

CANADIAN RESPIROLOGY TODAY

VOLUME 2
ISSUE 1
FALL 2026

Clinical Insights, Perspectives,
and Disease Management

EMERGING DIAGNOSTIC AND THERAPEUTIC APPLICATIONS OF REMOTE PATIENT MONITORING IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) CARE

Felix-Antoine Coutu, BSc
Armita Kalani
Seyedfakhreddin Nabavi, PhD
Bryan A. Ross, MD, FRCPC, MSc, BScH

A PATIENT-CENTRED APPROACH TO OPTIMIZING INHALED THERAPY: INTEGRATING PATIENT, DEVICE, DRUG AND DISEASE FACTORS

George Philteos, MBBCh, MSc, FRCPC, D. ABSM

CLINICAL AND SEROLOGICAL EVALUATION AND MANAGEMENT OF RHEUMATIC DISEASE- ASSOCIATED INTERSTITIAL LUNG DISEASE

Ophir Vinik, MD, FRCPC, MScCH

SINGLE-INHALER TRIPLE THERAPY IS JUST THE START

Sacha Bhinder, HBSc, MD, FRCPC

OPTIMIZING IN-HOSPITAL CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) CARE IN CANADA: CHALLENGES, EVIDENCE, AND FUTURE DIRECTIONS

Mathieu D. Saint-Pierre, MD, FRCPC Respiriology

ISSN 2819-2621 (Print)
ISSN 2819-263X (Online)

Editorial Board



Mathieu D. Saint-Pierre, MD, FRCPC Respiriology
University of Ottawa, Ottawa, ON
Montfort Hospital, Ottawa, ON
Institut du Savoir Montfort, Ottawa, ON



Sacha Bhinder, HBSch, MD, FRCPC
Scarborough Health Network, Centenary Site, Toronto, ON
Toronto Lung Care Clinic, Toronto, ON
Heart Health Institute, Toronto, ON
Lecturer, Division of Respiriology, University of Toronto, Toronto, ON



George Philteos, MBBCh, MSc, FRCPC, D. ABSM
Lakeridge Health, Durham Region
Durham Institute of Respiriology
President of Dynamic Drug Advancement

Table of Contents

Emerging Diagnostic and Therapeutic Applications of Remote Patient Monitoring in Chronic Obstructive Pulmonary Disease (COPD) Care 5
Felix-Antoine Coutu, BSc
Armita Kalani
Seyedfakhreddin Nabavi, PhD
Bryan A. Ross, MD, FRCPC, MSc, BScH

A Patient-Centred Approach to Optimizing Inhaled Therapy: Integrating Patient, Device, Drug and Disease Factors 12
George Philteos, MBBCh, MSc, FRCPC, D. ABSM

Clinical and Serological Evaluation and Management of Rheumatic Disease-Associated Interstitial Lung Disease..... 19
Ophir Vinik, MD, FRCPC, MScCH

Single-Inhaler Triple Therapy Is Just The Start 25
Sacha Bhinder, HBSch, MD, FRCPC

Optimizing In-Hospital Chronic Obstructive Pulmonary Disease (COPD) Care in Canada: Challenges, Evidence, and Future Directions 31
Mathieu D. Saint-Pierre, MD, FRCPC Respiriology

Canadian Respiriology Today is published 3 times per year.

To contribute to a future issue, email us at info@catalytichealth.com. Submission guidelines and editorial policies are available on the journal website, canadianrespirologytoday.com.

To subscribe to Canadian Respiriology Today and more open access scientific specialty journals published by Catalytic Health, please visit catalytichealth.com/crct.

The content of this journal qualifies for Section 2 (self-learning) CPD credits under the Royal College’s Maintenance of Certification (MOC) program. For more information on how journal articles can meet your CPD needs, please consult the Royal College’s website. For more personalized support, please contact the Royal College Services Centre (1-800-461-9598) or your local CPD Educator.

Canadian Respiriology Today is an open access journal, which means all its content is freely available without charge. Users are permitted to copy and redistribute the material in any medium or format for any noncommercial purpose, provided they cite the source.

© 2026 Canadian Respiriology Today. Licensed under CC BY-NC-ND 4.0.
To learn more about our policies please visit canadianrespirologytoday.com.

About the Authors



Felix-Antoine Coutu, BSc

Felix-Antoine Coutu is currently completing his medical training at McGill University with a strong clinical interest in pulmonary medicine and chronic obstructive pulmonary disease (COPD). He is involved in multiple clinical research projects investigating the population with COPD, with a specific interest in Digital Health. He presented innovative research on remote patient monitoring in COPD at the national level and has published in widely recognized peer-reviewed journals.

Affiliations: Respiratory Epidemiology and Clinical Research Unit, Centre for Outcomes Research and Evaluation, Research Institute of the McGill University Health Centre, Montreal, QC, Canada. Department of Medicine, McGill University, Montreal, QC, Canada.



Armita Kalani

Armita Kalani is completing her medical training at McGill University, with a strong clinical interest in respiratory medicine, particularly chronic obstructive pulmonary disease (COPD). She is actively involved in clinical research at the McGill University Health Centre, with a focus on COPD and digital health, including work in remote patient monitoring and contributions to clinical trials evaluating oscillatory positive expiratory pressure (OPEP) therapy in patients with COPD. Her work centers on improving patient-centered care and outcomes in chronic respiratory disease.

Affiliations: Respiratory Epidemiology and Clinical Research Unit, Centre for Outcomes Research and Evaluation, Research Institute of the McGill University Health Centre, Montreal, QC, Canada. Department of Medicine, McGill University, Montreal, QC, Canada.



Seyedfakhreddin Nabavi, PhD

Seyedfakhreddin Nabavi is a Research Associate at the Research Institute of the McGill University Health Centre (RI-MUHC), where his work sits at the intersection of digital health and respiratory medicine. His research focuses on the clinical translation of remote patient monitoring (RPM) technologies for chronic obstructive pulmonary disease (COPD), with particular emphasis on integrating innovative sensing and data-driven approaches into real-world care pathways. Dr. Nabavi has authored and co-authored several peer-reviewed publications and has presented his research at national and international conferences.

Affiliations: Respiratory Epidemiology and Clinical Research Unit, Centre for Outcomes Research and Evaluation, Research Institute of the McGill University Health Centre, Montreal, QC, Canada.

About the Authors



Bryan A. Ross, MD, FRCPC, MSc, BScH

Dr. Bryan A. Ross is a Clinician-Scientist at the Research Institute of the McGill University Health Centre (RI-MUHC), Respiriologist at the MUHC, and Assistant Professor at McGill University in Montreal. He is Co-Director of the renowned COPD and Pulmonary Rehabilitation clinical program at the Montreal Chest Institute (MCI) of the MUHC, and Director of the McGill Accredited COPD and Pulmonary Rehabilitation Clinical Fellowship Training Program. He holds national and international leadership positions within the Canadian Thoracic Society and American Thoracic Society and is the recent recipient of the 2026 Pulmonary Rehabilitation Early Career Achievement Award of the American Thoracic Society. His innovative clinical research program, funded by the Fonds de recherche du Québec Santé (FRQS) and by the Canadian Institutes of Health Research (CIHR), addresses the determinants and management of COPD, with a focus on Digital Health and Exacerbations.

Affiliations: Respiratory Epidemiology and Clinical Research Unit, Centre for Outcomes Research and Evaluation, Research Institute of the McGill University Health Centre, Montreal, QC, Canada. Department of Medicine, McGill University, Montreal, QC, Canada. Division of Respiratory Medicine, Department of Medicine, McGill University Health Centre, Montreal, QC, Canada. Montreal Chest Institute, McGill University Health Centre, Montreal, QC, Canada.

Emerging Diagnostic and Therapeutic Applications of Remote Patient Monitoring in Chronic Obstructive Pulmonary Disease (COPD) Care

Felix-Antoine Coutu, BSc
Armita Kalani
Seyedfakhreddin Nabavi, PhD
Bryan A. Ross, MD, FRCPC, MSc, BScH

Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality, with prevalence projected to rise by nearly 25% between 2020 and 2050 to reach approximately 600 million people worldwide.¹ COPD is characterized by persistent airflow limitation, leading to chronic dyspnea and reduced exercise

capacity. Patients experience exacerbations of COPD (ECOPDs), clinically significant acute episodes characterized by increased airway inflammation and sudden worsening of breathlessness, which contribute substantially to lung function decline and are strongly associated with mortality.² Exacerbations account for the vast majority of COPD-related healthcare use, driving hospital admissions, healthcare costs, long-term

functional decline, and mortality risk.² Despite progress in inhaled and biologic therapies, the management of recurrent exacerbations remains a significant challenge, and in fact, admissions for COPD are uniquely increasing rather than decreasing when compared with other chronic diseases after adjusting for population growth and aging in Canada.³ This highlights two important clinical realities: 1) that the current approach to COPD care is failing, and 2) that for both patients and health systems alike, there is a pressing need for innovative strategies to address and reduce the burden of COPD exacerbation admissions and readmissions.

What is Remote Patient Monitoring?

Remote patient monitoring (RPM) has emerged as a promising method to potentially address many ongoing clinical challenges in COPD care, including key individual (dyspnea, mobility) and logistical (rural/isolated populations, winter seasonal care) accessibility gaps,⁴ as well as the overarching need for prompt and timely prevention-oriented strategies (Figure 1). RPM involves the systematic collection and real-time transmission of health-related data from the comfort of the patient’s home environment, allowing for the detection of warning signs,

particularly among COPD sub-populations who experience frequent and/or severe exacerbations and hospitalization/re-hospitalization.⁵ Recent technological advances have led to the development of increasingly compact and sophisticated wearable^{4,5} and portable⁶ devices that are capable of continuous, multi-parameter data collection and transmission. ‘Wearables’ are available in nearly any format, including wristbands, armbands, vests, upper thorax bands, and rings,⁴ and can enable continuous daytime and nighttime monitoring of relevant physiological parameters including respiratory rate (RR), oxygen saturation (SpO₂), heart rate (HR), physical activity, sleep quality, and autonomic function.⁷ Complementing these technologies, portable handheld devices allow for independent home-based measurement and transmission of lung function and lung mechanical changes.^{6,8} A summary of the principal equipment and strategies used in RPM for COPD is presented in Table 1.

A New Approach to Exacerbation Definition and Classification

Alongside rapid advances in wearable and portable technologies, the current artificial intelligence (AI)/machine learning (ML) ‘renaissance’ has enabled the processing

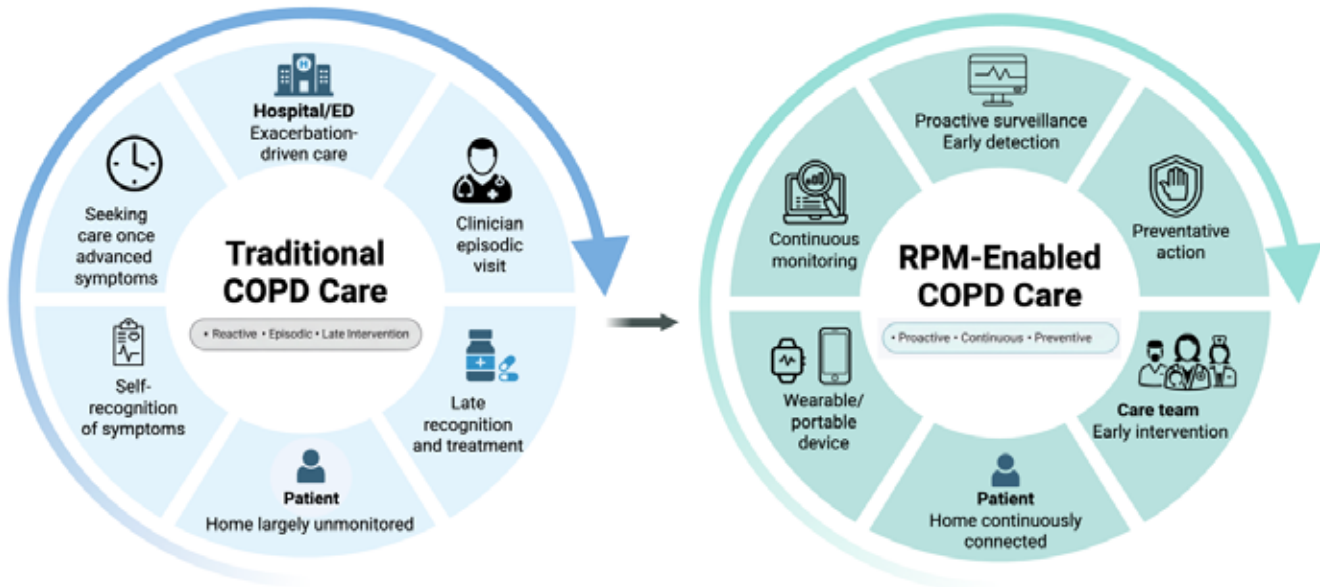


Figure 1. Traditional care model vs remote patient monitoring care model in COPD; courtesy of Felix-Antoine Coutu, BSc, Armita Kalani, Seyedfakhreddin Nabavi, PhD, Bryan A. Ross, MD, FRCPC, MSc, BScH

Abbreviations: COPD: chronic obstructive pulmonary disease; ED: Emergency Department; RPM: remote patient monitoring

of incredibly large volumes of continuous, multiparametric physiologic data at an unprecedented scale. By leveraging ML to interpret complex physiological signatures, clinicians can improve diagnostic accuracy⁹ while supporting a more personalized approach to care. Historically, COPD exacerbations have been diagnosed based on patient-reported increases in classic symptoms such as dyspnea, sputum production, and cough, with exacerbation severity classified retrospectively, according to treatment decisions and care settings rather than underlying mechanisms or the degree of physiological derangement.^{2,10} These persistent limitations in diagnosis and severity classification have prompted the formulation of a new framework—the Rome Proposal adopted by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) in 2023—whereby severity classification is defined by objective and measurable parameters, including validated dyspnea scores, RR, SpO₂, HR, C-reactive protein, and blood gas values.¹⁰

This framework provides a useful and objective foundation not only for advancing exacerbation research but also for developing and deploying clinical COPD RPM platforms. Reflecting the progress made to date in this field, the 2026 edition of the GOLD Report has, for the first time, included a chapter dedicated to AI and emerging technologies in COPD.²

Diagnostic Applications of Remote Patient Monitoring

Given that COPD exacerbations are characterized by an acute pro-inflammatory burst within the airways,¹⁰ and that emerging evidence identifies the prodromal (pre-symptomatic) period as a key and potentially multi-day window for prompt intervention,¹¹⁻¹³ pre-emptive monitoring strategies in high-risk patients may have a profound impact on health resource use, quality of life, lung function worsening, and mortality.

RPM Domain	Modality	Data Captured	Clinical Application	Strengths	Limitations
Continuous Physiological Monitoring	Wearable sensors	Respiratory, cardiac, activity, sleep, autonomic metrics	Early detection of exacerbations, characterization of exacerbation trajectories	Continuous, passive, home environment, high patient acceptability	Signal variability, possible artefact, requires validation of alert thresholds
	Portable/handheld oscillometers	Airway resistance, lung mechanical changes	Disease monitoring, risk stratification, complement to wearable data	Effort-independent, autonomous home use	Non-continuous (interval) measurements, limited temporal resolution, technique-dependent
Monitoring of Standard COPD Therapy	Smart inhalers/device attachments	Inhaler actuation, technique, adherence	Optimization of therapy, early detection of deterioration	Objective adherence data, actionable feedback	Device-specific, cost considerations
Therapeutic Delivery	Virtual pulmonary rehabilitation programs	Activity metrics, exercise adherence, safety monitoring	Maintenance of PR benefits, symptom improvement	Expands access, scalable	Digital literacy requirements

Table 1. Remote Patient Monitoring Domains and Modalities in COPD; courtesy of Felix-Antoine Coutu, BSc, Armita Kalani, Seyedfakhreddin Nabavi, PhD, Bryan A. Ross, MD, FRCPC, MSc, BScH

Abbreviations: COPD: chronic obstructive pulmonary disease; RPM: remote patient monitoring; PR: pulmonary rehabilitation.

