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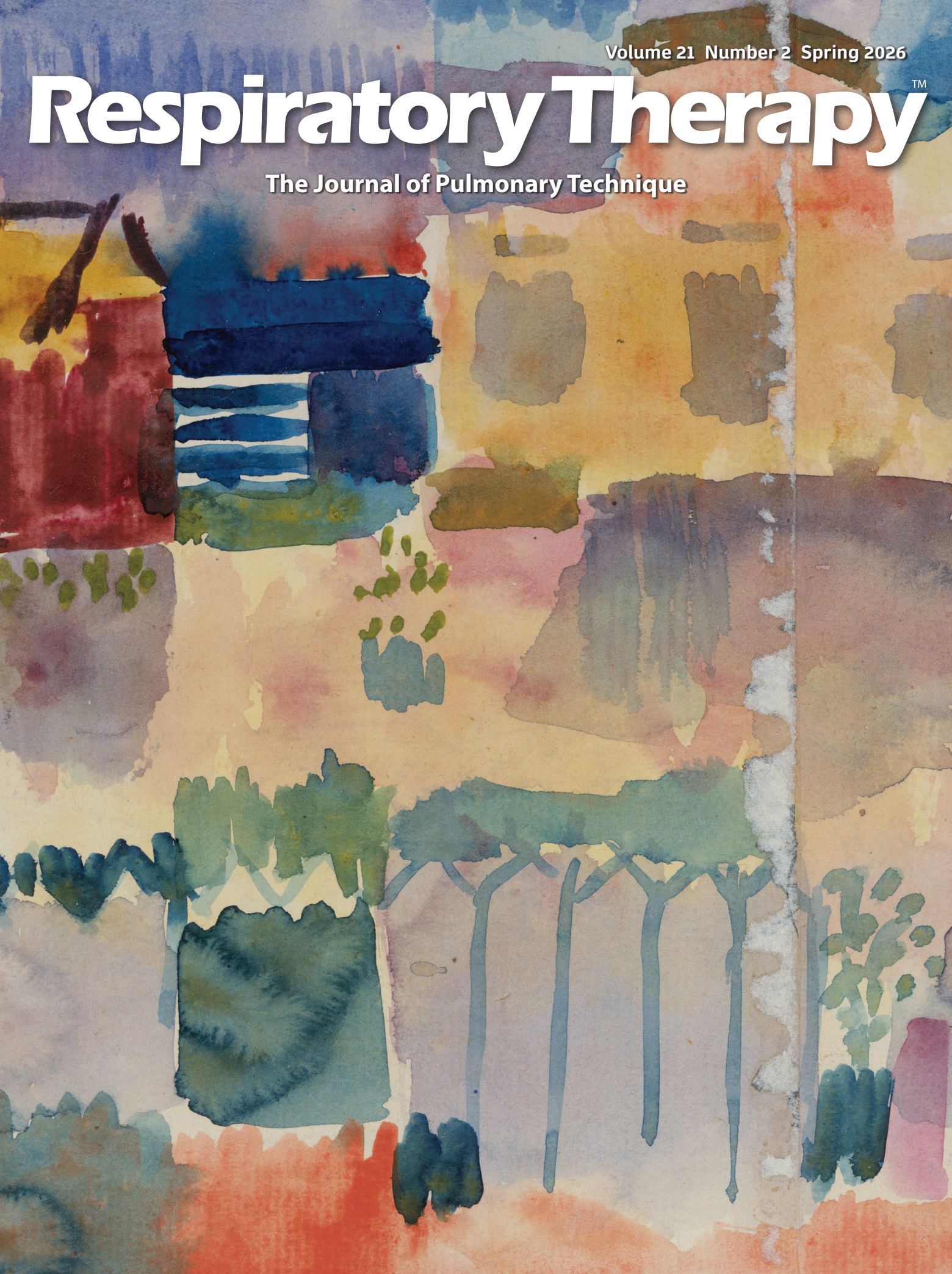
Respiratory Therapy™

The Journal of Pulmonary Technique



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News

■ Spring 2026

Collaborative Care Planning for Sleep and Respiratory Disease

While drifting off to sleep may be calm and restful for many, as muscles in the upper airway relax, some patients begin to experience breathing difficulty. Those who live with any of the more than 80 identified sleep disorders may experience disruptions in their sleep, threatening everything from energy and cognition to emotional and mental well-being as well as overall health. Among the most common disorders are a group of respiratory conditions known as sleep-disordered breathing (SDB), a spectrum of diagnoses defined by the American Thoracic Society that includes sleep hypopnea (increased resistance to airflow through the upper airway, heavy snoring, and marked reduction in airflow) and sleep apnea (complete cessation of breathing). As the clinical understanding of the relationship between sleep and respiratory health has become elucidated, pulmonologists and other respiratory care professionals are commonly collaborating with sleep health professionals in the diagnosis and treatment of SDB for patients of all ages and comorbidities. "We now view sleep and respiratory not as separate systems, but as interconnected networks that influence each other," Rupali Drewek, MD, a pediatric pulmonologist, sleep medicine specialist, and co-medical director of the sleep medicine program at Phoenix Children's Hospital, Phoenix, said. "Another major discovery is how breathing interruptions during sleep raise stress hormones and inflammation that can lead to a multitude of problems, including worsening of underlying asthma. Understanding this connection is valuable for prevention and improved treatment." As education has advanced and treatments have evolved, Drewek and other clinicians are suggesting that screening and care planning continue to trend toward collaborative care planning. Approximately 50-70 million people in the US live with at least one sleep disorder, with an estimated 1 in 3 adults regularly not get the recommended amount of uninterrupted sleep to protect their health, according to the National Heart, Lung, and Blood Institute. Obstructive sleep apnea (OSA) is said to be the most common and severe form of SDB, affecting up to 1 billion adults globally, although some 40 million Americans are undiagnosed. OSA is caused by a physical blockage within the airway while central sleep apnea is a condition in which the brain fails to appropriately signal muscles that control the body's breathing. This inaccurate signaling is more common as people grow older. "Aging changes the body's internal clock and sleep architecture," explained Drewek. "It makes sleep lighter and causes nighttime awakenings."

Saline Succeeds for Children With Sleep-Disordered Breathing

A daily spray of saline in each nostril significantly improved symptoms of obstructive sleep-disordered breathing (OSDB) in children, researchers in Australia found. The nasal spray was as effective as a steroid spray in helping children breathe and sleep better, potentially avoiding the need for surgery and specialist care, said Gillian M. Nixon, MD, adjunct clinical professor at Monash Children's Hospital in Clayton, Australia, who led the research. Although adenotonsillectomy is often the first-line treatment for obstructive sleep apnea (OSA), the demand for ear, nose, and throat specialists outweighs their availability, Nixon said. "The current study was specifically designed to use saline as a first-line treatment and to test whether those that did not respond to saline would respond to steroid spray, but we again found that saline worked as well as steroid [spray]," Nixon said. Older studies, such as a randomized controlled trial from 2001, showed treating OSA with intranasal steroids improved symptom severity. A 2023 Australian study showed equivalent improvement among children with OSDB treated with intranasal steroids and those treated with intranasal saline for 6 weeks. In the new study, published in *JAMA Pediatrics*, Nixon and

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her team analyzed the data of 139 children aged 3-12 years with OSDB who were on the waitlists at otolaryngology, sleep, or respiratory medicine clinics. All participants received once-daily intranasal saline for a 6-week run-in period, with 29.5% showing resolution of their symptoms. The remaining 93 children (mean age, 6.2 years; 62% boys; 54.1% White) with persistent symptoms were randomly assigned to continue once-daily intranasal saline or switched to a once-daily intranasal steroid (50 µg mometasone furoate) for another 6 weeks. After this second period, approximately one third of the children in both the steroid and saline groups saw their symptoms resolved (35.6%; 95% CI, 22.9%-50.6% and 36.4%; 95% CI, 23.5%-51.6%, respectively), with no significant difference between the groups. Secondary outcomes included behavior, quality of life, and parental perception of need for surgery, and no significant differences appeared between the groups. In a subgroup analysis, neither treatment arm stood out as more or less likely to respond to either method.

Preterm Birth Raises Risk for Severe RSV, Even at 36 Weeks

Preterm children, even those born at gestational ages as late as 36 weeks, are more at risk for serious cases of respiratory syncytial virus (RSV), resulting in severe outcomes such as admission to ICUs, compared to those born at full term. The findings "add to the evidence that young infants, and especially preterm infants, are at high risk of hospitalization and complications from RSV," said Daniele Gusland, MD, a pediatric infectious disease physician at UCSF Benioff Children's Hospitals, who was not associated with the study. RSV is the leading cause of infant hospitalization in the United States. RSV infections in early life are associated with health consequences such as chronic respiratory disease and asthma later in life. Researchers conducted a study of 5844 children (56.5% male; 20.8% born preterm) younger than 2 years who were hospitalized with RSV at seven medical centers across the United States between 2016 and 2023. Preterm children experienced a greater risk for hospitalization lasting at least 3 days (adjusted risk ratio (aRR), 1.3; 95% CI, 1.2-1.4), ICU admission (aRR, 1.2; 95% CI, 1.1-1.4), and assisted ventilation (aRR, 1.8; 95% CI, 1.3-2.4) compared to children born at full term. Infants who were born before 37 weeks of gestation tended to be hospitalized at later ages than those born at full term (median age, 6 vs 4 months; $P < .001$). Premature children accounted for 8.8% of hospitalizations for RSV at less than 1 month of age but made up 30.1% of hospitalizations by 23 months of age. More preterm children developed bronchopulmonary dysplasia (BPD), which is a risk factor for contracting the virus, compared to term children (6.6% vs less than.1%; $P < .001$). Preterm children with BPD showed heightened risk for hospitalization past 3 days compared to term children (aRR, 2.0; 95% CI, 1.7-2.4), with this elevated risk lasting up until 23 months of age. The paper highlights the heightened risk for preterm children born at gestational ages above 29 weeks, said Areej Qadri, MD, a neonatologist and assistant professor in the Department of Pediatrics at Rutgers New Jersey Medical School in Newark, New Jersey, who was not associated with the study. Gusland said that the findings support vaccination recommendations from the American Academy of Pediatrics (AAP), which advise administering the RSV vaccine to all infants under 8 months of age, depending on their mother's vaccination status. An additional dose is advised for infants with chronic lung disease of prematurity or if they have risk factors.

Noninvasive Home Monitoring May Aid Pediatric Asthma Care

A digital, noninvasive home-monitoring system — integrating home spirometry, smartwatch data, and medical feedback — showed promise for managing pediatric asthma. Nocturnal heart rate monitoring was associated with asthma control and may serve as a promising noninvasive marker for deterioration. Researchers conducted a prospective study involving 38 children with asthma (median age, 9 years; 68.4% boys) to evaluate whether real-time digital monitoring at home could detect early signs of disease deterioration and improve asthma control. Children were monitored for 12 weeks using a certified healthcare platform, a wrist-worn wearable to monitor heart rate and activity, and a home spirometer for weekly lung function measurements. The healthcare platform provided educational content, measurement overviews, automated reminders, secure text-based communication with clinicians, and tailored monitoring protocols. Automated alerts were sent to the healthcare team when asthma was poorly controlled, or when forced expiratory volume in 1 second dropped > 10% from the reference value; the app then queried symptoms and routed families to the appropriate protocol. The primary endpoint was asthma control assessed via Asthma Control Test questionnaires; a score of ≤ 19 indicated poorly controlled or uncontrolled asthma. An increase in nocturnal heart rate above the age-appropriate median was significantly associated with worsening Asthma Control Test scores (odds ratio [OR], 2.11; $P = .032$); the association was significant even after adjusting for rescue medication use. More frequent home spirometry was significantly associated with worsening Asthma Control Test scores (OR, 2.94; $P < .001$). Childhood Asthma Control Test scores at baseline for children aged 6-11 years tended toward improvement after 12 weeks, but lung function measurements did not change significantly. Adherence to home monitoring declined over time, with wear-time compliance for the wrist-worn device falling from 80% to about 50%, indicating that sustained engagement with monitoring devices is challenging. "These advances [remote alerts, optional monitoring, and minimal burden] signal a shift toward individualized, technology-driven approaches for early detection and quantitative control assessment," the authors wrote.

Study Looks at Lung Monitoring

Strados Labs, a medical technology company advancing respiratory care through wearable technologies, today announced an observational research study evaluating remote lung sound monitoring in patients with chronic obstructive pulmonary disease (COPD) using its FDA 510(k) cleared RESP Biosensor. The study, titled SL-RS-SHORE, will take place at Jefferson Einstein Philadelphia Hospital and affiliated outpatient pulmonary clinics. Enrollment began in January, with plans to enroll up to 20 adults with COPD following a recent exacerbation. COPD exacerbations are a leading cause of hospitalization and readmission in the United States, yet clinicians have limited tools to assess respiratory status once patients return home. While traditional stethoscope auscultation plays a central role in inpatient evaluations, it is largely absent from telehealth

and remote monitoring. This study will evaluate whether continuous, passive monitoring of cough and lung sounds using a stethoscope-based wearable device can help extend respiratory assessments into the home environment with the goal of preventing unnecessary readmissions. Led by Sadia Benzaquen, MD, Chair of Pulmonary, Critical Care, and Sleep Medicine at Jefferson Einstein Philadelphia Hospital, the observational study will follow patients for 90 days after hospital discharge or post-exacerbation outpatient follow-up. The primary objective is to assess the feasibility of remote lung sound monitoring, including patient adherence, compliance, and retention using the Strados Labs RESP Biosensor. Secondary and exploratory objectives will explore associations between data captured by the RESP Biosensor, such as cough frequency, wheeze, rhonchi, respiratory rate and sleep/wake, and standard measures of COPD symptom burden, including the EXACT® questionnaire, pulse oximetry, and spirometry. The study will also explore whether changes in RESP-acquired measures precede or correlate with acute COPD exacerbations. "Home monitoring has already shown promise in improving self-management and detecting exacerbations." Said Sadia Benzaquen, MD, Principal Investigator at Jefferson Health. "This study will help provide additional information to determine if this technology could offer a simpler and more continuous way to keep patients and providers informed in real-time. The RESP Biosensor will be used primarily to measure cough and lung sounds during sleep as well as during structured breathing and exertional activities. Data will be transferred via a companion mobile phone to a secure cloud platform for analysis alongside standard measures including pulmonary function tests and questionnaire results. "COPD has long been an important focus for us at Strados, in part because it remains such a difficult disease to manage effectively outside the clinic." Said Nick Delmonico, CEO & Cofounder at Strados Labs. "After discharge, clinicians have limited visibility into how patients are really doing day to day. We're excited to build on our previous COPD research and further explore how continuous monitoring of cough and lung sounds may provide valuable information during this high-risk period for so many patients." The study is expected to run for approximately 12 months, including start-up, enrollment, and data analysis phases. Findings from the SHORE study are anticipated to inform future studies evaluating remote lung sound monitoring strategies in COPD and other chronic respiratory diseases.

Alpha-1 Antitrypsin Deficiency Likely Underdiagnosed in COPD Patients

Chronic obstructive pulmonary disease (COPD) remains highly prevalent among veterans, but the contribution of alpha-1 antitrypsin deficiency (AAT deficiency or AATD) to this patient population remains unclear and likely underdiagnosed, according to data from more than 2 million veterans presented at the American College of Chest Physicians (CHEST) 2025 Annual Meeting. AATD is a genetic condition increases the risk for both lung disease and liver

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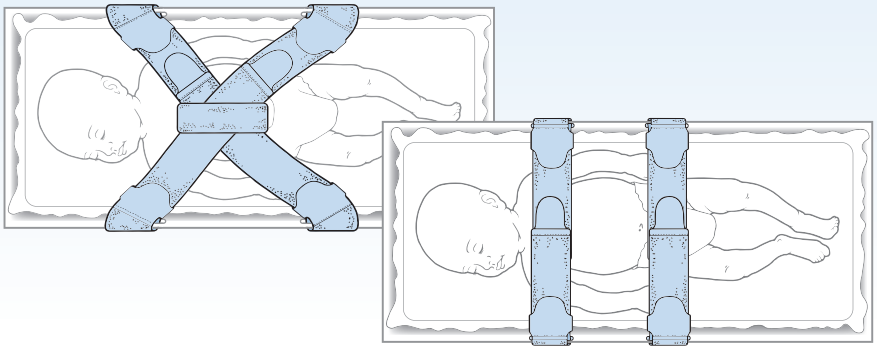

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Why Integrated Cardiorespiratory Diagnostics Matter More Than Ever in Respiratory Therapy

The Editors of Respiratory Therapy

The role of respiratory therapy in modern health care has undergone a steady, but profound transformation. Once focused primarily on bedside care and routine pulmonary testing, respiratory therapists are now central participants in diagnostic evaluation, physiologic monitoring, and longitudinal disease management across a wide spectrum of cardiopulmonary conditions. This expanded scope has elevated expectations for diagnostic technology. Today, relevance is no longer defined by whether a system can perform spirometry or exercise testing, but by how reliably it supports physiologic accuracy, clinical decision-making, and the day-to-day realities of respiratory therapy practice.

In this evolving environment, integrated diagnostic platforms such as the Meridian Series from MGC Diagnostics reflect a broader shift in how cardiorespiratory assessment is delivered. Respiratory therapists are increasingly responsible for performing, troubleshooting, and quality-checking a continuum of tests that range from basic lung mechanics to complex cardiopulmonary exercise testing (CPET). Systems designed to support this full spectrum within a unified architecture are particularly relevant as laboratories seek to balance clinical rigor with operational efficiency.

At the foundation of respiratory therapy diagnostics lies physiologic integrity. Spirometry remains one of the most frequently performed tests in pulmonary medicine, yet its value depends entirely on precision and reproducibility. Poor coaching, inconsistent calibration, or subtle equipment variability can significantly alter results, leading to misclassification of disease severity or inappropriate clinical decisions. For respiratory therapists, who are often the final safeguard for test quality, diagnostic systems must support consistent adherence to established standards while minimizing operator-dependent variability.

As diagnostic practice expands beyond spirometry, the technical demands increase substantially. CPET introduces breath-by-breath gas exchange analysis, ventilatory efficiency indices, and integrated cardiovascular response metrics that require stable instrumentation and robust signal processing. Respiratory therapists conducting these tests must manage patient safety, ensure protocol fidelity, and monitor complex physiologic responses in real time. Platforms that maintain accuracy across both low-intensity and high-demand testing environments support therapist confidence in the data produced and strengthen the clinical value of these assessments.

The relevance of integrated systems also becomes evident when considering longitudinal patient care. Many patients undergo repeated pulmonary function testing over months or years to track disease progression, therapeutic response, or surgical readiness. Consistency in measurement methodology is critical when interpreting trends over time. Diagnostic platforms that unify testing modalities and standardize data acquisition may reduce inter-test variability and improve confidence in longitudinal comparisons, a key consideration for respiratory therapists involved in chronic disease management programs.

Beyond measurement accuracy, workflow integration plays an increasingly important role in defining relevance. Respiratory therapy departments face persistent pressures related to staffing, scheduling, and documentation, often while being asked to expand diagnostic services. Fragmented diagnostic environments, where spirometry, gas exchange testing, and CPET require separate systems, can introduce inefficiencies, increase training burdens, and complicate quality control processes. For therapists, navigating multiple platforms may increase cognitive load and the potential for error.

Integrated diagnostic systems may address these challenges by consolidating testing capabilities into a single workflow framework. From a respiratory therapy perspective, this can translate into more predictable setup procedures, standardized calibration routines, and consistent reporting formats. These operational efficiencies are not merely administrative; they directly influence test quality and patient experience. Reduced setup time allows therapists to focus more fully on patient instruction and monitoring, which in turn improves test performance and data reliability.

The growing utilization of CPET further underscores the need for adaptable diagnostic solutions. Once confined largely to specialized research or tertiary care centers, CPET is now widely used to evaluate unexplained dyspnea, exercise intolerance, preoperative risk, heart failure, pulmonary hypertension, and complex cardiopulmonary interactions. In many institutions, respiratory therapists are the primary operators of CPET laboratories, responsible for test execution, physiologic monitoring, and coordination with interpreting clinicians.

