogeneity into respective convection and acinar components, offer insight into ventilation physiology that LCI alone cannot provide, warranting further investigation in paediatric populations where peripheral airway dysfunction and acinar involvement are characteristics of early-life disease pathogenesis. Establishing disease-specific minimal clinically important differences will be critical for guiding clinical decision-making; the existing 15% absolute LCI threshold requires prospective validation against patient-centred outcomes such as exacerbation frequency, symptom burden, and structural disease progression across specific age and disease groups.

Finally, translation of MBW into routine clinical practice will depend on successful implementation of standardised reference equations within commercially available systems and demonstration that MBW-guided management improves clinical outcomes. As these challenges are addressed, MBW is likely to transition from a physiological measurement confined to specialised centres, to an integral component of routine paediatric respiratory assessment.

Conclusions

MBW provides a non-invasive assessment of ventilation distribution by quantifying the efficiency of gas mixing in the lung. Because the test does not rely on forced expiratory manoeuvres, but instead requires only normal tidal breathing, it is particularly well suited for infants and children. The principal measure obtained from MBW, LCI, has demonstrated high sensitivity for detecting early abnormalities in ventilation distribution, enabling identification of changes in lung function that occur in the early stages of obstructive lung disease that may not be apparent using conventional spirometry alone. Advances in equipment, signal processing, standardisation, and global reference equations in recent years have facilitated broader adoption of MBW beyond specialised research centres. MBW has evolved over the past 20 years and continues to transition to mainstream clinical measurement; it is now well positioned to integrate into routine clinical practice to complement traditional measures of lung function and contribute to earlier detection and more comprehensive monitoring of paediatric lung disease.

Author contributions

LW, LH, and CDB reviewed the available literature and drafted and finalised the manuscript. All authors approved the final version of the manuscript.

Ethical policy and Institutional Review Board statement

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Review Article

Assessing the Efficacy and Implementation of Nirsevimab for RSV Prevention in Infants: Global Insights and Recommendations for Hong Kong

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Abstract

Respiratory syncytial virus (RSV) is a leading cause of lower respiratory tract infection (LRTI) and hospitalization in infants globally, including in Hong Kong (HK), yet preventive options remain limited. Although palivizumab has historically been used for high-risk infants, its high cost and monthly dosing have restricted broader applicability. Nirsevimab, a long-acting monoclonal antibody that provides season-long protection after a single dose, has shown substantial efficacy against RSV-associated LRTI and hospitalization in clinical trials and real-world studies, and is now being rolled out in various high-income countries. However, implementation in HK poses unique challenges related to the city's prolonged and variable RSV seasonality, public health infrastructure, and cost-effectiveness thresholds. This narrative review examines the clinical evidence, global implementation experience, and the ethical, epidemiological, and economic considerations relevant to the potential introduction of nirsevimab in HK. It argues that a localized implementation model—featuring timing based on birth month and seasonal risk, delivery integrated through Maternal and Child Health Centers and District Health Centers, and phased introduction supported by district-based pilot testing and comprehensive post-marketing surveillance—may offer a pragmatic, sustainable, and equity-oriented pathway for introducing nirsevimab into HK's infant preventive healthcare strategy.

Keywords: Hong Kong, immunoprophylaxis, infants, nirsevimab, respiratory syncytial virus

Introduction

Respiratory syncytial virus (RSV) is a major cause of lower respiratory tract infections (LRTIs) in infants, especially those under 1 year of age. Globally, RSV leads over 33 million episodes of LRTIs annually, resulting in up to 3.6 million hospital admissions in children under 5 years of age.[1] In the United States (U.S.) alone, RSV causes approximately 58,000–80,000 hospitalizations each year in this age group, with a disproportionately high burden in infants under 6 months.[2] In Hong Kong (HK), RSV accounts for a substantial share of pediatric respiratory hospitalizations. A surveillance study from 2013 to 2015 found that RSV was responsible for 43% of all respiratory virus-related hospitalizations across four public hospitals, with infants under 1 year comprising nearly half of such cases. Despite a low overall case-fatality rate of around 0.14%, the implications for healthcare resource utilization, morbidity, and caregiver distress are substantial.[3]

Until recently, the mainstay of RSV prophylaxis has been palivizumab, a monoclonal antibody administered monthly during the RSV season. However, its high cost (from United States Dollar [USD] $1500 per dose) and limited indication to high-risk infants have restricted its widespread use.[4] The development and introduction of nirsevimab, a

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long-acting monoclonal antibody that provides season-long protection through a single injection, represents an important development in RSV prevention. As a passive immunizing agent rather than a vaccine, it provides direct antibody-mediated protection without eliciting an active immune response. Following regulatory approval in multiple jurisdictions, including Europe, North America, and parts of Asia, nirsevimab is now being integrated into infant RSV prevention programs in a growing number of high-income settings. This study evaluates the clinical evidence behind nirsevimab, compares its performance to palivizumab and maternal RSV vaccination, and critically assesses its potential implementation in HK, where local RSV dynamics differ substantially from the temperate regions where most clinical trials were conducted.

Materials and Methods

This study is a narrative review based on a targeted, non-systematic literature search undertaken to inform discussion of nirsevimab implementation in HK. Relevant materials were identified through searches of PubMed, Google Scholar, UpToDate, and official public health or regulatory websites, including documents from the World Health Organization, the Centers for Disease Control and Prevention (CDC), the European Center for Disease Prevention and Control, the Center for Health Protection (CHP) of Hong Kong, and other relevant government agencies. Eligible sources included peer-reviewed clinical trials, observational and real-world effectiveness studies, health economic analyses, surveillance reports, government publications, and policy guidance. Sources were selected based on relevance, recency, and contribution to the paper's central themes, namely RSV burden in infants, comparative evidence on nirsevimab and palivizumab, international implementation models relevant to HK or comparable high-income settings, HK-specific epidemiology and service delivery considerations, and economic and ethical issues relevant to policy adoption. This review ultimately aimed to assess the feasibility and implications of implementing nirsevimab within HK's healthcare system.

Nirsevimab: mechanism and duration

Nirsevimab is a long-acting monoclonal antibody that targets the prefusion conformation of the RSV F protein, neutralizing the virus before it can fuse with host cell membranes. Its engineered constant region (Fc) prolongs its half-life, allowing a single intramuscular dose to confer protection for at least 5 months, sufficient to cover a typical RSV season.[5]

Clinical efficacy and real-world evidence

Several large-scale trials have demonstrated its robust efficacy. The Phase 2b trial involving over 1400 preterm infants (29–34 weeks and 6 days gestational age) reported a 70.1% reduction in medically attended RSV LRTIs and a 78.4% reduction in RSV-related hospitalizations compared to placebo.[6] The Phase 3 MELODY trial, also including over 1400 healthy term infants, showed a 74.5% reduction in RSV-associated LRTIs.[7] Furthermore, evidence is exemplified in the HARMONIE trial, a pragmatic Phase 3b real-world study across more than 200 sites in France, Germany, and the UK, in which 8058 infants were enrolled; this trial found an 83.2% reduction in RSV-related hospitalizations and a 75.7% reduction in very severe RSV cases.[8] Collectively, these studies demonstrate consistent efficacy across trial phases, infant populations, and care settings. The Phase 2b and MELODY trials established efficacy in preterm and broader infant populations, whereas HARMONIE provided pragmatic real-world evidence supporting the effectiveness and scalability of nirsevimab for wider implementation and in routine care.

Comparison with palivizumab and maternal vaccination

Palivizumab, by contrast, has been the only effective pharmaceutical RSV preventive in the last 25 years until recent developments with nirsevimab.[9] In earlier studies, palivizumab has shown around 55% efficacy in reducing RSV hospitalizations, but is limited to high-risk populations. Its repeated monthly dosing imposes a logistical and financial burden on healthcare systems and families.[10] Consequently, palivizumab is not scalable for universal infant use, particularly in middle- and high-income countries that lack federal subsidies. The high cost of palivizumab presents a substantial financial burden, and its complex production may limit supply. Furthermore, guidelines recommend its use primarily for high-risk infants, which helps focus resources effectively.[11] Without federal subsidies, insurance coverage may be inadequate, leaving many families without access. These factors collectively hinder the practical implementation of palivizumab as a universal treatment for infants. In HK, palivizumab is reserved for a small number of infants with chronic lung disease or congenital heart defects[3] while the majority of infants remain without access to pharmaceutical RSV prophylaxis. This limitation identifies an important public health gap in RSV prevention for which nirsevimab may offer a broader and potentially more scalable preventive option, as its universal application could protect a larger population of infants who are healthy, full-term, premature, or have specific health conditions.[12]

Nirsevimab should also be considered within the broader landscape of emerging RSV prevention strategies, particularly maternal RSV vaccination. Whereas maternal vaccination is an active immunization approach administered during pregnancy to enhance transplacental transfer of vaccine-induced antibodies to the infant,[13]

nirsevimab provides passive immunization directly to the infant after birth. Although maternal vaccination may offer advantages through integration into routine antenatal care, its effectiveness depends on uptake during pregnancy, timing of administration relative to delivery, and adequate placental antibody transfer. By contrast, nirsevimab offers a direct infant-level intervention that is independent of maternal vaccine uptake and may therefore be particularly relevant when considering broader implementation through infant preventive services. As this review focuses on infant delivery strategies in HK, the following discussion centers on nirsevimab while recognizing that maternal vaccination may represent a complementary component of future RSV prevention policy.

Global implementation models

Global implementation experiences provide useful insight into how nirsevimab could be deployed effectively in routine care. The European Commission was among the first major regulatory authorities to approve nirsevimab for infant RSV prevention.[12] Spain subsequently emerged as one of the earliest adopters of a universal seasonal nirsevimab strategy for eligible infants under 6 months of age. This approach included administration before hospital discharge for newborns born during the RSV period (October to March) and catch-up delivery through hospitals and primary care services. The reported national coverage in Spain surpassed 90%, with RSV-related hospitalizations and intensive care admissions down by over 80%.[14]

In 2023, the United States Food and Drug Administration approved nirsevimab, and the CDC recommended its use for all infants under 8 months of age entering their first RSV season. The U.S. strategy aligns administration with local seasonal viral circulation, recommending a dose during the fall (typically October to November), particularly for infants born during or entering the season. Modeling by the CDC suggested that nirsevimab could prevent up to 300,000 outpatient visits and over 14,000 hospitalizations annually.[15]

Other high-income settings have adopted similar approaches. The United Kingdom has incorporated nirsevimab into its national RSV prevention program, emphasizing early administration during the RSV season. Public health campaigns are also in place to educate parents and healthcare providers about the vaccine's benefits.[16] Sixteen European Union/ European Economic Area countries, including France and Germany, have adopted comparable universal immunization strategies, backed by both public procurement and inclusion in national schedules.[17] China has also approved nirsevimab and has begun hospital-based rollout in selected urban settings.[18] Collectively, these experiences suggest that nirsevimab can be implemented successfully, although delivery models remain highly dependent on local epidemiology, financing arrangements, and healthcare system organization.