Foundational studies of RPM in COPD used to leverage ‘fixed’ non-wearable home equipment (home oxygen, non-invasive ventilation) to demonstrate that subtle changes in RR could precede acute exacerbations by up to 5 days.^{12,13} Subsequent studies used biometric wearable chest bands to collect daytime ambulatory (non-tethered) parameters for several weeks after an exacerbation. These investigations demonstrated both the feasibility of prolonged monitoring as well as a progressive normalization of RR over time in the recovery period, suggesting a possible application for RPM in ‘high-risk’ patients at discharge and monitoring to prevent re-hospitalizations.¹⁴

More recently, smaller and more comfortable wearables, such as biometric rings and wristbands, have been used to demonstrate the feasibility of non-invasive, continuous recording of parameters in the unperturbed ambulatory home setting during COPD exacerbations over periods of several weeks. These investigations have shown that excellent quality data could be captured and transmitted autonomously by older adults with advanced disease (i.e., the target population most likely to benefit from RPM platforms in real-world clinical practice).⁵ These studies have also demonstrated that the scientific community is starting to leverage wearable devices to better address the fundamental question of ‘what exactly is an exacerbation?’. More recently, wearable devices (biometric rings and wristbands) have been used to characterize the trajectory of exacerbations over 3 consecutive weeks, capturing subtle longitudinal changes in respiratory, cardiac, activity, sleep, and autonomic parameters (*exacerbation characterization*), while also identifying patients who ultimately recover (“recovered” subgroup) from those with persistent symptom worsening (“persistent-worsening” subgroup). This work has delineated distinct pathophysiological patterns (“*clinical subgroup signatures*”).⁷ The former (*exacerbation characterization*) serves as the foundation to construct and validate the sophisticated COPD RPM platforms using prospectively collected data from a large cohort of patients with COPD with a history of frequent exacerbations, such as the ePredictAECOPD trial ([ClinicalTrials.gov NCT06802003](#)). These platforms are designed to detect the very early prodromal period of an exacerbation, allowing for prompt trajectory-altering intervention. In parallel, clear and distinct patterns that differentiate clinically recovered

from non-recovered patients (“clinical subgroup signatures”)⁷ are being integrated into RPM alert algorithms to support monitoring of high-risk patients after hospital or emergency department discharge.

Handheld portable devices are increasingly being used and incorporated into RPM platforms for chronic disease monitoring in COPD, due in part to concomitant technological advances that have allowed lighter, more compact, and user-friendly designs. These advancements also address the need to complement wearable-derived vital sign-based metrics with daily lung function-based metrics. Portable oscillometry devices are often preferred over spirometry for home monitoring, as they can be used more reliably and autonomously without the need for a skilled technician or uncomfortable repeated forced respiratory manoeuvres, an advantage that is particularly important when the patient is acutely unwell.¹⁵ The feasibility and practicality of home-based oscillometry was demonstrated in the CHROMED randomized controlled trial, which also reported a reduction in healthcare costs as an exploratory outcome following the incorporation of this lung function monitoring intervention.⁸ Following this trial, smaller handheld portable devices designed for estimating large and small airway resistance have been tested and validated against conventional oscillometry. These devices demonstrated a comparable, and in some cases superior, ability to discriminate disease severity alongside excellent user-reported experience scores among patients with COPD.⁶

Therapeutic Applications of Remote Patient Monitoring

The applications of RPM in COPD management extend well beyond diagnosis and monitoring. The COVID-19 pandemic emphasized the relevance of therapeutic RPM-based solutions, as remote modalities became essential for maintaining standard-of-care interventions, such as pulmonary rehabilitation (PR) programs, during periods when in-person care was restricted or even prohibited.¹⁶ This rapid and, initially, forced clinical transition from traditional in-person PR to virtual or hybrid alternatives, adopted during the COVID-19 pandemic and sustained thereafter, has been complemented by research demonstrating these approaches to be both feasible and safe, with similar clinical outcomes comparable to those of in-person programs, including effects on

symptom burden and quality of life.¹⁷ In addition, a recent systematic review and meta-analysis evaluating the addition of wearable-based activity tracking into PR programs reported a significant increase in daily step count compared with usual care, although no clear additional benefits were observed for quality of life or functional capacity. Overall, these findings support the integration of RPM modalities within virtual PR programs.¹⁸

Digital ‘smart’ inhalers and other connected therapeutic devices represent an additional avenue through which RPM can be used as an adjunct to existing standard-of-care COPD therapies. These technologies support the monitoring of objective inhaler-related metrics, and provide direct feedback on inhaler technique, supporting optimized medication delivery and improved adherence to controller therapy. In a recent prospective observational study of 40 patients with COPD, smart inhaler sensors detected reductions in core inhalation characteristics (volume, duration, and peak inspiratory flow) up to 2 weeks before an exacerbation. These findings suggest that smart inhalers have the ability to identify not only issues related to proper technique and adherence, but also may help identify the prodromal/early therapeutic window for acute intervention.¹⁹ Building on this premise, an ongoing prospective clinical trial (ClinicalTrials.gov NCT06614959) is investigating the integration of a ‘smart’ attachment to an oscillatory positive expiratory pressure device. This technology collects parameters related to both the quality of the technique (time of use, number of use, pressure gradient generated) and the quality and technical parameters of use (including frequency and amplitude of pressure oscillations and the sum of oscillations over a predefined threshold). These parameters, transmitted without any “active” participation whatsoever from the patient to the clinical care team, have the potential to remotely identify nonadherence, poor technique, and even early signs of deterioration. Collectively, “smart” inhalers and connective device attachments have the potential to complement, and even enhance, existing COPD therapeutic strategies.

Finally, app-based delivery of educational modules and self-management training for COPD is being developed and implemented. Recent studies have shown that these digital interventions can significantly improve self-management behaviours and quality of life. Motivational and peer-support features embedded within

these applications appear to contribute to their effectiveness,²⁰ and have been shown to improve physical activity, adherence to exercise, and reductions in depression scores.²¹

Barriers to Implementation

The actual implementation of RPM innovations into frontline clinical practice remains limited by both perceived and genuine barriers to health system integration. In contrast to in-person monitoring methods, RPM relies on the patient’s adherence and ability to operate the devices in the home setting, including wearing and using the device, recharging it, and transmitting data.²² Therefore, end-user (patient) ease of use and comfort from prolonged wear become important factors.^{23,24} Moreover, because RPM occurs outside the hospital or clinic, and generates large volumes of continuous, multiparametric data, many platforms rely on third-party cloud-based storage solutions.²⁵ These considerations raise significant concerns about data privacy and confidentiality. Aside from data collection and storage, achieving the primary goal of RPM, which is prompt intervention, requires trained healthcare professionals to triage alerts and notify physicians promptly. Especially during early implementation, ‘false-positive’ alerts may lead to unnecessary use of limited resources. Continuous monitoring also increases the likelihood of detecting unrelated pathological findings, raising questions about medico-legal liability, particularly if an acute event occurs outside of routine care hours. At the same time, patients enrolled in RPM platforms may feel continuously monitored and may inappropriately delay seeking urgent inpatient care. Finally, the transition from small-scale passive data collection for research purposes to large-scale, real-time clinical monitoring will require substantial infrastructure and personnel.

Conclusion

RPM has substantial potential to support a more proactive and sophisticated approach to chronic disease management in patients with COPD. Advances in continuous monitoring technologies, parallel progress in “hardware” (devices) and “software” (ML-based models), and the introduction of more objective diagnostic and severity classification criteria for exacerbations have converged over the same time period. Together, these developments enable a range of

clinical applications, including earlier detection of clinical deterioration, monitoring post-discharge of high-risk patients in the recovery period, creating novel home-based therapeutic interventions, and strengthening the effectiveness of existing standard-of-care COPD therapies. Achieving a broader implementation of RPM in frontline clinical practice will require robust evidence of clinical efficacy beyond current standards of care, as well as seamless integration into an already overburdened, stagnant, and failing “traditional” healthcare system.

Correspondence

Bryan A. Ross, MD, FRCPC, MSc, BScH
Email: bryan.ross@mcgill.ca.

Financial Disclosures

F.C.: None declared.

A.K.: None declared.

S.N.: None declared.

B.R.: Speaker Honoraria and/or Consultant compensation from the Canadian Thoracic Society (CTS), CHEST, Respiplus, Alberta Kinesiology Association (AKA), Association des Pneumologues de la Province du Québec (APPQ), McGill University Continuing Professional Development (CPD), GSK, AstraZeneca (AZ), COVIS, Sanofi, and Trudell Medical International (TMI), and Chiesi; **Research funding as Principal Investigator** from the McGill University Health Centre (MUHC) Department of Medicine Contract Academic Staff (CAS) Research Award, TMI; Unrestricted Investigator-Initiated Operating Grant, AstraZeneca **Unrestricted Investigator-Initiated Operating Grant**, GSK Medical Grant, the Quebec Respiratory Health Network (QRHN), Ministère de l'Éducation et le Ministère de l'Enseignement Supérieur Innovation and Office of Innovation + Partnerships (I+P: McGill University); Thorasys Thoracic Medical Systems, Inc.), the McGill Interdisciplinary Initiative in Infection and Immunity (MI4) Early Career Investigator Award, the MUHC Foundation/MCI Respiratory Research Campaign Innovation Grant, the Dept. of Medicine Scholarly Quality Award, and the Accelerating Clinical Trials-Clinical Trials Unit (ACT-CTU) Flagship Clinical Trial Feasibility Project Award, the RI-MUHC Sustaining Excellence Grants Program, the Fonds de Recherche du Québec – Santé (FRQS), and the Canadian Institutes of Health Research (CIHR);

In-kind support for research from Amazentis, Thorasys Inc., Restech, TMI, and DiaSorin.

References

- Boers E, Barrett M, Su JG, Benjafield AV, Sinha S, Kaye L, et al. Global burden of chronic obstructive pulmonary disease through 2050. *JAMA Netw Open*. 2023;6(12):e2346598-e. doi:10.1001/jamanetworkopen.2023.46598
- Global Initiative for Chronic Obstructive Lung Disease - GOLD. Global strategy for the diagnosis, management, and prevention of COPD: 2026 Gold Report [Internet]. 2026 [cited 2026 March 26]. Available from: https://goldcopd.org/wp-content/uploads/2026/01/GOLD-REPORT-2026-v1.3-8Dec2025_WMV2.pdf
- Amegadzie JE, Lee TY, Sadatsafavi M, Lynd LD, Sin DD, Johnson KM. Trends in hospital admissions for chronic obstructive pulmonary disease over 16 years in Canada. *CMAJ*. 2023;195(35):E1172-E1179. doi:10.1503/cmaj.221051
- Coutu FA, Iorio OC, Ross BA. Remote patient monitoring strategies and wearable technology in chronic obstructive pulmonary disease. *Front Med (Lausanne)*. 2023;10:1236598. doi:10.3389/fmed.2023.1236598
- Iorio OC, Coutu F-A, Malaeb D, Ross BA. Feasibility, functionality, and user experience with wearable technologies for acute exacerbation monitoring in patients with severe COPD. *Front Sig Proc*. 2024;4:1362754. doi:10.3389/frsip.2024.1362754.
- Coutu FA, Malaeb D, Iorio OC, Nabavi S, McFarland T, Lundblad LKA, et al. Measuring lung mechanics in patients with COPD using the handheld portable rapid expiratory occlusion monitor (REOM): a cross-sectional study. *Physiol Rep*. 2025;13(7):e70307. doi:10.14814/phy2.70307
- Coutu FA, Iorio OC, Nabavi S, Hadid A, Jensen D, Pamidi S, et al. Continuous characterisation of exacerbation pathophysiology using wearable technologies in free-living outpatients with COPD: a prospective observational cohort study. *EBioMedicine*. 2024;110:105472. doi:10.1016/j.ebiom.2024.105472
- Walker PP, Pompilio PP, Zanaboni P, Bergmo TS, Prikk K, Malinovsky A, et al. Telemonitoring in chronic obstructive pulmonary disease (CHROMED). A randomized clinical trial. *Am J Respir Crit Care Med*. 2018;198(5):620-628. doi:10.1164/rccm.201712-2404OC
- Glyde HMG, Morgan C, Wilkinson TMA, Nabney IT, Dodd JW. Remote patient monitoring and machine learning in acute exacerbations of chronic obstructive pulmonary disease: dual systematic literature review and narrative synthesis. *J Med Internet Res*. 2024;26:e52143. doi:10.2196/52143
- Celli BR, Fabbri LM, Aaron SD, Agustí A, Brook R, Criner GJ, et al. An updated definition and severity classification of chronic obstructive pulmonary disease exacerbations: the Rome Proposal. *Am J Respir Crit Care Med*. 2021;204(11):1251-1258. doi:10.1164/rccm.202108-1819PP
- Al Rajeh AM, Hurst JR. Monitoring of physiological

parameters to predict exacerbations of chronic obstructive pulmonary disease (COPD): a systematic review. *J Clin Med*. 2016;5(12):108. doi:10.3390/jcm5120108.

- Yañez AM, Guerrero D, Pérez de Alejo R, Garcia-Rio F, Alvarez-Sala JL, Calle-Rubio M, et al. Monitoring breathing rate at home allows early identification of COPD exacerbations. *Chest*. 2012;142(6):1524-1529. doi:10.1378/chest.11-2728
- Borel JC, Pelletier J, Taleux N, Briault A, Arnol N, Pison C, et al. Parameters recorded by software of non-invasive ventilators predict COPD exacerbation: a proof-of-concept study. *Thorax*. 2015;70(3):284-285. doi:10.1136/thoraxjnl-2014-206569
- Rubio N, Parker RA, Drost EM, Pinnock H, Weir CJ, Hanley J, et al. Home monitoring of breathing rate in people with chronic obstructive pulmonary disease: observational study of feasibility, acceptability, and change after exacerbation. *Int J Chron Obstruct Pulmon Dis*. 2017;12:1221-1231. doi:10.2147/COPD.S120706
- Stanojevic S, Kaminsky DA, Miller MR, Thompson B, Aliverti A, Barjaktarevic I, et al. ERS/ATS technical standard on interpretive strategies for routine lung function tests. *Eur Respir J*. 2022;60(1):2101499. doi:10.1183/13993003.01499-2021
- Foppiani A, Calcaterra V, Montanari C, Bertoli S, Battezzati A, Zuccotti G. Active home surveillance system (COD19) in managing chronic obstructive pulmonary disease: lessons and future perspectives from the COVID-19 pandemic experience. *Ther Adv Respir Dis*. 2025;19:17534666251346097. doi:10.1177/17534666251346097
- Qu M, Yang L, Liu K, Tang T, Sun X, Chen Y, et al. The effectiveness and feasibility of virtual pulmonary rehabilitation in patients with chronic respiratory diseases: a systematic review and meta-analysis. *Respir Med*. 2025;244:108159. doi:10.1016/j.rmed.2025.108159
- Oliveira TRA, do Nascimento Sales Figueiredo Fernandes AT, Santino TA, da Silva Menescal FEP, de Miranda Silva Nogueira PA. Effects of wearable devices on physical activity monitoring in pulmonary rehabilitation programs for chronic respiratory diseases: a systematic review and meta-analysis. *Sci Rep*. 2025;15(1):44767. doi:10.1038/s41598-025-28554-w
- Drummond MB, Hemphill CC, Hill T, Boe A, Yu D, Ohar JA. Use of a digital inhaler to assess COPD disease variability and identify impending acute COPD exacerbations: a pilot study. *Chronic Obstr Pulm Dis*. 2025;12(3):250-259. doi:10.15326/jcopdf.2024.0555
- Wang L, Guo Y, Wang M, Zhao Y. A mobile health application to support self-management in patients with chronic obstructive pulmonary disease: a randomised controlled trial. *Clin Rehabil*. 2021;35(1):90-101. doi:10.1177/0269215520946931
- Benzo R, Houlst J, McEvoy C, Clark M, Benzo M, Johnson M, et al. Promoting chronic obstructive pulmonary disease wellness through remote monitoring and health coaching: a clinical trial. *Ann Am Thorac Soc*. 2022;19(11):1808-1817. doi:10.1513/AnnalsATS.202203-214OC
- Nabavi S, Lundblad LKA, Ross BA. Susceptibility

assessment of oscillometry parameters to motion artifact. *Annu Int Conf IEEE Eng Med Biol Soc*. 2024;2024:1-4. doi:10.1109/EMBC53108.2024.10782180

- Fan KG, Mandel J, Agnihotri P, Tai-Seale M. Remote patient monitoring technologies for predicting chronic obstructive pulmonary disease exacerbations: review and comparison. *JMIR Mhealth Uhealth*. 2020;8(5):e16147. doi:10.2196/16147
- Hawthorne G, Greening N, Eslinger D, Briggs-Price S, Richardson M, Chaplin E, et al. Usability of wearable multiparameter technology to continuously monitor free-living vital signs in people living with chronic obstructive pulmonary disease: prospective observational study. *JMIR Hum Factors*. 2022;9(1):e30091. doi:10.2196/30091
- Waleed M, Kamal T, Um TW, Hafeez A, Habib B, Skouby KE. Unlocking insights in IoT-based patient monitoring: methods for encompassing large-data challenges. *Sensors (Basel)*. 2023;23(15):6760. doi:10.3390/s23156760.