Prepared by the editors of Respiratory Therapy. All editorial content is independently authored and does not require advertiser legal review.

For these programs to function effectively, diagnostic platforms must balance technical sophistication with usability. Systems that integrate CPET into a broader pulmonary diagnostics framework may lower barriers to adoption, particularly in mid-sized hospitals and outpatient centers where resources are limited. From a respiratory therapy standpoint, this integration supports role continuity, allowing therapists to apply consistent skills and protocols across different levels of testing rather than transitioning between disparate systems.

Another dimension of relevance lies in adaptability over time. Respiratory therapy laboratories operate within health-care environments that are constantly evolving, influenced by changing clinical guidelines, reimbursement structures, and patient demographics. Diagnostic systems that are modular or upgradeable may help departments respond to these changes without repeated capital reinvestment. For therapists, continuity of platform familiarity supports standardized training, competency maintenance, and sustained quality assurance practices.

Training and staff development are often overlooked when evaluating diagnostic technology, yet they are central to respiratory therapy practice. New graduates and experienced therapists alike must maintain proficiency across a growing range of diagnostic procedures. Systems that provide consistent interfaces and workflows across testing modalities may reduce the learning curve and support more effective onboarding. Over time, this continuity can contribute to stronger laboratory performance and reduced variability in test quality.

The relevance of integrated diagnostics also extends to interdisciplinary collaboration. Respiratory therapists routinely work alongside pulmonologists, cardiologists, surgeons, and rehabilitation specialists who rely on accurate physiologic data to guide care. Diagnostic platforms that produce clear, consistent, and interpretable results facilitate communication across disciplines. When data integrity is trusted, respiratory therapists become not just test operators, but key contributors to clinical interpretation and patient management discussions.

Importantly, relevance in respiratory therapy is not defined by novelty alone. New technology must ultimately serve the practical needs of clinicians and patients. Diagnostic systems that emphasize precision, efficiency, and adaptability align with the profession's ongoing shift toward evidence-based practice and outcome-driven care. As respiratory therapists assume greater responsibility for complex diagnostic evaluation, the tools they use must support both technical excellence and clinical judgment.

Taken together, the growing complexity of cardiopulmonary diagnostics places respiratory therapists at the center of physiologic assessment. Integrated platforms that support routine spirometry, advanced gas exchange testing, and CPET within a cohesive framework reflect the realities of modern practice. Their relevance lies not in isolated features, but in their ability to support accurate measurement, efficient workflows, and long-term clinical adaptability.

As respiratory therapy continues to evolve, diagnostic solutions designed around integration and physiologic fidelity are increasingly central to delivering high-quality care. In this context, systems that align with the expanding diagnostic responsibilities of respiratory therapists play an important role in shaping the future of cardiorespiratory assessment.

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BioMed Devices OxyMinder Pro: Patient-Level Oxygen and Pressure Monitoring in Neonatal Bubble CPAP

The Editors of Respiratory Therapy

Bubble CPAP is a foundational mode of noninvasive respiratory support in neonatal intensive care, particularly for preterm and low birth-weight infants with respiratory distress syndrome, evolving lung disease, or post-extubation support needs. Its physiologic benefit lies in the maintenance of functional residual capacity (FRC), promotion of alveolar recruitment, and reduction in work of breathing—all while avoiding the risks associated with invasive ventilation. However, the effectiveness of Bubble CPAP depends not on prescribed settings alone, but on the **oxygen concentration and distending pressure actually delivered to the infant at the patient interface**.

In routine practice, clinicians often infer delivered therapy based on system setup—blender settings, flow rates, and water column depth. Yet in neonatal Bubble CPAP systems, delivered oxygen concentration and pressure are highly sensitive to interface fit, circuit integrity, leaks, condensation, and infant movement. As a result, discrepancies between intended and delivered support may go undetected until late physiologic signs emerge.

The OxyMinder Pro from BioMed Devices is designed to address this clinical blind spot by focusing on **direct measurement at the patient level**, rather than upstream system conditions.

The primary function of the OxyMinder Pro is to **verify the oxygen concentration actually being delivered to the infant**. In neonatal care, small deviations in FiO_2 can have outsized physiologic consequences, particularly in extremely preterm infants with limited oxygen reserve and narrow therapeutic margins. While oxygen concentration is typically set upstream, delivered FiO_2 may vary due to circuit leaks, prong displacement, or inconsistent flow dynamics. By measuring oxygen concentration closer to the patient interface, the OxyMinder Pro provides confirmation that the infant is receiving the intended oxygen support, rather than relying on assumptions based on system settings.

Equally important is the device's role in **measuring the pressure delivered to the infant**, rather than estimating pressure based solely on Bubble CPAP setup parameters. Although water submersion depth establishes a theoretical pressure target, actual distending pressure at the nares can fluctuate with interface seal, tubing resistance, and patient activity. In neonates, even modest reductions in delivered pressure may lead to partial alveolar collapse, loss of FRC, increased work of breathing, and escalating oxygen requirements.

The OxyMinder Pro continuously monitors this **delivered distending pressure**, offering clinicians a more physiologically relevant indicator of CPAP effectiveness than upstream system measurements alone.

A key clinical feature of the OxyMinder Pro is its **pressure deviation alarm**, which alerts caregivers when delivered pressure varies outside the desired range. This early-warning capability is particularly relevant in neonatal care, where traditional indicators of CPAP failure—oxygen desaturation, increased apnea, or bradycardia—often represent **late manifestations of lung derecruitment or respiratory instability**. By identifying pressure interruptions or losses at the patient interface earlier in the process, clinicians may intervene before significant physiologic deterioration occurs.

This distinction is clinically meaningful. In many NICUs, troubleshooting Bubble CPAP systems is reactive, triggered by changes in vital signs rather than by real-time awareness of delivered support. Pressure alarms tied to patient-level measurements shift this paradigm toward earlier detection of interface problems, circuit disruptions, or unintentional pressure loss—events that may otherwise remain silent until the infant becomes unstable.

It is important to clarify that the OxyMinder Pro **does not measure or verify source gas pressure or upstream system pressure**. Its relevance lies specifically in monitoring **delivered pressure at the patient interface**, which is the pressure that directly influences lung mechanics, alveolar stability, and breathing effort. When used with an appropriate neonatal interface, the device functions as a safeguard against unnoticed loss of effective CPAP support rather than as a system calibration tool.

From a neonatal practice standpoint, the OxyMinder Pro aligns with lung-protective care strategies that emphasize stability, consistency, and early intervention. By confirming delivered oxygen concentration and continuously monitoring delivered pressure—with alarms to prompt timely response—the device supports Bubble CPAP therapy without altering its fundamental simplicity or workflow.

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In settings where Bubble CPAP is used across varying gestational ages and staffing experience levels, patient-level monitoring tools may help reduce variability in delivered support and enhance situational awareness at the bedside. The OxyMinder Pro's clinical relevance is grounded in this pragmatic objective: ensuring that the therapy intended is the therapy received.

In summary, within the neonatal intensive care environment, the BioMed Devices OxyMinder Pro is relevant for its ability to **verify delivered oxygen concentration**, **measure delivered CPAP pressure**, and **alert clinicians to pressure deviations before late physiologic signs such as desaturation or bradycardia occur**. Used appropriately, it serves as an early detection monitor that complements Bubble CPAP by reinforcing the link between prescribed support and actual patient delivery.

Patients with Tracheostomies: Ethical Considerations and Benefits of Restoring Their Voice

Gabriela Ortiz, BSRT, RCP

Voice is a fundamental aspect of human identity, autonomy, and dignity, yet it is often unintentionally stripped from individuals who require a tracheostomy and mechanical ventilation. Recognizing voice as a human right compels health-care professionals to prioritize communication access as an ethical obligation rather than a convenience.

For patients receiving mechanical ventilation, the quality of communication directly influences comfort, perceived safety, and emotional well-being.[1-2] These findings highlight the need to intentionally integrate communication strategies into routine critical care practice. Bartlett et al. (2008) further reports that patients with communication impairments are at greater risk of experiencing preventable adverse events than those who can communicate for assistance.[3]

The Americans with Disabilities Act (ADA) enforced by the US Department of Justice, establishes requirements to ensure effective communication for individuals with disabilities in all public facilities, including hospitals, long-term care facilities, and physician offices. The ADA mandates that individuals with vision, hearing, or speech disabilities be provided with accommodations that support understanding, participation in care, and preservation of dignity.[4] For example, individuals who are blind may give and receive information audibly rather than in writing, individuals who are deaf may communicate through writing or sign language rather than speech, and patients with tracheostomies may communicate verbally rather than through gestures or writing.

Gabriela Ortiz earned her Respiratory Care Practitioner license in 2006. She has extensive experience managing patients at different stages of care, including acute, sub-acute, sleep therapy, and homecare. As the Respiratory Clinical Director and General Manager at a respiratory care provider, Gabriela managed all company operations, including patient assessment and case management for pediatric and adult patient populations. With her clinical knowledge, Gabriela advanced into clinical training and sales for critical care ventilation products for the ICU and PICU within acute and subacute hospitals. Gabriela has combined her clinical experiences to support others through education and is a regularly invited speaker for university programs, Better Breather's Club, and ALS support groups. She has authored and co-authored multiple peer-reviewed papers on respiratory topics such as the progression of ALS, the effects of a tracheostomy in neonates, and respiratory care plans for patients in homecare. Gabriela is currently a full-time Clinical Specialist with Passy-Muir, Inc.

One practical way health-care providers can fulfill these legal and ethical obligations for patients with tracheostomies is through interventions that restore verbal communication, such as using the Passy Muir® Valve Tracheostomy and Ventilator Swallowing and Speaking Valve (PMV®), which enables patients with tracheostomies to regain their voice. The PMV, a one-way speaking valve, restores airflow through the upper airway during exhalation, allowing phonation. This enables patients to express needs, report symptoms, and participate actively in clinical decision-making, reinforcing both patient safety and dignity.

Consequences of Impaired Verbal Communication in Healthcare

Patients who are unable to use their voice in healthcare settings often experience significant emotional and psychological challenges.[1] Clinically, these psychological impacts are well-documented and have important implications for care delivery.

From an emotional and psychological standpoint, loss of voice frequently leads to frustration, anxiety, fear, and feelings of helplessness.[1] Patients may feel isolated or ignored when they are unable to communicate pain, discomfort, or urgent needs. Many report loss of autonomy and dignity, particularly when they must rely on others to interpret gestures or anticipate needs.[5] This communication barrier can also contribute to depressive symptoms and heightened stress, especially during prolong hospitalizations or critical illness.

From a clinical and safety perspective, the inability to communicate effectively increases the risk of unmet needs, delayed symptom reporting, and medical.[5] Patients may struggle to alert staff of pain or pain level. Respiratory distress, or changes in condition, can compromise timely intervention. This limitation can also hinder informed consent, shared decision-making, and accurate assessment of symptoms.

Socially and from an interpersonal perspective, patients without a voice often experience a feeling of disconnection from caregivers and family, which may further exacerbate emotional distress. Clinicians may unintentionally reduce interactions due to time constraints or communication difficulties, reinforcing feelings of invisibility or loss of personhood.

Overall, the absence of a functional voice in health-care settings not only affects communication but also patient safety, emotional well-being, and engagement in care. This underscores the importance of patient-centered interventions that restore

communication, such as speaking valves and alternative strategies, to support connection and self-sufficiency.

Clinical Example: Patient Without a Voice

A Speech-Language Pathologist (SLP) contacted the nursing team to obtain additional background information on a tracheostomized patient who was unable to vocalize. The SLP explained that a Passy Muir Valve trial was being considered and that a physician's order had already been obtained.

During the discussion, nursing staff expressed concerns about proceeding with the PMV, noting that the patient was frequently irritable and verbally aggressive after losing his voice. They shared that they were apprehensive about restoring his voice, stating they did not want to hear the patient shout offensive or hostile remarks.

The SLP acknowledged these concerns and offered an alternative perspective, explaining that the patient's agitation and apparent hostility might be related to frustration from being unable to communicate effectively. The SLP emphasized that restoring the patient's ability to speak may potentially reduce distress, improve cooperation, and enhance overall communication between the patient and care team.[5]

Clinical Considerations for Valve Placement

There is additional guidance under civil rights laws (ADA), which affirms that hospitals and other health-care facilities must meet patients' communication needs. Under the ADA, patients who require communication tools or support due to speech-related disabilities are recognized as being at greater risk for discrimination, exclusion, and isolation when appropriate accommodations are not provided.[4] When the patient's ability to communicate is limited or denied, whether intentional or unintentionally, this can result in unequal access to care, increased distress, and compromised patient safety.[6]

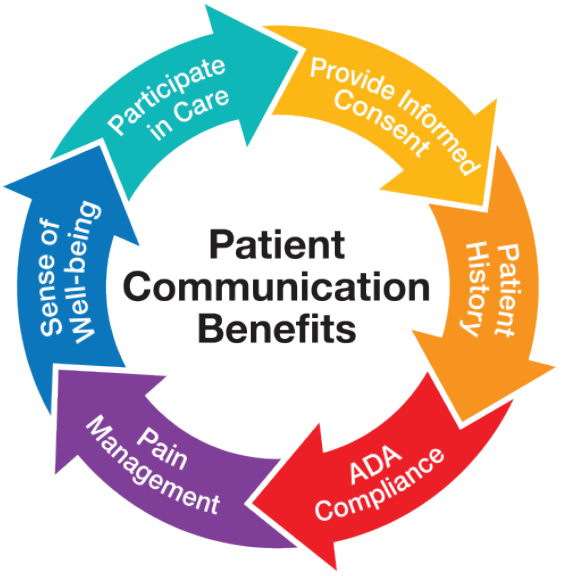
In the context of the clinical example above, discouraging the use of a prescribed communication intervention secondary to concerns about patient behavior underscores the importance of reframing communication access as a civil right and clinical necessity, rather than a discretionary comfort measure. Ensuring access to voice and communication supports not only ethical practice, but also federal mandates designed to protect patients with disabilities.

From a clinical standpoint, the timing of PMV placement is often cited as a barrier to implementation. Traditional recommendations suggest that Valve placement may be considered 48-72 hours following a surgical tracheostomy, once the patient is medically stable and has met appropriate airway criteria.

However, emerging evidence and clinical practice demonstrate that earlier valve use is feasible and safe in select patients, including those with percutaneous tracheostomies, with documented cases of successful placement less than 24 hours post-procedure.[7] These findings stress that Valve candidacy should be based on physiologic readiness and interdisciplinary assessment, rather than a subjective time threshold alone.

Conclusion

Who wants to be a JoÚ Doe with an unknown medical history? Imagine waking up in a hospital bed, surrounded by unfamiliar



faces, unable to speak your name or explain what your body needs. You cannot warn them about the medication you are allergic to or the condition that could change everything about your treatment. Decisions are being made for you, about you, but without you.

Alternative forms of communication exist, but they are often not used and not as effective as a patient's primary communication method.

In these moments, the harm is not physical; it is deeply emotional. Your identity, your history, and your voice are absent with an open tracheostomy tube, and without them, this also may change a patient's sense of dignity. The fear of being unseen and unheard compounds the vulnerability of illness.

When patients cannot speak for themselves, the responsibility shifts to the health-care system to listen differently. Refusing or overlooking alternative means of communication does not erase a patient's voice; it erases their right to be recognized as an individual. Honoring communication in all its forms is not optional; it is essential to humane and ethical care.

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Inactivated Mycobacterial Vaccine Nebulized Inhalation: An Effective Therapy for the Prevention and Treatment of Respiratory Diseases?

Xiaohong Jiang,[1] Qixiang Sun,[1] Yujia Huang,[2] Yuetian Deng,[3] and Chaoqian Li[4]

Abstract

Nebulized inhalation therapy is an important method in the prevention and treatment of respiratory diseases, and inactivated mycobacterial vaccine nebulized inhalation has received a wide attention recently, but the roles and mechanisms are still not fully understood. A literature search showed there is a strong scientific rationale and evidence that nebulized inhalation of inactivated mycobacterial vaccine is effective in the prevention and treatment of respiratory diseases. Clinically available mycobacterial vaccines include *Mycobacterium phlei* (*M. phlei*), BCG, and *Mycobacterium vaccae* (*M. vaccae*). Nebulized inhalation of inactivated mycobacterial vaccine, especially *M. vaccae*, has been used in the prevention and treatment of respiratory diseases, such as asthma, respiratory syncytial virus (RSV), coronavirus disease 2019 (COVID-19), and sepsis. It acts on the respiratory tract directly, thus stimulating the body to produce an immune response, enhance respiratory immunity, and achieve prevention and treatment effects. Nebulized inhalation of inactivated mycobacterial vaccine will be an effective therapy in the prevention and treatment of respiratory diseases.

Nebulized Inhalation Therapy History

Nebulized inhalation therapy is a direct administration method with the respiratory tract and lung as the target organs. It offers rapid onset of action and is associated with minimal systemic exposure, therefore reducing the risk of adverse effects.[1] So, it has been used as an important treatment method for respiratory diseases. It uses physical means, such as ultrasonic vibration, compressed gas dynamics, or mesh vibrations, to convert the liquid drug into aerosol form to form fine particles that can be inhaled by the patient through the natural breathing process.

These particles can penetrate deep into the respiratory tract and reach the alveoli to achieve a highly effective local therapeutic effect, improving the efficacy of the drug while reducing systemic side effects.[2] It is especially suitable for the management of acute attacks; compared with oral or intravenous administration, nebulization can reduce systemic drug exposure and reduce the risk of adverse reactions, and it is suitable for a wide range of people, from infants to elderly patients.

Nebulized inhalation medications for the treatment of respiratory diseases have a long history,[3] and the nebulizer development has also gone through a long process.[4] Nebulized inhalation therapy for asthma and other complaints origins date back 4000 years.[5] It is a very old method of drug delivery.[3] In 1928, antiseptic inhalations were advocated for the treatment of tuberculosis;[4] in 1946, penicillin nebulization was used in bronchopulmonary diseases such as bronchiectasis and infection.[6]

Inactivated Mycobacterial Vaccines and Their Immunological Basis

Mycobacterium is intertwined with human life; among approximately 190 species in this genus, mainly *Bacillus Calmette–Guérin* (BCG) and *Mycobacterium tuberculosis* (*M*tb) are studied intensively.[7] To date, clinically available mycobacterial vaccines include *Mycobacterium phlei* (*M. phlei*), BCG, and *Mycobacterium vaccae* (*M. vaccae*).