Hong Kong epidemiology/seasonality and scheduling implications

These contextual differences are especially important when considering implementation in HK, where RSV transmission patterns may not mirror those observed elsewhere. In contrast to most high-income countries, which typically experience winter-centric RSV seasons, HK's subtropical climate results in year-round RSV activity, with peaks often occurring between June and October but without a consistent, predictable seasonality

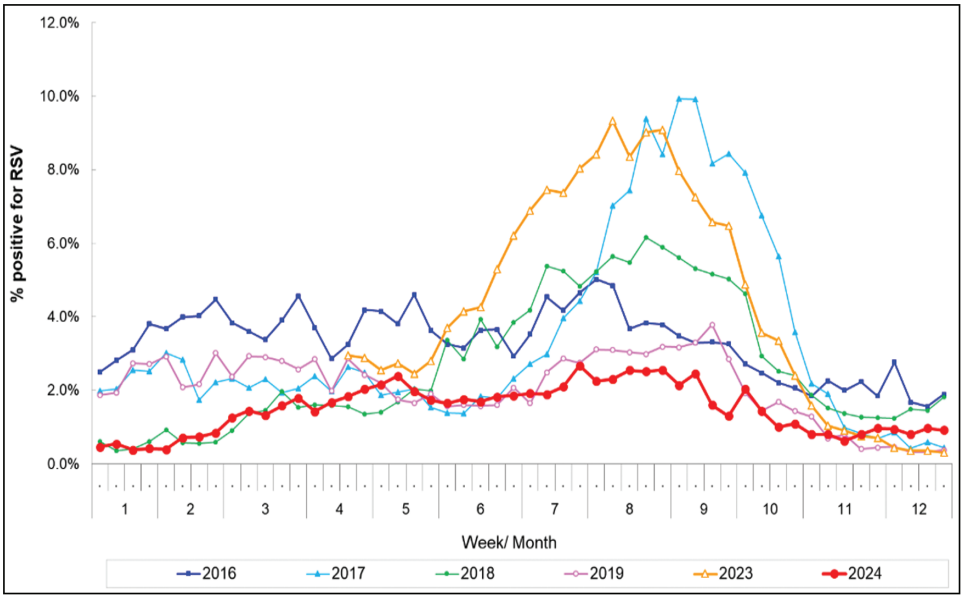

Figure 1: Weekly respiratory syncytial virus positivity (%) in Center For Health Protection and Hospital Authority specimens, 2016–2024 (excluding 2020–2022): activity varies by year with peaks in some summers, but no consistent seasonality—circulation occurs year-round[19]

[see Figure 1].[20] Other local studies similarly describe peak activity around March to August or April and November in HK, but these estimates fall within a broadly extended spring–summer window.[21,22] Surveillance data indicate that over 87% of RSV-related hospitalizations in HK occur between January and September.[3] Figure 1 also shows that the RSV surges observed in 2023 and 2024 were more irregular than many pre-pandemic patterns, with marked increases in positivity and less predictable timing. These disruptions may partly reflect "immunity debt" following pandemic-related suppression of RSV circulation, together with shifts in social mixing and healthcare utilization. Taken together, these findings suggest that a fixed U.S.-style model of fall immunization within the first week of life may not align with actual infection risk in HK. Instead, a catch-up or rolling immunization strategy informed by birth month and projected seasonal peaks in surveillance data would likely be more appropriate. Such an approach would allow protection to be aligned more closely with evolving epidemic timing. For example, infants born in November may face their highest risk several months later, between March and August, necessitating prophylaxis beyond the traditional RSV "season," while preserving flexibility in the face of ongoing year-to-year variability.

Economic considerations in Hong Kong

Cost remains a central consideration. Although the per-dose cost of nirsevimab (list price of around USD $495–$520 per dose) is substantially lower than that of palivizumab, universal provision to all infants in HK would still represent a considerable budgetary commitment. Based on annual births in the range of approximately 35,000–45,000 infants, a universal strategy would cost between USD $17 and $23 million annually.[23] A 2024 cost-effectiveness study in HK suggests that under current pricing, all modeled strategies exceeded the local willingness-to-pay threshold of USD $50,000 per quality-adjusted life year (QALY). However, the same modeling indicates that more targeted approaches, including a seasonal or catch-up strategy—targeting infants just before high-risk months—showed a more favorable cost-effectiveness profile, especially if the per-dose price could be negotiated down to around USD $105.[24] These findings suggest that while universal administration may be fiscally challenging under current pricing, targeted strategies could be both economically viable and clinically impactful.

Moreover, the potential public health value of RSV prophylaxis extends beyond immediate cost offsets from avoided hospitalizations. Indirect benefits include fewer parental or caregiver work absences, reduced pressure on pediatric inpatient services during surge periods, lower antibiotic use, and possible longer-term downstream respiratory benefits such as reduced risks of recurrent wheezing and asthma in children following severe RSV infections—outcomes that may not be fully captured in short-term economic analysis. In a densely populated city like HK, where hospital resources are stretched during seasonal surges, even modest reductions in RSV-related admissions could meaningfully alleviate pressure on pediatric wards and intensive care units. The broader preventive value of nirsevimab may, therefore, justify higher upfront costs, particularly within a universal healthcare system like HK. Accordingly, a phased approach combining economic evaluation with real-world implementation data may represent the most appropriate path for HK.

Implementation strategy for Hong Kong

Despite strong evidence and a strong medical rationale, several practical barriers remain to implementing nirsevimab in HK. First, regulatory approval is pending. Without endorsement from the Pharmacy and Poisons Board in HK, nirsevimab cannot be prescribed outside of research settings. Second, clinical familiarity with the drug remains low. Most pediatricians are accustomed to prescribing palivizumab in rare, high-risk cases. Expanding usage of nirsevimab to healthy infants will require education, training, and updated clinical guidelines. Third, public awareness of RSV appears limited. RSV, often perceived as a routine illness, remains less well recognized than influenza and Coronavirus disease 2019 (COVID-19); in one U.S. study, 67.3% of respondents rarely considered RSV as a cause of cold/flu-like symptoms, and a separate 2017 survey reported that 57% of physicians rarely suspected RSV and 73% perceived influenza as more severe - highlighting persistent awareness gaps.[25] Without sustained education campaigns, parental demand may remain low, affecting uptake even if nirsevimab becomes available.

HK's healthcare infrastructure, nevertheless, offers several advantages that could support implementation. The city's Maternal and Child Health Centers (MCHCs) provide centralized and accessible preventive services for infants. These centers could serve as effective hubs for nirsevimab administration, especially if integrated into routine well-baby visits or immunization schedules. Additionally, HK's digital health infrastructure could support implementation beyond simple record-keeping. If integrated with routine public healthcare surveillance, it could enable near real-time monitoring of program coverage, timeliness of administration, and reported adverse events following immunization, while also helping to identify patterns of missed uptake or clusters of parental refusal that may signal emerging hesitancy toward infant RSV immunoprophylaxis. Such surveillance would be particularly important during the early phase of program introduction, when transparent monitoring of safety, acceptance, and program performance is essential for maintaining public trust in a new preventive intervention.

From a policy perspective, the decision to adopt nirsevimab should also consider both quantitative and qualitative factors. While an incremental cost-effectiveness ratio provides a benchmark for economic efficiency, policymakers must also weigh social values, public demand, and institutional readiness. The inclusion of nirsevimab in other high-income jurisdictions signals a growing international consensus on its value. HK, as a high-income city, can draw from these experiences while tailoring its strategy to local epidemiology, fiscal constraints, and service delivery structures. The phased introduction of nirsevimab—starting with high-risk or seasonally vulnerable infants—could allow for careful evaluation and gradual expansion.

Negotiated pricing would likely be pivotal to any sustainable program, such as for nirsevimab. HK has prior experience incorporating newer vaccines through public-sector planning and phased adoption, including pneumococcal conjugate (PCV15) and human papillomavirus (HPV) vaccination initiatives. While the procurement arrangements for these products differ from those for nirsevimab, they nonetheless demonstrate that price reduction through volume-based purchasing, staged introduction, and public financing mechanisms is feasible in principle. This precedent strengthens the argument that local cost-effectiveness may improve materially if procurement negotiations lower the effective per-dose price.

Nirsevimab's adoption in various high-income countries also provides a valuable basis for evaluating its suitability in HK. The United Kingdom and France followed similar approaches, launching national programs through centralized procurement and integrating nirsevimab into their existing infant immunization infrastructure. However, these countries also have clear RSV seasonality and established cost-sharing mechanisms that are not directly transferable to HK's setting. Thus, a successful HK rollout must account for local seasonality, integrate smoothly into the MCHC network, and work within HK's universal healthcare funding constraints.

First, the timing of administration must be localized. In contrast to temperate countries, where RSV peaks in winter and prophylaxis is clustered in the fall, HK experiences prolonged RSV circulation with variable peaks. A novel scheduling model–based on birth month rather than season—may be optimal. For example, infants born from October to March may receive nirsevimab during an early well-baby visit to ensure protection during spring and summer peaks. Conversely, infants born in the middle of the high-incidence window (e.g., April to August) may benefit from immediate postnatal administration before hospital discharge. Integrating predictive modeling and yearly modifications like influenza, informed by historical RSV trends and real-time virological surveillance, could support dynamic scheduling and targeted public health advisories.

Second, program delivery should leverage HK's robust primary care and child health infrastructure. The city's MCHCs already deliver essential immunizations and developmental screenings to over 90% of infants.[26] Administering nirsevimab through District Health Centers (DHCs) and MCHCs would minimize administrative burden and capitalize on existing appointment structures. Nurses and pediatricians within these centers could be trained to administer the injection during routine visits, supplemented by digital reminders and tracking through the eHealth App. This integration avoids the need for separate scheduling or hospital-based distribution, which would pose equity and access challenges.