About the Author



George Philteos, MBBCh, MSc, FRCPC, D. ABSM

Dr. George Philteos is a respirologist and sleep specialist at Lakeridge Health and Durham Institute of Respirology. He is the principal investigator for Dynamic Drug Advancement Clinical Research Center and his research interests spread from severe asthma, COPD, Chronic cough, to ILD trials. His clinics operate in the Durham Respiratory and Sleep Center, the Ellesmere Sleep Center and Sleep Wake Sleep Center. He has contributed to the development and presenting of CME activities, chairing respirology journal clubs and the development of guidelines.

Affiliations: Lakeridge Health, Durham Region
Durham Institute of Respirology
President of Dynamic Drug Advancement.

A Patient-Centred Approach to Optimizing Inhaled Therapy: Integrating Patient, Device, Drug and Disease Factors

George Philteos, MBBCh, MSc, FRCPC, D. ABSM

Abstract

Inhaled medications are crucial for the management of respiratory conditions such as chronic obstructive pulmonary disease and asthma, although their efficacy is contingent upon selecting the most appropriate inhaler and medication for each patient. Consideration should be given to factors such as inhaler technique, patient preference, coordination, inspiratory flow, small airway disease, and medication-related side effects. A patient-centred approach can maximize the benefits of inhaled therapy while minimizing potential risks.

Introduction

Respiratory conditions, such as asthma and chronic obstructive pulmonary disease

(COPD), represent significant causes of morbidity worldwide and frequently require long-term pharmacological management. While inhaled therapies are fundamental to the treatment of many respiratory conditions, their clinical efficacy can be highly dependent on proper administration. Consequently, patient education and evaluation of inhaler device technique are critical components of care. The Global Initiative for Obstructive Lung Disease (GOLD) emphasizes that it is essential to consider both the patient's ability to use the device effectively and their individual preferences when selecting an inhaler device.¹ These considerations set the stage for a more detailed exploration of the underlying factors that influence successful inhaler use.

Patient Characteristics and Device

Inspiratory flow rate, flow acceleration, and inhaled air volume are key patient characteristics that can affect the delivery of particles from inhaler devices to the lower respiratory tract.¹ Different inhaler devices, such as pressurized metered-dose inhalers (pMDIs) and soft mist inhalers (SMIs), require a slow, deep inhalation, whereas dry powder inhalers (DPIs), require a rapid and forceful inhalation.¹ Therefore, the patient's cognitive abilities, dexterity, and physical strength should be considered when selecting and prescribing inhaler therapy.

The Canadian Thoracic Society (CTS) recommends assessing a patient's peak inspiratory flow (PIF) when evaluating the suitability of a DPI.¹ In clinical practice, PIF can be readily measured using an In-Check DIAL.² To achieve effective medication delivery, the patient must generate sufficient force to produce the required PIF to overcome the internal resistance of the DPI and to separate the active drug from its carrier molecules.³ For most DPIs, a PIF of 60 L/min is considered optimal for adequate powder deaggregation.⁴ However, suboptimal PIF is common among hospitalized patients with COPD. A real-world study conducted by Mahler et al.⁵ reported that 44.6% of hospitalized COPD patients who were using a DPI demonstrated suboptimal PIF. Similarly, a real-world study conducted by the Montreal Chest Institute reported suboptimal PIF in 28% of stable outpatients with COPD.⁶ Three factors associated with suboptimal PIF included the degree of severity of airflow obstruction (40.5% in GOLD 4), female sex (suboptimal PIF was observed in 49% females versus 8% of males), and a low body mass index.⁶

Patient Behaviour

The CTS recommends administering triple inhaler therapy through a single inhaler.⁷ Single-inhaler triple therapy (SITT) is preferred over multiple-inhaler triple therapy due to its potential for increased benefits, improved adherence, and reduce inhaler technique errors.^{7,8}

Patient's Level of Consciousness and Coordination

Metered-dose inhalers (MDI) require patients to coordinate device actuation with inhalation,

and to inhale slowly (count of 5) and deeply.¹ For patients who are unable to perform a conscious inhalation manoeuvre, a pressurized metered-dose inhaler (pMDI) with a spacer or a nebulizer is recommended. In conscious patients with poor coordination and insufficient PIF, suitable options include a pMDI with a spacer, a soft mist inhaler, a nebulizer, or a breath-actuated MDI.^{9,10}

Disease and Drug Factors

Both asthma and COPD are airway diseases commonly treated with inhaled medications. To achieve optimal therapeutic benefit, it is essential that these medications are delivered to the sites of disease activity within the respiratory tract. This is particularly pertinent given the recognized role of small airway disease (SAD) in the pathophysiology of both COPD and asthma. Small airways, defined as airways with a diameter of less than 2 mm, serve as an important anatomical bridge between conductive larger airways and gas exchanging peripheral airways of the lung. Thus, optimizing the delivery of inhaled medications to the smaller airways may be an important consideration for the management of COPD and asthma.

In asthma, SAD contributes to overall airway resistance.¹¹ Histopathology studies have confirmed the presence of small airway abnormalities in asthma, irrespective of the severity of the disease.^{12,13} In COPD, the small airways are considered to be the primary site of disease progression. The prevalence of SAD increases with disease severity, affecting an estimated 51% of patients with GOLD stage 2 COPD and 95% of those with GOLD stage 4 disease.¹⁴ SAD has also been observed in pre-COPD patients, smokers, and patients with normal spirometry. Evidence of ventilation inhomogeneity and peripheral acinar inhomogeneity has been observed in patients with SAD,¹⁵ while histopathologic sampling of micro computed tomography (CT) imaging studies have demonstrated SAD in pre-COPD patients who exhibit symptoms or structural/physiological abnormalities despite non-obstructive spirometry.^{16,17}

Over the past several decades, growing attention has focused on the early origins of lung diseases. Research into these origins has identified that small airway inflammation may be a potential driver of disease progression.¹⁸ A variety of methods are available to assess SAD, with oscillometry increasingly recognized as a

non-invasive, reproducible physiologic tool for its assessment.^{19,20} Oscillometry enables the measurement of opposition to oscillatory airflow using the formula: **Impedance = Resistance + Reactance**

Resistance reflects the peripheral airway diameter and reactance reflects the stiffness (elastance) of the lung (**Figure 1**). More negative reactance values are indicative of small airway dysfunction, as airway narrowing or closure reduces the number of communicating lung units and increases the elastic stiffness of the lungs (**Figure 1**). Thus, reactance measured at 5 HZ (X5) may indicate SAD.²¹ Resistance measured at 5 HZ (R5) represents total airway resistance, while resistance at 20 HZ (R20) reflects resistance within the central airways. The difference (R5-R20) is a useful index of small airway resistance.²²

A growing understanding of SAD and advances in its assessment have increasingly

influenced inhaler selection by gauging the device's ability to deliver medication to the small airways.²³ The presence of SAD can influence COPD patient outcomes. Measures of quality of life and dyspnea have been shown to correlate more strongly with SAD as assessed by oscillometry than with forced expiry volume in 1 second (FEV1).²⁴ In addition, functional SAD identified by CT analysis has been recognized as an independent risk factor for future exacerbations.²⁵ Patients who experience frequent exacerbations also demonstrate significantly greater acinar zone inhomogeneity compared to those with infrequent exacerbations.²⁶ Small airway dysfunction has been associated with an increased risk of all cause, cardiovascular, respiratory, and neoplasm-related mortality, supporting a role for SAD as a prognostic marker of mortality.²⁷ In addition, functional SAD identified by CT in the early stages of COPD independently predicted accelerated loss

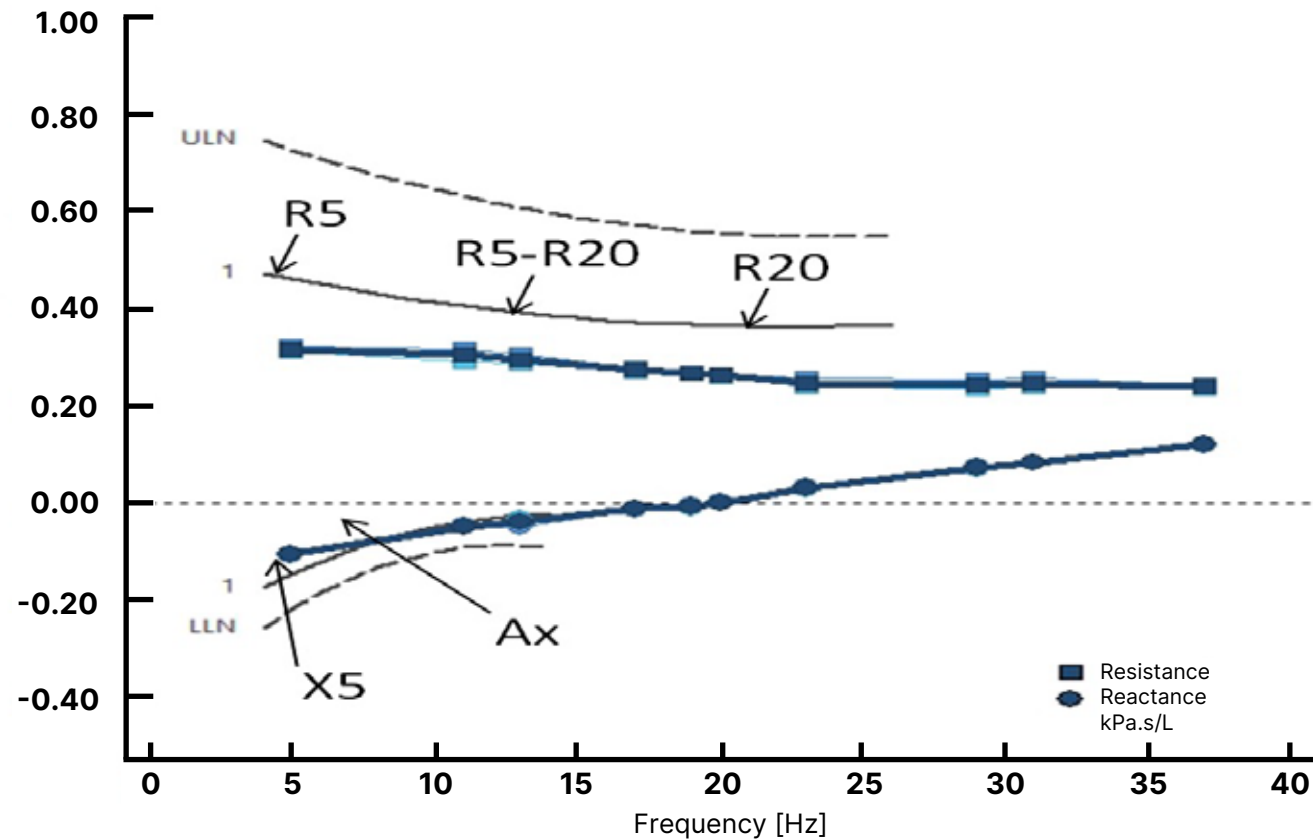


Figure 1. The representative resistance and reactance spectrum obtained during forced oscillation in a healthy adult's lungs. R5: Resistance at 5 Hz, reflecting airflow obstruction; R20: Resistance at 20 Hz, indicating an obstruction at the level of the central airways; R5-R20: Differences in resistance between R5 and R20 indicating an obstruction at the small airway level; X5: Reactance at 5 Hz, with a lower X reflecting a decrease in compliance; and Ax: Reactance area under the curve, with larger Ax values indicating an increase ventilation heterogeneity and greater lung stiffness, often resulting from an airway obstruction or collapse that reduces the volume of the aerated area of the lung; courtesy of George Philteos, MBBCh, MSc, FRCPC, D. ABSM

of lung function.²⁸ CT-detected functional SAD was also independently associated with an accelerated decline in FEV1 over a median follow-up period of 32 months among younger smokers with normal spirometry.²⁹

Potential Impact of SAD Evaluation on the Selection of Inhaled Therapies

To assess the impact of SAD on the selection of inhaled medication, Verbanck et al.³⁰ compared peripheral acinar ventilation inhomogeneity, as measured by forced oscillometry, between a DPI and an SMI. The SMI demonstrated significantly greater improvements in ventilation compared to the DPI. These improvements in ventilation was attributed to enhanced small airway function secondary to improvements in peripheral deposition, which is facilitated by the smaller particle size delivered by the SMI.³¹ Particle size is considered to be the critical factor of pulmonary deposition, with extra-fine particles, defined by a mass median aerodynamic diameter (MMAD) of <2.1 µm, achieving more effective delivery to the peripheral airways.³²

Usmani et al.³³ have shown that extra-fine SITT formulations achieved superior peripheral distribution and airway penetration compared with non-extra-fine formulations in patients with moderate to severe COPD. Similarly, co-suspension delivery using Aerosphere® technology, which employs porous particles made of phospholipids of 1 to 2 µm in size was shown to increase peripheral drug deposition.³⁴ Consistent with these findings, Tzani et al.³⁵ showed that extra fine particle formulations were more effective than conventional formulations in reducing gas trapping and improving dyspnea in patients with COPD and hyperinflation.