M. phlei, a gram-positive acid-fast mycobacterium from the *Actinomycetes Mycobacteriaceae* family, was first discovered by German scientists in 1889; it has no spores or flagella and has a few 1.0- to 2.0-μm-long rod-shaped branches. *M. phlei* has the cell wall structure of both gram-positive (G^+) and gram-negative bacteria (G^-), and it is found widely in soil, plants, and drinking water.[8] Its cell structure is quite similar to that of prokaryotic bacteria except for the unique cell wall.[9] Normally, *M. phlei* is nonpathogenic to humans and other animals practically, but its cell wall and other components have strong immune regulation, growth promotion, anti-infection, and other effects after

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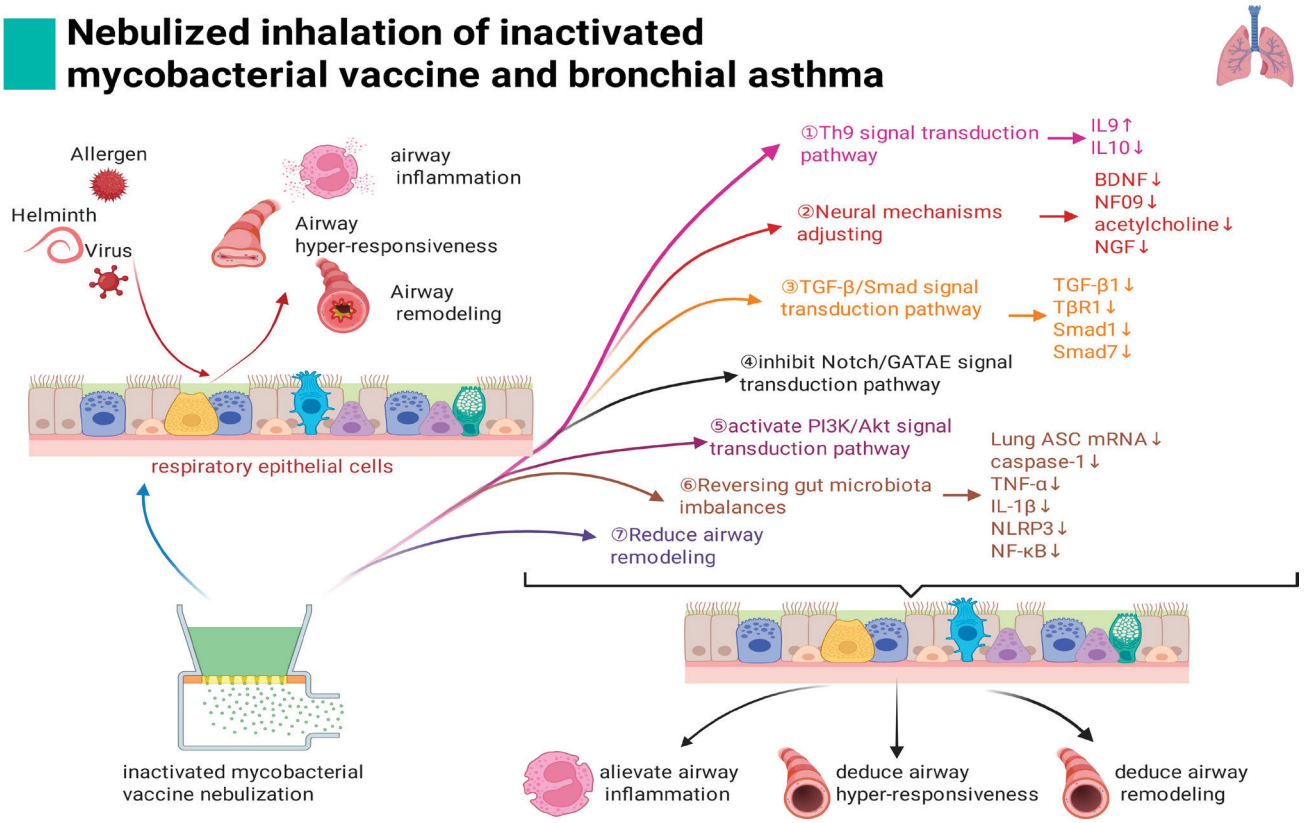

Figure 1. The mechanisms of nebulized inhalation of inactivated mycobacterial vaccine and bronchial asthma.

inactivation. A large number of experiments have demonstrated that *M. phlei* bacteria, cell wall, DNA, unmethylated CpG, polysaccharides, and so on have antitumor, antiradiation, and other effects and are very potential immunomodulators, which are widely used in clinical practice; it can treat many chronic diseases and tumors, such as recurrent respiratory tract infections, bronchial asthma, drug-resistant tuberculosis, and malignant tumors (like as non–small-cell lung cancer, gastric cancer, and bladder cancer).

BCG vaccine, an attenuated strain of *Mycobacterium bovis*, is obtained by serial passage, whereas in 1908, *M. bovis* was isolated by Albert Calmette and Camille Guérin firstly.[10] BCG is widely used as a vaccine,[11] it still was the gold-standard treatment therapy for nonmuscle-invasive bladder cancer for more than 40 years.[12] On the other hand, it not only can be used for the prevention of tuberculosis but also has a nonspecific protective effect on humans called "trained immunity" mediated by innate immune cells such as monocytes, macrophages, and natural killer cell.[13] There still has been research improving that BCG vaccination was unable to cause a long-term reinforcement of Th1 response in asthmatic children, although it could avoid the increased Th2 response observed in control patients.[14] BCG is also used to decrease recurrent respiratory tract infections and acute chronic bronchitis.[15] However, the side effects of BCG, such as allergic reactions and fever, have affected its application; scientists have tried to find alternatives that have no side effects and good immune effects, so people have focused their research on *M. phlei* that are not pathogenic, but unfortunately, *M. phlei is* not produced now.

M. vaccae, a nonpathogenic species belonging to the same genus as *M. tuberculosis*, is commonly found in soil and water and was first described in 1964.[16] It is a preparation with bidirectional immunomodulatory effect made by high-temperature inactivation and purification of *M. bovis* by high temperature. It is available in injectable form in China (Anhui Longkema Biological Pharmaceutical Co., China) and is approved in China as an immunotherapeutic agent.[17] It is often used in the treatment of respiratory diseases such as asthma and tuberculosis[18-20] and also used in the treatment of lung cancer,[21] and it is the only immunotherapeutic agent that is recommended by WHO in the Tuberculosis Strategic Development Plan of 1991.[17]

To date, the mycobacterial vaccines like *M. phlei*, BCG, and *M. vaccae* are widely used in respiratory diseases and bladder cancer, mainly through intramuscular injection. From literature research, we found that nebulized inhalation of inactivated mycobacterial vaccines has a strong treatment and prevention effects on respiratory diseases.

Nebulized Inhalation of Inactivated Mycobacterial Vaccine and Respiratory Diseases

The details of this method are as follows: nebulized with 22.5-μg *M. vaccae* (Anhui Longkema Biological Pharmaceutical Co., Anhui, China) mixed with 10-mL phosphate-buffered saline (PBS) once daily for five consecutive days.[22]

Nebulized Inhalation of Inactivated Mycobacterial Vaccine and Bronchial Asthma

Bronchial asthma is a serious global health problem, affecting approximately 300 million people around the world and causing around 1000 deaths per day.[23] It is a heterogeneous disease, usually characterized by chronic airway inflammation, airway hyperresponsiveness, and airway hypersecretion, defined

by the recurrent attacks of respiratory symptoms, such as cough, wheeze, shortness of breath, and chest tightness. The symptoms vary over time and in intensity, together with variable expiratory airflow limitation. The main pathogenesis of asthma includes hyperresponsiveness, airway inflammation, and high mucus secretion. Professor Li's research team from China has investigated the effect of nebulized inactivated mycobacterial vaccine on asthma from the basic and clinical perspectives. They found it can significantly alleviate airway inflammation, airway hypersecretion, and improve the clinical symptoms of asthma in both asthmatic patients and mice.

Back in 2012, Zhang et al. found that the nebulized inhalation of *M. phlei* can alleviate airway inflammation in asthmatic mice; this is attributed to its immunomodulatory effect on regulating IL-4, IL-10, and IFN-γ secretion,[24] also correlated with modulating γδT cell function. It showed that the expression of IL-10$^+$γδT cells, IFN-γ$^+$γδT cells, and Vγ4 mRNA were significantly increased after nebulized inhalation of inactivated *M. phlei.*[25] It is known that γδT cells are important modulators of airway hyperresponsiveness and allergic inflammation. Researchers demonstrated that Vγ1$^+$γδT cells can increase eosinophilic airway inflammation and airway hyperresponsiveness, while Vγ4$^+$γδT cells reduce airway hyperresponsiveness.[26] Subsequently, they made discoveries in clinical research and demonstrated that nebulized inhalation of inactivated *M. phlei*, to some extent, improved asthmatic symptoms, reduced the need for rescue medication, and reduced acute exacerbation in adult asthmatic patients. It played the same role as inhaled Seretide treatment in reducing airway hyperresponsiveness.[27] Immediately afterwards, Ming et al. showed the same effect in moderately asthmatic children.[28] Through animal research, they also proved further mechanisms of nebulized inhalation of inactivated *M. phlei* in asthmatic mice. It can significantly reduce the IL-5 and IL-13 levels in lung and IgE level in BALF,[29] modulate the balance of CD4$^+$CD25$^+$ regulatory T cells and Th17 cells,[30] and reduce the IL-17$^+$γδT cell-mediated immune response of asthma in mice.[31] These studies proved that *M. phlei* nebulized inhalation may be accepted as an alternative method in asthmatic treatment with less risk of adverse reactions.

On the other hand, the other inactivated mycobacterial vaccine, called *M. vaccae*, attracted the attention of the researchers gradually. There was a research that showed that *M. vaccae* intratracheal administration exerted a lasting ameliorating effect on airway histopathologic features of asthmatic mice.[32] Vaccination with *M. vaccae* in OVA-sensitized pregnant BALB/c mice can prevent Th2 immune responses by enhancing IFN-γ secretion and lowering IL-5 levels during pregnancy, and this effect persisted during the postnatal period in offspring[33] and so on. So, in 2016, Li et al. first used nebulized inhalation therapy of *M. vaccae* in the treatment and prevention of asthma in mice; the results demonstrated that both the airway inflammation and airway hyperresponsiveness in asthmatic mice were alleviated and reduced after being treated with nebulized inhalation of *M. vaccae*. The mechanisms could involve the Th9 signal transduction pathway, *M. vaccae*-mediated effects on the induction of IL-9 secretion, and suppression of IL-10 secretion from γδT cells.[22] From then on, this research team began a series of studies on the relationships between nebulized inhalation therapy of *M. vaccae* and asthma. Their research results showed that nebulized inhalation of *M. vaccae* could indeed alleviate airway inflammation, reduce airway hyperresponsiveness, and airway remodeling in asthmatic mice. The mechanisms include (Figure 1): (1) Th9 signal transduction pathway. It has been described as above. (2) Neural mechanisms adjusting. It was proven that the expression of BDNF, NF09, acetylcholine, and the level of NGF mRNA were decreased in the asthmatic mice after treatment with *M. vaccae.*[34] (3) TGF-β/Smad signal transduction pathway.[35] It showed that after nebulized inhalation of *M. vaccae*, the expression of TGF-β1, TβR1, Smad1, and Smad7 of the TGF-β/Smad signal transduction pathway was deregulated in asthmatic mice. (4) Notch/GATA3 signal transduction pathway. The result demonstrated that the *M. vaccae*-primed γδT cells can alleviate asthmatic symptoms in mice by reversing lung Th2 polarization and inhibiting the Notch/GATA3 signaling transduction pathway.[36] (5) PI3K/Akt signal transduction pathway. The newest research from Xiao et al. proved that nebulized inhalation of *M. vaccae* can decrease eosinophil counts; alleviate airway inflammation, mucus secretion, and airway remodeling in asthmatic mice through autophagy inhibition; and reduce the levels of IgE, IL-5, IL-13, and TNF-α by inhibiting autophagy; it can also suppress autophagy in IL-13-stimulated BEAS-2B cells. *M. vaccae* nebulization may protect against asthma by activating the PI3K/Akt signaling pathway.[37] (6) Reversing gut microbiota imbalances. We know that host immunity can influence the composition of the gut microbiota and affect disease progression consequently. It is proven that this method can alleviate airway inflammation and hyperresponsiveness in asthmatic mice by reversing imbalances in gut microbiota.[38] Xiao et al. also proved that *M. vaccae* nebulized inhalation can inhibit the mRNA expression of lung ASC, caspase-1, TNF-α, and IL-1β, and also inhibit the expression of lung NLRP3 and NF-κB protein during allergen sensitization or challenge.[39] (7) Reduce airway remodeling. Xiao et al. demonstrated that the expression of IL-1β, TNF-α, NF-κB, and WISP1 mRNA in the pulmonary tissue of asthmatic mice was downregulated, while β-catenin, WISP1, and Wnt1 protein were inhibited, and glycogen synthase kinase-3 beta (GSK-3β) was upregulated after nebulized inhalation of *M. vaccae*. Nebulized inhalation of *M. vaccae* can reduce airway remodeling in asthmatic mice.[39] These mechanistic insights are expected to pave the way for therapeutic strategies for asthma.

Nebulized Inhalation of Inactivated Mycobacterial Vaccine and Respiratory Syncytial Virus (RSV)

RSV is the leading cause of acute lower respiratory tract infection, especially in young children.[40] Former research demonstrated that *M. vaccae* nebulization can protect against allergic asthma, as RSV infection and bronchial asthma are closely related.[41] We further hypothesized whether nebulized inhalation of *M. vaccae* can protect against pulmonary RSV infection. Therefore, we investigated the effect of *M. vaccae* nebulization on RSV infection in BALB/c mice. One week before the RSV infection mouse model was established, the mice in the RSV infection group were all nebulized with *M. vaccae* once a day for five consecutive days. The results showed that after 1 week of *M. vaccae* intervention, in the RSV infection group, the mice's airway inflammation was alleviated, the pulmonary mRNA levels of RSV, NF09, acetylcholine, and EGFR expression were decreased considerably, whereas the TLR7 and TLR8 mRNA levels were increased significantly. It further proved the effect of *M. vaccae* nebulization on RSV infection; the mechanism may be the effect of *M. vaccae* on the regulation of neurotransmitters and expression of TLR7, TLR8, and EGFR.[42]

Nebulized Inhalation of Inactivated Mycobacterial Vaccine and Coronavirus Disease 2019 (COVID-19)

During the COVID-19 pandemic, the research team of Professor Li also explored the efficacy, safety, and effect of inactivated mycobacterial vaccine inhalation on the treatment of COVID-19. They conducted a randomized, double-blind, and placebo-controlled clinical trial; a total of 31 adult patients with moderate COVID-19 were included. They were randomly divided into two groups. The primary outcome was the time interval from admission to viral RNA negative conversion (in this study, the oropharyngeal swabs were used), the secondary outcomes included chest computed tomography (CT), mortality, the length of hospital stay, and complications during the treatment. Patients were followed up to 4 weeks after discharge (viral RNA were reexamined, chest CT, etc.). The results showed that *M. vaccae* nebulized inhalation shortened the time interval from admission to viral RNA negative conversion, which might be beneficial to the prevention and treatment of COVID-19.[43]

Nebulized Inhalation of Inactivated Mycobacterial Vaccine and Sepsis

Sepsis often causes acute lung injury and has a high clinical mortality rate; it is thought to be related to a variety of inflammatory mediators, but the pathogenesis remains unclear.

M. phlei cell wall, polysaccharides, and other components have immunomodulatory functions. As an inactivated mycobacterium, can *M. phlei* alleviate lung injury in sepsis? Professor Gu from China demonstrated that *M. vaccae* nebulized inhalation can reduce lung damage by reducing the levels of sepsis-related inflammatory factors and pathway proteins. It has certain clinical significance.

Nebulized Inhalation of Inactivated Mycobacterial Vaccine and Other Diseases

To date, our literature search results have not found reports of nebulized inhalation of inactivated mycobacterial vaccines for other diseases.

Summary and Prospects

Nebulized inhalation of inactivated mycobacterial vaccine has the advantages of noninvasiveness, simple operation, and safety; it is suitable for the majority of patients. This method can prevent and treat a variety of respiratory diseases and has a wide range of applications. Immunomodulation may be the main mechanism. The most studied currently was the *M. vaccae* nebulized inhalation effect on respiratory diseases. In bronchial asthmatic mice, it can alleviate airway inflammation, deduce hyperresponsiveness, reduce airway modeling, and so on. In RSV infection mice, it can reduce the RSV mRNA level. In COVID-19 patients, it can shorten the time interval from admission to viral RNA negative conversion.

This method, nebulized inhalation of inactivated mycobacterial vaccine, has been granted patents in China and has been applied in clinical practice. With further research, nebulized inhalation of inactivated mycobacterial vaccine may become an important means for the prevention and treatment of respiratory diseases and will provide new ideas and methods for the prevention and treatment of respiratory diseases.

However, despite its many advantages, there are still some challenges and problems. For example, the specific mechanism of this method still needs to be further studied; at the same time, more clinical trials are needed to verify the differences in efficacy between different populations and different disease types.

Author Contributions

Xiaohong Jiang: writing – original draft. **Qixiang Sun:** writing – original draft. **Yujia Huang:** writing – review and editing. **Yuetian Deng:** writing – review and editing. **Chaoqian Li:** writing – review and editing, funding acquisition. All authors read and approved the final manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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How Do Airway Clearance Therapies Work Together?

A 'Prepare → Mobilize → Evacuate' Framework for Clinical Practice

Leah Noaeill

The patient's chart says it all: bronchiectasis, daily productive cough, multiple exacerbations this year, and yet another admission for pneumonia. For bedside RTs and clinicians building daily care plans, the question is not whether airway clearance matters — it's what combination of therapies will actually help this patient.

Chronic lung disease, neuromuscular weakness, and postoperative changes each affect lung volume, mucus properties, and cough strength in different ways. As new technologies emerge, clinicians are left to sort through marketing claims and historical habits to answer a basic question: How does this therapy fit into airway clearance, and how does it compare to the other options available?

Although the goal is simple — to move mucus out of the lungs — the way we get there can be complex. Over the past several decades, airway clearance approaches have evolved from manual chest physiotherapy to a wide range of patient-directed techniques and system-based therapies. With so many options, clinicians need a practical way to evaluate whether a patient's current regimen is complete or whether critical steps are being missed.

The Framework: Prepare → Mobilize → Evacuate
One way to organize these options is to think of airway clearance as a three-step process. Each step addresses a distinct physiologic objective, and skipping a step can limit the effectiveness of the therapies that follow.

Prepare: Recruit Volume and Open Airways
Before mucus can be mobilized effectively, the lungs need to be open. Patients with chronic lung disease, atelectasis, or postoperative changes often have collapsed or poorly ventilated regions where mucus accumulates but airflow cannot reach. If a mobilization therapy is applied to a lung that has not been adequately expanded, oscillation or percussion may not reach the distal airways where secretions are trapped.

The Prepare phase uses lung expansion, sustained positive pressure, or deep-breathing techniques to recruit collapsed alveoli, improve ventilation distribution, and open airways ahead of mucus-mobilizing therapies.

Techniques that address the Prepare phase include: positive expiratory pressure (PEP), oscillating lung expansion (OLE) systems, lung expansion maneuvers within the active cycle of breathing technique (ACBT), and incentive spirometry in cooperative patients.

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Clinical implication: When a patient is adherent to a mobilization therapy but still retaining secretions, the Prepare phase is the first place to look. Is the lung adequately expanded before oscillation or percussion is applied?

Mobilize: Move Mucus from Distal to Central Airways
Once airways are open and ventilation is distributed, the goal shifts to moving mucus from the peripheral airways toward the central airways where it can be cleared. Mucus mobilization relies on creating shear forces at the airway wall through oscillation, vibration, or percussion.

Different therapies generate these forces through different mechanisms. External approaches, such as high-frequency chest wall oscillation (HFCWO), transmit energy through the chest wall. Internal approaches, such as intrapulmonary percussive ventilation (IPV) and OLE systems, deliver high-frequency oscillations directly to the airway via a mouthpiece, mask, or tracheostomy interface. Patient-directed techniques, such as the forced expiration technique within ACBT and oscillatory PEP devices, use the patient's own breathing to help generate expiratory flow bias.

Each approach has practical tradeoffs in session time, patient tolerance, care setting, caregiver requirements, and whether a pressurized gas source is needed. The comparison table in this article maps these differences across common therapies.

Clinical implication: Mobilization is the phase clinicians most commonly address — but mobilization alone does not complete airway clearance. Mucus that is loosened but not evacuated can migrate back to distal airways.

Evacuate: Clear Secretions from the Upper Airways
The final step is removing mobilized secretions from the central and upper airways. For patients with adequate cough strength, a spontaneous or huff cough is sufficient. For patients with neuromuscular weakness or an ineffective cough — common in conditions such as ALS, muscular dystrophy, spinal cord injury, and post-extubation — mechanical insufflation–exsufflation (MIE) or suctioning may be required.

This phase is often assumed rather than assessed. A care plan that includes mobilization without a plan for evacuation may move mucus centrally without clearing it, leading to mucus plugging or reaccumulation in dependent airways.