Third, public education should address the perceived benign nature of RSV. In public discourse, RSV is often dismissed as a "common cold" in infants, unlike diseases such as influenza or pertussis that are widely feared, with heightened vaccine hesitancy. A successful rollout requires targeted education campaigns to enable a broader audience to improve understanding that RSV is a leading cause of infant hospitalization and a preventable source of morbidity. Testimonials from parents whose children were hospitalized for RSV, patient advocates, infographics comparing RSV burden to other preventable pediatric infections, and communication from pediatricians and professional bodies could enhance trust and uptake.

Fourth, if HK were to scale up nirsevimab toward universal immunization, a district-based pilot would be a pragmatic first step before territory-wide implementation. A demographically and operationally manageable urban district such as Kowloon City District could be considered as a possible pilot site, given it represents a sizable yet manageable urban population (412,500 residents in 2024, accounting for 5.5% of HK's population)[27] and has accessible MCHC service infrastructure capable of supporting infant immunization delivery. In addition, the district benefits from HK's established RSV surveillance from the CHP of the Department of Health (DH), and its integration with existing hospital and surveillance networks, particularly within the Hospital Authority's Kowloon Central Cluster, may facilitate linkage between immunization records and RSV-related hospitalization and laboratory data for outcome evaluation. A 1-year pilot delivering nirsevimab to a defined birth cohort born between January and June could assess logistical feasibility, uptake, timeliness of administration, cost, parental acceptance, and early safety monitoring, amongst other implementation metrics, to generate locally relevant implementation evidence before broader rollout.

Fifth, HK should explore co-financing models to ensure fiscal sustainability. Although a full public subsidy would

best support equitable access, increased budget constraints with the city's rising deficit may necessitate innovative approaches. Means-tested co-payment systems, private–spublic partnerships with insurers, or phased inclusion in the Childhood Immunization Program could reduce fiscal pressure. Negotiated volume-based pricing, as successfully pursued with pneumococcal and HPV vaccines, would be crucial for long-term viability. A cost threshold closer to Hong Kong dollar (HKD) $700 per dose (down from ~HKD $4000 list price) would likely meet the cost-effectiveness benchmark of HKD $390,000 per QALY.[24]

Additionally, HK can draw on experience with COVID-19 vaccine implementation, particularly in coordinating across public and private sectors. During COVID-19, HK effectively deployed multiple vaccine platforms through community centers, hospitals, and mobile units. The vaccination campaign demonstrated the system's capacity to manage appointment scheduling, cold-chain logistics, stock distribution, and digital reporting at scale. These operational lessons could inform a nimble, adaptable nirsevimab rollout, especially if implementation requires flexibility across birth settings, outpatient services, and periods of fluctuating RSV activity. Public confidence in immunization programs and health consciousness has increased post-pandemic, and this momentum can also be leveraged for RSV prevention.[28]

Finally, implementation must be guided by evidence and data to cultivate trust from a highly educated population. DH or the Health Bureau should mandate routine reporting of adverse events, real-time tracking of coverage rates by district, and post-market effectiveness evaluations. Establishing a real-world evidence platform—referenced from overseas examples such as the U.S. Vaccine Safety Datalink—could support continuous learning and inform adjustments. For instance, if coverage gaps emerge in lower-income districts like Sham Shui Po, targeted outreach through DHCs or home visits could be implemented in tandem.

Conclusion

Ultimately, the question is not whether nirsevimab is clinically effective, but how HK can introduce it in a manner that is affordable, acceptable, and aligned with local epidemiology. Given the high burden of RSV, the limitations of existing preventive options, and the readiness of infrastructure in the centralization of healthcare services and robust primary healthcare, a tailored nirsevimab program appears feasible in principle in HK. Entailing a localized scheduling model incorporating birth-month-based timing, delivery through MCHCs and DHCs, phased introduction, targeted public education, and robust post-implementation surveillance can propel its effective implementation. If shown to be feasible, acceptable, and cost-effective locally, such an approach could protect thousands of infants each year, reducing RSV-related morbidity and healthcare utilization while strengthening HK's commitment to evidence-informed pediatric care.

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Author contribution

KWEY: concepts, design, definition of intellectual content, literature search, data acquisition and analysis, manuscript preparation, editing and review, and guarantor.

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Original Article

Cranial Ultrasound Study Among Preterm Neonates Admitted in NICU in a Tertiary Care Hospital and Its Correlation with Perinatal Risk Factors

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Abstract

Background: Prematurity is a major global cause of neonatal mortality and long-term disabilities. Preterm neonates are highly vulnerable to neurological injuries, which can be effectively detected by cranial ultrasonography (CUS). Understanding the correlation between CUS findings and perinatal risk factors is crucial for improving neonatal outcomes, especially in resource-limited settings. Therefore, this study aims to determine the prevalence of cranial ultrasound abnormalities and their association with perinatal risk factors in preterm neonates admitted to the neonatal intensive care unit in a tertiary healthcare center. **Methods:** A prospective observational study was conducted over a period of 2 years, including 100 preterm neonates who underwent CUS within the first week of life. Maternal and neonatal data were collected, and CUS images were interpreted by independent radiologists. Statistical analysis was performed to assess associations between perinatal risk factors and CUS findings. **Results:** Among 100 preterm neonates, most were born at 33–37 weeks (55%) and had a birth weight of 2–2.5 kg (50%). Germinal matrix hemorrhage (27%) and periventricular hyper-echogenicity (22%) were the most common CUS abnormalities. Pregnancy-induced hypertension (23%) and anemia (17%) were the common maternal risk factors, whereas birth asphyxia (17%) and respiratory distress (15%) were the frequent neonatal complications. Birth weight showed a significant association with neonatal outcome ($P < 0.001$), whereas CUS abnormalities were not significantly associated with outcomes ($P = 0.630$). **Conclusions:** Lower birth weight was significantly associated with increased neonatal mortality, whereas CUS findings were not directly related to mortality. Early identification and management of perinatal risk factors are essential to improve survival and neurological outcomes among preterm neonates.

Keywords: Abnormalities, cranial ultrasonography, neonates, prematurity, risk factors

Introduction

Prematurity is a leading global cause of mortality among children under 5 years of age, with preterm birth and low birth weight (LBW) presenting substantial health challenges worldwide. Preterm births may occur spontaneously or result from medically indicated interventions such as early labor induction or cesarean delivery.[1,2] Despite advancements in obstetric and neonatal care, preterm neonates admitted to the neonatal intensive care unit (NICU) continue to present a higher risk of mortality and long-term morbidities.[3] Therefore, ongoing investigations are urgently needed to improve clinical outcomes and reduce associated complications in premature infants.

According to the World Health Organization, an estimated 13.4 million babies were born prematurely in 2020, with complications resulting in approximately

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900,000 deaths in 2019.[2,4,5] Survivors often endure lifelong challenges, including learning disabilities, neurological impairments, and sensory deficits.[4,5] The neonatal period is particularly critical due to vulnerabilities such as respiratory distress syndrome, hypoglycemia, sepsis, and cerebral injury, which are exacerbated by immature cerebral autoregulation and fragile vasculature.

In modern neonatology, cranial ultrasonography (CUS) has become an essential diagnostic modality. This advanced diagnostic tool facilitates the evaluation of brain anatomy and pathologies, such as intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), and ventriculomegaly, which are key determinants of neurodevelopmental outcomes. This imaging diagnostic tool is predominantly valuable in the NICU for early detection of brain injuries or anomalies, aiding early intervention and improved prognosis.[6-10]

Perinatal risk factors, including maternal health conditions, delivery mode, LBW, and neonatal complications, are closely associated with adverse CUS findings in preterm infants.[6] Accurate knowledge and understanding of these correlations are important for enhancing neonatal care, especially in resource-limited settings. However, limited studies have explored these associations in Maharashtra. Addressing this gap, this study aims to assess cranial ultrasound abnormalities in preterm neonates admitted to a tertiary care hospital NICU and to analyze their correlation with perinatal risk factors.

Materials and Methods

Study design and subject

This prospective observational study was conducted at a tertiary care center over a period of 2 years. Ethical approval was obtained from the Institutional Ethics Committee (MUHS/Medical/MUHS-053704/2019 [dated February 29, 2024]), and informed consent was obtained from the guardians of all participants. Preterm infants admitted to the NICU who required cranial ultrasound were included. Exclusion criteria encompassed infants or families unwilling to participate, those discharged against medical advice (DAMA), patients who withdrew consent, and those with incomplete data. Furthermore, all preterm infants admitted to the NICU who required a cranial ultrasound were included. Participants who were unwilling to participate, those who DAMA or were discharged early, those who withdrew consent, and those with incomplete data were excluded from the study.

Data collection and measurements of cranial ultrasound scans

A total of 100 preterm neonates, from birth to 28 days of age, were enrolled based on specific perinatal risk factors. Demographic data, clinical status, cranial ultrasound findings, and immediate outcomes were extracted from medical records. The cranial ultrasound scans (EDAN Acclarix LX3 Diagnostic Ultrasound System, Edan Instruments Inc., Shenzhen, China) were performed using digital high-frequency transducers (7.5–10 MHz) through the anterior fontanel, capturing standard coronal and sagittal views.

To ensure accuracy, scans were interpreted independently by two radiologists blinded to the clinical details. In cases of discrepancies, a third radiologist provided a consensus opinion. Key findings, such as IVH, parenchymal echolucency, or moderate-to-severe ventriculomegaly, were documented. White matter damage was defined as the presence of hypoechoic zones or ventriculomegaly on late scans performed after 2 weeks of life. Data analysis focused on identifying correlations between cranial ultrasound abnormalities and perinatal risk factors, enabling a comprehensive evaluation of neurodevelopmental risks in preterm neonates.

Statistical analysis

Statistical analysis for categorical variables was conducted by presenting the number and percentage of patients. These variables were compared across groups using Pearson's chi-square test for independence of attributes. For continuous variables, the mean and standard deviation were reported. The analysis was performed using the Statistical Package for the Social Sciences software, version 20 (IBM, Armonk, NY, USA), with an alpha level set at 5%. A P value of <0.05 was considered statistically significant.