Lipworth et al.³⁶ evaluated the potential of inhaled products used in asthma and COPD to penetrate the small airways, highlighting the clinical implications of small airway dysfunction, including poor disease control and worse health status. They used impactor analysis to assess inhaled particle size based on MMAD (**Figure 2**). Extra-fine particle fraction, defined as particles with a diameter <2 µm, was calculated as a percentage of the delivered dose. Smaller particles are more likely to penetrate the small airways

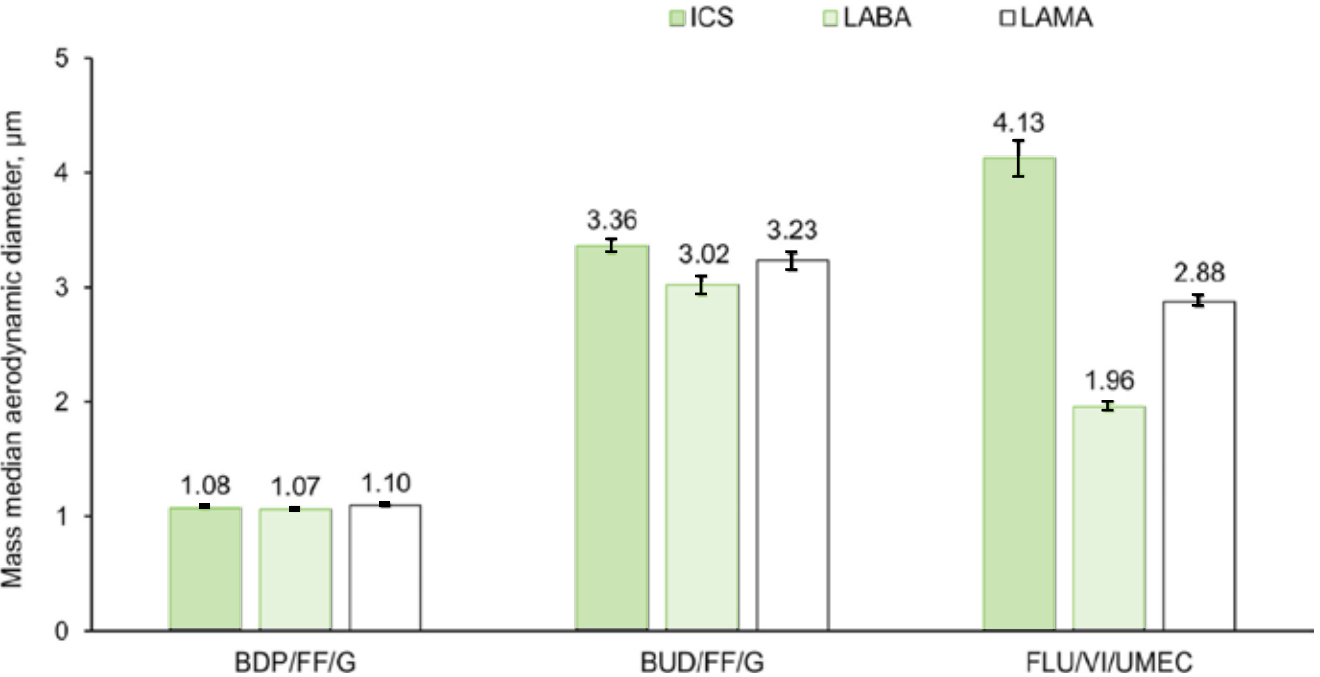


Figure 2. The mass median aerodynamic diameter (MMAD) of the three inhaled triple-therapy formulations. Mean values are presented with 95% CI. BDP/FF/G, n=54; BUD/FF/G, n=6; and FLU/VI/UMEC, n=6; courtesy of George Philteos, MBBCh, MSc, FRCPC, D. ABSM

Abbreviations: BDP: beclomethasone dipropionate; BUD: budesonide; CI: confidence interval; FF: formoterol fumarate; FLU: fluticasone furoate; G: glycopyrronium; ICS: inhaled corticosteroid; LABA: long-acting β₂-agonist; LAMA: long-acting muscarinic antagonist; UMEC: umeclidinium; VI: vilanterol (Lipworth et al., 2026).²⁰

(Figure 2). However, the authors emphasized the need for prospective randomized clinical trials to confirm whether treatment with extra-fine particle formulations can better target the small airways and subsequently improve disease control in patients with asthma and COPD.

Impact of Health Status and Comorbidities on the Selection of Inhaled Corticosteroids

Inhaled corticosteroids (ICSs) play an important role in the management of asthma and are recommended for use in selected patients with COPD. However, the clinical benefits of ICS should be weighed against the risk of local and systemic adverse effects, particularly in patients with relevant comorbidities. Evidence suggests that ICS use may be associated with an increased risk of respiratory infections, cataracts, and reductions in bone mineral density.³⁷ Systemic exposure to ICS can occur through both gastrointestinal absorption of the swallowed fraction and direct absorption from the lungs, which may increase the risk of systemic adverse effects. The likelihood of systemic side effects varies among ICS agents.³⁸ As noted by Baptist and Reddy,³⁹ lower bioavailability is generally associated with reduced systemic side effects. They noted that among ICSs, ciclesonide has a particularly low bioavailability, while ciclesonide and mometasone exhibit high serum protein binding, further reducing systemic effects. Moreover, fluticasone has low oral bioavailability due to fast metabolism in the liver.

Other adverse effects of ICSs are localized to the oropharynx, and include dysphonia, pharyngitis, and oropharyngeal candidiasis. Dysphonia affects up to 58% of patients using ICSs.⁴⁰ Williams et al.⁴¹ postulated that dysphonia may result from bilateral vocal cord adductor myopathy, identified as bowing in the vocal folds, secondary to local deposition of ICS. Notably, ciclesonide and beclomethasone are administered as prodrugs that undergo activation in the lungs. Ciclesonide requires hydrolyzation by esterases in the lung tissue to form the active metabolite, while exhibiting a low rate of transformation to the active metabolite in the mouth.⁴² Similarly, beclomethasone is activated by hydrolysis in the lung tissue.⁴³ Due to these properties, both ciclesonide and beclomethasone are postulated to exhibit a lower occurrence rate of oropharyngeal side effects. In summary, when selecting ICS

prescribers should consider the pharmacokinetic properties and potential adverse effects alongside patient-specific tolerance to inform the selection of appropriate inhaled therapies.

Conclusion

Inhaled therapies retain a central role in the management of respiratory conditions such as asthma and COPD, providing targeted delivery of medication directly to the lungs. However, the effectiveness of these therapies depends on factors beyond the pharmacological properties of the medication alone. Appropriate inhaler technique, adherence to treatment, particle size, and consideration of the pharmacokinetic properties and potential adverse effects of inhaled medications are important factors in optimizing treatment outcomes. When selecting inhaled therapy, prescribers should consider individual patient characteristics, preferences, and treatment tolerability. Ensuring that patients receive adequate education and ongoing assessment of their inhaler technique may further improve medication delivery and therapeutic effectiveness. Ultimately, optimal inhaled therapy selection for each patient requires an individualized approach that integrates patient, device, drug, and disease factors to achieve the best possible clinical outcomes.

Correspondence

George Philteos, MBBCh, MSc, FRCPC, D. ABSM
Email: drgphilteos@gmail.com

Financial Disclosures

G.P.: None declared.

References

1. Global initiative for chronic obstructive lung disease. 2026 GOLD report and pocket guide [Internet]. 2026 [cited 2026 August 31]. Available from: <https://goldcopd.org/2026-gold-report-and-pocket-guide/>

2. Dal Negro RW. Dry powder inhalers and the right things to remember: a concept review. *Respir Med.* 2015;10(1):13. doi:10.1186/s40248-015-0012-5

3. Ghosh S, Ohar JA, Drummond MB. Peak inspiratory flow rate in chronic obstructive pulmonary disease: implications for dry powder inhalers. *J Aerosol Med Pulm Drug Deliv.* 2017;30(6):381-387. doi:10.1089/jamp.2017.1416

4. Mahler DA. The role of inspiratory flow in selection and use of inhaled therapy for patients with chronic

obstructive pulmonary disease. *Respir Med.* 2020;161:105857. doi:10.1016/j.rmed.2019.105857

5. Mahler DA, Demirel S, Hollander R, Gopalan G, Shaikh A, Mahle CD, et al. High prevalence of suboptimal peak inspiratory flow in hospitalized patients with COPD: a real-world study. *Chronic Obstr Pulm Dis.* 2022;9(3):427-438. doi:10.15326/jcopdf.2022.0291

6. Pankovitch S, Frohlich M, AlOthman B, Marciniuk J, Bernier J, Paul-Emile D, et al. Peak inspiratory flow and inhaler prescription strategies in a specialized COPD clinical program. *Chest.* 2025;167(3):736-745. doi:10.1016/j.chest.2024.09.031

7. Bourbeau J, Bhutani M, Hernandez P, Aaron SD, Beauchesne MF, Kermelly SB, et al. 2023 Canadian Thoracic Society guideline on pharmacotherapy in patients with stable COPD. *Chest.* 2023;164(5):1159-1183. doi:10.1016/j.chest.2023.08.014

8. Bosnic-Anticevich S, Chrystyn H, Costello RW, Dolovich MB, Fletcher MJ, Lavorini F, et al. The use of multiple respiratory inhalers requiring different inhalation techniques has an adverse effect on COPD outcomes. *Int J Chron Obstruct Pulmon Dis.* 2016;12:59-71. doi:10.2147/COPD.S117196. Erratum in: *Int J Chron Obstruct Pulmon Dis.* 2019;14:1739. doi:10.2147/COPD.S156325

9. Dekhuijzen PN, Vincken W, Virchow JC, Roche N, Agusti A, Lavorini F, et al. Prescription of inhalers in asthma and COPD: towards a rational, rapid and effective approach. *Respir Med.* 2013;107(12):1817-1821. doi:10.1016/j.rmed.2013.09.013

10. Nelson HS. Inhalation devices, delivery systems, and patient technique. *Annals of Allergy, Ann Allergy Asthma Immunol.* 2016;117(6):606-612. doi:10.1016/j.anai.2016.05.006

11. Wagner EM, Liu MC, Weinmann GG, Permutt S, Bleecker ER. Peripheral lung resistance in normal and asthmatic subjects. *Am Rev Respir Dis.* 1990;141(3):584-588. doi:10.1164/ajrccm/141.3.584

12. Hamid Q, Song Y, Kotsimbos TC, Minshall E, Bai TR, Hegele RG, Hogg JC. Inflammation of small airways in asthma. *J Allergy Clin Immunol.* 1997;100(1):44-51. doi:10.1016/s0091-6749(97)70193-3

13. Mauad T, Silva LF, Santos MA, Grinberg L, Bernardi FD, Martins MA, et al. Abnormal alveolar attachments with decreased elastic fiber content in distal lung in fatal asthma. *Am J Respir Crit Care Med.* 2004;170(8):857-862. doi:10.1164/rccm.200403-305OC

14. Crisafulli E, Pisi R, Aiello M, Vigna M, Tzani P, Torres A, et al. Prevalence of small-airway dysfunction among COPD patients with different GOLD stages and its role in the impact of disease. *Respiration.* 2017;93(1):32-41. doi:10.1159/000452479

15. Verbanck S, Schuermans D, Meysman M, Paiva M, Vincken W. Noninvasive assessment of airway alterations in smokers: the small airways revisited. *Am J Respir Crit Care Med.* 2004;170(4):414-419. doi:10.1164/rccm.200401-037OC

16. Verleden SE, Hendriks JMH, Snoeckx A, Mai C, Mentens Y, Callebaut W, et al. Small airway disease in pre-chronic obstructive pulmonary disease with emphysema: a cross-sectional study. *Am J Respir Crit Care Med.* 2024;209(6):683-692. doi:10.1164/rccm.202301-0132OC

17. Martinez FJ, Agusti A, Celli BR, Han MK, Allinson JP,

Bhatt SP, et al. Treatment trials in young patients with chronic obstructive pulmonary disease and pre-chronic obstructive pulmonary disease patients: time to move forward. *Am J Respir Crit Care Med.* 2022;205(3):275-287. doi:10.1164/rccm.202107-1663SO

18. Stolz D, Mkorombindo T, Schumann DM, Agusti A, Ash SY, Bafadhel M, et al. Towards the elimination of chronic obstructive pulmonary disease: a Lancet commission. *Lancet.* 2022;400(10356):921-972. doi:10.1016/S0140-6736(22)01273-9

19. Kaminsky DA, Simpson SJ, Berger KI, Calverley P, de Melo PL, Dandurand R, et al. Clinical significance and applications of oscillometry. *Eur Respir Rev.* 2022;31(163):210208. doi:10.1183/16000617.0208-2021

20. Lipworth BJ, Jabbal S. What can we learn about COPD from impulse oscillometry? *Respir Med.* 2018;139:106-109. doi:10.1016/j.rmed.2018.05.004

21. Milne S, Jetmalani K, Chapman DG, Duncan JM, Farah CS, Thamrin C, et al. Respiratory system reactance reflects communicating lung volume in chronic obstructive pulmonary disease *J Appl Physiol* (1985). 2019;126(5):1223-1231. doi:10.1152/jappphysiol.00503.2018

22. King GG, Bates J, Berger KI, Calverley P, de Melo PL, Dellacà RL, et al. Technical standards for respiratory oscillometry. *Eur Respir J.* 2020;55(2):1900753. doi:10.1183/13993003.00753-2019

23. Toumpanakis D, Kim Y, Usmani OS. Small airways disease in patients with COPD: a question-and-answer approach for everyday clinical practice. *Chest.* 2026;169(3):641-651. doi:10.1016/j.chest.2025.07.002

24. Haruna A, Oga T, Muro S, Ohara T, Sato S, Marumo S, et al. Relationship between peripheral airway function and patient-reported outcomes in COPD: a cross-sectional study. *BMC Pulm Med.* 2010;10:10. doi:10.1186/1471-2466-10-10

25. Han MK, Quibrera PM, Carretta EE, Barr RG, Bleecker ER, Bowler RP, et al. Frequency of exacerbations in patients with chronic obstructive pulmonary disease: an analysis of the SPIROMICS cohort. *Lancet Respir Med.* 2017;5(8):619-626. doi:10.1016/S2213-2600(17)30207-2

26. Day K, Ostridge K, Conway J, Cellura D, Watson A, Spalluto CM, et al. Interrelationships among small airways dysfunction, neutrophilic inflammation, and exacerbation frequency in COPD. *Chest.* 2021;159(4):1391-1399. doi:10.1016/j.chest.2020.11.018

27. Quintero Santofimio V, Knox-Brown B, Potts J, Bartlett-Pestell S, Feary J, Amaral AFS. Small airways obstruction and mortality: findings from the UK biobank. *Chest.* 2024;166(4):712-720. doi:10.1016/j.chest.2024.04.016

28. Bhatt SP, Soler X, Wang X, Murray S, Anzueto AR, Beaty TH, et al. Association between functional small airway disease and fev1 decline in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2016;194(2):178-184. doi:10.1164/rccm.201511-2219OC

29. Ritchie AI, Donaldson GC, Hoffman EA, Allinson JP, Bloom CI, Bolton CE, et al. Structural predictors

of lung function decline in young smokers with normal spirometry. *Am J Respir Crit Care Med*. 2024;209(10):1208-1218. doi:10.1164/rccm.202307-1203OC. Erratum in: *Am J Respir Crit Care Med*. 2024;210(2):249. doi:10.1164/rccm.v209erratum11

30. Verbanck S, Schuermans D, Vincken W. Small airways ventilation heterogeneity and hyperinflation in COPD: response to tiotropium bromide. *Int J Chron Obstruct Pulmon Dis*. 2007;2(4):625-634.

31. Biddiscombe M, Saleem A, Meah S, Mak V, Usmani, O. Efficacy of the device in targeting tiotropium to the small airways in COPD. *European Respiratory Journal*. 2018;52:Suppl. 62, PA1017 <https://doi.org/10.1183/13993003.congress-2018.pa1017>

32. Usmani OS, Biddiscombe MF, Barnes PJ. Regional lung deposition and bronchodilator response as a function of β_2 -agonist particle size. *Am J Respir Crit Care Med*. 2005;172(12):1497-504. doi:10.1164/rccm.200410-1414OC

33. Usmani OS, Scichilone N, Mignot B, Belmans D, Van Holsbeke C, De Backer J, et al. Airway deposition of extrafine inhaled triple therapy in patients with COPD: a model approach based on functional respiratory imaging computer simulations. *Int J Chron Obstruct Pulmon Dis*. 2020;15:2433-2440 doi:10.2147/COPD.S269001

34. Usmani OS, Roche N, Jenkins M, Stjepanovic N, Mack P, De Backer W. Consistent pulmonary drug delivery with whole lung deposition using the aerosphere inhaler: a review of the evidence. *Int J Chron Obstruct Pulmon Dis*. 2021;16:113-124. doi:10.2147/COPD.S274846

35. Tzani P, Crisafulli E, Nicolini G, Aiello M, Chetta A, Clini EM, et al. Effects of beclomethasone/formoterol fixed combination on lung hyperinflation and dyspnea in COPD patients. *Int J Chron Obstruct Pulmon Dis*. 2011;6:503-509. doi:10.2147/COPD.S23746

36. Lipworth B, Zambelli E, Agazzi R, Piraino A. Relative particle size and distribution of inhaled triple therapies. *Ann Allergy Asthma Immunol*. 2026;136(5):545-549. doi:10.1016/j.ana.2025.12.016

37. Patel R, Naqvi SA, Griffiths C, Bloom CI. Systemic adverse effects from inhaled corticosteroid use in asthma: a systematic review. *BMJ Open Respir Res*. 2020;7(1):e000756. doi:10.1136/bmjresp-2020-000756

38. Pandya D, Puttanna A, Balagopal V. Systemic effects of inhaled corticosteroids: an overview. *The Open Respir Med J*. 2014;8:59-65. doi:10.2174/1874306401408010059

39. Baptist AP, Reddy RC. Inhaled corticosteroids for asthma: are they all the same? *J Clin Pharm Ther*. 2009;34(1):1-12. doi:10.1111/j.1365-2710.2008.00970.x

40. Galván CA, Guarderas JC. Practical considerations for dysphonia caused by inhaled corticosteroids. *Mayo Clin Proc*. 2012;87(9):901-904. doi:10.1016/j.mayocp.2012.06.022

41. Williams AJ, Baghat MS, Stableforth DE, Cayton RM, Shenoi PM, Skinner C. Dysphonia caused by inhaled steroids: recognition of a characteristic laryngeal abnormality. *Thorax*. 1983;38(11):813-821. doi:10.1136/thx.38.11.813

42. Burioka N, Fukuoka Y, Koyanagi S, Miyata M, Takata M, Chikumi H, et al. Asthma: chronopharmacotherapy and the molecular clock. *Adv Drug Deliv Rev*. 2010;62(9-10):946-955. doi:10.1016/j.addr.2010.03.012

43. Yi W, Wu M, Chen F, Zhou Z. Chapter 31 - Glucocorticoid compounds in drug discovery by targeting glucocorticoid receptor protein. *Privileged Scaffolds in Drug Discovery*. 2023;781-793. <https://doi.org/10.1016/b978-0-443-18611-0.00017-6>

About the Author



Ophir Vinik, MD, FRCP, MScCH

Dr. Vinik completed internal medicine and rheumatology training at the University of Toronto. He works as a staff Rheumatologist and General Internist at St. Michael's Hospital in Toronto. Dr Vinik is a clinician teacher recognized for excellence and innovation in medical education. Head of the Myositis program, a national center of clinical, teaching and research excellence providing multi-disciplinary care to patients with inflammatory myopathies.