Clinical implication: Evacuation should be explicitly addressed in the care plan. For patients with marginal cough strength, assess whether assisted cough tecÚiques or MIE should be added.

Where Common Therapies Fit: Prepare → Mobilize → Evacuate

Therapy / Technique	Prepare	Mobilize	Evacuate	What It Mainly Does	Typical Patients / Settings	Practical Considerations	HCPCS
Active Cycle of Breathing Techniques (ACBT)	■	■	■	Alternates relaxed breathing, deep breaths with holds, and huff coughing to create expiratory flow bias.	Motivated, instructed patients with preserved cognition and some muscle strength.	Requires patient engagement and coaching; may fatigue weak patients.	N/A
PEP / Oscillatory PEP (OPEP) Devices	■	■	□	Exhalation against resistance (with or without oscillation) to maintain airway patency and move mucus centrally.	Cystic fibrosis, bronchiectasis, chronic mucus producers in hospital or home.	Portable and relatively low cost; effectiveness depends on regular use and correct technique.	E0484
Oscillating Lung Expansion (OLE) Systems	■	■	□	Combines lung expansion and internal high-frequency oscillations, along with an integrated aerosol delivery in one circuit.	Cystic fibrosis, bronchiectasis, COPD with secretions, neuromuscular disease, atelectasis risk; used in hospital and home.	Therapy typically delivered in ~10-minute sessions; may be repeated multiple times daily.	E0469
Chest Physiotherapy (CPT)	□	■	□	Manual percussion and postural drainage to loosen mucus and move it toward larger airways.	Acute care, pediatrics, cystic fibrosis, bronchiectasis; bedside or home with a trained caregiver.	Highly technique-dependent and labor-intensive; harder to sustain long term at home.	N/A
High-Frequency Chest-Wall Oscillation (HFCWO "vest")	□	■	□	External chest-wall compressions generate airflow changes that mobilize mucus toward central airways.	Cystic fibrosis and non-CF bronchiectasis; chronic secretion retention; used in hospital and home	Sessions are often 20–30 minutes; some patients cannot tolerate or wear a vest.	E0483
Intrapulmonary Percussive Ventilation (IPV)	□	■	□	Delivers small bursts of pressurized gas to provide internal percussions that loosen and clear mucus from distal airways.	Hospital or long-term care; spontaneously breathing or ventilated patients with mucus retention.	Requires a pressurized gas source and trained users; home access can be limited.	E0481
Mechanical Insufflation–Exsufflation (MIE "cough assist")	□	□	■	Applies positive pressure to simulate a deep breath, then rapid negative pressure to simulate a cough and clear upper-airway secretions.	Neuromuscular disease or weak cough to deliver an assisted cough; used in hospital and home	Does not mobilize mucus from distal airways; often paired with a mobilization therapy (e.g., OLE, HFCWO, IPV, CPT).	E0482
Spontaneous / Huff Cough (with or without suction)	□	□	■	Uses forced exhalation or cough to clear secretions from central and upper airways, sometimes assisted by suction.	Broad use across populations whenever patients can cough or be suctioned.	Final common pathway for most ACT; effectiveness depends on cough strength or access to suction.	N/A

Identifying Gaps: Is Your Protocol Covering All Three Phases?

The framework above is not only a way to categorize therapies — it is a practical tool for evaluating whether a patient's current airway clearance regimen is complete.

Clinicians can audit an existing care plan by asking three questions:

1. **Are we addressing the Prepare phase — or going straight to Mobilize?**
   Many commonly prescribed airway clearance therapies focus primarily on mucus mobilization. If a patient's regimen begins with oscillation or percussion without first recruiting lung volume or opening airways, the mobilizing forces may not reach the areas where secretions are most problematic. This is especially relevant in patients with atelectasis, low tidal volumes, or heterogeneous ventilation distribution.

2. **If the patient is on a Mobilize-only therapy, what is covering Prepare?**
   Some patients are prescribed a single mobilization therapy as their entire airway clearance regimen. The framework prompts clinicians to consider whether a separate preparation step — or a therapy that integrates Prepare and Mobilize functions — would improve the effectiveness of their current plan. Reviewing the table, clinicians can identify which therapies address one phase versus multiple phases.

3. **Can the patient effectively Evacuate, or do they need cough assistance?**
   This is the most frequently overlooked gap. A patient who is mobilizing mucus effectively but cannot generate an adequate cough may be moving secretions centrally without clearing them. Patients with neuromuscular disease, post-extubation weakness, heavy sedation, or pain-limited cough should be assessed for MIE or suction as part of the clearance plan.

Clinical Example

Consider a patient with non-CF bronchiectasis who has been prescribed HFCWO vest therapy at home. The patient is adherent — using the vest twice daily for 20-minute sessions — but continues to experience frequent exacerbations, persistent daily sputum production, and two hospitalizations in the past year. The patient also performs nebulized bronchodilator and hypertonic saline treatments separately from vest sessions, bringing total daily therapy time to over 60 minutes.

Using the framework, the clinician would observe that the current regimen addresses Mobilize (vest) and Evacuate (the patient has adequate cough strength) but does not include a dedicated Prepare phase. The lungs may not be optimally expanded before oscillation begins, potentially limiting mucus transit from distal airways. Additionally, the separation of nebulized therapy from airway clearance adds to the daily therapy burden — a well-documented driver of poor long-term adherence in bronchiectasis.

The framework would prompt the clinician to consider whether adding or substituting a therapy that addresses the Prepare phase — or one that integrates Prepare, Mobilize, and aerosol delivery — could improve both clinical outcomes and therapy sustainability.

Conclusion: Key Takeaways for Therapy Selection

Airway clearance is rarely a single-step intervention. Most patients benefit from a combination of therapies — or an integrated approach — that addresses all three phases:

- **Prepare** the lungs by recruiting volume and improving airway patency.
- **Mobilize** mucus from the distal to upper airways using oscillation, vibration, and/or expiratory flow bias.
- **Evacuate** secretions from the upper airways with effective cough or suction.

By mapping therapies onto this Prepare → Mobilize → Evacuate framework, clinicians can identify gaps in a patient's current airway clearance regimen and build protocols that match each patient's diagnosis, care setting, and ability to participate.

When a patient is adherent to therapy but still symptomatic, the answer may not be more of the same — it may be that a phase is missing. The framework gives clinicians a structured way to ask that question and a practical path to answering it.

The Essential Role of Caregivers in Pulmonary Hypertension: A Patient Advocacy Perspective on Support, Resources, and the Unique Challenges Facing Families

Seth Hall, MBA, RRT, RRT-ACCS, RRT-NPS

Abstract

Pulmonary hypertension (PH) is a group of rare, progressive, and debilitating conditions that impose substantial burdens on both patients and their caregivers. This article examines the critical yet often overlooked role of caregivers in the management of PH, synthesizing evidence from patient advocacy organizations alongside peer-reviewed scientific literature. The physical, emotional, social, and financial dimensions of caregiver burden are explored, while highlighting the unique challenges faced by caregivers managing supplemental oxygen therapy. Special attention is devoted to the sandwich generation phenomenon, in which middle-aged adults simultaneously provide care to aging parents with PH while raising their own children. Additionally, this article examines the increased burden experienced by caregivers in rural communities, who face significant barriers including long travel distances to specialty care centers, time away from employment, and substantial out-of-pocket expenses for transportation and lodging. The article highlights awareness of caregivers as essential members of the care team and the importance of developing targeted solutions that address their specific needs.

Introduction

Pulmonary hypertension (PH) is a group of rare, progressive conditions characterized by elevated blood pressure in the pulmonary arteries, leading to progressive right heart failure and diminished quality of life (Galie et al., 2015). Classified into five distinct groups by the World Health Organization, PH varies in etiology and treatment approach but universally demands complex therapeutic regimens that may include continuous intravenous infusion, inhaled delivery, or careful oral medication management, along with frequent medical monitoring and often supplemental oxygen therapy as disease severity progresses (Humbert et al., 2022). The disease burden imposed on patients has been compared to that of chronic obstructive pulmonary disease, renal failure, and treatment-resistant cancer (Ferrari et al., 2015).

The impact of PH extends far beyond the individual patient, creating what researchers have termed a "ripple effect" that touches family members, particularly those who assume caregiving responsibilities (Hwang et al., 2011). For caregivers, the specific classification of their loved one's PH may be less salient than the shared realities of managing a progressive, life-limiting illness. Symptom monitoring, medication management, coordination of specialty care, and emotional support represent universal caregiving demands regardless of the diagnostic category. Despite their critical role, caregivers remain a frequently overlooked population whose needs warrant focused attention from healthcare systems, communities, and policymakers.

This article provides an examination of the caregiver experience in PH, drawing upon scientific literature to advocate for enhanced recognition, support, and resources for this critical population. By centering patient advocacy principles, this article identifies pathways toward family-centered care models that recognize caregivers not simply as background support but as key partners in the care process.

The Burden of Caregiving in Rare Disease

Physical and Practical Demands

Caregivers of individuals with pulmonary hypertension assume substantial physical and practical responsibilities that evolve as disease severity progresses. International survey data revealed that 57 percent of caregivers found the demands of caregiving physically draining, with caregiving activities affecting their other daily responsibilities (Ferrari et al., 2012). Practical tasks commonly assumed by caregivers include medication administration (54 percent), household chores (61 percent), transportation to medical appointments, and assistance with personal care activities.

Patient advocacy resources specifically address practical considerations for caregivers, noting that responsibilities may include helping patients prevent infections, recognizing early signs of illness, and knowing when to restrict visitors or avoid crowded environments. These resources emphasize that caregivers must be prepared to assume responsibilities that patients may no longer be able to manage independently, requiring anticipatory planning and ongoing role adaptation.

Emotional and Psychological Impact

The psychological toll of caregiving in rare disease contexts has been extensively documented. A systematic literature review examining psychosocial impacts on caregivers of individuals with rare diseases found consistent patterns of increased psychological distress, lower quality of life, and elevated caregiver burden (Anderson et al., 2024). In the PH-specific context, Hwang et al. (2011) found that lower levels of social support were associated with increased depressive symptoms in

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at least 14 percent of caregivers, with emotional support deficits playing a particularly significant role in caregiver wellbeing.

The International PH Patient and Carer Survey documented that two-thirds of caregivers reported feeling fearful about the future, while 22 percent frequently felt stressed by caregiving demands (Ferrari et al., 2015). Additional concerns included uncertainty about appropriate patient care (19 percent), worry about inadequate care provision (21 percent), and self-doubt regarding caregiving competence (20 percent). Both patients (55 percent) and caregivers (approximately one-third) reported social isolation stemming from limited public understanding of PH, compounding emotional burden with social disconnection.

Financial Burden

The economic impact of pulmonary hypertension on families represents a significant yet often underappreciated aspect of caregiver burden. Research from multiple countries has documented substantial financial strain affecting both patients and caregivers. A Chinese national survey found that both patients and caregivers reported major impacts on family finances and employment, with the financial burden of treatment often overwhelming family resources (Zhai et al., 2017). The study highlighted that financial difficulties were especially pronounced, affecting work conditions for more than half of participants.

A recent Scientific Reports study examining rare disease caregiving found that financial well-being significantly moderated the relationship between caregiver burden and quality of life, with caregivers reporting greater financial security experiencing reduced burden impact on their perceived quality of life (Kowalczyk et al., 2025). This finding highlights the importance of addressing financial support needs as part of caregiver intervention strategies.

Rural Healthcare Access: The Hidden Burden on Caregivers

The challenges facing caregivers of pulmonary hypertension patients are complicated in rural communities, where geographic isolation can create serious barriers to accessing specialty care. Pulmonary hypertension, as a rare and complex disease, requires management by specialized PH centers, often located exclusively in metropolitan academic medical centers. For families residing in rural areas, this geographic distribution of expertise translates to significant travel burdens that compound the already substantial demands of caregiving.

The Travel Burden: Distance and Time

Rural caregivers frequently face round-trip journeys spanning hundreds of miles to reach PH specialty centers. In regions of the United States such as Central Appalachia, patients and their caregivers may travel three to four hours or more each way for routine appointments, transforming what would be a half-day commitment in urban settings into multi-day expeditions. Research on healthcare access barriers in rural communities has documented that these distances create layered challenges: the physical demands of long drives on patients already experiencing dyspnea and fatigue, the need for caregivers to navigate unfamiliar urban environments, and the logistical complexity of transporting oxygen equipment over extended distances.

The time investment required for these journeys extends far beyond driving hours. Caregivers must allocate time for pre-appointment preparation, including ensuring adequate oxygen supplies, packing medications, and arranging for any mobility assistance devices. Post-appointment recovery time may also be necessary, as the physical toll of travel on patients with compromised cardiopulmonary function can worsen symptoms and require rest before the return journey. For caregivers managing employment alongside their caregiving role, these time demands often necessitate using paid or unpaid time off, reducing hours, or in some cases, leaving the workforce entirely.

Employment and Income Loss

The intersection of caregiving responsibilities and employment represents a critical pressure point for rural PH caregivers. Each specialty appointment may require one to two full days away from work, with patients typically requiring quarterly visits during stable periods and more frequent monitoring during treatment adjustments or disease progression. For hourly workers without paid leave benefits, a common employment situation in rural communities, these absences translate directly to lost income. Even for salaried employees, the cumulative effect of repeated absences may jeopardize job security or advancement opportunities.

The Family and Medical Leave Act (FMLA) provides job-protected leave for qualifying caregivers, but this protection applies only to employers with 50 or more employees, a threshold that excludes many rural employers. FMLA leave is also unpaid, meaning that even protected caregivers face income reduction during absences. Research has shown that caregivers with lower income are more likely to provide financial support to their care recipients, creating a difficult situation in which those least able to absorb income loss are most likely to experience it (Lei et al., 2022).

Out-of-Pocket Expenses: Gas, Lodging, and Meals

Beyond lost wages, rural caregivers incur substantial direct expenses associated with medical travel. Fuel costs for roundtrips exceeding 200 to 400 miles can amount to $100 or more per appointment at current fuel prices, a significant burden when multiplied across multiple annual visits. For appointments requiring early morning arrival or spanning multiple days for testing, overnight lodging becomes necessary, adding $100 to $200 or more per night depending on proximity to medical centers. Meal expenses during travel further compound these costs.

Consider a representative scenario: a caregiver from rural Appalachia traveling 180 miles each way to a PH specialty center for a patient's quarterly appointment where they also are scheduled for a right heart catheterization. Sometimes the procedure may require an overnight stay for pre-procedure preparation and post-procedure monitoring. Direct costs might include fuel ($80 to $120 round trip), two nights of hotel accommodation ($200 to $400), meals for two people over two days ($80 to $120), and parking at the medical center ($10 to $30). This single appointment could cost the family $400 to $700 in direct expenses, not including lost wages. Across four quarterly visits, annual out-of-pocket travel costs alone may exceed $2,000 to $3,000, resulting in a substantial burden for families.

Systemic Implications and Advocacy Opportunities

The geographic barriers facing rural caregivers represent a healthcare equity issue deserving focused advocacy attention.

Patient advocacy organizations have begun addressing these disparities through initiatives such as telemedicine advocacy, travel assistance programs, and support for satellite clinic development. Existing networks of specialty care centers, while concentrated in metropolitan areas, provide a model for distributed specialty care that could be expanded to reduce travel burden. Policy interventions that could meaningfully reduce rural caregiver burden include expanded telehealth reimbursement allowing for remote monitoring and follow-up visits, travel reimbursement programs through Medicaid and Medicare, support for mobile health units bringing specialty care to underserved regions, and incentive programs encouraging PH specialists to practice in rural areas.

The Sandwich Generation: Dual Caregiving Responsibilities

Among the most vulnerable caregiver populations are those belonging to the "sandwich generation," a term describing middle-aged adults simultaneously providing care to aging parents while raising their own children. According to the Pew Research Center, nearly half of adults aged 40 to 59 find themselves in this dual caregiving role (Pew Research, 2022). The National Study of Caregiving found that approximately 24 percent of adult child caregivers also care for minor children, representing an estimated 2.5 million individuals in the United States alone (Lei et al., 2022).

Research published in the Journal of the American Geriatrics Society documented that sandwich generation caregivers were more likely to report substantial financial difficulty (23.5 percent vs. 12.2 percent) and more likely to report substantial emotional difficulty (44 percent vs. 32 percent) compared to caregivers without minor children (Lei et al., 2022). Despite these heightened burdens, sandwich generation caregivers provided similar hours of care to their older adults (approximately 75 hours monthly) while simultaneously managing childcare and maintaining higher rates of workforce participation (69 percent vs. 54 percent).

The Mental Health America organization notes that sandwich generation caregivers face unique challenges in managing competing priorities, often experiencing guilt about divided attention and difficulty meeting their own standards for either caregiving role (MHA, 2024). A qualitative study examining coping strategies among sandwich generation caregivers identified three primary approaches: diversifying responses to meet varied needs, self-soothing through spiritual practices and enjoyable activities, and strategic distancing from caregiving situations to preserve psychological well-being (Mohammadi et al., 2024).

When the care recipient has pulmonary hypertension, the complexity intensifies. The unpredictable nature of PH symptoms, the need for vigilant monitoring, and the potential for rapid decompensation create additional stress layers for caregivers already stretched between generations. The Caregiver Action Network emphasizes that 60 percent of sandwich generation caregivers are women, who on average spend 45 additional minutes daily on caregiving tasks compared to male counterparts (CAN, 2024).

The rural dimension further compounds sandwich generation challenges. A caregiver managing both aging parents with pulmonary hypertension and school-aged children might have to coordinate long-distance medical travel around school schedules, arrange childcare during multi-day absences, and manage the competing financial demands of children's educational expenses and parents' medical costs. The combination of sandwich generation status, rural residence, and rare disease caregiving creates a set of overlapping burdens that calls for targeted research and intervention development.

Managing Oxygen Therapy: A Critical Caregiver Responsibility

As pulmonary hypertension progresses, many patients develop hypoxemia that requires supplemental oxygen therapy. Clinical guidance explains that people with PH need their heart and lungs to work harder to obtain adequate oxygen, leading to symptoms such as fatigue and breathlessness that supplemental oxygen can help alleviate. Data from the REVEAL registry demonstrated that 57 percent of patients used supplemental oxygen, with usage associated with more advanced disease and worse prognostic factors (Farber et al., 2018).

For caregivers, oxygen management is a significant practical and logistical responsibility. The American Thoracic Society clinical practice guidelines emphasize that patients and their caregivers should receive instruction and training on the use and maintenance of all oxygen equipment, along with education regarding oxygen safety, including smoking cessation, fire prevention, and tripping hazards (Jacobs et al., 2020). The guidelines specifically acknowledge the substantial body of evidence regarding patient and caregiver burden associated with ambulatory oxygen use, including managing equipment weight and bulk, embarrassment and perceived stigma, fear of cylinders running out, and reduced ability to travel outside the home.

Types of Oxygen Equipment

Caregivers must become proficient with multiple oxygen delivery systems. Standard oxygen concentrators, weighing approximately 50 pounds and typically mounted on wheels, represent the most common home-based option, filtering room air to deliver concentrated oxygen. Portable oxygen concentrators, under 20 pounds and battery-powered, enable greater patient mobility but require charging management and battery monitoring. Compressed gas cylinders offer portability but present weight challenges and require careful supply management, with cylinder duration being limited by the patient's liter flow of oxygen.

Safety Considerations and Rural Challenges

Patient advocacy resources provide guidance regarding oxygen therapy access and safety, noting that patients may face challenges obtaining appropriate equipment that fits their lifestyle. Caregivers must understand that oxygen cylinders should remain at least five feet from open flames, heat sources, or electrical devices, and that smoking presents significant fire risk in oxygen-enriched environments. The nasal mucosa may become dry with prolonged use, potentially causing nosebleeds, while skin irritation around masks or cannulas requires monitoring.