Results

In this prospective observational study of 100 preterm neonates, the majority of mothers were aged 25–30 years (53%), followed by 18–24 years (21%). Most neonates were born at 33–37 weeks of gestation (55%) and were male (57%). Nearly half of the neonates were examined between 24 and 72 h of life (49%). The most common birth weight category was 2–2.5 kg (50%), and most neonates had Apgar scores >5 at both 1 min (56%) and 5 min (64%). Among maternal complications, pregnancy-induced hypertension (23%) and anemia (17%) were most frequent. Birth asphyxia (17%) and respiratory distress (15%) were the most common neonatal complications. The majority of neonates were discharged (89%), whereas 8% left against medical advice and 3% died [Table 1].

Cranial ultrasound findings were similar in neonates with gestational age > 32 weeks and ≤32 weeks. Germinal matrix hemorrhage was the most common abnormality, followed by periventricular hyper-echogenicity and intraventricular hemorrhage, with no significant difference between the groups ($P = 0.990$) [Table 2].

Table 1: Clinical characteristics of the 100 enrolled subjects stratified by maternal and infant characteristics

Characteristics	Frequency	Percentage (%)
Mother		
Age (years)		
18–24	21	21.00
25–30	53	53.00
31–35	15	15.00
>35	11	11.00
Gestational age (weeks)		
≤28	7	7.00
29–32	38	38.00
33–37	55	55.00
Neonate gender		
Male	57	57.00
Female	43	43.00
Neonatal hours of life		
<24	18	18.00
24–72	49	49.00
≥72	33	33.00
Birth weight (kg)		
<1	8	8.00
1–1.5	13	13.00
1.5–2	29	29.00
2–2.5	50	50.00
Apgar score—1 min		
<3	5	5.00
3–5	39	39.00
>5	56	56.00
Apgar score—5 min		
<3	4	4.00
3–5	32	32.00
>5	64	64.00
Maternal complication		
PIH	23	23.00
Anemia	17	17.00
APH	14	14.00
Polyhydramnios	11	11.00
GDM	7	7.00
Eclampsia	6	6.00
Oligohydramnios	5	5.00
Neonatal complication		
Birth asphyxia	17	17.00
Respiratory distress	15	15.00
Hypoglycemia	6	6.00
Birth trauma	5	5.00
Neonatal seizures	4	4.00
Neonatal sepsis	3	3.00
Hypocalcemia	2	2.00
Outcome		
Discharged	89	89.00
DAMA	8	8.00
Death	3	3.00

DAMA = discharged against medical advice, PIH = pregnancy-induced hypertension, APH = antepartum hemorrhage, GDM = gestational diabetes mellitus

Table 2: Comparison of the prevalence of cranial ultrasound findings categorized by gestational age groups

Cranial ultrasound findings	GA > 32 weeks	GA ≤ 32 weeks	*P* value
	Frequency (%)	Frequency (%)	
Germinal matrix hemorrhage	16 (29.1%)	12 (26.7%)	0.990
Periventricular hyper-echogenicity	12 (21.8%)	10 (22.2%)	
Intraventricular hemorrhage	8 (14.5%)	7 (15.6%)	
Cystic periventricular leukomalacia	5 (9.1%)	4 (8.9%)	
Parenchymal bleed	4 (7.3%)	3 (6.7%)	
Hypoxic ischemic encephalopathy	3 (5.5%)	3 (6.7%)	
Ventriculomegaly	3 (5.5%)	2 (4.4%)	
Cerebral edema	2 (3.6%)	2 (4.4%)	
Cysts	2 (3.6%)	2 (4.4%)	

GA = gestational age

Table 3: Comparisons of birth body weight and abnormal cranial ultrasound findings categorized by neonatal outcomes

Characteristics	Outcome (frequency) (%)			*P* value
	Discharged	DAMA	Death	
Birth body weight (kg)				
<1	5 (5%)	0 (0%)	3 (3%)	*P* < 0.001
1–1.5	13 (13%)	0 (0%)	0 (0%)	
1.5–2	23 (23%)	6 (6%)	0 (0%)	
2–2.5	50 (50%)	0 (0%)	0 (0%)	
Cranial ultrasound findings				
Germinal matrix hemorrhage	27 (27%)	0 (0%)	1 (1%)	*P* = 0.630
Periventricular hyper-echogenicity	22 (22%)	0 (0%)	0 (0%)	
Intraventricular hemorrhage	14 (14%)	0 (0%)	1 (1%)	
Cystic periventricular leukomalacia	9 (9%)	0 (0%)	0 (0%)	
Parenchymal bleed	7 (7%)	0 (0%)	0 (0%)	
Hypoxic ischemic encephalopathy	5 (5%)	0 (0%)	1 (1%)	
Ventriculomegaly	5 (5%)	0 (0%)	0 (0%)	
Cerebral edema	4 (4%)	0 (0%)	0 (0%)	
Cysts	4 (4%)	0 (0%)	0 (0%)	

DAMA = discharged against medical advice

Birth weight was significantly associated with outcomes ($P < 0.001$), with deaths mainly in neonates weighing <1 kg. Cranial ultrasound abnormalities showed no significant association with outcomes ($P = 0.630$) [Table 3].

Discussion

Preterm birth is associated with a higher risk of various types of brain injuries. The probability of such injuries increases as gestational age decreases. These brain injuries are critical factors contributing to substantial morbidity

and mortality among preterm infants. The prognostic outcomes for preterm brain injury remain unpredictable, which continues to be an area of ongoing research. CUS has been demonstrated as an effective tool for the assessment of neonatal brain health. This noninvasive, rapid, and cost-efficient technique provides a viable alternative to other neuroimaging methods, particularly due to its minimal radiation exposure. As a bedside diagnostic tool, CUS can be readily performed and repeated, making it an invaluable imaging modality in NICUs.

In this study, the cohort consisted of 57 male neonates and 43 female neonates. These demographic findings are similar to a previous study,[11] which also observed a male predominance in their study population. Additionally, in this analysis, all neonates were designated as LBW. Prior studies reveal that 20% of neonates are classified as very low birth weight (VLBW). Additionally, all neonates included in this analysis were classified as LBW; one previous study shows 20% of neonates were categorized as VLBW.[11] Other research found that the majority of neonates (40.67%) had a birth weight between 1.5 and 2 kg, with a mean birth weight of 1.8 ± 0.54 kg.[10] Also, abnormal CUS findings were significantly associated with birth weights <2000 g, as well as with adverse perinatal and maternal factors, with all *P* values being <0.05.[12]

The current research demonstrated that abnormal findings in cranial ultrasound were significantly linked to lower Apgar scores and negative maternal and perinatal outcomes.[8] Based on these findings, we recommended that early neuroimaging be incorporated as part of the assessment of brain health, especially for preterm neonates, to identify risk factors. This was comparable with some studies,[12,13] which observed strong associations between abnormal CUS findings and conditions such as microcephaly, low Apgar scores at 5 min, and related complications, including the need for mechanical ventilation, surfactant therapy, and neurological disorders.

In this study, the majority of cases were associated with pregnancy-induced hypertension (23 cases), followed by anemia (17 cases), antepartum hemorrhage (APH) (14 cases), polyhydramnios (11 cases), gestational diabetes mellitus (7 cases), eclampsia (6 cases), and oligohydramnios (5 cases). These findings were in accordance with a previous study, which found that among 108 normal patients, 35 patients were observed with maternal risk factors, and among 42 abnormal patients, 23 patients were observed with maternal risk factors.[10] Pregnancy-induced hypertension and prelabor rupture of membranes were high among subjects with abnormal cranial findings.

In this study, the most common neonatal complications were birth asphyxia (n = 17), respiratory distress (n = 15), hypoglycemia (n = 6), birth trauma (n = 5), neonatal seizures (n = 4), and hypocalcemia (n = 2). This was comparable with the previous study,[7] which reported similar results with respiratory distress syndrome (25.53%), neonatal sepsis (21.27%), birth asphyxia (17.02%), neonatal seizures (8.51%), and necrotizing enterocolitis (6.38%). Additionally, another study found that, among 75 preterm neonates, CUS abnormalities were present in 25.4%, including periventricular hyper-echogenicity (10.6%), GMH–IVH (8%), PVL (4%), and cerebral edema (2.4%).[14] CUS findings were linked to gestational age, birth weight, and complications such as APH and birth asphyxia. These findings were supported in their study.[12]

In this study, the most common CUS finding was germinal matrix hemorrhage (n = 27), followed by periventricular hyper-echogenicity (n = 22) and intraventricular hemorrhage (n = 15), whereas the remaining abnormalities are presented in Table 3. Similar findings have been reported in previous studies, which documented abnormalities such as hydrocephalus (12%), intracranial hemorrhage (6%), brain edema (6%), and PVL (2%) among preterm neonates.[15] Other studies also reported that a considerable proportion of neonates had abnormal CUS findings, including intracranial hemorrhage (12%) and periventricular echogenicity (13%).[9] Furthermore, it has been observed that out of 200 neonates, 76 (38%) had abnormal CUS findings, whereas 124 (62%) had normal CUS findings.[12] Similarly, another study reported abnormal CUS findings in 26% of neonates.[11]

In this study, neonatal clinical outcomes revealed that 89% discharged, 8% DAMA, and 3% mortality. This was comparable with a previous study,[10] which reported that among 42 (28%) neonates with abnormal outcomes, 35 (83.3%) recovered, 6 (14.28%) were discharged on request/DAMA, and 1 (2.38%) died. The correlation between birth weight and neonatal mortality was statistically significant ($P < 0.05$) in this study. Abnormal CUS findings were significantly associated with birth weights <2000 g and adverse perinatal factors ($P < 0.05$).[12]

Conclusion

The findings of this study shed light on the significant impact of birth weight on neonatal outcomes, with lower birth weights being associated with higher mortality rates. In contrast, no significant association was observed between cranial ultrasound abnormalities and neonatal mortality. This suggests that while perinatal risk factors, particularly birth weight, play a critical role in determining neonatal outcomes, cranial ultrasound findings may not be as robust a predictor of mortality. These results offer valuable insights into the factors affecting neonatal health in NICU settings and may inform clinical practices aimed at improving neonatal care and prognosis. CUS was mainly performed within the first week of life, so late-appearing

abnormalities may have been missed. The study also relied on available medical records, which may contain incomplete information. Additionally, long-term neurodevelopmental outcomes were not assessed, restricting the ability to link early CUS findings with later neurological status.