Affiliations: Assistant Professor of Medicine, University of Toronto, Division of Rheumatology, Myositis Program, St. Michael's Hospital, Toronto, ON.

Clinical and Serological Evaluation and Management of Rheumatic Disease-Associated Interstitial Lung Disease

Ophir Vinik, MD, FRCP, MScCH

Introduction

In 2011, the American Thoracic Society (ATS) recommended that antibody testing be included in the evaluation of patients with interstitial lung disease (ILD) to assess for an underlying connective tissue disease, particularly in cases of lingering diagnostic uncertainty, such as differentiating ILD from idiopathic pulmonary fibrosis.¹ Specifically, the ATS endorsed routine testing for antinuclear antibodies (ANA), rheumatoid factor (RF), and anti-cyclic citrullinated peptide (anti CCP) antibodies.

However, autoantibody testing in isolation is rarely diagnostic and results must be interpreted within a clinical context. Accordingly, the interpretation of autoantibody testing and its implications for the diagnosis and management of rheumatic disease-associated ILD remain central to optimizing care in this patient population.

Serology testing is best utilized as an adjunct rather than a standalone diagnostic tool. Over reliance on antibody results without

clinical correlation can result in misdiagnosis and inappropriate treatment. It is therefore important to integrate serologic data into the broader diagnostic workup of systemic autoimmune rheumatic disease-associated ILD.

Rheumatoid Factor and Anti Cyclic Citrullinated Peptide in Rheumatoid Arthritis

RF is an autoantibody, usually of the IgM isotype, directed against the Fc portion of IgG. RF demonstrates a sensitivity of approximately 70–80% and a specificity of 80–90% for rheumatoid arthritis (RA); however, 10–15% of RA patients remain seronegative. Seronegativity is particularly common early in the disease course of RA, with up to 40% of patients testing negative for these antibodies during the first year.² In addition, RF can be detected in 5–10% of healthy individuals and in many other clinical contexts, such as

infections and malignancies, thereby limiting its specificity.

CCP antibodies target citrullinated peptides formed by post translational modification of arginine residues and are measured using enzyme-linked immunosorbent assays (ELISA). While anti CCP antibodies have a sensitivity comparable to RF (67% vs 69%), they demonstrate a higher specificity for RA (90–95%), yet their presence alone is not diagnostic.²

According to the American College of Rheumatology (ACR) classification criteria for RA,³ the diagnosis requires that patients have findings of synovitis with additional factors such as joint symptom duration and elevations in inflammatory markers to suggest a possible diagnosis of RA.

Antinuclear Antibody and Connective Tissue Disease Serology

ANA testing is highly sensitive (95–100%) for systemic lupus erythematosus (SLE) but lacks specificity.⁴ ANA positivity can also be observed in other autoimmune conditions, infections, malignancies, medication-related side effects, and a substantial portion of the healthy population. This highlights the importance of interpretation within a clinical context. While a strongly positive ANA result (e.g., immunofluorescence titer of >1:640) may increase suspicion for an autoimmune disease, there is no specific diagnostic cut off. Moreover, ANA titers do not reliably correlate with disease activity or guide longitudinal disease monitoring.

Classic ANA staining patterns on immunofluorescence are not sufficiently specific to distinguish connective tissue disease subtypes and cannot replace disease specific testing. Additional serologic studies, including anti-double-stranded DNA (dsDNA) antibodies, extractable nuclear antigen (ENA) panels, and complement levels, can further assist in elucidating the underlying diagnosis once SLE is suspected based on clinical assessment and a positive ANA result.

Anti-dsDNA antibodies show high specificity for SLE (approximately 95%) but only moderate sensitivity (70%) and their levels may display either concordance or discordance with disease activity.⁴ ENA testing covers a range of antibodies, which may vary by laboratory but commonly include anti-Ro and anti-La (associated with Sjogren's syndrome), anti-Jo1 (associated with anti-synthetase syndrome), anti histone antibodies (associated with drug induced lupus), and anti Scl-

70 (associated with diffuse systemic sclerosis). These antibodies can assist in establishing the diagnosis and identifying disease phenotypes, although none are diagnostic in themselves.

Serum complement levels, specifically C3 and C4, may be elevated in acute and chronic inflammation but are particularly informative when decreased, as this could indicate SLE disease activity. Complement levels tend to fluctuate with disease activity in SLE and are therefore useful both in supporting the diagnosis and monitoring disease activity.

Myositis Antibodies

Myositis-specific antibodies were not included in the 2011 ATS recommendations but are increasingly utilized to assist in the diagnosis of Idiopathic Inflammatory Myopathies (IIM). These antibodies are commonly tested as part of a panel that includes a variety of antibodies associated with distinct IIM phenotypes.⁵ Amongst the many myositis antibodies, anti MDA5 and anti synthetase antibodies typically carry the strongest association with ILD as a clinical manifestation. In contrast, ILD is rare in association with other myositis antibodies, such as TIF1-gamma.⁵

Several anti MDA5 clinical phenotypes have been described with varying degrees of muscle involvement, ranging from significant myositis to no muscle involvement (i.e., amyopathic).⁶ Distinctive cutaneous manifestations can occur in the form of tender palmar violaceous lesions that can provide an early clinical clue to the diagnosis. Digital ulcerations, reflecting a significant underlying vasculopathy, are also a common dermatological manifestation. A particularly concerning manifestation is rapidly progressive ILD, which is associated with high rates of morbidity and mortality, particularly among Asian and Mediterranean populations.

Anti synthetase antibodies constitute a group of antibodies targeting aminoacyl tRNA synthetase enzymes. They can be categorized into anti-Jo1 and non-Jo1 antibodies. Non-Jo1 antibodies, including anti-PL-7, PL-12, OJ, and EJ, are typically associated with a higher risk of more severe lung disease.⁷ The clinical phenotype of anti-synthetase syndrome is diverse and may include varying degrees of involvement of the skin, Raynaud's phenomenon, muscle, joints, and lungs.⁷ While some patients present with multiple features, others may manifest with isolated lung involvement. The severity of organ

involvement, including lungs, also varies widely, from asymptomatic interstitial lung abnormalities detected on imaging to rapidly progressive ILD.⁷

Diagnosis of Rheumatic Conditions Affecting the Lung

Serologic evaluation is recommended in patients with ILD to identify the possibility of an underlying rheumatic disease. However, serological findings must be interpreted within a holistic clinical context of rheumatic disease extra pulmonary manifestations.

Rheumatoid Arthritis-associated Interstitial Lung Disease

Rheumatoid arthritis-associated ILD is common, with a global pooled prevalence of approximately 21.4%.⁸ A usual interstitial pneumonia pattern occurs more frequently than a nonspecific interstitial pneumonia (NSIP).⁸ The 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria for RA incorporates joint distribution, serological markers (RF and anti CCP), symptom duration, and acute phase reactants, with a score of 6 or more supporting classification as RA. This classification framework can be a useful reference for the Respiriologist when RA ILD is under consideration.³

RF and anti CCP antibodies are often present in RA and may correlate with the risk of ILD; however, their primary validated roles are in diagnosis and prediction of erosive joint disease. Of note, a subset of RA patients test positive for these antibodies, and the diagnosis of RA can be made in the absence of these antibodies based primarily on joint manifestations. Therefore, assessment of joint symptoms and related physical examination findings in a patient with new ILD could facilitate early diagnosis of RA-ILD. Early diagnosis then allows timely initiation of treatment strategies tailored to both joint and pulmonary involvement that may reduce disease progression and damage.

Systemic Lupus Erythematosus and Systemic Sclerosis-associated Interstitial Lung Disease

SLE EULAR/ACR classification criteria for SLE includes pleural effusion as the principal lung manifestation.⁹ However, ILD is another possible

manifestation estimated to occur in approximately 5–10% of SLE patients, typically with an NSIP pattern on imaging.¹⁰ Given the multisystem nature of SLE, no one single test or physical examination finding is sufficient to immediately establish the diagnosis in isolation.

Systemic sclerosis carries a substantially higher burden of ILD, with prevalence estimates of 30–50%, usually with an NSIP pattern.¹¹ ILD is a leading cause of mortality in this patient population, emphasizing the importance of early identification of ILD in systemic sclerosis. Current classification criteria for systemic sclerosis incorporates clinical features such as skin tightening, digital ischemia, and gastrointestinal manifestations along with serologic markers such as anti-topoisomerase I-70 (Scl 70) and anti centromere antibodies.¹² These features, along with skin findings, help to distinguish diffuse from limited scleroderma phenotypes. Screening ILD patients for skin and gastrointestinal manifestations may assist in diagnosis. Of note, while skin involvement is typical, scleroderma sine sclerosis can occur in approximately 5–10 % of patients who have no skin involvement.¹³

Idiopathic Inflammatory Myopathies–Associated Interstitial Lung Disease

IIM are acquired autoimmune conditions with diverse clinical, serological, and pathological phenotypes.¹⁴ Proximal muscle weakness is the typical pattern of muscle involvement, while severe muscle involvement can also result in dysphagia and respiratory muscle weakness. Typical skin rashes may include malar rash, Gottron's papules, and Shawl- and V neck signs.

Screening ILD patients for clinical manifestations of IIM including skin rashes and muscle weakness may facilitate diagnosis. Measurement of creatine kinase (CK) with blood testing can also aid the diagnostic process; however, diagnosis often requires additional muscle specific testing such as electromyography, magnetic resonance imaging, and muscle biopsy.

Amyopathic disease can occur in which IIM manifests with extra-muscular manifestation such as ILD in the absence of muscle involvement. Similarly, a normal CK level does not exclude the possibility of inflammatory myopathy.

Given the broad phenotypic diversity of IIM, it has become clear that the dichotomous paradigm of dermatomyositis and polymyositis is obsolete, highlighting the broad spectrum of potential IIM

manifestations.¹⁴ This marked heterogeneity has resulted in difficulty developing encompassing classification criteria, including the 2017 ACR/EULAR criteria for inflammatory myopathies,¹⁵ requiring caution in applying these criteria in clinical practice.

Approach to Treatment of Rheumatic Disease-associated Interstitial Lung Disease

General Treatment Principles

Inflammation in rheumatic disease is reversible, whereas chronic sequela, such as joint damage, muscle atrophy with fibrosis, and fatty replacement, may lead to irreversible functional limitation and disability. Early initiation of effective therapy, both non-pharmacological and pharmacological, aimed at achieving disease control and ultimately remission, is paramount. Non-pharmacologic measures, such as physiotherapy, occupational therapy, speech-language pathology, respiratory therapy, and structured rehabilitation are vital and should be an integral part of the treatment plan, tailored to the individual patient’s needs.

A common challenge with rheumatic disease treatment is the multisystem involvement that results in multiple therapeutic targets. While systemic glucocorticoids typically provide benefit across multiple systems, disease-modifying, steroid-sparing agents (DMARDs) typically demonstrate variable affinity to different organs and related manifestations. Furthermore, the severity of involvement may differ across organs, requiring careful balancing of the risks and benefits of immunosuppressive therapies.

A “treat-to-target” approach, in which medications are tailored to the individual patient based on specific disease manifestations and their severity, can provide a useful therapeutic framework. This approach involves identifying which disease manifestations are present and their severity, considering medication contraindications, and, if feasible, selecting medications that target multiple involved systems to limit polypharmacy. This approach is particularly relevant for complex presentations, such as anti-synthetase syndrome, in which lung, joint, skin, and muscle involvement may occur and evolve asynchronously.

Pharmacologic Treatment Modalities

Glucocorticoids are typically the cornerstone of initial management, with dosing determined by organ involvement and severity. While lower doses of prednisone could be sufficient to achieve a response in RA joint involvement, significant proximal muscle weakness in IIM may require initial dosing of up to 1 mg/kg/day followed by a slow taper over several months. High-dose glucocorticoids are especially critical in high-risk settings, such as rapidly progressive ILD, where early aggressive therapy may alter prognosis in a potentially life-threatening condition. Long-term monotherapy with glucocorticoids, however, is generally avoided owing to multiple potential side effects and the availability of steroid-sparing medications.

The selection of steroid-sparing medication depends on the diagnosis and the specific organ systems involved. Multiple treatment guidelines for rheumatic conditions have been published, typically focusing on isolated disease manifestations such as joint, kidney, or lung involvement. However, the approach for managing the patient with multisystem concurrent involvement remains challenging, given the paucity of data to guide clinicians in selecting optimal medications.¹⁶

Organ-targeted Disease-modifying, Steroid-sparing Agent Strategies

Pragmatic “target organ efficacy” profiles can help match disease-modifying agents with organ involvement. Methotrexate (MTX), for example, has established efficacy for joints, muscle, and skin in rheumatic disease,^{16,17} but is frequently avoided in the presence of lung involvement due to potential side effects. It is absolutely contraindicated during pregnancy and in patients with renal impairment.

In contrast, mycophenolate mofetil (MMF), azathioprine, and calcineurin inhibitors such as tacrolimus have demonstrated efficacy for lung and muscle involvement,^{16,18} but may not benefit inflammatory joint disease. In conditions such as anti-synthetase syndrome, where both joint and lung manifestations are present, these medications may provide benefit for the lung disease, while joint disease persists, necessitating the addition of a joint targeting medication.

Alternatively, a medication such as rituximab, which targets both lung and joint disease, could be considered. Rituximab has demonstrated efficacy in lung, joint, and muscle involvement, though its

effectiveness for skin involvement in IIM appears more limited, with higher rates of skin relapse reported.¹⁹ Therefore, in a patient with lung, joint, muscle, and skin disease, a combination DMARD approach might be needed.

Cyclophosphamide is typically reserved for severe or refractory lung and muscle manifestations of rheumatic disease and is commonly an important part of induction therapy for patients with rp-ILD.²⁰

Intravenous immunoglobulin (IVIg) has established efficacy as adjuvant therapy in patients with severe inflammatory myopathy involving muscle and skin. However, its benefit for lung involvement has not been clearly established.²¹

Emerging therapies such as Janus kinase/signal transducer and activator of transcription (JAK-STAT) inhibitors and interferon-targeting therapies are the focus of growing attention as their indications expand across a range of rheumatic conditions and may show benefit for lung involvement. However, clinical practice patterns, approved indications, and accessibility can vary widely across the world. For example, JAK-STAT inhibitors are commonly used for patients with MDA 5 with lung involvement in Asia,²² whereas IIMs are not currently recognized as an approved indication for these medications in Canada.