For rural caregivers, oxygen management presents additional challenges. Oxygen supply companies may have limited delivery areas or infrequent delivery schedules in remote regions, requiring caregivers to maintain larger stockpiles or travel to pick up supplies. During long-distance medical appointments, caregivers must calculate oxygen needs for the entire journey,

accounting for delays and ensuring backup supplies. Power outages, more common in rural areas with aging infrastructure, can disable oxygen concentrators, making emergency backup plans and battery-powered alternatives necessary.

The Role of Patient Advocacy in Caregiver Support

Patient advocacy organizations serving the pulmonary hypertension community have developed extensive support infrastructure for caregivers. These organizations provide a range of resources including support groups, peer mentoring programs, dedicated caregiver support lines, and centralized resource portals offering guidance for newly diagnosed patients and their families. Many maintain large networks of both in-person and online support groups to accommodate geographic constraints, while providing educational materials covering treatment options, disease management, and resource navigation that benefit both patients and their caregivers.

Targeted caregiver programs offered by these organizations include guides on effective caregiving practices, the importance of self-care, and strategies for sustainable long-term caregiving. Help centers provide patients, caregivers, and healthcare providers with current medical information, support service availability, and resource connections. Virtual support groups specifically designed for caregivers to enable participation regardless of geographic location, a feature of particular importance for rural families.

Some organizations raise awareness and funding for PH research through community engagement events, offering caregivers unique avenues for emotional expression and community connection that transform feelings of helplessness into purposeful advocacy. Others use digital media platforms, including podcasts and social media campaigns, to share caregiver stories and build online communities of support that reach across geographic barriers. For caregivers managing patients with connective tissue disease-associated PH, specialty organizations provide educational resources and advocacy initiatives addressing the unique intersection of autoimmune disease and pulmonary hypertension, helping caregivers navigate the complex care coordination required between multiple specialties.

Collectively, these advocacy organizations continue building infrastructure to reach underserved populations, expanding networks of care centers, and developing digital tools to connect isolated caregivers with the support they need.

Advocacy Organization Resources

The following are examples, not an exhaustive list, of organizations that provide resources, support, and advocacy for patients with pulmonary hypertension, pulmonary fibrosis, scleroderma, and related conditions, as well as their caregivers and families.

Pulmonary Hypertension Association (PHA)
https://phassociation.org

PHA Europe
https://www.phaeurope.org

PHA Canada
https://www.phacanada.ca

PHA UK
https://www.phauk.org

phaware Global Association
https://www.phaware.global

Team PHenomenal Hope
https://www.teamphenomenalhope.org

Pulmonary Fibrosis Foundation (PFF)
https://www.pulmonaryfibrosis.org

European Pulmonary Fibrosis Federation (EU-PFF)
https://www.eu-pff.org

National Scleroderma Foundation
https://scleroderma.org

World Scleroderma Foundation
https://worldsclerofound.org

Scleroderma Research Foundation
https://srfcure.org

Sociedad Latina de Hipertensión Pulmonar (SLHP)
https://sociedadlatinahp.org

Pulmonary Hypertension Association Australia (PHAA)
https://phaaustralia.com

Lung Foundation Australia
https://lungfoundation.com.au

Pulmonary Vascular Research Institute (PVRI)
https://pvrinstitute.org

Conclusion

Caregivers of individuals with pulmonary hypertension fill an essential yet frequently invisible role in disease management. Whether navigating complex medication regimens, managing oxygen therapy logistics, advocating for appropriate specialty care, or simply providing emotional support through the uncertain trajectory of a progressive illness, these individuals make possible the quality of life that therapeutic advances promise. When caregivers are also managing responsibilities to younger generations, residing in rural communities far from specialty centers, or confronting financial constraints that limit access to support, their burden can become unsustainable without targeted intervention.

Patient advocacy organizations have demonstrated leadership in recognizing and addressing caregiver needs, developing resources that acknowledge caregivers not as peripheral support but as central partners in the therapeutic journey. The continued expansion of these resources, combined with healthcare system changes that formalize caregiver inclusion and policy modifications that address structural barriers such as geographic access and financial strain, offers a pathway toward truly family-centered PH care.

As the field advances therapeutic options for pulmonary hypertension, parallel attention to the people who support patient care, the caregivers, becomes increasingly important. Their wellbeing directly influences patient outcomes, treatment adherence, and quality of life. Investing in caregiver support is not only compassionate but also clinically sound. The path forward requires collaborative effort among healthcare providers, researchers, advocacy organizations, industry partners, and policymakers, all working toward a vision where no caregiver feels alone in their journey and every family affected by pulmonary hypertension has access to the support they need to thrive.

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Integrating Orofacial Myofunctional Therapy Into Airway Care

Clinical Implications for Respiratory Therapy Practice

The Editors of Respiratory Therapy

Airway management extends beyond lower respiratory mechanics alone. A growing body of evidence demonstrates that upper-airway function, breathing pattern, and neuromuscular coordination exert direct and clinically meaningful influence on respiratory health, sleep quality, airway hygiene, and infection risk. Chronic oral breathing—once dismissed as a benign behavioral habit—is now recognized as a physiologically consequential breathing pattern that alters airway resistance, mucociliary clearance, microbial balance, and oxygenation. For respiratory therapists (RTs), this evolving understanding highlights upstream airway factors that may limit the effectiveness and durability of conventional respiratory interventions.

At rest, nasal breathing is the physiologically preferred breathing pattern, supporting air conditioning, filtration, humidification, mucociliary clearance, and normal upper-airway function. While oral breathing may occur during periods of increased ventilatory demand or acute nasal obstruction, persistent reliance on oral breathing represents a deviation from normal physiology and is increasingly associated with adverse respiratory consequences.

The nasal passages warm, humidify, and filter inspired air while facilitating exposure to endogenous nitric oxide (NO) generated within the paranasal sinuses. Nitric oxide plays a recognized role in antimicrobial defense, modulation of bronchial tone, regulation of vascular perfusion, and optimization of ventilation–perfusion matching. Disruption of nasal airflow therefore has implications that extend beyond airflow resistance or patient comfort alone.

Chronic oral breathing bypasses these nasal functions, resulting in reduced air filtration and humidification, drying of airway mucosa, and impaired mucociliary transport. In patients with underlying airway disease, postoperative vulnerability, prolonged device use, or neuromuscular compromise, these changes may materially impair airway defense mechanisms. Compromised mucociliary clearance and mucosal integrity increase susceptibility to upper and lower respiratory infections and may contribute to inefficient gas exchange in the setting of chronic upper-airway dysfunction.

RTs routinely manage patients whose clinical outcomes are influenced by factors extending beyond lung parenchyma. Individuals with obstructive sleep apnea (OSA), chronic rhinosinusitis, recurrent respiratory infections, or intolerance to positive airway pressure therapy frequently demonstrate persistent oral breathing patterns. Despite appropriate device settings and adherence, these patients may continue to experience nocturnal desaturation, fragmented sleep, mouth leak, or excessive work of breathing. Recognizing oral breathing as a modifiable contributor to airway instability has direct relevance for respiratory assessment and care planning.

Chronic oral breathing is associated with altered upper-airway neuromuscular coordination and diminished airway stability. Reduced tongue-to-palate contact, inadequate lip seal, and altered resting muscle tone may decrease upper-airway support and increase collapsibility, particularly during sleep. In pediatric populations, persistent oral breathing has been associated with altered craniofacial growth and airway development. In adults, these neuromuscular and structural adaptations may contribute to residual hypoxemia, persistent flow limitation, and suboptimal response to positive airway pressure therapy.

Upper-airway biofilms represent an additional clinically relevant consideration. Biofilms within the oral cavity and nasopharynx function as protected microbial reservoirs, harboring pathogens associated with recurrent sinus disease, otitis media, and pneumonia. In patients with impaired airway defenses or increased aspiration risk, these reservoirs may contribute to ongoing airway contamination and recurrent infection. Once mature, biofilms demonstrate marked resistance to antibiotics and antiseptics, and repeated broad-spectrum antimicrobial exposure may disrupt commensal microbial balance, exacerbating mucosal inflammation and airway dysbiosis.

Xylitol-based interventions are increasingly discussed as biofilm-modulating rather than bactericidal strategies. Evidence from dental, otolaryngologic, and microbiologic research indicates that xylitol interferes with carbohydrate metabolism in early colonizing bacteria, limiting adhesion and biofilm maturation without sterilizing the mucosa. This distinction is clinically relevant, as reducing early biofilm development may decrease protected niches for pathogenic organisms while preserving beneficial microbial diversity.

Clinical relevance is supported by human data. A prospective study conducted in Israel demonstrated a 75% reduction in recurrent otitis media among pediatric patients using xylitol-containing nasal spray compared with controls. These findings

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suggest that targeted modulation of nasopharyngeal biofilm ecology can meaningfully reduce upper-airway infection burden and reinforce the role of nasal hygiene and microbial balance in preventing recurrent airway infections.

Xlear® nasal spray, a xylitol-based formulation, is described as a tool used clinically to support nasal patency and mucociliary clearance. Evidence suggests that xylitol-containing nasal irrigation can thin nasal secretions, enhance mucociliary transport, and improve nasal airflow. By supporting nasal hydration and patency, such interventions may help preserve normal nasal physiology, including sustained exposure to endogenous nitric oxide. In a randomized controlled pilot study involving patients with chronic rhinosinusitis, xylitol nasal irrigation was associated with increased nasal nitric oxide levels and inducible nitric oxide synthase (iNOS) expression compared with saline irrigation. For RTs involved in airway clearance, sinus care, or postoperative ENT management, maintaining nasal patency is essential for supporting physiologic breathing patterns and reducing reliance on oral breathing.

Orofacial myofunctional therapy (OMT) is presented as a complementary approach aimed at restoring neuromuscular coordination of the upper airway. OMT emphasizes tongue posture, lip seal, nasal breathing, and coordinated oropharyngeal muscle function. While RTs do not typically deliver myofunctional therapy, awareness of its role is increasingly relevant when managing patients with persistent sleep-disordered breathing, CPAP intolerance, unexplained nocturnal desaturation, or refractory mouth leak.

From a sleep-medicine perspective, OMT may improve upper-airway tone and reduce collapsibility during sleep. RTs frequently encounter barriers to effective positive airway pressure therapy—such as dryness, discomfort, and mouth leak—that are exacerbated by chronic oral breathing. Recognizing neuromuscular dysfunction or nasal obstruction as contributors to therapy failure allows for earlier referral and interdisciplinary collaboration.

Clinical observations suggest that surgical correction or device therapy alone may be insufficient when nasal patency, airway hygiene, and breathing pattern are not addressed. Patients with severe sinus obstruction and sleep apnea may experience markedly different postoperative courses depending on airway hygiene practices and support for nasal breathing. Xylitol-based nasal hygiene products have been incorporated into broader supportive care strategies in these settings, underscoring the importance of addressing airway health along the entire respiratory continuum.

For RTs, the relevance lies in assessment, observation, and coordination of care. Identifying chronic mouth breathing, nasal obstruction, or signs of impaired mucociliary clearance can guide referrals to ENT specialists, dental professionals, or certified myofunctional therapists. Such interdisciplinary collaboration may improve outcomes in patients with recurrent infections, chronic hypoxemia, or sleep-disordered breathing resistant to standard interventions.

As respiratory care continues to evolve toward chronic disease management and preventive models, integrating upper-airway considerations aligns with evidence-based practice. Airway health exists on a continuum, and strategies that support nasal breathing, mucociliary function, and microbial balance may enhance the effectiveness, tolerance, and durability of respiratory therapies already in use.

In summary, integrating awareness of orofacial myofunctional therapy and xylitol-based nasal interventions such as Xlear® supports a more comprehensive and physiologically aligned approach to airway management. While further controlled studies are warranted to refine patient selection and protocols, respiratory care professionals are well positioned to identify upstream airway dysfunction and facilitate interdisciplinary care. Addressing these factors may improve therapy tolerance, reduce infection risk, and contribute to more durable respiratory outcomes across clinical settings.

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Inhaled Biologics for Respiratory Diseases: Clinical Potential and Emerging Technologies

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Abstract

The pulmonary route has gained significant attention as a drug delivery method, particularly for managing respiratory diseases. This approach provides several benefits, such as rapid therapeutic action, minimized systemic exposure, improved patient adherence, and the ability to deliver high drug concentrations directly to the lungs. Advances in inhalation devices, including pressurized metered-dose inhalers (pMDIs), dry powder inhalers (DPIs), and nebulizers, have established the pulmonary route as effective for administering both small-molecule drugs and complex biologics. Recent research has showcased the successful use of inhaled biologics such as monoclonal antibodies, nanobodies, and protein-based treatments in conditions like asthma, chronic obstructive pulmonary disease (COPD), pulmonary fibrosis, COVID-19, and respiratory syncytial virus (RSV). These treatments employ innovative mechanisms, such as muco-trapping and immune modulation, to optimize site-specific drug delivery and minimize systemic side effects. As technologies for pulmonary administration continue to evolve, they provide a non-invasive and highly promising platform for enhancing respiratory therapies and broadening the applications of biologics.

Introduction

Since the global pandemic of SARS-CoV-2 arose, awareness of pulmonary diseases has emerged, reshaping priorities in respiratory health. Hence, pulmonary administrative delivery has garnered renewed attention for most pulmonary diseases. Inhaled therapeutics have been used for decades to treat lung diseases. It is the gold standard for the administration of low molecular-weight drugs.[1] However, the potential for expanding pulmonary delivery beyond traditional small molecules into the realm of complex biologics is now being seriously reconsidered.

Pulmonary administration has become one of the most favourable and non-invasive drug delivery techniques due to its ability to target lungs directly, reducing exposure of the used drugs to other locations.[2] Pulmonary therapeutic delivery enables administration of lower drug doses with reduced incidence of systemic adverse effects while also facilitates rapid onset of action for certain therapeutic agents.[3] Delivering therapeutics via inhalation requires navigating a highly complex biological landscape. For pulmonary delivery, the particle must cross several airway bifurcations. While promising, there are a few setbacks in delivering therapeutics through inhalation. An example of the complexity of this system is the defence mechanism of the respiratory tract that has been established to prevent inhaled contaminants from entering the lungs and to remove or inactivate them after they have been deposited. Furthermore, an inhaling device or medium would be needed and used correctly to ensure ideal drug delivery.[3] The physical and immunological barriers in the lung are made up of mucus, the epithelial cell layer, surface fluid that is antimicrobial-rich, and neutralising immunoglobulins.[4] This barrier's main function is to shield the airway from external hazards, but it also prevents effective drug administration. Despite these challenges, the unique physiology of the pulmonary system characterized by a vast surface area and proximity to the systemic circulation offers significant advantages for therapeutics that require rapid absorption and action, such as corticosteroids.[5] This biological "gateway" has driven increasing research interest in pulmonary delivery for more sophisticated agents, particularly biologics.

Biological therapeutics (biologics) cover a broad spectrum of products, including vaccines, blood-based substances, recombinant proteins, and somatic cells. They can be sourced from human, animal, or microbial origins and are frequently manufactured using advanced biotechnological processes. Cutting-edge treatments, such as gene-based or cell-based therapies, are at the forefront of biomedical innovation. In contrast to chemically synthesized drugs with distinct and fixed structures, many biologics are intricate blends that cannot be easily characterized. Biologics generally exhibit high specificity and lower toxicity levels compared to conventional drugs.[6]

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An example of a biological therapeutic is local-acting protein therapies such as Pulmozyme, a nebulized recombinant human DNAse[1] which has been commercialised for the treatment of cystic fibrosis (CF). Among protein-therapeutics, studies of antibodies-based therapeutics have also been increasing as antibodies are one of the prominent biological elements used for the targeted administration of drugs due to their framework's stability, selectivity, and adaptability.[7] The ability of antibodies to accumulate in the target organ or tissue in a targeted, quantifiable manner regardless of the administration site and method is referred to as the use of antibodies in targeted drug delivery.[8]

The goal of developing targeted pulmonary delivery systems is not merely to treat disease but to do so more safely by decreasing side effects and dosage requirements, efficiently by increasing plasma residence duration, and precisely by increasing the drug concentration at the target site, hence also improving biodistribution.[9] Nevertheless, while inhaled antibodies have shown promising preclinical and early clinical outcomes, no inhaled antibody therapies have yet been approved by major regulatory bodies such as the U.S. Food and Drug Administration (FDA) or European Medicines Agency (EMA). This gap between scientific promise and clinical approval highlights both the challenges and the untapped potential within this evolving field. Given the advancements in formulation strategies and delivery technologies, inhaled biologics are increasingly being explored as therapeutic options across a wide range of respiratory diseases. This review critically discusses recent developments in inhaled biologic therapies across various disease contexts, such as asthma, pulmonary fibrosis, chronic obstructive pulmonary disease (COPD), COVID-19 and respiratory syncytial virus (RSV). By evaluating the technologies and strategies specific to each condition, this review aims to highlight both the current progress and the future directions of inhaled biologic delivery.

Pulmonary drug delivery as preferred route for respiratory diseases

The lungs are equipped with an extensive vascular system, holding about 500 mL of blood.[10] Their structure includes a vast epithelial surface spanning over 100 m^2 and a thin alveolar barrier less than 1 μm thick, enabling efficient gas exchange.[11] While the lungs have robust defence mechanisms, the pulmonary route for drug delivery remains highly promising and offers great potential to address unmet medical challenges.

The pulmonary drug delivery route ensures quick symptom relief due to the rapid onset of action, which is especially important during acute exacerbations.[11] In clinical settings, the rapid therapeutic onset provided by inhalation could be critically advantageous, especially in managing acute respiratory distress events where systemic drug administration might be too slow. Inhalation therapy requires a smaller dose compared to systemic administration, and it minimizes systemic exposure, significantly lowering the likelihood of side effects affecting the entire body.[12]

A review comprising the administration of monoclonal antibodies via systemic administrations on COVID-19 has reported that the concentration of monoclonal antibodies (mAbs) in the lungs is typically reduced by 500–2000 folds than in the bloodstream.[13-15] Hence, inhalation delivery offers a more effective approach as it allows a significantly higher proportion of the administered mAbs to reach the target area directly within the airways.[16] This striking inefficiency of systemic administration strongly supports the argument for shifting towards direct inhalation methods to maximize therapeutic availability at the infection site. This approach ensures elevated and longer-lasting drug levels at the disease site, eliminating the need for large doses administered systemically.

Administering drugs directly to the lungs through inhalation can achieve both local and systemic therapeutic effects. Importantly, this dual-action capability underscores the versatility of pulmonary delivery, suggesting it could bridge the gap between targeted and systemic therapies, depending on the disease. Compared to other administration routes, pulmonary inhalation offers significant advantages such as a large absorption area with a thin alveolar epithelial cell membrane that facilitates rapid absorption and high permeability. This ensures rapid concentration of medication at the target site while keeping systemic drug levels low.[17] Considering how pulmonary route is particularly advantageous, when compared to oral delivery, albeit the convenience and non-invasive technique, it is often related to its poor bioavailability due to enzymatic degradation and first-pass metabolism in the liver, making it unsuitable for many biologics specifically the proteins and peptides.[18] In contrast to inhaled delivery route as it bypass hepatic first-pass metabolism primarily due to their route of administration, as they are directly delivered to the respiratory tract rather than absorbed via the gastrointestinal system. This results in reduced systemic metabolism and allows for higher local drug concentrations at the site of action, potentially improving therapeutic efficacy and also reduces systemic exposure.[19]

If compared to intravenous and subcutaneous administrations, both are invasive in nature but has differences in their pharmacokinetic profiles. Intravenous delivery provides 100% bioavailability and rapid systemic distribution, but it requires clinical supervision and often fails to achieve sufficient drug concentration in the lungs, particularly for monoclonal antibodies targeting respiratory infections.[20] In contrast, subcutaneous injections, though more convenient than IV, are associated with delayed absorption and similarly result in limited pulmonary drug levels.[21] Hence, from a patient-centric perspective, the non-invasive nature of inhalation paired with the potential for dose reduction and fewer systemic side effects may enhance therapeutic adherence compared to injectable regimens.[22] These advantages make pulmonary delivery an attractive alternative for administering biologics.