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Author contributions

NJP: conceptualization, formal analysis, and resources. KB: validation, methodology, and formal analysis. SM: writing original draft, formal analysis, writing—review, methodology, and resources.

Ethical policy and Institutional Review Board statement

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board, Reg. no. MUHS/Medical/MUHS-053704/2019 (dated February 29, 2024).

Data availability statement

The data are available from the corresponding author.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

Utility of Inhaled Antibiotics in Children with Exacerbations of Non-Cystic Fibrosis Bronchiectasis: A Pilot Study

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Abstract

Background: Inhaled antibiotics are an accepted treatment strategy in cystic fibrosis. We aimed to explore the effect of inhaled antibiotics with and without systemic antibiotics in children experiencing an exacerbation of non-cystic fibrosis bronchiectasis (NCFBE). **Methods:** This prospective pilot study included children with an exacerbation of NCFBE. Inhaled antibiotics were prescribed based on the bacterial antibiogram for 3 months or 1 month if they had a tracheostomy. Systemic antibiotics were prescribed at the physician's discretion. We assessed respiratory bacterial culture and Parent Cough-specific Quality-of-Life (PC-QoL) and cough scores at recruitment, after 3 months of treatment, and 3 months postcessation of treatment. **Results:** Thirty-seven participants were recruited with a median (interquartile range) age of 3.19 (1.55, 6.74) years. One-quarter (n = 9, 24.3%) had a tracheostomy; the majority had isolated *Pseudomonas aeruginosa* (59.5%) and received antibiotics (n = 28, 75.6%). Bacterial eradication was achieved in 75.7%, with lower eradication rates in children with a tracheostomy (odds ratio [OR]: 0.27, 95% confidence interval [CI]: 0.05–1.39) and in those treated without systemic antibiotics (OR: 0.24, 95% CI: 0.04–1.50), although these findings were not statistically significant. Significant improvements in PC-QoL scores and cough scores after 3 months of treatment were observed in patients who received both systemic and inhaled antibiotics (P = 0.002 and P = 0.003, respectively), but not in patients who received inhaled antibiotics alone (P = 0.09 and P = 0.89, respectively). Bacterial recrudescence occurred in 16.2% (n = 6) of participants at 3 months postcessation, with *P. aeruginosa* (n = 5) being the most common organism, and when systemic antibiotics (n = 1) were not used. **Conclusion:** Inhaled antibiotics alone are not effective in managing children with exacerbations of NCFBE.

Keywords: Antibiotics, nebulization, non-cystic fibrosis bronchiectasis, tracheostomy

Introduction

Non-cystic fibrosis bronchiectasis (NCFBE) is characterized by recurrent acute exacerbations of lung disease that impacts morbidity, mortality, and healthcare costs.[1] Frequent flare-ups of bronchiectasis due to bacterial infection, especially with *Pseudomonas aeruginosa*, were among the factors associated with higher mortality in patients with NCFBE.[2,3] Irreversible bronchiectasis may develop due to persistent inflammation and tissue damage resulting from an untreated underlying respiratory tract infection.[4] Delivery of antibiotics via inhalation or nebulization offers significant advantages over systemic antibiotic therapy, as it can achieve high concentrations in lung tissue while reducing the risk of systemic side effects.[5,6] Furthermore, it can help overcome the antagonistic effect of purulent sputum on the drug's biological activity, reduce the number of hospitalizations, improve the quality of life (QoL), and make home therapy possible.[7]

Guidelines for adults support the use of inhaled antibiotics in NCFBE,[8-10] and studies have shown improved

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eradication rates of *P. aeruginosa* with the use of inhaled plus systemic antibiotics.[11,12] In children with NCFBE, guidelines suggest that inhaled antibiotics in combination with systemic antibiotics should be used in selected patients colonized with *P. aeruginosa*.[13] However, the evidence is lacking, especially in children colonized with other bacteria, such as *Haemophilus influenzae* and other Gram-negative organisms.[13] In a small, double-blind, randomized controlled, crossover trial, stable participants with NCFBE receiving inhaled gentamicin showed a significant decrease in bacterial density ($P < 0.001$) and a significant reduction in *H. influenzae* sputum growth (27% vs. 80%, $P = 0.002$).[14] They also showed that the inhaled gentamicin significantly reduced the likelihood of children receiving additional antibiotics for respiratory exacerbations while on inhaled antibiotics (odds ratio [OR]: 0.19, 95% confidence interval [CI]: 0.10–0.33, $P < 0.001$).[14]

This pilot study aimed to explore the effect of inhaled antibiotics in children with an exacerbation of NCFBE colonized with various bacteria, with and without systemic antibiotics. The following outcomes were assessed: (i) bacterial eradication and associated factors, (ii) QoL, (iii) number of unscheduled healthcare visits, (iv) bacterial recrudescence in respiratory cultures 3 months after cessation of treatment, and (v) incidence of adverse events. Our hypothesis was that inhaled antibiotics alone are efficacious in managing children with an exacerbation of NCFBE, with an improvement in both bacterial and QoL outcomes.

Materials And Methods

Study population and data collection

This prospective pilot study involved participants with NCFBE who were followed up by the Pediatric Respiratory Unit at a tertiary care hospital in Malaysia. Participants were recruited from June 1, 2023, to May 31, 2024. We included participants diagnosed with NCFBE at <18 years of age, who were having an exacerbation and either had chronic bacterial colonization in the respiratory tract or had a first isolate of *P. aeruginosa*. Exacerbation was defined as the presence of increased cough or change in cough characteristics for ≥3 days.[15] Bacterial colonization was defined as any bacteria isolated from two respiratory cultures over the past year. We excluded participants or parents who refused to participate in this study or participants who could not proceed with inhaled antibiotics due to allergies, who did not have a nebulizer machine, or who had received inhaled antibiotics within 3 months of recruitment. Participants with missing data on bacterial eradication and QoL were also excluded.

This study obtained approval from the local Research Ethics Committee (MREC ID No.: 2023330-12319) on March 30, 2023, and was conducted following the Declaration of Helsinki and ethical standards for research involving children. All participants' parents/guardians had given their written informed consent to participate in this research. The ClinCalc calculator (https://clincalc.com/stats/samplesize.aspx) was used to estimate the study's sample size. Based on the study by Twiss *et al.*,[14] in which the difference in cough score was 2.53 after nebulized antibiotics, a sample size of 32 was required. After considering a 20% dropout rate (lost to follow-up), nonparticipation rate, and possible missing data (excluded during data cleaning), we aimed for a sample size of 38 participants.

Study flow and instruments

All eligible participants were identified during hospital admission or clinic presentation. Informed consent was obtained before any study procedure. Subsequently, nebulized antibiotics were prescribed for 1 month for participants with a tracheostomy or 3 months for participants without a tracheostomy. The shorter duration for participants with a tracheostomy was decided due to the possibility of increased risk of systemic absorption of inhaled antibiotics, as shown in intubated adult participants treated with aminoglycosides.[16,17] Parents/guardians were required to answer the language-appropriate Parent Cough-specific Quality-of-Life (PC-QoL) questionnaire. A sputum/respiratory sample for culture was collected from participants at recruitment.

Parents were encouraged to complete a daily cough diary to monitor the severity of the cough at home.[18] Sociodemographic data were collected from the parents and/or electronic medical records. Participants/parents were reviewed at 3 and 6 months, during which they were again required to answer the PC-QoL questionnaire; repeat sputum cultures were obtained; and anthropometric measurements, cough symptoms, adverse events, number of unscheduled doctor visits, and side effects related to treatment were assessed. The PC-QoL questionnaire was validated and translated into Malay.[19,20] A minimal important difference of 0.9 was suitable for the PC-QoL questionnaire, confirming its validity and responsiveness in assessing QoL changes in children experiencing chronic cough. The maximum score on the PC-QoL questionnaire was 56, where higher scores reflected a better QoL.

The cough diary was used to assess the severity of the cough.[18] Parents were instructed to gauge the severity of their child's daytime and nocturnal cough daily in a diary for the duration of the study. The scores ranged from 0 to 5, with 0 indicating no cough and 5 indicating severe coughing that significantly disrupted daily activities or sleep. The cough score was calculated as the mean of daytime, nocturnal, and overall cough scores over that month. A lower mean score indicated a better clinical outcome.

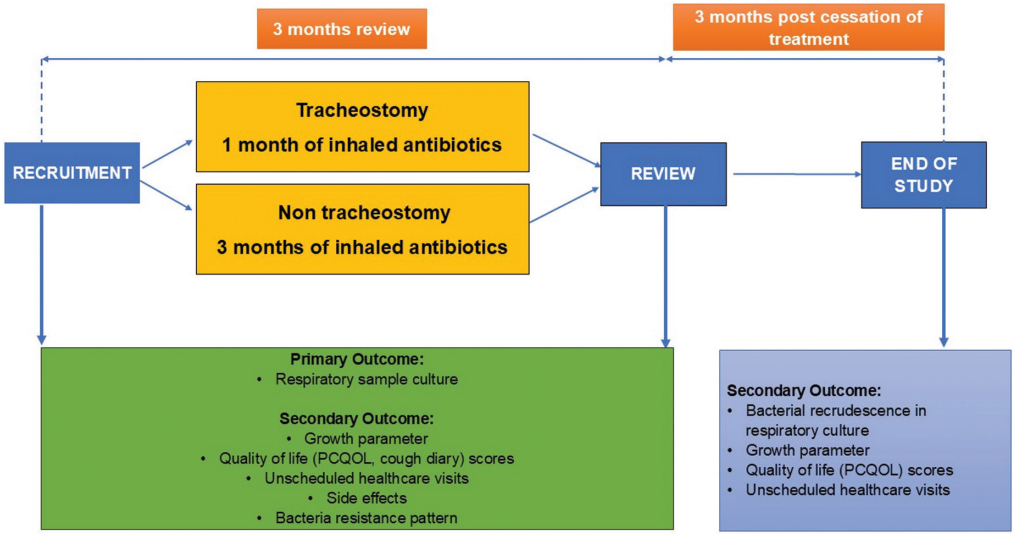

Figure 1: Flow diagram of the study design. PC-QoL = Parent Cough-specific Quality of Life

Definition of study outcomes

Respiratory samples for bacteriology were collected at three time points: at recruitment, 3 months after treatment, and 3 months postcessation of treatment [Figure 1]. Bacterial eradication was defined as the absence of growth in the respiratory culture at the 3-month review for the causative bacteria identified in the baseline respiratory culture.[21] Failed bacterial eradication occurred when the causative bacteria found in the respiratory culture at baseline persisted in follow-up cultures at the 3-month review.[21] Recrudescence of bacteria referred to the reisolation of the same pathogen at the 6-month review, that is, 3 months postcessation of treatment, irrespective of the clinical outcome of the infection. Cough QoL was assessed using the PC-QoL questionnaire[19] at three time points: at recruitment, 3 months post-treatment, and 3 months postcessation of treatment, as detailed below.