Antifibrotic Lung-directed Therapies

In addition to immunosuppressive therapy, lung-targeted antifibrotic therapies play an increasing role in managing rheumatic disease-associated lung involvement, particularly when lung fibrosis is a dominant feature. Nintedanib, a tyrosine kinase inhibitor, has demonstrated benefit in slowing forced vital capacity decline in progressive fibrosing ILD, including systemic sclerosis-associated ILD.²³ Nerandomilast, a phosphodiesterase-4B (PDE-4B) inhibitor, has also demonstrated benefit in preserving forced vital capacity in this context.²⁴ Antifibrotic options are generally used as adjuncts to immunomodulatory therapy, particularly when fibrosis is established and disease progression persists despite adequate control of systemic inflammation.

Conclusion

Serologic testing can support diagnosis, phenotyping, and risk stratification in rheumatic disease-associated ILD; however, results must

always be interpreted within a well-defined clinical context. Therefore, detailed history and physical examination focused on stigmata of rheumatic disease are paramount in establishing the clinical context for interpreting antibody findings.

Evolving classification paradigms, particularly in IIM, recognize a broad spectrum of clinical, serological, and pathological phenotypes. The wide variability in disease severity and organ involvement poses potential diagnostic pitfalls such as IIM-ILD in the absence of typical muscle or skin findings.

A “treat-to-target” framework that focuses on disease manifestations can assist in tailoring treatment to the individual patient. This framework is particularly relevant in multisystem organ involvement, where a single standard medication regimen is likely not feasible and high-quality evidence to guide management is frequently lacking. These complexities in diagnosis and management highlight the need for collaborative, multidisciplinary care to improve patient outcomes.

Correspondence

Ophir Vinik, MD, FRCPC, MScCH
Email: Ophir.Vinik@unityhealth.to

Financial Disclosures

O.V.: None declared.

References

1. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med.* 2011;183(6):788-824. doi:10.1164/rccm.2009-040GL

2. Nishimura K, Sugiyama D, Kogata Y, Tsuji G, Nakazawa T, Kawano S, et al. Meta-analysis: diagnostic accuracy of anti-cyclic citrullinated peptide antibody and rheumatoid factor for rheumatoid arthritis. *Ann Intern Med.* 2007;146(11):797-808. doi:10.7326/0003-4819-146-11-200706050-00008

3. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO 3rd, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum.* 2010;62(9):2569-2581. doi:10.1002/art.27584.

4. Alsaed OS, Alamlh LI, Al-Radideh O, Chandra P, Alemadi S, Al-Allaf AW. Clinical utility of ANA-ELISA vs ANA-immunofluorescence in connective tissue diseases. *Sci Rep.* 2021;11(1):8229. Published 2021 Apr 15. doi:10.1038/s41598-021-87366-w

5. Damoiseaux J, Mahler M. *Curr Rheumatol*

Rep. 2022;24(6):199-210.

6. Allenbach Y, Uzunhan Y, Toquet S, Leroux G, Gallay L, Marquet A, et al. Different phenotypes in dermatomyositis associated with anti-MDA5 antibody: Study of 121 cases. *Neurology*. 2020;95(1):e70-e78. doi:10.1212/WNL.00000000000009727.

7. Faghihi-Kashani S, Yoshida A, Bozan F, Zanframundo G, Rozza D, Loganathan A, et al. Clinical characteristics of anti-synthetase syndrome: analysis from the classification criteria for Anti-Synthetase Syndrome Project. *Arthritis Rheumatol*. 2025;77(4):477-489. doi:10.1002/art.43038

8. Prasanna H, Inderjeeth CA, Nossent JC, Almutairi KB. The global prevalence of interstitial lung disease in patients with rheumatoid arthritis: a systematic review and meta-analysis. *Rheumatol Int*. 2025;45(2):34. Published 2025 Jan 18. doi:10.1007/s00296-025-05789-4.

9. Aringer M, Costenbader K, Daikh D, Brinks R, Mosca M, Ramsey-Goldman R, et al. 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. *Ann Rheum Dis*. 2019;78(9):1151-1159. doi:10.1136/annrheumdis-2018-214819.

10. Volkman ER, Kreuter M, Hoffmann-Vold AM, Wijsenbeek M, Smith V, Khanna D, D, et al. Dyspnoea and cough in patients with systemic sclerosis-associated interstitial lung disease in the SENSICIS trial. *Rheumatology (Oxford)*. 2022;61(11):4397-4408. doi:10.1093/rheumatology/keac091

11. Bergamasco A, Hartmann N, Wallace L, Verpillat P. Epidemiology of systemic sclerosis and systemic sclerosis-associated interstitial lung disease. *Clin Epidemiol*. 2019 Apr 18;11:257-273. doi: 10.2147/CLEP.S191418. PMID: 31114386; PMCID: PMC6497473.

12. Van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A, et al. 2013 classification criteria for systemic sclerosis: an American college of rheumatology/European league against rheumatism collaborative initiative. *Ann Rheum Dis*. 2013;72(11):1747-1755. doi:10.1136/annrheumdis-2013-204424.

13. Lescoat A, Huang S, Carreira PE, Siegert E, de Vries-Bouwstra J, Distler JHW, et al. Cutaneous manifestations, clinical characteristics, and prognosis of patients with systemic sclerosis sine scleroderma: data from the International EUSTAR Database. *JAMA Dermatol*. 2023;159(8):837-847. doi:10.1001/jamadermatol.2023.1729

14. Allameen NA, Ramos-Lisbona AI, Wedderburn LR, Lundberg IE, Isenberg DA. An update on autoantibodies in the idiopathic inflammatory myopathies. *Nat Rev Rheumatol*. 2025 Jan;21(1):46-62. doi: 10.1038/s41584-024-01188-4. Epub 2024 Nov 28. PMID: 39609638.

15. Lundberg IE, Tjälrlund A, Bottai M, Werth VP, Pilkington C, Visser M, et al. 2017 European League Against Rheumatism/American College of Rheumatology classification criteria for adult and juvenile idiopathic inflammatory myopathies and their major subgroups. *Ann Rheum Dis*. 2017;76(12):1955-1964. doi:10.1136/annrheumdis-2017-211468.

16. Paik JJ, Werth VP, Chinoy H, Masri KR, Jambekar A, Hasan F, et al. Treatment guidelines for idiopathic inflammatory myopathies in adults: a comparative review. *Rheumatology (Oxford)*. 2025;64(6):3288-3302. doi:10.1093/rheumatology/keaf116.

17. Hazlewood GS, Pardo JP, Barnabe C, Schieir O, Barber CEH, Proulx L, Canadian Rheumatology Association Living Guidelines for the pharmacological management of rheumatoid arthritis with disease-modifying antirheumatic drugs. *J Rheumatol*. 2022;49(10):1092-1099. doi:10.3899/jrheum.220209.

18. Johnson SR, Bernstein EJ, Bolster MB, Chung JH, Danoff SK, George MD, et al. 2023 American College of Rheumatology (ACR)/American College of Chest Physicians (CHEST) Guideline for the treatment of interstitial lung disease in people with systemic autoimmune rheumatic diseases. *Arthritis Rheumatol*. 2024;76(8):1182-1200. doi:10.1002/art.42861.

19. Fasano S, Gordon P, Hajji R, Loyo E, Isenberg DA. Rituximab in the treatment of inflammatory myopathies: a review. *Rheumatology (Oxford)*. 2017;56(1):26-36. doi:10.1093/rheumatology/kew146.

20. Barnes H, Holland AE, Westall GP, Goh NS, Glaspole IN. Cyclophosphamide for connective tissue disease-associated interstitial lung disease. *Cochrane Database Syst Rev*. 2018;1(1):CD010908. Published 2018 Jan 3. doi:10.1002/14651858.CD010908.pub2.

21. Marie I, Chérin P, Michallet M, Pelus E, Dantal J, Crave JC, et al. Prise en charge des événements indésirables chez les patients sous traitement par immunoglobulines : recommandations pour la pratique clinique [Management of adverse effects related to human immunoglobulin therapy: recommendations for clinical practice]. *Rev Med Interne*. 2017;38(5):312-319. doi:10.1016/j.revmed.2016.10.390 .

22. Fujimoto M, et al. *Ther Adv Respir Dis*. 2024;18:1 9.

23. Flaherty KR, Wells AU, Cottin V, Devaraj A, Walsh SLF, Inoue Y, Richeldi L, et al. Nintedanib in progressive fibrosing interstitial lung diseases. *N Engl J Med*. 2019;381(18):1718-1727. doi:10.1056/NEJMoa1908681.

24. Scleroderma Research Foundation. New ILD clinical trial reaches key milestone. Scleroderma Research Foundation. 2026 [accessed January 30, 2026] Available from: <https://srfcure.org/research/bi-ild-trial/>.

About the Author



Sacha Bhinder, HBS, MD, FRCP

Dr. Bhinder is an adult respirologist in Toronto practicing at the Scarborough Health Network Centenary site, the Toronto Lung Care Clinic, and the Heart Health Institute. After having completed his MD degree, he went on to pursue training in Internal Medicine and a fellowship in Adult Respiratory, all at the University of Toronto. He is a lecturer in the Division of Respiratory at the University of Toronto. For the Scarborough Health Network (SHN), he has served in a number of leadership roles on the Corporate HSMR, Palliative, and Quality of Care Committees, as well as the Co-Chair of the Corporate Medical Education Committee and SHN Education representative for the Toronto Academic Health Sciences Network. Recently he completed a term in the role of Corporate Chief and Medical Director for the Department of Medicine.

Affiliations: Scarborough Health Network, Centenary Site, Toronto, ON
Toronto Lung Care Clinic, Toronto, ON
Heart Health Institute, Toronto, ON
Lecturer, Division of Respiratory, University of Toronto, Toronto, ON

Single-Inhaler Triple Therapy Is Just The Start

Sacha Bhinder, HBS, MD, FRCP

New Era in Congestive Obstructive Pulmonary Disease (COPD)

The emergence of biologic therapies for reducing exacerbations of COPD heralds a new era in pharmacologic management and optimal patient care. Through pathophysiologic pathway and trajectory alterations, disease modification, and stability, biologic therapies in the setting of COPD raise the possibility of disease control. While asthma and COPD remain clinically distinct diseases, evolving insights into their underlying pathophysiology reveals areas of overlap and complexity.

In contemporary practice, key components of COPD management, including screening and case finding, diagnosis, clinical risk stratification, initial pharmacologic therapy, exacerbation management, action plan implementation, vaccination, pulmonary rehabilitation, and chronic

bronchitis management, largely fall within the domain of primary care. Although specialist respiratory consultation continues to support these fundamental aspects of COPD management, the advent of biologic therapies creates new possibilities for respiratory specialists to focus on therapies beyond single-inhaler triple therapy.

Current State of COPD Outcomes

Exacerbations of COPD remain disease-altering events in a patient's life course. Longitudinal cohort studies have demonstrated a 50% mortality within 5 years among patients experiencing one or two acute exacerbations requiring hospitalization per year, with mortality exceeding 50% within 3 years among those experiencing three or more exacerbations. Indeed, even exacerbations managed in the outpatient setting increase the risk of future hospitalization

by 21% following a single moderate exacerbation and the risk of death is 80% following two moderate exacerbations.^{1,2}

Severe exacerbations of COPD are associated with substantial mortality. Globally, 20% of patients will die within one year of their first hospitalization for a COPD exacerbation.²⁻⁴ In Ontario, the one-year mortality rate reaches 28% among those aged 65 years or older.⁵

Challenges related to healthcare system funding, resource availability, and workload remain persistent. Within these limitations, management of COPD in the modern era is more often task-based or event-driven by patients experiencing worsening respiratory symptoms, exacerbations, or a combination of worsening factors affecting respiratory status that prompt patients to seek care. Although targeted case finding of early and undiagnosed COPD using spirometry, supported by the Canadian Lung Health Test, is recommended, implementation remains challenging. Limited access to spirometry, difficulties with test interpretation among non-respiratory specialists, and barriers to adopting a preventive approach to case finding continue to hinder widespread uptake.⁶

Canadian Thoracic Society 2023 Guidelines for Pharmacotherapy in Stable COPD

In the modern era, the 2023 Canadian Thoracic Society (CTS) guidelines for pharmacotherapy in stable COPD place single-inhaler triple therapy as the preferred pharmacologic option, placing it in over 60% of the possible pharmacologic options within the framework.⁷ Given current healthcare system constraints and the challenges associated with proactive case finding and early diagnosis, it is reasonable to anticipate that single-inhaler triple therapy will serve as the initial and final pharmacologic therapy for many patients with COPD.

Dyspnea remains a prominent symptom burden in COPD, with modified MRC class 2 dyspnea remaining common. Across patient cohorts, 40 to 60% of patients exhibit a modified MRC dyspnea score of two or higher. Consequently, COPD patients often remain quite dyspneic on exertion.⁸

Spirometric severity distributions in real-world COPD patient cohorts are generally weighted toward more advanced disease. Indeed,

70 to 80% of patients often present with moderate, severe, or very severe COPD.^{9,10}

Exacerbations are common among patients with COPD, with up to 75% experiencing at least one moderate or severe exacerbation within a three-year period.¹¹ A substantial proportion of exacerbations go unreported, with studies from both local and international settings suggesting that 40 to 80% of exacerbations may be missed despite active monitoring.¹¹⁻¹³

The CTS 2023 pharmacologic framework for pharmacotherapy in patients with stable COPD places significant emphasis on high-risk symptoms, spirometric severity, and a high risk of acute exacerbation of COPD based on exacerbation history, all of which are associated with an increased risk of mortality. Given the high prevalence of significant symptoms, spirometric severity, and frequency of exacerbations, newly-diagnosed COPD patients will most likely be candidates for single-inhaler triple therapy as first-line pharmacotherapy.

Considering this, chance favours the prepared mind. Prompt initiation of single-inhaler triple therapy in COPD following a severe exacerbation is associated with reductions in all-cause readmission and COPD-related readmission.¹⁴ Indeed, initiating therapy within 14 to 30 days of exacerbation appears to be superior compared to delaying treatment beyond 30 days.^{14,15} Each 30-day delay in initiation of single-inhaler triple therapy following a severe exacerbation is associated with a 10% risk of subsequent exacerbation.¹⁶

While once daily regimens are typically preferred over twice-daily regimens and are associated with improved patient adherence,¹⁷ overall adherence to COPD pharmacotherapy remains suboptimal.

Challenges related to inhaler devices persist, including correct dry powder inhaler technique, differences between metered dose inhaler devices, perceptions of treatment effectiveness of molecules with respect to longevity of symptom reduction and benefit, as well as regimen complexity and dosing frequency. Collectively, these factors contribute to the challenges associated with device-based therapy compared with oral pharmacotherapy.

Compounding these challenges is the reality that COPD therapies offer improvement of symptoms, quality of life, functional capacity, and exertional tolerance, yet even with optimal therapy, technique, and adherence, restoration

of normal respiratory function is not a reasonable objective. Consequently, long-term persistence with pharmacotherapy remains a challenge for many patients. Indeed, real-world evidence comparing once daily fluticasone furoate/umeclidinium/vilanterol (Trelegy 100) with twice-daily budesonide/glycopyrrolate/formoterol (Breztri) demonstrated a 43% increased likelihood of adherence with Trelegy 100. However, despite this advantage, overall adherence at 12 months remained low, reaching only 35% with Trelegy 100 and 25% with Breztri in a monitored real-world effectiveness study.¹⁸ This finding demonstrates an ongoing challenge of ensuring baseline foundational pharmacotherapy compliance and persistence in symptomatic patients with COPD. Although inhaled treatments are unable to eliminate symptoms completely, single-inhaler triple therapy remains central in COPD management, reducing exacerbation risk and serving as a therapeutic foundation upon which biologic therapies may be added for patients who continue to experience exacerbations.

Modelling studies demonstrate that the implementation of the 2023 CTS guideline for single-inhaler triple therapy could reduce exacerbation and mortality rates in Canada, increase life expectancy by 1.7 years, and over a 10 year period, reduce mortality rates by 22.2% while preventing up to 180,000 deaths. Taken together, these findings support the well-established benefits of single-inhaler triple therapy.¹⁹

Beyond Single-Inhaler Triple Therapy

While additional guideline-supported therapies toward exacerbation reduction are available for exacerbation prevention, including N-acetylcysteine, prophylactic macrolide, and Phosphodiesterase-4 (PDE4) inhibitor, challenges remain.