The first traction of pulmonary drug delivery was in the 1950s specifically for asthma treatment and has become a widely accepted approach for managing respiratory conditions since. While initially developed for asthma management, the maturation of inhalation technologies now offers much broader therapeutic possibilities, extending well beyond classical respiratory conditions. Utilizing devices to spray or nebulize drug aerosols, this technique enables patients to breathe in medication, allowing faster achievement of peak lung concentration (Cmax).[23] Animal studies have highlighted the superior efficiency of the inhalation drug delivery route as compared to intravenous or intraperitoneal administration for delivering mAbs targeting respiratory viruses like influenza and RSV. Furthermore, researchers observed that 1.7% of inhaled mAb 1212C2, a strong neutralizing antibody

Table 1 Shows a comparison of pulmonary drug delivery devices

Device type	Mechanism/description	Advantages	Disadvantages	Suitability range	References
Pressurized metered-dose inhalers (pMDIs)	Propellant-driven canister releases aerosol upon actuation. Often used with spacers.	-Portable and convenient -Delivers accurate doses -Widely available	-Requires hand-breath coordination -High oropharyngeal deposition -Propellant-protein compatibility issues	Adults and adolescents with good inhalation coordination	[26, 30, 39]
Dry powder inhalers (DPIs)	Breath-actuated, releases powder formulation. Some use external energy for deagglomeration	-Suitable for nanobodies and peptides with stabilizers -Propellants are not needed, stable dry formulation -Breath-activated -Useful in asthma and COPD	-Requires strong inspiratory effort -Sensitive to humidity -Less effective in severe airflow limitation -Sheer stress may denature proteins	Asthma and/or COPD patients with sufficient inspiratory capacity	[30, 32, 40, 41]
Breath-activated inhalers (BAIs)	Combines pMDI and DPI benefits, dose released automatically upon inhalation	-Eliminates coordination need -Higher user-friendliness -Preferred by many patients	-Less availability -Higher cost -Fewer formulations	Children, elderly or cognitively impaired patients	[42]
Nebulizers	Converts liquid formulation to aerosol for inhalation, used during tidal breathing	-High lung deposition -Mesh type, gentle on proteins -Minimal coordination required -Suitable for high doses -Versatile for biologics	-Bulky -Longer treatment times -Requires cleaning and maintenance	Paediatric, geriatric or hospitalized patients	[26, 30, 45, 46]

against SARS-CoV-2, reached the bronchoalveolar lavage fluid (BALF) of hamsters within 30 min of inhalation. In contrast, the intraperitoneal route resulted in less than 0.1% lung deposition of the same antibody.[24] These findings offer compelling preclinical validation that pulmonary delivery not only improves drug targeting efficiency but may also enable substantial dose reductions, minimizing costs and potential systemic side effects.

Device considerations for inhaled biologics: bridging formulation and function

Effective pulmonary drug delivery depends not only on therapeutic agent, but also on the delivery method used. Various inhalation devices have been developed to optimize drug deposition in the lungs, particularly for patients with respiratory diseases such as asthma and COPD. Understanding the physiological requirements and device-speicific characteristics is crucial for achieving targeted delivery and therapeutic success. The following section outlines key considerations and the strengths and limitations of each delivery platform as shown in Table 1.

The physicochemical characteristics of aerosols, such as their shape, size, density, and hygroscopicity, play a crucial role in determining how inhaled particles are deposited within the lungs.[25] Among these factors, the aerodynamic diameter of particles is particularly significant for dictating their distribution across various regions of the respiratory system. In order to establish an effective pulmonary delivery, inhaled biologics must be able reach and remain in the intended region of the lung. This is largely determined by the aerodynamic diameter of the particles. Particles with diameters ranging from 1 to 5 μm have been found to deposit more effectively in the lungs, which in turn enhances their potential therapeutic efficacy.[26,27] Particles smaller than 1 μm may be exhaled before deposition, while those larger than 5 μm tend to deposit in the oropharyngeal region, thereby failing to reach deeper lung tissues.[28,29] This structure of size depositions of inhaled particles in the respiratory system is shown in Figure 1.[30]

Once deposited, the pharmacokinetics of the therapeutic agent are influenced by its molecular size and biochemical properties. Inhaled agents must also overcome shifts in humidity, penetrate the airway lining, and bypass various cellular defence mechanisms. The pulmonary immune landscape includes resident immune cells that play essential roles in maintaining airspace integrity, clearing inhaled particles, and initiating localized immune responses. Among these, alveolar macrophages, CD11b + and CD103 + dendritic cells, and interstitial macrophages are of particular interest, as they are involved in numerous respiratory pathologies.[33]

In addition to deposition, effective pulmonary delivery requires adequate residence time within the lungs.[34] The retention and clearance of inhaled biologics can vary significantly depends on their size and structure. Monoclonal antibodies, due to their large molecular weight (~ 150 kDa), often show prolonged retention in the lung interstitium but are more prone to enzymatic degradation or uptake by alveolar macrophages.[35-37] In contrast, nanobodies and peptides, owing to their smaller sizes exhibit improved tissue penetration but shorter half-lives,[38] necessitating formulation strategies like PEGylation[37,38] or encapsulation[38] to enhance stability and residence time.

Methods of pulmonary delivery include pressurized metered-dose inhalers (pMDIs), dry powders for inhalation (DPIs), and nebulizers[25] as shown in Figure 2. Deciding between various options involves careful consideration of multiple aspects, such as the physicochemical characteristics of the drug, the simplicity of its application, the patient's age, and the feasibility of manufacturing on an industrial scale.[26] Inhaler and the formulation design must also account for lung physiology, including mucociliary clearance, surface liquid thickness and alveolar macrophage activity, all of which influence particle retention and absorption.[21] Therapeutic aerosols must meet specific criteria regarding their aerodynamic particle size to be effective.

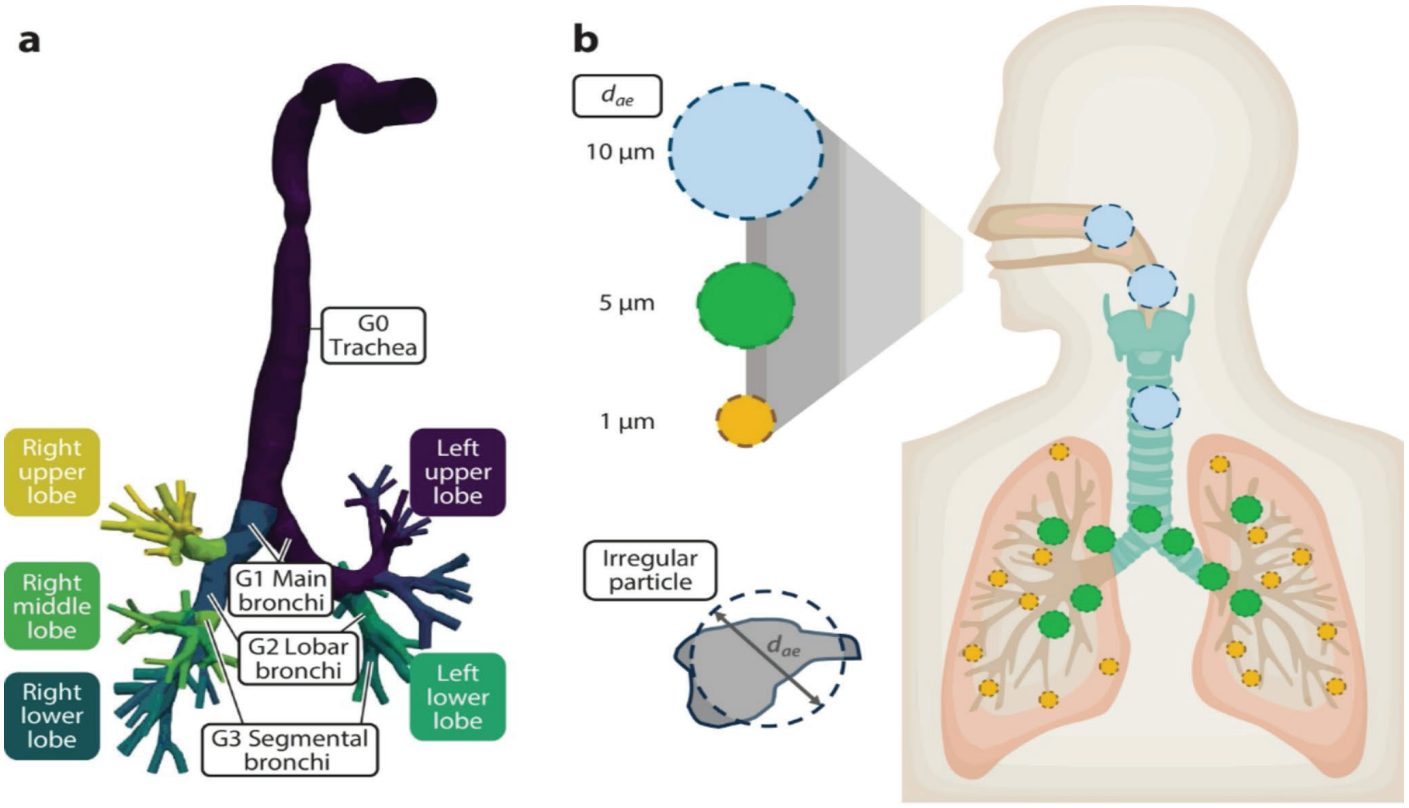

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Figure 1. Illustration of size depositions of inhaled particles in the respiratory system. (a) Structure of the upper airway of the human lung. Mouth inlet is idealized, while the trachea and bronchi are obtained from a healthy adult male.[31] Generations 0–3 (G0–G3) are labeled, and representative generations are indicated for the lobar and segmental bronchi. (b) Diagram depicting the role of aerodynamic diameter (dae) in generational deposition within the lung, where ~10-µm aerosols deposit in the oropharynx and trachea, ~5-µm aerosols deposit in the upper conducting airways, and ~1-µm aerosols reach the respiratory airways.[28] Illustration adapted from[32]

pMDIs include a pressurized canister containing a drug-propellant mixture that delivers medication in a fine mist upon actuation. It is often used with spacers to improve drug deposition. The advantages of using pMDIs are the portability, hand-held design, and the ability to deliver accurate doses with each actuation. However, reports have shown that excessive drug deposition was found in the oropharyngeal region, necessitating higher dosage levels to achieve therapeutic effects at the target site when using this device.[26,39] DPIs have been manufactured to aid patients mainly suffering from asthma and COPD. Several manufacturers of DPIs produce active systems equipped with an external energy source to aid in the deagglomeration of the powder. These devices are particularly beneficial for individuals with reduced breathing capacity, such as children, critically ill patients, and those suffering from severe COPD or asthma.[40] The first researchers to introduce the use of DPI technology were Bell et al., where they demonstrated the ability of the device to dispense size-graded fractions of lactose, in the range of 4–400µ.[41]

The emerging technology of the development of pressurized breath-activated inhalers (BAIs) aim to integrate the advantages of pMDIs and DPIs while addressing their shortcomings. For instance, devices such as Synchro-breathe™ operate by detecting low efforts of inhalation and synchronizing dose delivery with the breathing process, thereby eliminating the challenge of coordinating the two actions.[42] BAIs offer various benefits, including user-friendliness, efficient therapeutic delivery to the lungs, and greater patient preference. The future of medicine is set to prioritize tailored biological therapies and advancements in drug delivery systems. Smart inhalers integrated with sensors are also emerging, which track inhalation parameters and adherence, offering personalized dosing and real-time feedback for improved clinical outcomes.[43,44]

Nebulizers consist of three different categories which are jet nebulizers, ultrasonic nebulizers, and mesh nebulizers where the technology depends on the properties of drug solution into aerosols.[26,45] The introduction of early nebulizers dates back to the mid-19th century, marking the initial step in aerosol medicine delivery. Later, between the 1930s and 1950s, advancements led to the creation of both electric nebulizers and hand-bulb models, further revolutionizing respiratory therapy.[46] Nebulizers operate effectively with tidal breathing and do not demand extensive patient training or cooperation. They are generally used for diseases that require high pulmonary doses and patients who are unable to achieve the necessary flow rate. As a result, they are particularly beneficial not only in emergencies but also for elderly and paediatric patients who may have cognitive or physical challenges.[26,45]

pMDIS are typically not suitable for delivering biologics due to the propellant-protein compatibility issues.[30] When administering drugs, the formulation would only content

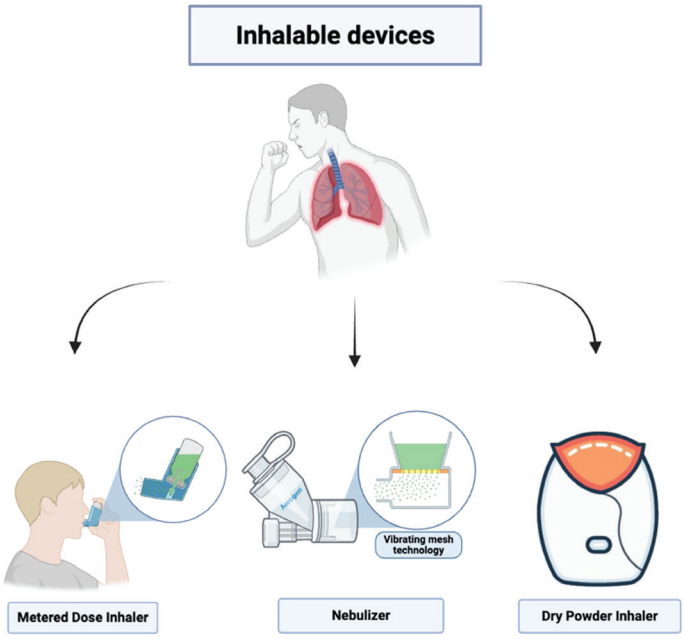

Figure 2. Types of inhalable devices for pulmonary delivery.

approximately 1% of the active drug with typically delivering less than 0.5 mg of medication per actuation.[47,48] Studies have reported that only 10–20% of the drug dosage deposited by pMDIs is concentrated in the lungs.[49] DPIs on the other hand have better stability to deliver biologics with the ability to effectively aerosolize large masses (25–100 mg) of spray dried powder formulations.[50,51] In comparison with nebulizers, they are capable of administering significantly large doses, often exceeding 100 mg, making them more suitable for therapies requiring higher drug loads.[48] Hence, more new developments of aerosol medications and most biologics involved requires nebulizer delivery.

The selection of an inhaler is also influenced by various patient-specific factors. This includes the patient's inspiratory flow rate and volume, severity of the condition, presence of other health issues, and the patient's ability to use the device.[52] It is also influenced by the properties of the developed formulation in consideration of the particle size and aerosol velocity generated by the device as well as the regimen complexity of inhalation therapy.[53]

Inhaled biologics across respiratory pathologies: current strategies and emerging evidence

When delivering biologics specifically proteins, a main concern is protein degradation during administration. When proteins lack stability in their solution form, they can be enhanced with stabilizing agents before undergoing freeze-drying or spray-drying processes for preservation.[54,55] These approaches allow the proteins to be reconstituted effectively, making them suitable for delivery through nebulizers. Studies have shown that aerosols produced using mesh nebulizers specifically the vibrating mesh technology significantly minimize protein degradation compared to jet or ultrasonic nebulizers, which rely on heating elements[14,56] While traditional jet nebulizers deliver medication with an efficiency of approximately 10%, newer vibrating mesh nebulizers (VMNs) surpass 60% efficiency, tackling challenges often seen in dry powder formulations for proteins such as hygroscopic growth and protein aggregation. Additionally, these devices eliminate the need for synchronized breathing techniques that are frequently required with dry powder inhalers or metered dose inhalers, which can pose difficulties for both elderly and paediatric users.[14,15]

Limitation of MDI that may occur to delivering biologics are such as the hydrophilic nature of most biologics and poorly soluble in the non-polar hydrofluoroalkane (HFA) propellants used in MDIs. This poor solubility limits the formulation possibilities and the dose range that can be delivered per actuation.[57] Besides that, MDIs often result in high oropharyngeal deposition and require precise coordination between actuation and inhalation. This can lead to suboptimal lung deposition, especially in patients who have difficulty with inhaler techniques.[58] Hence, nebulizers are highly favoured for administering proteins due to the simplicity of their formulations and the compatibility with soluble proteins, which require minimal use of additives.

Given the continuous advancements in formulation techniques and delivery technologies, inhaled biologics are emerging as promising therapeutic options for a wide range of respiratory disorders. This section provides a comprehensive analysis of recent developments in inhaled biologic therapies, focusing on diseases such as asthma, pulmonary fibrosis, COPD, COVID-19, and respiratory syncytial virus (RSV). By evaluating the specific delivery strategies and technologies for each condition, this review aims to highlight both current progress and future directions in the field. A summary of the key findings discussed is presented in Table 2.

Inhaled biologics for asthma: direct targeting of TSLP and IL-13 pathways

Asthma is a common and persistent respiratory illness that impacts millions worldwide. Its symptoms include wheezing, breathing difficulties, chest tightness, and coughing. The condition has a far-reaching effect, with approximately 262 million people affected in 2019, predominantly children, resulting in significant mortality and economic burdens. Recent data from the Global Initiative for Asthma (GINA) 2024 Report indicates the global asthma population has now approached 300 million individuals.[76]

The pharmacological management of asthma is divided into several categories such as rescue therapies, controller treatments, and, for severe cases, add-on options. Reliever medications play a key role in addressing acute symptoms, while controller therapies are designed to minimize airway inflammation. For patients with severe asthma, particularly those with an eosinophilic phenotype, biologic treatments are often recommended. These patients typically continue to experience symptoms and frequent exacerbations despite using high-dose inhaled corticosteroids (ICS) combined with long-acting beta-agonists (LABA). Current biologic therapies target molecules such as immunoglobulin E (IgE), IL-4, IL-5, IL-13, and thymic stromal lymphopoietin.[77] The EMA and the U.S. FDA have approved six biological treatments, including omalizumab (anti-IgE), benralizumab, mepolizumab, reslizumab (anti-IL5/IL5R), dupilumab (anti-IL-4Rα/IL-13), and tezepelumab (anti-TSLP).[78-82] While systemic biologics have made significant strides, it is notable that inhaled options could offer a transformative step forward by delivering treatment directly to the site of inflammation with reduced systemic exposure. However, all approved biological therapies are

Table 2 Shows a summary of the key findings discussed in section below

Respiratory disease	Biologics involved	Type of biologics	Mechanism of action	Development status	References
Asthma	Ecleralimab	mAb fragment	Anti-TSLP therapy	Phase II clinical trial	[16, 59]
	CDP7766	mAb fragment	Prevents IL-13 from binding to its receptor, IL-13Rα1	Preclinical animal-model study	[60]
Pulmonary fibrosis	OM-85	Bacterial lysate	Promote a Th1-biased immune environment by increasing interferon-gamma (IFN-γ) and reducing interleukin-4 (IL-4)	Preclinical animal-model study	[61]
	PRS-220	Protein	Blocks CCN2, preventing the over-activation of fibroblasts and the excessive deposition of extracellular matrix components	Preclinical ex-vivo human study	[62]
	Lung spheroid cell secretomes or exosomes	Biologic mixture or nanoparticle-based biologic	Modulates fibrosis, inflammation, and tissue repair processes	Preclinical animal-model study	[63]
COVID-19	Pittsburgh inhalable Nanobody 21 (PiN-21)	Single-domain antibody fragment	Bioengineered into a trimeric form for higher affinity towards SARS-CoV-2	Preclinical animal-model study	[64]
	SNG001	Protein (recombinant cytokine)	Increases high concentrations of interferon-β in the lungs resulting in a robust local antiviral response	Phase II clinical trial	[65]
	HH-120	Multivalent, recombinant fusion protein	High binding affinity to the viral S protein, increasing ability of viral neutralization	Preclinical animal-model study	[66]
	IN-006	mAb	Immobilizes SARS-CoV within the airway mucus, preventing the trapped virions from diffusing through the mucus to reach and infect host cells (Muco-trapping)	Preclinical animal-model study	[67]
Chronic Obstructive Pulmonary Disease (COPD)	Progesterone (P4)	Hormone	Modulate pathological balance in the lungs with significant anti-inflammatory and antioxidant properties	Preclinical animal-model study	[68, 69]
	Patchouli essential oil (PEO)	Plant extract	Reduces inflammatory cell infiltration and decreases the levels of pro-inflammatory cytokines such as IL-6 and TNF-α	Preclinical animal-model study	[70]
	Immunoantimicrobial nanoparticles (IMAMs)	Peptides	Reduces airway bacterial burden, decreases pro-inflammatory cytokine levels and suppress TLR9 signalling	Preclinical animal-model study	[71]
Respiratory syncytial virus (RSV)	Mota-MT	mAb	Muco-trapping therapy, neutralizing monoclonal antibody targeting the RSV F	Preclinical animal-model study	[72]
	ALX-0171	Nanobody	Targets the F protein of RSV to block the virus from entering host cells	Phase I/IIa clinical trial	[73–75]

administered via systemic routes, including intravenous and subcutaneous methods.