Unscheduled doctor visit was defined as the need for any unscheduled healthcare visit for cough, shortness of breath, or any other respiratory-associated symptom that required oral or intravenous antibiotics, and this information was obtained at the 3- and 6-month review.

Adverse events

The following symptoms were explicitly sought at the 3-month review: cough, hemoptysis, sore throat, throat burning, chest tightness or difficulty breathing, and hoarseness of voice. Bacterial resistance of respiratory cultures isolated at the 3-month review was reported. This was defined as multidrug-resistant (MDR), extended-spectrum beta-lactamase–resistant, or methicillin-resistant *Staphylococcus aureus*.

Sociodemographic data included the participants' age (years), gender, ethnicity, and monthly household income (B40 [<RM 5,250], M40 [RM 5,251–RM 11,819], and T20 [>RM 11,820]). Growth parameters (weight, height, and body mass index) were interpreted as *z* scores according to the World Health Organization classification.[22]

Study treatments

The inhaled antibiotic dosage was based on the local hospital's formulary (UniversitiMalaya Medical Centre).[23] The choice of inhaled antibiotics was based on the implicated bacterial antibiogram. If more than one type of bacteria was isolated from the respiratory sample, the heavily growing organism or Gram-negative bacteria, such as *P. aeruginosa*, was designated as the pathogenic bacterium for treatment. Tobramycin was not available in our hospital. Intravenous antibiotics were given for moderate-to-severe symptoms, that is, those requiring admission, while mild symptoms were treated in the outpatient clinic, with or without oral antibiotics, depending on the treating physician. Further details on the inhaled medications used and dosages are available in Supplementary Information.

The antibiotics were mixed with normal saline to make up a total volume of 4 mL and administered via a jet nebulizer. All participants were advised to perform airway clearance first. Pretreatment with two puffs of metered-dose inhaler salbutamol was performed before administering inhaled antibiotics. The duration of nebulized antibiotics was 1 month for participants with a tracheostomy and 3 months for participants without a tracheostomy. The shorter duration of antibiotics for participants with a tracheostomy was to avoid toxicity, as shown in intubated participants treated with aminoglycosides.[16,17]

Statistical analysis

Data were stored securely and analyzed using the Statistical Package for Social Sciences (SPSS) software (version 29.0;

IBM Corporation, Armonk, NY). Descriptive statistics were used to characterize the study population. The distribution of continuous variables was checked using skewness, kurtosis, histogram, and the Shapiro–Wilk test. Continuous variables were presented as mean ± standard deviation if the data were normally distributed, and median (interquartile range [IQR], i.e., 25th–75th percentiles) if non-normally distributed. Categorical variables were presented as frequencies and percentages. Changes in growth were calculated using a paired-samples *t* test, while changes in PC-QoL and cough score were calculated using a Wilcoxon signed-rank test. The effect size was measured using Cohen's *d* for analyzing changes in growth parameters and Phi for analyzing significant factors associated with bacterial eradication. For Cohen's *d*, a value of 0.2 to <0.5 indicated a small effect size, 0.5 to <0.8 indicated a medium effect size, and ≥0.8 indicated a large effect size.[24] As for the Phi coefficient (Φ), a value of 0.1 to <0.3 indicated a small effect size, 0.3 to <0.5 indicated a medium effect size, and 0.5–1.0 indicated a large effect size.[24] The association between categorical data was tested using the Pearson chi-squared test or Fisher's exact test. A *P* value of <0.05 was considered statistically significant.

Results

Participant recruitment and characteristics

A total of 40 children were eligible for recruitment. Two parents refused to participate, leaving 38 children who were finally recruited. During the study, one participant withdrew due to a new diagnosis, resulting in a final number of 37 subjects who completed the study and on whom analysis was performed [Figure 2]. The median (IQR) age of the participants was 3.19 (1.55–6.74) years. The most frequently isolated bacterium was *P. aeruginosa* (59.5%), with *H. influenzae* isolated in only one participant (2.7%). Inhaled gentamicin and amikacin were the most prescribed antibiotics. The majority (75.7%) were prescribed systemic antibiotics.

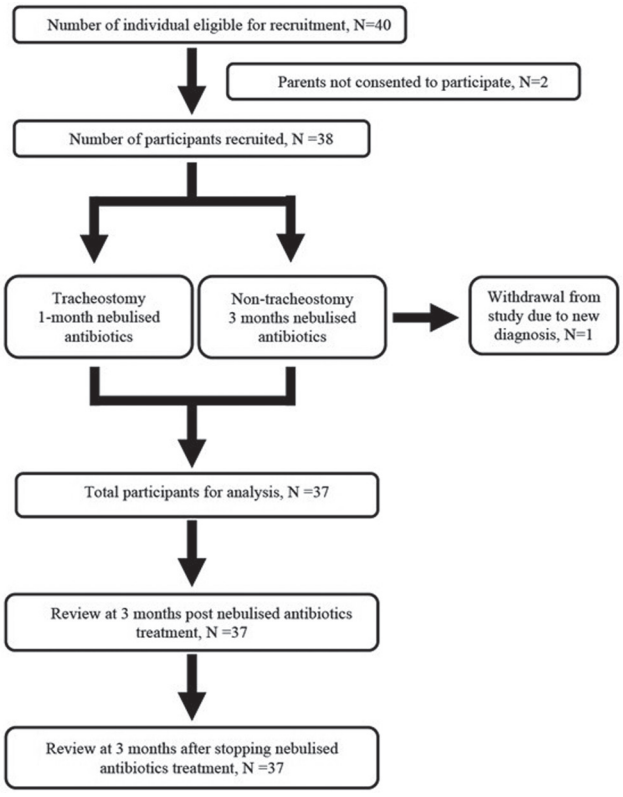

Figure 2: Participant recruitment process of this study

Bacterial eradication after 3 months of inhaled antibiotics and factors associated with successful eradication

The majority (*n* = 28, 75.7%) achieved bacterial eradication post-inhaled antibiotic treatment. Bacterial eradication rates were lower in children with a tracheostomy than in those without (55.6% vs. 82.1%, *P* = 0.18); however, this difference was not statistically significant. Similarly, systemic antibiotics did not significantly increase eradication rates (*P* = 0.38), indicating no statistically significant effect [Tables 1 and 2].

Changes in PC-QoL scores, cough scores, and unscheduled healthcare visits after 3 months of inhaled antibiotics

The PC-QoL score improved significantly from recruitment to 3 months post-inhaled antibiotics in patients treated with both systemic and inhaled antibiotics [Figure 3]. Cough scores improved significantly in children treated with both systemic and inhaled antibiotics [Figure 4]. Unscheduled healthcare visits were required in 18.9% (*n* = 7): 4 received systemic antibiotics at recruitment and 3 were on tracheostomy. Out of the seven,six participants had prior P. *aeruginosa* isolation. Subsequently, all received systemic antibiotics.

Bacterial recrudescence at 3 months postcessation of antibiotics

There were six participants (16.2%) with bacterial recrudescence at 3 months postcessation of inhaled antibiotics; two (33.3%) had a tracheostomy, and the predominant isolate was *P. aeruginosa* (83.3%), which was not MDR. All these participants were compliant with nebulized treatment. Bacteria isolated at different time points are listed in Supplementary Table 1.

Outcomes and changes in PC-QoL-8 scores and unscheduled healthcare visits at 3 months postcessation of inhaled antibiotics

Comparison of PC-QoL scores at recruitment and 3 months postcessation showed significant improvement in patients treated both with systemic and inhaled antibiotics (*P* = 0.003) and with inhaled antibiotics alone

Table 1: Demographic characteristics of the participants

Characteristics	Total *N* = 37*
Age in years, median (IQR)	3.14 (1.52–6.72)
Gender, *n* (%)	
Male	20 (54.1)
Female	17 (45.9)
Ethnicity, *n* (%)	
Malay	20 (54.1)
Chinese	11 (29.7)
Indian	3 (8.1)
Others	3 (8.1)
Age of symptom onset, year, median (IQR)	0.67 (0.19–3.13)
Duration since diagnosis, year, median (IQR)	1.41 (0.65–3.06)
Number of children in the family, median (IQR)	3 (1–3)
Number of family members in the household, median (IQR)	5 (4–6)
Number of parents working, *n* (%)	
Only one	22 (59.5)
Both	15 (40.5)
Total family income bracket, *n* (%)	
B40 (<RM 5,250)	18 (48.6)
M40 (RM 5,251–11,819)	13 (35.1)
T20 (>RM 11,820)	6 (16.2)
Tracheostomy, *n* (%)	
Yes	9 (24.3)
No	28 (75.7)
Respiratory support, *n* (%)	
Yes	23 (62.2)
No	14 (37.8)
Type of respiratory support, *n* (%)	
CPAP and BiPAP	19 (51.4)
Room air	14 (37.8)
Oxygen	4 (10.8)
Etiology of bronchiectasis, *n* (%)	
Postinfectious	10 (27.0)
Neuromuscular disease	9 (24.3)
Tracheostomy-related recurrent infection	9 (24.3)
Immunodeficiency	5 (13.5)
Lower airway structural anomaly	2 (5.5)
Craniofacial syndrome	1 (2.7)
Others	1 (2.7)
Severity of symptoms	
Mild	26 (70.3)
Moderate to severe	11 (29.7)
Bacteriology of respiratory sample, *n* (%)	
Pseudomonas aeruginosa	22 (59.5)
Klebsiella pneumoniae	6 (16.2)
Acinetobacter baumannii	2 (5.4)
Staphylococcus aureus	2 (5.4)
Streptococcus spp.	1 (2.7)
Escherichia coli	1 (2.7)
Haemophilus influenzae	1 (2.7)
Stenotrophomonas maltophilia	1 (2.7)
Proteus mirabilis	1 (2.7)
Systemic antibiotics at recruitment, *n* (%)	
Yes	28 (75.7)
No	9 (24.3)
Type of nebulized antibiotics, *n* (%)	
Gentamicin	20 (54.1)
Amikacin	14 (37.8)
Ceftazidime	2 (5.4)
Colistin	1 (2.7)
Compliance with nebulized antibiotics, *n* (%)	
Yes	34 (91.9)
No	3 (8.1)
PC-QoL score at recruitment, median (IQR)	28 (20.5–42.5)
Cough score, median (IQR)	
Daytime	0.55 (0.11–1.05)
Nocturnal	0.4 (0.12–1.00)
Total	1.00 (0.31–2)