Daily azithromycin has demonstrated a relative risk reduction of exacerbation of 27% compared to placebo.²⁰ Unfortunately, cardiac concerns with respect to QTc prolongation, decreased auditory acuity, and tinnitus, in addition to gastrointestinal tolerability may limit its widespread use. Additionally, only 49% of patients in the seminal publication received triple therapy, which raises questions of real-world effectiveness in contemporary practice, where single-inhaler triple therapy is considered foundational therapy.²¹

PDE4 inhibition with roflumilast (Daxas) presents several challenges, including cost due to limited coverage across provincial and territorial formularies, variable access to private insurance coverage among older adults with COPD, and gastrointestinal tolerability. Similarly, real-world effectiveness in contemporary COPD practice remains a challenge. In the pivotal study, roflumilast reduced the annual exacerbation rate by 17% compared to placebo; however, inhaled corticosteroid therapy was discontinued at randomization, and only approximately half of the participants were receiving a long-acting beta agonist, which raises questions regarding the relevance of these efficacy findings to modern COPD care that includes single-inhaler triple therapy.²¹

While single-inhaler triple therapy is firmly established as the foundation of treatment for patients with symptomatic, exacerbating COPD, exacerbation reduction remains incomplete. Nearly half of patients receiving single-inhaler triple therapy will experience another moderate or severe exacerbation in the 12 months following initiation of single-inhaler triple therapy.²² This risk is also observed in the Kaplan Meier curves in the IMPACT and ETHOS trials.^{23,24}

Although asthma and COPD are recognized as distinct clinical entities, the underlying pathophysiologic processes underlying the development of fixed airway obstruction may share areas of overlap. However, the extent of this overlap remains incompletely understood. Considering the spirometric pattern seen in both of these clinical entities, peripheral blood eosinophil count has emerged as an established biomarker of T2 inflammation and a predictor of the efficacy of T2 biologic therapy in COPD. Importantly, the prevalence of elevated peripheral blood eosinophil counts are common among patients with COPD.²⁵⁻²⁷

Eosinophilic inflammation of the airways is present in up to 40% of patients with COPD, with peripheral blood eosinophil levels serving as a biomarker of this inflammatory phenotype. Elevated blood eosinophil levels are associated with increased eosinophil counts in sputum, bronchoalveolar lavage fluid, and bronchial submucosa tissue, and are associated with a greater benefit from corticosteroid-containing regimens for exacerbation reduction.²⁵⁻²⁷ In a real-world Canadian cohort, 35% of patients treated for a severe acute exacerbation of COPD had a peak peripheral blood eosinophil count of 0.3 or higher in the previous 12 months.²⁸ Indeed, in a

prospective Canadian cohort, the presence of an elevated peripheral blood eosinophil count of 0.3 or higher identified patients set to experience an accelerated loss of lung function over time.

Dupilumab and mepolizumab are Health Canada-approved biologic therapies for patients with COPD who continue to experience exacerbations despite treatment with single-inhaler triple therapy. Eligibility includes those who have experienced two or more moderate or one severe exacerbation of COPD in the prior 12 months, together with evidence of type 2 inflammation, as indicated by one or more peripheral blood eosinophil counts measuring 0.3 or higher.

In the NOTUS and BOREAS phase 3 randomized controlled trials, dupilumab reduced the annual rate of moderate or severe COPD exacerbations by 34% and 30%, respectively, over 52 weeks. Similarly, in the MATINEE phase 3 randomized controlled trial involving mepolizumab, a 21% reduction in moderate or severe exacerbations was observed over a 104 week treatment period.^{29,30}

An indirect treatment comparison of mepolizumab and dupilumab in patients with exacerbation-prone COPD evaluated patients from the METREX, METREO, and MATINEE trials who met eligibility criteria for the NOTUS and BOREAS trials. This analysis demonstrated comparable efficacy between the two biologics, with similar effects on the annualized rate of moderate or severe exacerbations, time to first moderate or severe exacerbation, and the annualized rate of severe exacerbations.³¹ These findings further support the efficacy of T2 biologic therapy with dupilumab and mepolizumab in reducing exacerbations of COPD in symptomatic, exacerbation-prone patients on single-inhaler triple therapy, with an elevated peripheral blood eosinophil count of 0.3 or higher. Importantly, the analysis highlights the comparative efficacy of the two biologics with respect to exacerbation reduction.³¹

Future of COPD Care Begins Today

Advances in medical science drive innovation in pharmacotherapy and disease management. Accordingly, continued scientific progress can be expected to translate into meaningful changes in medical practice.

Single-inhaler triple therapy is firmly established as the foundation for

pharmacotherapy management of COPD in the modern era, recognizing system limitations, and the prevalence of symptomatic, non-mild, and exacerbation-prone COPD in real-world populations. The emergence of biologic therapy in COPD raises the prospect of a new era of disease modification that perhaps will parallel the transformative impact biologics have had in asthma.

Undoubtedly, the vast majority of those with COPD are managed in primary care settings. The central role of single-inhaler triple therapy in the pharmacotherapy armamentarium for COPD is supported by the 2023 CTS guidelines, real-world patient characteristics, widespread adoption by respiratory specialists, and modelling studies showing favourable outcomes with broader implementation. Importantly, respiratory specialists are not required for single-inhaler triple therapy. For most patients, evidence-based COPD care can be delivered by primary care until consideration of biologic therapy arises.

Respiratory specialists are the gatekeepers for biologic therapy in COPD. Recognizing that pharmacologic and non-pharmacologic management of COPD short of biologic therapies can and should occur within primary care, specialists can focus on evaluating patients for disease-modifying injectable therapies and advocating their potential benefits among referring clinicians. For patients who continue to exacerbate despite optimized treatment, these therapies offer an important opportunity to further improve outcomes.

Given that even a single moderate or severe exacerbation places a patient in a high risk category according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD),³² and recognizing the likelihood of exacerbation risk despite single-inhaler triple therapy, treatment goals should extend beyond acceptance of recurrent events. For patients who exacerbate on single-inhaler triple therapy, pursuing additional therapies is essential to improving outcomes.

Nothing changes if nothing changes. The emergence of biologic therapies in COPD presents an opportunity to advance pharmacologic management and to drive change in respiratory clinical practice toward the broader integration of biologic therapy.

Our foremost responsibility is to the patient before us. The emergence of biologic therapies represents a call to action to prevent the exacerbations that continue to drive morbidity and

mortality in COPD. By acting today, we have the opportunity to improve outcomes and provide our patients with more tomorrows.

Correspondence

Sacha Bhinder, HBSc, MD, FRCPC
Email: sbhinder@shn.ca

Financial Disclosures

S.B.: Consulting fees/advisory board memberships: Boehringer-Ingelheim, AstraZeneca, Merck/Organon, Novartis, Bayer, GSK, Covis, Sanofi, Valeo, CPD, ICEBM, Trudell, LIV, Meducom, Regeneron, CTS, Ardeane, Agence Unik, Methapharm, Pfizer; **Speakers' bureau/honoraria:** Boehringer-Ingelheim, AstraZeneca, Merck/Organon, Novartis, Bayer, GSK, Covis, Sanofi, Valeo, CPD, ICEBM, Trudell, LIV, Meducom, Regeneron, CTS, Ardeane, Agence Unik, Catalytic Health, East GTA Family Health Group, Humber River Hospital, Pfizer, Methapharm

References

1. Soler-Cataluña JJ, Martínez-García MA, Román Sánchez P, Salcedo E, Navarro M, Ochando R. Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. *Thorax*. 2005;60(11):925–931. doi:10.1136/thx.2005.040527
2. Rothnie KJ, Müllerová H, Smeeth L, Quint JK. Natural history of chronic obstructive pulmonary disease exacerbations in a general practice-based population with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2018;198(4):464–471. doi:10.1164/rccm.201710-2029OC
3. Ho TW, Tsai YJ, Ruan SY, Huang CT, Lai F, Yu CJ. In-hospital and one-year mortality and their predictors in patients hospitalized for first-ever chronic obstructive pulmonary disease exacerbations: a nationwide population-based study. *PLoS One*. 2014;9(12):e114866. doi:10.1371/journal.pone.0114866
4. García-Sanz MT, Cánive-Gómez JC, Senín-Rial L, Aboal-Viñas J, Barreiro-García A, López-Val E, et al. One-year and long-term mortality in patients hospitalized for chronic obstructive pulmonary disease. *J Thorac Dis*. 2017;9(3):636–645. doi:10.21037/jtd.2017.03.34
5. Nie JX, Wang L, Upshur RE. Mortality of elderly patients in Ontario after hospital admission for chronic obstructive pulmonary disease. *Can Respir J*. 2007;14(8):485–489. doi:10.1155/2007/425248
6. O'Donnell DE, Hernandez P, Kaplan A, Aaron S, Bourbeau J, Marciniuk D, et al. Canadian Thoracic Society recommendations for management of chronic obstructive pulmonary disease - 2008 update - highlights for primary care. *Can Respir J*. 2008;15 Suppl A(Suppl A):1a–8a. doi:10.1155/2008/641965
7. Bourbeau J, Bhutani M, Hernandez P, Aaron SD,

- Beauchesne M-F, B. Kermelly S, et al. 2023 Canadian Thoracic Society Guideline on pharmacotherapy in patients with stable COPD. *Canadian Journal of Respiratory, Critical Care, and Sleep Medicine*. 2023;7(4):173–191. doi:10.1080/24745332.2023.2231451
8. Punekar YS, Mullerova H, Small M, Holbrook T, Wood R, Naya I, et al. Prevalence and burden of dyspnoea among patients with chronic obstructive pulmonary disease in five European countries. *Pulmonary Therapy*. 2016;2(1):59–72. doi:10.1007/s41030-016-0011-5
9. Bednarek M, Maciejewski J, Wozniak M, Kuca P, Zielinski J. Prevalence, severity and underdiagnosis of COPD in the primary care setting. *Thorax*. 2008;63(5):402–407. doi:10.1136/thx.2007.085456
10. Haughney J, Gruffydd-Jones K, Roberts J, Lee AJ, Hardwell A, McGarvey L. The distribution of COPD in UK general practice using the new GOLD classification. *Eur Respir J*. 2014;43(4):993–1002. doi:10.1183/09031936.00065013
11. Hurst JR, Vestbo J, Anzueto A, Locantore N, Müllerova H, Tal-Singer R, et al. Susceptibility to exacerbation in chronic obstructive pulmonary disease. *N Engl J Med*. 2010;363(12):1128–1138. doi:10.1056/NEJMoa0909883
12. Han MK, Quibrera PM, Carretta EE, Barr RG, Bleecker ER, Bowler RP, et al. Frequency of exacerbations in patients with chronic obstructive pulmonary disease: an analysis of the SPIROMICS cohort. *Lancet Respir Med*. 2017;5(8):619–626. doi:10.1016/s2213-2600(17)30207-2
13. Tashkin DP, Celli B, Senn S, Burkhart D, Kesten S, Menjoge S, et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med*. 2008;359(15):1543–1554. doi:10.1056/NEJMoa0805800
14. Ismaila AS, Haeussler K, Czira A, Youn J-H, Malmenäs M, Risebrough N, et al. Network meta-analysis of the efficacy of fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) Versus other triple therapies for the treatment of chronic obstructive pulmonary disease (COPD): a comparison of annual moderate and severe exacerbations. *American Journal of Respiratory and Critical Care Medicine*. 2022;205(Supplement_1):A1454–A1454. doi:10.1164/ajrccm-conference.2022.205.1_MeetingAbstracts.A1454
15. Bogart M, Germain G, Huang S, Ismaila AS, Jung Y, Laliberté F, et al. Benefit of prompt versus delayed initiation of single inhaler triple therapy on exacerbations and healthcare costs among patients with chronic obstructive pulmonary disease in the United States. *American Journal of Respiratory and Critical Care Medicine*. 2021;203(Supplement_1):A2252–A2252. doi:10.1164/ajrccm-conference.2021.203.1_MeetingAbstracts.A2252
16. Tkacz J, Evans KA, Touchette DR, Portillo E, Strange C, Staresinic A, et al. PRIMUS - Prompt Initiation of Maintenance Therapy in the US: a real-world analysis of clinical and economic outcomes among patients initiating triple therapy following a COPD exacerbation. *Int J Chron Obstruct Pulmon Dis*.

2022;17:329–342. doi:10.2147/copd.S347735

17. De Keyser H, Vuong V, Kaye L, Anderson WC, 3rd, Szefer S, Stempel DA. Is once versus twice daily dosing better for adherence in asthma and chronic obstructive pulmonary disease? *J Allergy Clin Immunol Pract*. 2023;11(7):2087–2093.e2083. doi:10.1016/j.jaip.2023.03.053

18. Noorduyn S, Young C, Lee L, Germain G, Laliberté F, Lejeune D, et al. Adherence and persistence with fluticasone furoate/umeclidinium/vilanterol and budesonide/glycopyrrolate/formoterol fumarate among patients with chronic obstructive pulmonary disease: a real-world United States study. *American Journal of Respiratory and Critical Care Medicine*. 2024;209(Supplement_1):A3301–A3301. doi:10.1164/ajrccm-conference.2024.209.1_MeetingAbstracts.A3301

19. Bhutani M, Kaplan A, Kayaniyil S, Jamieson K, Ormsby R, Bell J, et al. Implementation of 2023 Canadian Thoracic Society Guidelines for Single-Inhaler Triple Therapy could reduce exacerbation and mortality rates in COPD: PROMETHEUS Canada. *Chronic Obstr Pulm Dis*. 2026;13(3):184–194. doi:10.15326/jcopdf.2025.0687

20. Albert RK, Connett J, Bailey WC, Casaburi R, Cooper JA, Jr., Criner GJ, et al. Azithromycin for prevention of exacerbations of COPD. *N Engl J Med*. 2011;365(8):689–698. doi:10.1056/NEJMoa1104623

21. Calverley PM, Rabe KF, Goehring UM, Kristiansen S, Fabbri LM, Martinez FJ. Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials. *Lancet*. 2009;374(9691):685–694. doi:10.1016/s0140-6736(09)61255-1

22. Vogelmeier CF, Worth H, Buhl R, Criée CP, Gückel E, Kardos P. Impact of switching from triple therapy to dual bronchodilation in COPD: the DACCORD ‘real world’ study. *Respir Res*. 2022;23(1):109. doi:10.1186/s12931-022-02037-2

23. Lipson DA, Barnhart F, Brealey N, Brooks J, Criner GJ, Day NC, et al. Once-daily single-inhaler triple versus dual therapy in patients with COPD. *N Engl J Med*. 2018;378(18):1671–1680. doi:10.1056/NEJMoa1713901

24. Rabe KF, Martinez FJ, Ferguson GT, Wang C, Singh D, Wedzicha JA, et al. Triple inhaled therapy at two glucocorticoid doses in moderate-to-very-severe COPD. *N Engl J Med*. 2020;383(1):35–48. doi:10.1056/NEJMoa1916046

25. Tworek D, Antczak A. Eosinophilic COPD - a distinct phenotype of the disease. *Adv Respir Med*. 2017;85(5):271–276. doi:10.5603/ARM.a2017.0045

26. Vedel-Krogh S, Nielsen SF, Lange P, Vestbo J, Nordestgaard BG. Blood eosinophils and exacerbations in chronic obstructive pulmonary disease. The Copenhagen general population study. *Am J Respir Crit Care Med*. 2016;193(9):965–974. doi:10.1164/rccm.201509-1869OC

27. Ko FWS, Xu X, Hon P, Ratnasingham P, Milea D, Hui DSC. Clinical characteristics of patients with COPD in Hong Kong. *European Respiratory Journal*. 62(suppl 67):PA1316. doi:10.1183/13993003.congress-2023.PA1316

28. Saint-Pierre MD, Abdounour J. Oral add-on therapies and blood eosinophils in severe acute exacerbations of chronic obstructive pulmonary disease: A real-world hospital chart review. *Canadian Journal of Respiratory, Critical Care, and Sleep Medicine*. 2024;8(6):254–259. doi:10.1080/24745332.2024.2396463

29. Bhatt SP, Rabe KF, Hanania NA, Vogelmeier CF, Bafadhel M, Christenson SA, et al. Dupilumab for COPD with blood eosinophil evidence of type 2 inflammation. *N Engl J Med*. 2024;390(24):2274–2283. doi:10.1056/NEJMoa2401304

30. Bhatt SP, Rabe KF, Hanania NA, Vogelmeier CF, Cole J, Bafadhel M, et al. Dupilumab for COPD with type 2 inflammation indicated by eosinophil counts. *N Engl J Med*. 2023;389(3):205–214. doi:10.1056/NEJMoa2303951

31. Bourbeau J, Min J, Kolterer S, Yang S, Hunger M, Wang X, et al. Indirect treatment comparison (ITC) of mepolizumab and dupilumab in treating COPD. *European Respiratory Journal*. 66(suppl 69):PA488. doi:10.1183/13993003.congress-2025.PA488

32. Cazzola M, Bajpai J, Calzetta L, Matera MG, Rogliani P. GOLD 2026: Transforming COPD management with early intervention, multi-dimensional assessment, and personalized care. *Drugs*. 2026;86(5):581–597. doi:10.1007/s40265-026-02303-3

About the Author



Mathieu D. Saint-Pierre, MD, FRCPC Respiriology

Dr. Mathieu Saint-Pierre is a Respiriologist at Montfort Hospital and a clinician-researcher at the Institut du Savoir Montfort. He is currently the research director for the Department of Medicine. He is also an Assistant Professor at the University of Ottawa. He operates outpatient Respiriology clinics at Montfort Hospital and in Orléans, Ontario (Orléans Cardiopulmonary Group). His research interests include respiratory physiology and pulmonary function testing, obstructive lung disorders, and the overlap of lung and cardiac disease. He has had several manuscripts and abstracts published, and he is frequently solicited to act as a reviewer for well-known Respiriology journals.