Systemic administration of biologics is associated with key limitations such as low pulmonary bioavailability due to distribution dynamics, reducing local efficacy.[83] Moreover, systemic exposure increases the risk of adverse effects including hypersensitivity reactions, generalized immunosuppression and potential toxicity. Biologics delivered systemically may also exhibit delayed onset due to longer absorption and distribution phases.[84] These limitations underscore the need for direct, localized delivery methods that can improve drug concentrations in lung tissue while minimizing systemic exposure. Such approaches may also enhance patient adherence by reducing the invasiveness and complexity of treatment regimens.

Thymic stromal lymphopoietin (TSLP), a cytokine produced by epithelial cells, plays a critical upstream role in the development of asthma. TSLP is involved in activating dendritic cells, which leads to the differentiation of naïve T cells into Th2 cells. These Th2 cells then produce cytokines such as IL-4, IL-5, and IL-13 (Fig. 3).[16] Research suggests that inhibiting TSLP with the monoclonal antibody Tezepelumab which is currently the only approved add-on treatment could benefit a wide range of asthma patients,[85] however, limited to systemic administration methods, necessitating regular injections. Reliance on systemic administration may hinder the full therapeutic potential of TSLP-targeting agents due to the difference in dosing schedules and limited drug targeting, inhaled biologic therapies targeting TSLP could offer a practical alternative by improving local pharmacodynamics and reducing systemic side effects.

A recent study reported by Gauvreau et al., has developed ecleralimab as the pioneering inhaled anti-TSLP therapy aimed at treating asthma.[16,59] Phase II clinical trial was done to evaluate its efficacy and safety which involves subjects with mild atopic asthma to proceed to development in severe asthmatic subjects. In this study, ecleralimab, a potent neutralizing antibody fragment belonging to the fragment antigen-binding (Fab) group and falls under the IgG1/λ isotype subclass, specifically targets human TSLP and is formulated as PulmoSol™, a powder

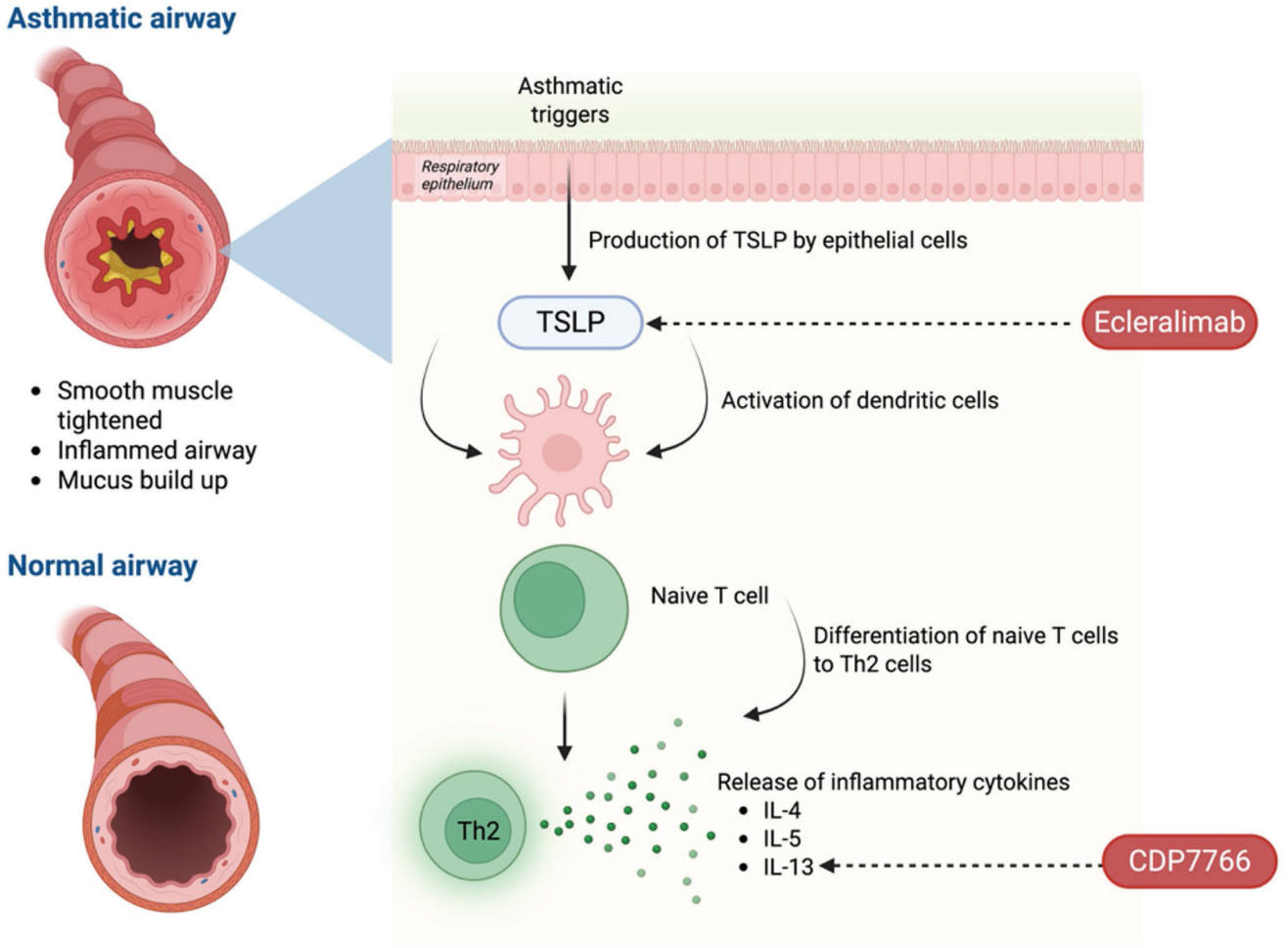

Figure 3. An illustration of asthmatic airways and the production of key cytokines involved. Ecleralimab targets the TSLP involved in anti-TSLP therapy while CDP7766 targets the IL-13 to effectively reduce IL-13 activity. (Created in Biorender.com)

designed for administration through a dry powder inhaler (DPI) device, using hard capsules. This antibody fragment comprises the antigen-binding components, including one constant and one variable domain from both the heavy and light chains, but it does not include the Fc region. The smaller size of Fab fragments (46.6 kDa compared to full antibodies at ~ 150 kDa) allows better penetration of lung tissue. With a molecular weight of 46.6 kDa, it is notably smaller compared to the approximately 150 kDa size of a complete antibody.[16]]. With no Fc region, Fab fragments are small enough to penetrate airway tissue, while maintaining antigen-binding specificity. Although a lack of Fc region means a shorter serum half-life, this is ideal for inhalation therapies as it gives a more localized therapeutic effect, targeting the airways in asthmatic patients and a faster elimination process reducing its side effects.[16,60] Results showed that ecleralimab effectively reduced bronchoconstriction and inflammation in the airways triggered by allergens. Moreover, it demonstrated a favourable safety profile in individuals with mild atopic asthma.[59]

Monoclonal antibodies (mAbs), a common biological agent are immunoglobulins with a high degree of specificity for the particular antigen or molecule for which they were developed.[86] The groundbreaking work of Kohler and Milstein, who successfully generated the first mAbs from a single B-cell hybridoma cell line using the hybridoma technique.[9] Notably, the FDA approved the first therapeutic mAbs, muromonab-CD3, which is adapted to transplantation procedures.[7] mAbs play a pivotal role in the treatment of a wide spectrum of conditions, including cancer therapy, autoimmune diseases, prevention of organ transplant rejection, and targeted drug delivery.[9] The increasing interest in inhaled mAbs reflects a broader trend in respiratory therapeutics aimed at achieving localized action while minimizing systemic risks.

IL-13, a cytokine significantly involved in the pathogenesis of severe allergic asthma, has also emerged as a promising target for inhalation-based therapies.[87] Research conducted by Lightwood et al. has developed CDP7766, a monoclonal fragment antigen-binding (Fab) antibody with high potency and is biophysically stable with strong specificity and affinity for IL-13. This functions by preventing IL-13 from binding to its receptor, IL-13Rα1, thereby inhibiting the formation of the high-affinity IL-13:IL-13Rα1:IL-4Rα signalling complex. In preclinical trials, inhaled CDP7766 using an ultrasonic nebulizer effectively reduced IL-13 activity, as well as the associated upregulation of cytokines and chemokines, and mitigated allergeninduced increases in pulmonary resistance. Importantly, no adverse effects from local irritation were observed.[60] These findings provide a strong basis for advancing the investigation of inhaled CDP7766 as a potential therapy for allergic asthma in humans. However, translation to clinical use requires further investigation in large-scale trials to confirm efficacy, safety and optimal delivery strategies. Nonetheless, the

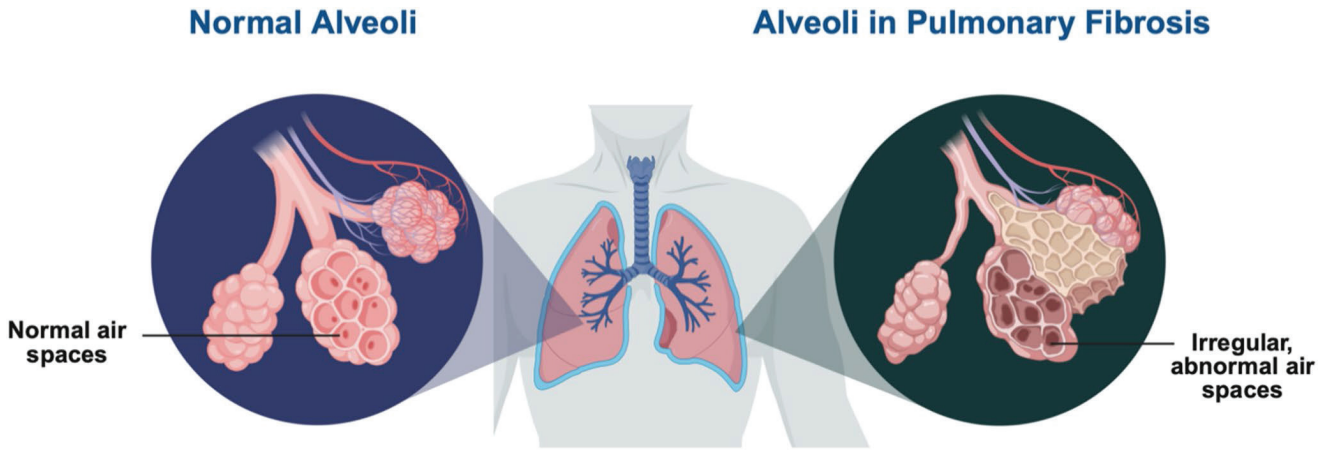

Figure 4. An illustration of normal alveoli and alveoli in pulmonary fibrosis. (Created in Biorender).

transition from systemic to inhaled biologics will require careful evaluation to ensure that the pharmacokinetics and bioactivity of the antibodies are not compromised. Hence, based on these findings, inhaled biologics offer a highly promising but still evolving frontier that warrants deeper exploration in both clinical and real-world settings.

Localized treatment strategies for pulmonary fibrosis: anticalins, exosomes, and immunomodulation

Idiopathic Pulmonary Fibrosis (IPF) is a chronic interstitial lung condition, primarily characterized by scarring of the alveolar-capillary interface (Fig. 4). Excessive apoptosis and injury of the alveolar epithelium caused by increased profibrotic factors disrupt the normal gas exchange and ultimately culminate in respiratory failure.[88,89] Despite extensive research, the main causative factor of IPF remains obscure. IPF is often diagnosed in older adults, with very poor prognosis, in which patients typically survive only 3 to 5 years following diagnosis. In contrast to other inflammatory lung diseases, IPF shows minimal to non-effective towards anti-inflammatory treatments, and in some cases, treatments lead to exacerbation of the condition.[90] Currently, the approved therapeutic regimes for IPF are nintedanib, a kinase inhibitor, and pirfenidone, which aim to inhibit extracellular matrix deposition and slow down the fibrotic processes.[91-93] However, these agents do not reverse fibrosis or even show any sign of cure. Among interstitial lung diseases, IPF garners particular clinical attention due to its severe progression, poor treatment outcomes, and high mortality rate.[94]

Given the limited efficacy of existing treatments, research is moving towards understanding the underlying mechanisms of fibrosis. It is hypothesized that the balance between T-helper subtypes, Th1 and Th2, plays a pivotal role in lung inflammation and fibrosis. Under normal physiological lung conditions, equal levels of Th1 and Th2 are crucial in maintaining cell immunity. In IPF, secretion of Th1/Th2 may suppress or increase the progression of pulmonary fibrosis, due to their regulatory roles.[95,96]

A recent study by Yu et al. utilized OM-85, which comprises bacterial lysates from bacterial pathogens, and evaluated its inhibitory effect in a mice pulmonary fibrosis model.[61] In this study, bleomycin-induced pulmonary fibrosis mice were given via aerosol exposure of OM-85 on days 42, 44, 46, 49, 51, and 53. Mice treated with aerosolized OM-85 exhibited significantly reduced fibrosis, as observed by decreased collagen accumulation, lower hydroxyproline content, and reduced inflammatory infiltration. Upon histopathological assessment, notable lung architecture was preserved and reduced Ashcroft scores were observed. OM-85 was shown to promote a Th1-biased immune environment by increasing interferon-gamma (IFN-γ) and reducing inter-leukin-4 (IL-4), thereby potentially regulating the fibro-genic Th2 shift induced by lung injury. OM-85 suppressed the expression of TGF-β1, Notch1, and Hes1, which are the key signalling molecules involved in fibrogenesis and fibro-blast activation. Importantly, inhalation treatment of OM-85 reversed the Th2-skewed immune shift. These findings highlighted OM-85 as a promising inhaled immunomodulatory therapy as a potential treatment for IPF.[61] Taken together, the dual mechanism, preclinical efficacy, and pulmonary delivery characteristics proved OM-85 as a strong candidate for a novel and localized therapeutic strategy for IPF management.

Other than treatments targeting Th1/Th2 balance in IPF, inhaled therapies targeting cellular communication network factor 2 (CCN2) have also emerged as a promising approach for treating pulmonary fibrosis. CCN2, also known as connective tissue growth factor (CTGF), holds an important role in fibrotic tissue remodelling, wherein, its over-expression in lung tissues directly contributes to the progression of IPF. PRS-220, an inhaled Anticalin® protein, is designed to specifically target CCN2 in the lungs, offering a novel approach to treating IPF and other fibrotic lung diseases. By blocking CCN2, PRS-220 prevents the over-activation of fibroblasts and the excessive deposition of extracellular matrix components. In preclinical concept studies by Neiens et al., pulmonary delivery of PRS-220 enables more efficient penetration to the site of action, the fibrotic lung tissue, when compared to systemic antibody.[62] With this localized delivery of PRS-220, a high concentration of PRS-220 can be reached with very minimal systemic exposure, thereby maximizing its therapeutic efficacy. PRS-220 was shown to accumulate in fibrotic lung tissue after inhalation, leading to a reduction in CCN2 levels and attenuation of the fibrotic processes.

These studies have shown that pulmonary delivery of treatments offers site-specific targeting, allowing effective treatment for pulmonary fibrosis when compared to systemic delivery. PRS-220, when delivered via inhalation, significantly reduced collagen deposition, fibrosis-associated proteins like α-SMA,

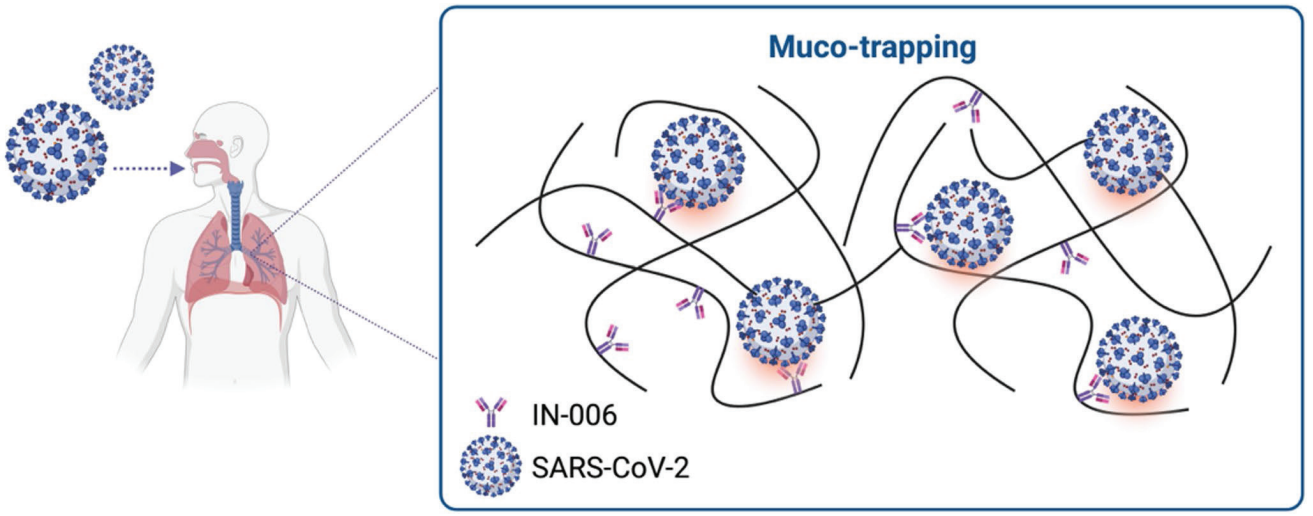

Figure 5. An illustration of muco-trapping mechanism illustrating SARS-CoV-2 moves freely in mucin matrix whereas Fc domain of antibody creates crosslinks with the mucin while Fab domain binds to virus. (Created in Biorender.com)

collagen I/III, and fibronectin, and improved lung architecture. Overall, the preclinical profile of PRS-220 supports the hypothesis that local pulmonary delivery of Anticalin® proteins is a promising therapeutic approach for pulmonary fibrosis.

In another preclinical study by Dinh et al., lung spheroid cell secretomes and exosomes were studied as a therapeutic approach to be delivered to the lungs of a fibrotic mice model.[63] Lung spheroid cells secrete a variety of regenerative factors, and their secretome, along with exosomes, was shown to have a significant impact on modulating fibrosis, inflammation, and tissue repair processes. Pulmonary fibrosis was induced in C57BL/6 mice using bleomycin, and the animals were then treated with inhaled lung spheroid cell secretomes or exosomes. Histological analysis revealed that the treated mice exhibited significant reductions in fibrotic lesions and collagen deposition when compared to the untreated group. In addition to fibrosis reduction, the inhaled treatments led to a decrease in the expression of fibrosis-related markers, such as collagen I/ III, α-SMA, and fibronectin, within the lung tissue. Furthermore, the treatments appeared to have a regenerative effect, promoting epithelial repair and enhancing alveolar architecture. Increased epithelial proliferation was observed, which is a sign of tissue repair, that may help counteract the damage caused by fibrosis. The inhaled exosomes and secretomes regulate the immune levels in the lungs to a more balanced immune response. Specifically, the treatments increased the levels of Th1 cytokines such as IFN-γ, while decreasing Th2 cytokines like IL-4. Following treatment of inhaled exosomes and secretomes, impaired lung function significantly showed improvement. Overall, this study highlighted the therapeutic potential of inhaled lung spheroid cell secretomes and exosomes as a promising strategy for treating pulmonary fibrosis.