B40 = the bottom 40% of income earners, BiPAP = bilevel positive airway pressure, CPAP = continuous positive airway pressure, IQR = interquartile range, M40 = the middle 40% of income earners, *N* = number of participants, PC-QoL = Parent Cough-specific Quality of Life, T20 = the top 20% of income earners

*Categorical variables were presented as numbers and percentages, and continuous variables were presented as medians and interquartile ranges

(*P* = 0.02) [Figure 3]. There were five (13.5%) participants who had unscheduled healthcare visits after cessation of treatment: four had achieved eradication at 3 months after inhaled therapy and had *P. aeruginosa* at recruitment, and one did not receive systemic antibiotics at recruitment. Of these, all required prescription of antibiotics: oral (*n* = 4) and intravenous (*n* = 1). Respiratory cultures of these participants, taken at 3 months postcessation, included the following isolates: normal flora (*n* = 4) and *Stenotrophomonas maltophilia* (*n* = 1). Two participants experienced an increase in the frequency of cough during the study period due to increased production of phlegm. There was no increase in resistant bacteria detected post-treatment: 21.6% pretreatment versus 18.9% post-treatment.

Discussion

This pilot study explored the effect of inhaled antibiotics, with and without systemic antibiotics, in eradicating respiratory pathogens and improving morbidity in children with an exacerbation of NCFBE. The majority of the children received both systemic and inhaled antibiotics. Bacterial eradication was achieved in three out of four participants. There was no significant reduction in bacterial eradication in children with a tracheostomy and in those who did not receive systemic antibiotics. However, PC-QoL scores after 3 months of inhaled antibiotics significantly improved only in children who

Table 2: Possible factors associated with bacterial eradication

Factors	Eradicated	Noneradicated	*P* value	OR (95% CI)	Phi value
	N = 28 (%)	*N* = 9 (%)			
Age					
<5 years	17 (60.7)	6 (66.7)	1	0.77	−0.05
>5 years	11 (39.3)	3 (33.3)		(0.16–3.75)	
Gender					
Male	17 (60.7)	3 (33.3)	0.251	3.09	0.24
Female	11 (39.3)	6 (66.7)		(0.64–15.00)	
Neuromuscular disorder					
Yes	6 (21.4)	3 (33.3)	0.657	0.55	−0.12
No	22 (78.6)	6 (66.7)		(0.10–2.85)	
Tracheostomy					
Yes	5 (17.9)	4 (44.4)	0.178	0.27	−0.27
No	23 (82.1)	5 (55.6)		(0.053–1.39)	
Systemic antibiotics					
Yes*	25 (89.2)	6 (66.7)	0.281	4.17	0.26
No	3 (10.8)	3 (33.3)		(0.67–26.01)	
Pseudomonas spp.					
Yes	16 (57.1)	6 (66.7)	0.711	0.67	−0.08
No	12 (42.9)	3 (33.3)		(0.14–3.221)	
Resistant *Pseudomonas* sp.					
Yes	1 (6.3)	0 (0)	>0.99	0.4	0.13
No	15 (94.7)	6 (100)		(0.02–7.48)	
Compliance with inhaled antibiotics					
Yes	25 (89.2)	9 (100)	0.99	0.93	−0.17
No	3 (10.8)	0 (0)		(0.03–9.91)	
Klebsiella spp.					0.11
Yes	6 (21.4)	1 (11.1)	0.656	2.18	
No	22 (78.6)	8 (88.9)		(0.23–21.04)	
Inhaled amikacin					−0.21
Yes	9 (32.1)	5 (55.6)	0.255	0.38	
No	19 (67.9)	4 (44.4)		(0.08–1.76)	
Inhaled gentamicin					0.24
Yes	17 (60.7)	3 (33.3)	0.251	3.09	
No	11 (39.3)	6 (66.7)		(0.64–15.00)	

*Included patients who required antibiotics during the unscheduled visits during the first 3 months while on inhaled therapy

received systemic antibiotics. Cough scores also improved significantly in children who received both systemic and inhaled antibiotics, but not in those treated with inhaled antibiotics alone. One of five participants still required unscheduled healthcare visits, and the majority had *P. aeruginosa*. Similarly, 16.2% had persistent bacteria at 3 months postcessation of inhaled antibiotics, and this occurred in children with *P. aeruginosa* isolates. The treatment was well-tolerated, with no significant side effects or increase in resistant bacteria.

The most common bacterial respiratory pathogen isolated in this study was *P. aeruginosa*, followed by *Klebsiella pneumoniae*, with only one participant having *H. influenzae*. The bacteriological profile in these participants differed from that reported in related studies of children with NCFBE, where *H. influenzae* was the most commonly isolated bacterium.[25-27] The low isolation rate of *H. influenzae* in this study, combined with the high isolation rate of *P. aeruginosa*, may be related to more severe disease in our participants.[28] We found that in participants with unscheduled visits and with bacterial recrudescence, *P. aeruginosa* was the most commonly isolated organism. *P. aeruginosa* has been reported to be associated with higher mortality (OR: 2.95, 95% CI: 1.98–4.40), increased hospitalization (OR: 6.57, 95% CI: 3.19–13.51), and exacerbations (mean difference: 0.97 per year, 95% CI: 0.64–1.30).[3]

Although the use of systemic antibiotics together with inhaled antibiotics did not achieve statistical significance, the trend in the effect size suggests that systemic antibiotics are important to achieve bacterial eradication too. In this study, the use of systemic antibiotics in addition to inhaled antibiotics, was at the discretion of the treating physician. To date, only two studies have investigated the use of

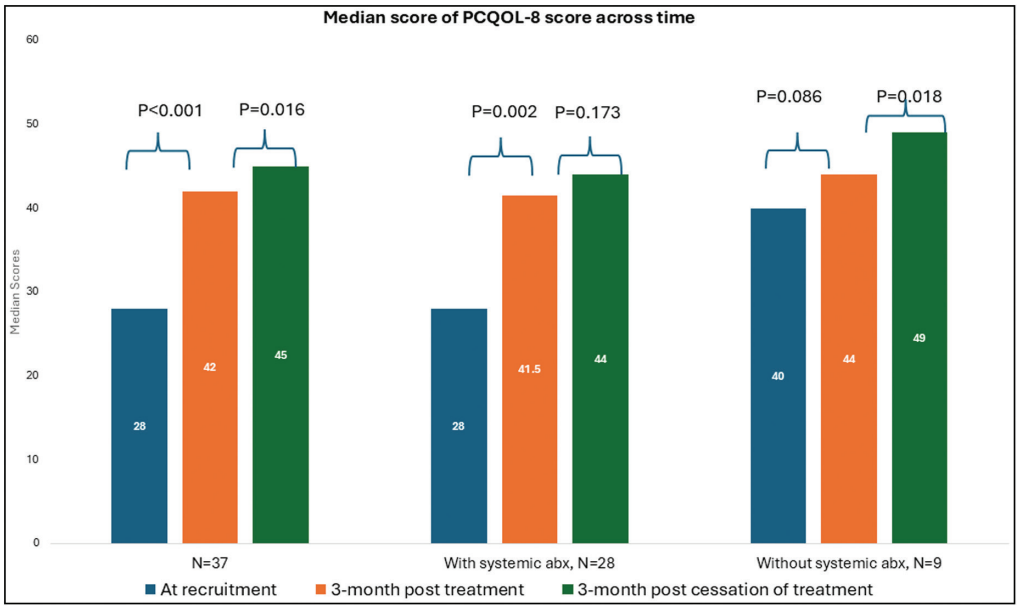

Figure 3: Bar charts showing median Parent Cough-specific Quality-of-Life (PC-QoL) scores for participants across the three time points (at baseline, after 3 months of inhaled therapy, and 3 months postcessation of inhaled therapy) in all patients categorized by with and without systemic antibiotics

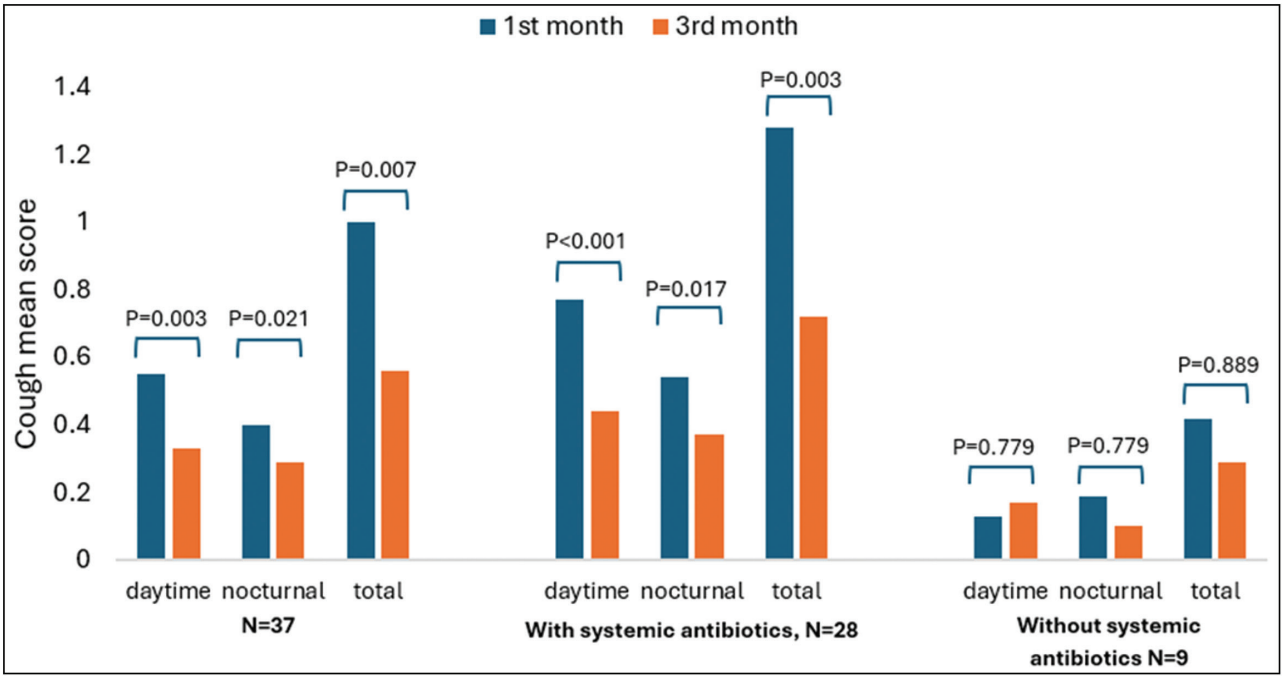

Figure 4: Bar charts showing mean cough scores (total, daytime, and nighttime) for participants across the two time points (at baseline and after 3 months of inhaled therapy) in all patients categorized by with and without systemic antibiotics

inhaled antibiotics in children with NCFBE.[14,29] Twiss *et al*.[14] performed a double-blind, placebo-controlled, crossover trial using inhaled gentamicin in stable children with NCFBE colonized with any bacteria and found that inhaled gentamicin was effective in reducing *H. influenzae* sputum growth and bacterial density, but not in reducing exacerbations. Kartsiouni *et al*.,[29] in their retrospective study of NCFBE children colonized with *Pseudomonas*, found that the use of inhaled colistin (between 1 and 3 months) was associated with successful eradication of *P. aeruginosa* (negative respiratory cultures taken during three consecutive follow-up visits), but no reduction in the number of exacerbations. Our study differs from the two studies mentioned above, as our population consisted of children with exacerbations. The European Respiratory Society guidelines for the management of children and adolescents with bronchiectasis advocate the use of inhaled antibiotics in children with NCFBE, but only if

they are colonized with *P. aeruginosa*, and also suggest the use of systemic antibiotics.[13]

In this study, one in six participants still experienced bacterial recrudescence at 3 months postcessation of inhaled antibiotics. The majority of participants had a tracheostomy and *P. aeruginosa* isolates or *P. aeruginosa* isolates alone, with only one participant having MDR *Pseudomonas*. *P. aeruginosa* is difficult to eradicate, as shown in studies of both cystic fibrosis and NCFBE. Kartsiouni *et al*.[29] reported that 34% of participants had failed eradication of *P. aeruginosa* after treatment with inhaled colistin. Biofilms formed by both *P. aeruginosa* and even *Klebsiella* spp. shield the bacteria from antibiotic therapy and the host's immunological response, making illnesses more difficult to cure.[30]

Managing infections in patients with a tracheostomy is challenging. In this study, only 55.6% of participants with a tracheostomy achieved eradication and 40% experienced recrudescence of the organism, specifically *P. aeruginosa* at 3 months postcessation of treatment. In infants with a tracheostomy and chronic airway colonization, Atag *et al*.[31] found that inhaled antibiotics decreased hospitalization, duration of stay in critical care units, and bacterial load without having a significant negative impact. This suggests that participants with a tracheostomy had a lower initial eradication success rate and a higher likelihood of bacterial recrudescence.

Furthermore, inhaled antibiotics have been administered to tracheostomized children for periods ranging from 2 weeks to 12 months in a few published trials; however, the ideal duration has not yet been determined.[31] We administered inhaled antibiotics for only 1 month to avert possible nephrotoxicity and ototoxicity. Therefore, further research is required to determine the optimal duration of inhaled antibiotic therapy without compromising safety.

We did not encounter any significant adverse effects in our participants, as all participants were prescribed prophylactic β2-agonists. This is similar to that reported by Twiss *et al*.,[14] although not reported in others.[29,32] All inhaled antibiotics can cause bronchospasm. Adults who received inhaled antibiotics were more likely to experience wheeze (OR: 6.74, 95% CI: 2.22–20.52, $P = 0.008$) and bronchospasm (OR: 2.84, 95% CI: 1.11–7.25, $P = 0.03$).[2] This may suggest that the risk of bronchospasm is probably more likely in adults than children.[33]

Antibiotic resistance is a significant concern associated with the use of inhaled antibiotics. Fortunately, this was not a finding in this study. A systematic review of stable NCFBE adults treated with inhaled antibiotics found a higher risk of resistant *P. aeruginosa* (risk ratio [RR]: 1.88, 95% CI: 1.46–2.42, $P < 0.001$, $I^2 = 0.0\%$),[34] although other studies found no increased risk (RR: 1.68, 95% CI: 0.62–4.52; $P = 0.30$, $I^2 = 15.7\%$).[35] Additional evidence suggests that inhaled antibiotics may aid in eradicating existing MDR organisms in intubated participants, reduce the risk of selecting new resistant organisms, and lower the need for systemic antibiotics.[36] In contrast, inhaled antibiotics have been shown to achieve sputum concentrations above the mutant prevention concentration, which may be difficult to achieve with systemic administration, indicating a clear benefit of this route of administration in minimizing antimicrobial resistance.[37] Finally, it has been shown that standard susceptibility testing correlates poorly with clinical effects.[38]

Strengths and limitations

This pilot study allowed us to explore possible factors associated with bacterial eradication in children with NCFBE. We know that inhaled antibiotic therapy was well-tolerated and safe, with no increase in resistant organisms. We also observed that systemic antibiotics should be used and cannot be replaced by inhaled antibiotics alone. Finally, in children with a tracheostomy, a longer duration of inhaled antibiotics is necessary. However, the limitations are the small sample size, as this study was powered to detect improvement in the PC-QoL. We did not randomize patients into those with and without inhaled treatment, as this was an exploratory study. The short duration of assessment of bacterial recrudescence may have an impact on the efficacy of inhaled antibiotics to successfully eradicate bacteria. The shorter duration of inhaled antibiotics in participants with tracheostomies, the inclusion of participants with tracheostomies, and the use of different antibiotics, both inhaled and systemic, may limit the generalizability of this study's findings. However, due to the various types of organisms isolated, with variable sensitivities, we could not standardize the antibiotics used.

Conclusion and recommendations

This study, which included children with an exacerbation of NCFBE, found that treatment with both inhaled and systemic antibiotics did not demonstrate significant bacterial eradication rates. However, PC-QoL scores and cough scores significantly improved only in children treated with both inhaled and systemic antibiotics. We recommend a randomized controlled trial in children with an exacerbation of NCFBE. Participants should receive a 2-week course of oral antibiotics and be randomly assigned to receive either inhaled gentamicin or 0.9% saline for 3 months. Bacterial eradication, QoL and cough scores, and need for unscheduled healthcare visits or oral antibiotics should be monitored at three time points: at recruitment, 3 months post-treatment, and 3 months postcessation of treatment.

Author note

This study was presented at the recent INSPIRED meeting 2025 in Barcelona, Spain.

Author contributions

Conceptualization: WTG, AMN, and SYH. Data curation: WTG and QA. Formal analysis: WTG, QA, and AMN. Funding acquisition: JAdB. Investigation: WTG, AMN, MSA, SYH, KPE, JAdB, and QYL. Methodology: WTG, AMN, and SYH. Project administration: WTG, AMN, and SYH. Resources and software; WTG, AMN, and QA. Supervision: AMN, MSA, SYH, KPE, JAdB, and QYL. Validation: AMN, MSA, SYH, KPE, and JAdB. Visualization; WTG and AMN. Roles/writing—original draft: WTG, AMN, QA, and SYH. Writing—review and editing: WTG, QYL, AMN, SYH, MSA, KPE, and JAdB. All authors have contributed significantly to this article and approved its content.

Data availability statement

All participant data were anonymized and stored on a password-protected computer, accessible only to the investigators.

Ethical policy and Institutional Review Board statement

Ethical approval (MREC ID No.: 2023330-12319) was obtained from the local hospital prior to the commencement of this study, and we obtained informed consent from all parents.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Supplementary Information

Choice of Inhaled Antibiotics

The recommended dosages for nebulized antibiotics were as follows: For gentamicin, children under two years old should receive 20mg twice daily (BD), those aged 2 to 8 years should receive 40mg BD, and those over eight years should receive 80mg BD. For Amikacin, the dosage is 62.5mg BD for children under one-year-old, 125mg BD for those aged 1 to 6 years, 250mg BD for those aged 6 to 12 years, and 500mg BD for those more than 12 years old. Ceftazidime was prescribed at a uniform dosage of 1g BD for all age groups. Lastly, for Colistin, children under two should receive 500,000 units BD, those aged 2 to 8 years should receive 1,000,000 units BD, and those over eight years should receive 2,000,000 units BD.

Supplementary Table 1: Respiratory samples at different time points

N=37	At recruitment	3 months post treatment	3 months post cessation of treatment
Bacteriology of respiratory sample, *n* (%)			
Pseudomonas aeruginosa	22 (59.5)	9 (24.3)	10 (27.0)
Klebsiella pneumoniae	6 (16.2)	4 (10.8)	4 (10.8)
Acinetobacter baumanii	2 (5.4)	1 (2.7)	0 (0)
Staphylococcus aureus	2 (5.4)	4 (10.8)	3 (8.1)
Streptococcus spp.	1 (2.7)	1 (2.7)	0 (0)
Escherichia coli	1 (2.7)	1 (2.7)	2 (5.4)
Haemophilus influenzae	1 (2.7)	0 (0)	0 (0)
Stenotrophomonas maltophilia	1 (2.7)	0 (0)	1 (2.7)
Proteus mirabilis	1 (2.7)	1 (2.7)	0 (0)
Normal flora	NA	16 (43.2)	17 (45.9)
Resistant organism, n(%)			
Yes	8 (21.6)	7 (18.9)	5 (13.5)
No	29 (78.4)	30 (81.1)	32 (86.5)
Resistant strain organism, *n*(%)			
MDR	4 (10.8)	3 (8.1)	4 (10.8)
ESBL	3 (8.1)	4 (10.8)	1 (2.7)
MRSA	1 (2.7)	0 (0)	0 (0)
No	29 (78.4)	30 (81.1)	32 (86.5)

NA = not applicable, MDR = multidrug resistant, ESBL = extended spectrum of bactam lactamase, MRSA = methicillin resistant Staphylococcus aureus.

*Categorical variables were presented in number and percentage