Inhaled biologics for COVID-19: nanobodies, interferons, and muco-trapping therapies

Biologics such as nanobodies, due to their lightweight molecular structure (approximately 15 kDa) and stable biophysical characteristics have emerged as significant potential therapeutics for nebulization in biological therapies. An ultrapotent homotrimer construct, Pittsburgh inhalable Nanobody 21 (PiN-21), has shown promising antiviral results as SARS-CoV-2 infectivity was efficiently blocked at below 0.1 ng/ml in vitro.[64] Researchers then continued to study the antiviral potential of PiN-21 in Syrian hamsters. Results showed that the aerosol administration using a vibrating mesh nebulizer of PiN-21 promotes effective distribution across the respiratory tract while enabling a reduced dosage of 0.2 mg/kg. This inhalation therapy not only expedites recovery from infection-induced weight loss in animals but also lowers lung viral titers by six logs, significantly alleviating lung damage and effectively preventing viral pneumonia.[97] The ability of PiN-21 to achieve such profound antiviral effects at ultra-low doses is particularly impressive and highlights the potential of nanobodies as next-generation inhalable antivirals.

Another formulation designed for nebulized inhalation is SNG001, a recombinant interferon beta formulation. In previous clinical trials, SNG001 has shown the ability to enhance lung antiviral defences in patients with asthma and/or COPD with or without respiratory viral infections.[98,99] The inhalation delivery method was preferred to achieve high concentrations of interferon-β in the lungs, promoting a strong localized antiviral response while minimizing systemic exposure, which is linked to flu-like symptoms.[98,100] In individuals with COVID-19, a diminished level of interferon-β was observed especially in the elderly or those with chronic respiratory illnesses. Combining the promising results of SNG001 on respiratory illness previously stated as well as the suppression of interferon-β by SARS-CoV-2, Monk et al.,[65] reported a phase II clinical trial on inhalation via nebuliser of SNG001 on COVID-19 patients. It was shown to be well-tolerated with no deaths as compared to three deaths for the placebo-treated group and had greater odds of improvement on the OSCI (WHO Ordinal Scale for Clinical Improvement) scale.[65]

Angiotensin-converting enzyme 2 receptor (ACE2) plays a significant role in the entry of SARS-CoV-2 into the host cells. The lungs have an abundance of ACE2 receptors making them the main target organ for COVID-19 as the S protein of SARS-CoV-2 binds to the ACE2 receptor for viral entry.[101-103] Proteins sourced from the extracellular domain of human ACE2 (hACE2) can act as decoys to block viruses from attaching to host cells. These soluble hACE2 proteins exhibit inherent resistance to viral mutational escape, making them

a robust tool in countering viral infections. The development of HH-120, a soluble hACE2 molecule engineered into an IgM-like multivalent Fc-fusion protein by Liu et al., highlights significant advancements in SARS-CoV-2 therapeutics.[66] HH-120 demonstrates exceptional binding affinity to the viral S protein ($> 1 \times 10 - 12$ M) and achieves substantial neutralization activity whereby approximately 88–265 times greater compared to hACE2-hIgG1, a bivalent ACE2 tagged with human IgG1 Fc when tested against the ancestral strain (IVDC-QD-11-2P2) in Vero cells.[66] In vivo studies using golden Syrian hamsters showed that inhaled aerosolized HH-120 via VMN for early treatment resulted in potent antiviral effects, reducing lung pathology scores and leading to ~ 3 log reductions in viral loads.[66] Hence, this formulation has paved the way for clinical development as a reliable, convenient treatment against SARS-CoV-2 variants and other emerging ACE2-utilizing coronaviruses.

An emerging yet underrecognized mechanism during pulmonary delivery is muco-trapping which involves the antibodies to combat viral infections on mucosal surfaces. This mechanism happens due to the presence of mucin, the predominant component of mucus covering the respiratory tract's luminal surface allowing viruses to move freely within its network of fibres.[13,73,104] Studies suggest that the Fc domain of IgG can create crosslinks with mucins, while the Fab domain binds specifically to viral antigens, effectively trapping the virus within the mucin structure (Fig. 5). This process aids in the clearance of viruses via mucus elimination pathways and prevents their entry into host cells during the early stages of infection.[73] An application of this mechanism is reported using IN-006,[67] a reformulated for nebulized delivery of regdanvimab, one of the approved neutralizing mAbs targeting SARS-CoV-2. IN-006 has demonstrated muco-trapping capabilities in human airway mucus where when nebulized using VMN to rats, the mAb level in the lungs was 100-fold greater as compared to the serum without compromising its activity. Substantial results have shown that after administration of IN-006, SARS-CoV was immobilized within the airway mucus, preventing the trapped virions from diffusing through the mucus to reach and infect host cells. These trapped virions will then be rapidly cleared from the respiratory tract through mucociliary action or cough-induced mucus elimination.[67] The muco-trapping mechanism employed by inhaled antibodies like IN-006 offers a fascinating and underexplored method for enhancing mucosal immunity, potentially adding a critical layer of defence at the earliest stages of infection.

Innovative pulmonary delivery for copd: hormones, plant extracts, and antimicrobial nanoparticles

Chronic Obstructive Pulmonary Disease (COPD) is a chronic inflammatory lung disease characterized by deterioration of lung function due to abnormal inflammatory reactions triggered by cigarettes or any airborne toxins. COPD is often associated with high morbidity and mortality, and is the third leading cause of death globally.[105] Despite the advancement of the use of inhaled bronchodilators and corticosteroids, these treatments only address symptoms rather than curing the disease progression, highlighting the urgent need for novel therapeutic approaches that can regulate and cure the pathogenesis of COPD.[106-108]

Recent evidence has highlighted the promising role of hormones in immune regulation, particularly progesterone (P4), a steroid hormone important in reproductive health. Beyond its endocrine functions, P4 exhibits significant anti-inflammatory and antioxidant properties.[68,69] A 2025 preclinical study by Xie et al., explored the therapeutic potential of progesterone in a murine model of cigarette smoke-induced COPD.[109] BALB/c mice were subjected to chronic smoke exposure and were given intranasal treatment of P4 to establish localized pulmonary administration. Pulmonary delivery of P4 was intended to maximize drug deposition in the lungs, limit systemic side effects, and directly target airway inflammation and oxidative stress of the COPD-induced mice model. Treatment with P4 revealed notable therapeutic outcomes. Histopathological examination revealed preserved alveolar architecture in the lungs, reduced neutrophilic infiltration, and reduced emphysematous changes in P4-treated animals. Inflammatory profiling of bronchoalveolar lavage fluid (BALF) indicated a significant reduction of pro-inflammatory cytokines such as TNF-α and IL-6, along with decreased activity of matrix metalloproteinase-9 (MMP-9), a key enzyme involved in extracellular matrix degradation. Moreover, P4 restored the oxidative balance by enhancing levels of endogenous antioxidants, superoxide dismutase (SOD), and catalase, while concurrently decreasing malondialdehyde (MDA), a lipid peroxidation marker. Altogether, this study has proven and revealed progesterone as a promising candidate for inhalation-based therapy in COPD, with its ability to modulate pathological balance in the lungs, other than the traditional anti-inflammatory treatments that only target disease symptoms.

Other than the pulmonary delivery of hormones as a therapeutic approach against COPD, growing interest in plant-derived compounds with bioactive properties as an alternative intervention. One such candidate is patchouli essential oil (PEO), extracted from *Pogostemon cablin*, traditionally used in herbal medicine for its anti-inflammatory, antimicrobial, and antioxidant effects. A recent experimental study by Zhang et al. evaluated the efficacy of inhaled PEO in a murine model of cigarette smoke-induced COPD.[70] Mice were exposed to chronic cigarette smoke to establish a COPD-mice model and were subsequently treated with PEO via inhalation to assess its direct impact on lung inflammation and tissue remodelling. Inhalation treatment of PEO produced significant improvements in the pulmonary area. PEO-treated mice showed significant reductions in inflammatory cell infiltration within bronchoalveolar lavage fluid (BALF), together with decreased levels of pro-inflammatory cytokines such as IL-6 and TNF-α. Histological analysis also revealed preservation of alveolar architecture and reduced signs of airway remodelling compared to untreated COPD mice controls. It was believed that PEO regulated the inflammatory pathways by modulating pathways involved in oxidative stress and cytokine production. Taken together, the study highlighted the novel, effective approach of inhaled patchouli essential oil as a natural, lung-targeted anti-inflammatory agent.

A recent inhalation study investigated the therapeutic potential of immunoantimicrobial nanoparticles (IMAMs) pulmonary delivery in the treatment of infection-driven COPD exacerbations.[71] The IMAMs consisted of negatively charged porous silica nanoparticles encapsulating ceftazidime and pH-responsive antimicrobial peptides (AMPs). These were specifically engineered to overcome the physical barriers of the respiratory tract, including mucus and bacterial biofilms, while maximizing therapeutic action at the disease site. In a

murine model of COPD-like lung infection, the IMAMs were administered via nebulization, allowing direct deposition into the lower airways and ensuring a high localized concentration of therapeutic agents. The nanoparticle surface charge and aerodynamic profile allowed for efficient mucus penetration and deep lung delivery. Upon reaching the acidic microenvironment of infected tissue, the AMP component underwent structural transformation, enhancing biofilm disruption and promoting bacterial eradication at the alveolar level. Pulmonary delivery of the IMAMs resulted in significant therapeutic benefits, including reduced airway bacterial burden, decreased pro-inflammatory cytokine levels in bronchoalveolar lavage fluid (BALF), and suppression of TLR9 signaling. Histological analysis confirmed reduced lung inflammation and damage in the IMAM-treated group. This inhalation approach not only ensured targeted delivery and retention within the lungs but also minimized systemic exposure and off-target effects. Strong preclinical evidence from the study supports the potential of nebulized IMAMs as a dual-function inhalation therapy for COPD.[71] By effectively navigating pulmonary barriers and delivering both antimicrobial and immunomodulatory payloads directly to the lungs, this strategy offers a promising avenue for disease modification in COPD beyond traditional symptomatic treatment.

To conclude, these recent preclinical studies highlight the growing potential of pulmonary delivery therapies as a localized and multifaceted approach for the management of COPD. Whether through the hormone anti-inflammatory and antioxidant characteristics, the bioactivity properties of essential oil, or immunoantimicrobial nanoparticles, each approach demonstrated that targeted pulmonary delivery not only enhances drug concentration at the disease site but also reduces overall systemic. These findings signal a paradigm shift from symptomatic control towards disease-control mechanisms.

RSV intervention via inhaled biologics: muco-trapping antibodies and nanobody-based antivirals

For respiratory infections, inhaling anti-infectious antibodies may be more effective than the traditional intravenous (IV) injection, as it allows for direct targeting of the infection site and enhances the therapeutic index of the antibodies.

Respiratory syncytial virus (RSV) is the leading cause of lower respiratory tract infections (LRTIs) in young children and significantly impacts morbidity and mortality among the immunocompromised and elderly.[110,111] Worldwide, RSV is responsible for around 35 to 40 million cases of acute LRTIs annually in children under the age of 5. In the United States, approximately 2 million children under 5 are affected by RSV infections each year, necessitating medical care, and about 2-3% of these cases (around 40,000-60,000) result in hospitalization.[72,112] Given the substantial global burden of RSV, particularly in vulnerable populations, it is imperative to develop more accessible and effective therapeutic strategies beyond prophylactic measures.

Given as a prophylactic treatment specifically to infants and/or babies born prematurely, babies with heart disease, and children with bronchopulmonary dysplasia; palivizumab also known as Synagis is an example of the first approved mAb given to target RSV F protein.[113] Besides that, nirsevimab, also sold under the brand name Beyfortus is another mAb that was later approved by the US FDA which helps prevent severe RSV in infants and young children.[114] However, both are mainly targeted at high-income countries, as the costs are expected to be prohibitively high for affordable global access to the product.[115] Moreover, despite the safety and moderate to good efficacy (approximately 50–70%) of palivizumab (Synagis) and nirsevimab—when used as prophylactic treatments, systemically administered mAbs have not been successful as a therapeutic option for RSV infections.[113]

Another muco-trapping study of combating RSV was reported using an inhaled motavizumab variant, known as Mota-MT, which is a highly effective neutralizing mAb targeting the RSV F protein.[72] Findings from this study demonstrated Mota-MT's efficacy in mice by capturing RSV within airway mucus through polyvalent Fc-mucin interactions, resulting in a 20–30-fold reduction in the movement of RSV particles in pediatric and adult mucus, dependent on the Fc-glycan mechanisms. Furthermore, Mota-MT rapidly eliminated the virus from the mouse airways. When administered daily via nebulization to RSV-infected neonatal lambs, the treatment achieved an astonishing reduction in RSV viral loads—10,000-fold in bronchoalveolar lavage fluid and 100,000-fold in lung tissues—compared to placebo controls.[72] The success of Mota-MT in preclinical models is particularly encouraging, suggesting that muco-trapping strategies could revolutionize the early intervention landscape for RSV infections. These substantial results demonstrated the immense potential of inhalable muco-trapping monoclonal antibodies as an innovative therapeutic strategy for RSV.

An antiviral study of nebulised ALX-0171, a novel trivalent nanobody with antiviral properties against RSV has been carried out which targets the F protein of RSV to block the virus from entering host cells.[73-75] When administered prophylactically or therapeutically through nebulization or intranasal delivery in cotton rats, ALX-0171 showed notable success in reducing viral loads. Its antiviral effect was more significant as compared to the systemic administration of palivizumab, an approved mAb for RSV treatment. A Phase I/IIa clinical trial found nebulized ALX-0171 was well-tolerated and effective in lowering nasal RSV viral titers among young children[74] Taken together, these findings reflect a growing consensus that inhaled biologics represent a viable and potentially superior alternative to systemic prophylaxis for respiratory viral infections like RSV.

Concluding remarks

Pulmonary drug delivery has evolved remarkably, shifting from traditional therapies to biologics-based approaches that target complex respiratory diseases. Inhalation therapies, once confined largely to small molecules for asthma and COPD, now show immense potential for delivering proteins, monoclonal antibodies, nanobodies, and even gene-based therapeutics. As the limitations of systemic biologic delivery become increasingly apparent, pulmonary administration offers a more localized, non-invasive and efficient therapeutic approach. It facilitates direct delivery to target site, enhances therapeutic efficacy and minimizes side effects, all while potentially improving patient adherence through ease of use.

These biologic agents exhibit distinct pharmacokinetic and pharmacodynamic profiles depending on their size and structure, necessitating tailored formulation and device strategies. Recent advances in formulation, such as PEGylation, encapsulation, and powder-based delivery, have helped to

overcome challenges related to biologic stability and tissue penetration. Similarly, innovations in inhaler design from DPIs and pMDIs to smart inhalers and mesh nebulizers are making it increasingly feasible to deliver sensitive biologic molecules effectively and reproducibly to the lungs.

However, despite these encouraging advancements, challenges remain. Achieving consistent aerosol delivery, preserving biologic stability during nebulization, ensuring uniform lung distribution, and overcoming mucosal and immunological barriers still require significant optimization. Encouragingly, emerging technologies such as mucopenetrating formulations, breath-actuated devices, and digitally monitored inhalers have shown potential in addressing some of these issues. However, translating pre-clinical success into consistent clinical efficacy remains a key barrier.

Ultimately, interdisciplinary collaboration across immunology, pulmonary medicine, pharmaceutical sciences, and device engineering will be essential to unlock the full potential of inhaled biologics. As more targeted therapies enter development and regulatory pathways begin to adapt to these novel delivery systems, inhaled biologics may soon become a widely adopted strategy in the management of complex respiratory diseases.

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Declarations

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disease, according to the National Library of Medicine. AAT is produced by the liver but helps the lungs defend against inflammation and outside irritants such as smoke or other environmental exposures. "COPD prevalence is especially high in the veteran population compared to the general population, making it essential to understand the rate of alpha-1 antitrypsin deficiency diagnosis and identify missed opportunities for screening in this group," said lead author Arianne K. Baldomero, MD, pulmonologist and assistant professor of medicine at the University of Minnesota, Minneapolis, in an interview. Baldomero and colleagues reviewed national data from Veterans' Administration electronic health records, from 2004 to 2024. The study population included 2,384,913 veterans with COPD and/or asthma, based on two or more International Classification of Diseases codes and/or spirometry (forced expiratory volume in 1 second/forced vital capacity of < 0.7). Overall, AATD was diagnosed in 8564 individuals (0.36% of the study population). Those diagnosed were significantly younger than the population overall, with a mean age of 57 years vs 64 years. A combination of COPD and asthma was more common among patients with AATD than those without AATD (20.8% vs 10.7%), while the proportion with either COPD or asthma alone was higher among patients without AATD (73.5% vs 64.4% and 15.8% vs 14.8%, respectively). Individuals with AATD also were more likely than those without AATD to have cirrhosis (21.59% vs 5.38%) but less likely to have coronary artery disease (35.1% vs 41.4%). The AATD group also had fewer active smokers and more never smokers than the group without AATD (24.39% vs 30.4% and 30.34% vs 26.4%, respectively). Although cirrhosis, hepatocellular carcinoma, and bronchiectasis were significantly associated with higher odds of an AATD diagnosis, active smoking compared to never smoking was associated with lower odds of AATD diagnosis. "The extremely low rate of AATD diagnosis was striking, but consistent with known testing gaps in clinical practice, highlighting systemic under-screening even within an integrated healthcare system," Baldomero said. "Clinicians should maintain a high index of suspicion for AATD in veterans with COPD, liver disease, or bronchiectasis and ensure guideline-recommended testing is performed regardless of smoking status or geography," she said.

The Potential Benefits of Sleep Medicine Hospitalists

As the hospitalist workforce grows, sleep medicine experts suggest that hospitals and their patients could benefit from having sleep medicine hospitalists available, too. Doing so will make it so "Healthcare providers can mitigate the adverse effects of OSA (obstructive sleep apnea) on patient recovery and long-term health outcomes," the authors of a 2024 exploration of the sleep medicine hospitalist wrote for *Current Pulmonology Reports*. One of the report's coauthors Kori Ascher, DO, described herself as enthusiastic about what she calls the "profound benefit" of sleep medicine hospitalists as a specialized inpatient service. "I think everyone realizes the benefits," said Ascher, an assistant professor in the Division of Pulmonary, Critical Care, and Sleep Medicine at the University of Miami, Miami. "It's operationally, how can it be executed?" Why now, one might ask. Research suggests that nearly 84 million adults in the US are living with obstructive sleep apnea, the most common form of sleep-disordered breathing and a serious condition associated with adverse health outcomes, such as cardiovascular disease (CVD), cognitive impairment, as well as an increased risk for early mortality. But the prevalence doesn't guarantee that patients will be monitored for sleep apnea while hospitalized. Currently, sleep apnea is underrecognized in hospitalized patients, according to Karin Johnson, MD, professor of neurology at the UMass Chan School of Medicine - Baystate in Springfield,Massachusetts. "There's still a lot of room for improvement," she said. If the electronic health record (EHR) isn't specifically configured to proactively ask patients about existing sleep disorders and their treatment, that information might not make it into their record, Ascher said. In fact, she recently submitted a request to her organization's information technology department, asking if continuous positive airway pressure use and settings could be incorporated into a patient's home medications list on the EHR. "If it's not part of what you do or the systems that are built into the electronic health record, it's easy to sort of miss," Johnson said.

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