Affiliations: University of Ottawa, Ottawa, ON
Montfort Hospital, Ottawa, ON
Institut du Savoir Montfort, Ottawa, ON

Optimizing In-Hospital Chronic Obstructive Pulmonary Disease (COPD) Care in Canada: Challenges, Evidence, and Future Directions

Mathieu D. Saint-Pierre, MD, FRCPC Respiriology

Introduction

Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) represent the leading cause of hospital admissions in Canada, second only to childbirth, with recent data showing an upward trend in hospitalizations since 2010.^{1,2} A substantial proportion of patients are also readmitted for AECOPD within the first 3 months after discharge.^{3,4} National spending for hospital-based care for AECOPD is estimated to exceed 4 billion Canadian dollars annually.⁵ AECOPD therefore represent a significant burden on the Canadian healthcare system. These events, which may be referred to in lay terms as “lung attacks”, are associated with considerable patient morbidity, including a higher risk of recurrent AECOPD, accelerated lung function decline, poorer

quality of life, and increased mortality.^{6–9} Indeed, previous reviews have reported all-cause mortality rates of up to 20–25% one year after a severe AECOPD and approximately 50% at 5 years.^{10,11} This paper aims to identify key barriers to optimal chronic obstructive pulmonary disease (COPD) management within the Canadian healthcare system for hospitalized patients and for those treated in the emergency department (ED).

Confirming The Diagnosis of COPD With Spirometry

Many patients who present to hospital with suspected AECOPD have not previously undergone pulmonary function testing. As a result, these patients are often treated empirically without confirmation of the underlying diagnosis.

Several alternative conditions, including asthma, congestive heart failure, and pneumonia, can present with similar symptoms.¹² Consequently, an incorrect diagnosis of AECOPD at the time of hospital admission is likely a significant contributor to recurrent hospital readmissions. Furthermore, these patients may receive inappropriate therapies.¹³ Ontario data have shown that the majority of patients (59%) with a reported diagnosis of COPD had not undergone peridiagnostic pulmonary function testing. These individuals were less likely to be prescribed long-acting therapy and had a higher risk of death or hospitalization for AECOPD.¹⁴ Expanding access to pulmonary function testing is therefore imperative. For some patients, spirometry may be feasible during hospitalization, which may be particularly beneficial for individuals who face barriers to accessing outpatient pulmonary function testing laboratories. Otherwise, all patients admitted for suspected AECOPD should be referred for pulmonary function testing if a COPD diagnosis has not previously been confirmed.

Standardizing In-hospital COPD Care and Discharge Instructions

Most Canadian hospitals now use electronic medical records with computerized physician order entry, creating opportunities to implement standardized inpatient order sets for the management of patients with AECOPD. These care pathways help ensure that hospitalists and ED physicians consistently follow evidence-based practices aligned with current COPD treatment recommendations. Order sets can include standardized prescriptions for oral corticosteroids, antibiotics, and appropriate inhaler therapy during acute care. Canadian data from Alberta have demonstrated that implementing such order sets can reduce the hospital length of stay for patients with AECOPD, with a median decrease of 1.15 days overall, without increasing readmissions.¹⁵

Discharge bundles provide an additional opportunity to ensure that recommended interventions are implemented before hospital discharge, including optimization of maintenance inhaler therapy, referral to pulmonary rehabilitation, administration of appropriate vaccinations to prevent respiratory infections (COVID-19, influenza, pneumococcal disease, and respiratory syncytial virus), and smoking cessation support.¹² Discharge bundles can also facilitate communication with outpatient care

providers, including primary care physicians (PCP) and respirologists. Evidence from a separate study in Alberta has shown that implementation of hospital discharge bundles reduced the risk of hospital readmission by 83% within 7 days and by 26% within 30 days after discharge, representing another important strategy to maximize limited hospital resources.¹⁶

Optimizing Maintenance Inhaler Therapy at The Time of AECOPD

Current Canadian Thoracic Society (CTS) COPD guidelines recommend inhaled triple therapy comprising a long-acting muscarinic antagonist (LAMA), a long-acting beta-agonist (LABA), and an inhaled corticosteroid, preferably delivered in a single inhaler, as initial maintenance therapy for patients at an increased risk of future AECOPD. This includes individuals who have experienced an ED visit or hospitalization for AECOPD within the previous 12 months. Compared with LAMA/LABA therapy, maintenance inhaled triple therapy lowers mortality in patients with a prior history of AECOPD, while also reducing the risk of future AECOPD, improving lung function, and decreasing COPD-related symptoms.¹⁷

Recent Canadian studies have shown, however, that many patients treated for AECOPD are not prescribed guideline-recommended maintenance inhaler therapy at discharge.¹⁸⁻²⁰ In an Ontario review, only 20% of patients were discharged from the hospital with appropriate pharmacotherapy consistent with the CTS guidelines. Common deviations from guideline recommendations included failure to escalate inhaler therapy (48%), discharge without any long-acting therapy (18%), and discharge on LAMA monotherapy (10%). Furthermore, patients who were not prescribed recommended inhaler therapy had a significantly higher risk of readmission for AECOPD within the first month after discharge (19% versus 0%, p=0.02).¹⁹ Additional studies have also shown that delaying optimization to inhaled triple therapy as per treatment recommendations is associated with an increased risk of future AECOPD.^{21,22}

Perceptions of clinicians’ roles in acute care settings may contribute to reluctance to intensify maintenance therapy. Some hospital-based physicians may assume that long-term COPD therapy can be adjusted by outpatient care providers shortly after hospital discharge. However, this approach has become increasingly

Optimizing In-Hospital COPD Care in Canada

CHALLENGES, EVIDENCE, AND FUTURE DIRECTIONS

5 STRATEGIC PILLARS FOR CARE IMPROVEMENT

- 1

DIAGNOSTIC ACCURACY

Confirm COPD diagnosis with spirometry and improve access to pulmonary function testing across clinical settings.
- 2

CARE STANDARDIZATION

Standardize in-hospital care and discharge instructions through the implementation of order sets and bundles.
- 3

THERAPEUTIC OPTIMIZATION

Prescribe guideline-recommended maintenance inhaler therapy at the time of AECOPD to improve patient outcomes.
- 4

ED CHALLENGES

Incorporate respiratory educators in the ED and provide specialized education for emergency physicians.
- 5

EMERGING THERAPIES

Raise awareness of advanced COPD therapies among hospitalists and ED physicians to improve future clinical outcomes.

impractical because many patients lack access to a PCP and specialist wait times remain lengthy. Hospital presentation with AECOPD should therefore be viewed as a critical opportunity to optimize maintenance inhaler therapy. In addition, public medication coverage criteria should be reviewed regularly to maintain alignment with the latest clinical guidelines and to avoid creating barriers to evidence-based prescribing.

Addressing Challenges Specific to The ED Setting

Traditionally, COPD guidelines have defined an ED visit for AECOPD as a severe event, prompting escalation of therapy.^{12,17} However, many patients treated exclusively in the ED for AECOPD might otherwise have been managed in an outpatient setting and therefore would have been categorized as having a less severe event. For example, limited access to a PCP has previously been identified as a risk factor for ED presentation during an AECOPD.²³ Consequently, a physiology-based classification of AECOPD severity may be more clinically meaningful than one based solely on healthcare utilization. Consistent with this perspective, the revised Global Initiative for Chronic Obstructive Lung Disease COPD recommendations now favour the Rome proposal criteria for determining AECOPD severity.^{12,24} This approach also shows promise for predicting return to hospital among patients treated in the ED, although further prospective validation is still required.²⁵

Optimizing care for patients with AECOPD in the ED remains challenging due to high patient volumes, time constraints, and insufficient access to allied healthcare professionals such as respiratory therapists.²⁶ Recent data from an academic hospital in Ontario show that only 5–10% of patients treated for AECOPD in the ED setting receive appropriate optimization of inhaler therapy at discharge.^{19,20} Integrating dedicated certified respiratory educators in this care setting could help to address these gaps. In addition, ongoing education for ED physicians regarding the importance of optimizing maintenance COPD pharmacotherapy remains essential to reduce the burden of AECOPD in the ED and improve patient outcomes. Timely referral to a respirologist should also be emphasized for patients who continue to experience AECOPD despite optimal inhaler therapy, allowing further diagnostic evaluation and consideration of advanced COPD treatments.²⁷

Incorporating Emerging Advanced COPD Therapies

Therapeutic options for COPD patients with recurrent AECOPD despite maximal inhaler therapy have historically been limited. Prophylactic azithromycin may reduce AECOPD in selected individuals, although the potential for adverse effects and drug interactions limits its use.^{28–32} Patients with the chronic bronchitis phenotype may also be considered for roflumilast, which is frequently associated with significant gastrointestinal side effects, or N-acetylcysteine.^{33–39}

Up to 40% of patients with COPD have elevated blood eosinophil counts (BEC) ($\geq 0.3 \times 10^9/L$), although the reported prevalence estimates vary by study population and methodology. This finding suggests the presence of underlying type 2 inflammation.^{40–42} Elevated BEC have been associated with an increased risk of readmission for AECOPD and a greater decline of lung function.^{40,43} Two biologic therapies targeting type 2 inflammation have demonstrated significant reductions in AECOPD frequency among patients with $BEC \geq 0.3 \times 10^9/L$: dupilumab (an anti-interleukin (IL)-4/13 monoclonal antibody) and mepolizumab (an anti-IL-5 therapy).^{44–46} Raising awareness of these new advanced therapies among hospitalists and ED physicians may improve identification of patients who could benefit from biologic treatment. Additional biologic medications are also under investigation. Tozorakimab (an anti-IL-33 monoclonal antibody) appears promising, regardless of BEC.^{47,48} Tezepelumab (an anti-thymic stromal lymphopoietin medication) and depemokimab (an ultra-long-acting anti-IL-5 therapy) are also currently being evaluated in COPD.³⁹

Conclusions

AECOPD continue to impose a substantial clinical and economic burden on the Canadian healthcare system, while also presenting a pivotal opportunity to improve long-term patient outcomes. Hospital admissions and ED visits should be viewed not only as episodes requiring acute management, but also as critical opportunities to confirm the diagnosis of COPD, implement standardized evidence-based care pathways, optimize guideline-directed maintenance therapy, and facilitate appropriate follow-up after discharge. Practical

interventions such as improving access to spirometry, incorporating standardized order sets and discharge bundles, initiating recommended therapy in eligible patients, and strengthening communication between acute and outpatient care providers have the potential to reduce recurrent AECOPD, hospital readmissions, and mortality.

Correspondence

Mathieu D. Saint-Pierre, MD, FRCPC Respiriology
Email: mathieuspierre@montfort.on.ca

Financial Disclosures

M.S.: None declared.

References

1. Canadian Institute for Health Information. Hospital stays in Canada 2022–2023. [Internet]. [Accessed 2026 July 30]. Available from: <https://www.cihi.ca/en/hospital-stays-in-canada-2022-2023>

2. Amegadzie JE, Lee TY, Sadatsafavi M, Lynd LD, Sin DD, Johnson KM. Trends in hospital admissions for chronic obstructive pulmonary disease over 16 years in Canada. CMAJ. 2023;195(35):E1172–E1179. doi:10.1503/cmaj.221051

3. Canadian Institute for Health Information. All-cause readmission to acute care and return to the emergency department [Internet]. Ottawa, ON; 2012 [Accessed 2026 July 30]. Available from: https://publications.gc.ca/collections/collection_2013/icis-cihi/H118-93-2012-eng.pdf

4. Saint-Pierre MD. Demographic and clinical characteristics predictive of hospital readmission for acute COPD exacerbation after 1 and 3 months post-discharge. Am J Respir Crit Care Med. 2024;209 Supplement_1:A1860. <https://doi.org/10.1164/ajrccm-conference.2024.209.1.MeetingAbstracts.A1860>

5. Canadian Lung Association. Pre-Budget Consultations House of Commons, 2011 [Internet]. 2011; [Accessed 2026 July 30]. Available from: https://www.ourcommons.ca/Content/Committee/411/FINA/WebDoc/WD5138047/411_FINA_PBC2011_Briefs/Canadian%20Lung%20Association%20E.html

6. Dransfield MT, Kunisaki KM, Strand MJ, Anzueto A, Bhatt SP, Bowler RP, et al. Acute exacerbations and lung function loss in smokers with and without chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2017;195(3):324–330. doi:10.1164/rccm.201605-1014OC

7. Watz H, Tetzlaff K, Magnussen H, Mueller A, Rodriguez-Roisin R, Wouters EFM, et al. Spirometric changes during exacerbations of COPD: a post hoc analysis of the WISDOM trial. Respir Res. 2018;19(1):251. doi:10.1186/s12931-018-0944-3

8. Hurst JR, Vestbo J, Anzueto A, Locantore N, Müllerova H, Tal-Singer R, et al. Susceptibility to exacerbation in chronic obstructive pulmonary disease. N Engl J Med. 2010;363(12):1128–1138. doi:10.1056/

NEJMoa0909883

9. Soler-Cataluña JJ, Martínez-García MÁ, Román Sánchez P, Salcedo E, Navarro M, Ochando R. Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. Thorax. 2005;60(11):925–931. doi:10.1136/thx.2005.040527

10. Ho TW, Tsai YJ, Ruan SY, Huang CT, Lai F, Yu CJ, et al. In-hospital and one-year mortality and their predictors in patients hospitalized for first-ever chronic obstructive pulmonary disease exacerbations: a nationwide population-based study. PloS One. 2014 9(12):e114866. doi:10.1371/journal.pone.0114866.

11. Sánta B, Tomisa G, Horváth A, Balázs T, Németh L, Gálffy G. Severe exacerbations and mortality in COPD patients: a retrospective analysis of the database of the Hungarian National Health Insurance Fund. Pulmonology. 2023;29(4):284–291. doi:10.1016/j.pulmoe.2022.11.001

12. Global Initiative for chronic obstructive lung disease. 2026 Gold report and pocket guide [Internet]. 2026; [Accessed 2026 July 30] Available from: <https://goldcopd.org/2026-gold-report-and-pocket-guide/>

13. Saint-Pierre MD, Abdulnour J, Sabbagh R. Inhaler prescription in congestive heart failure patients without evidence of obstructive lung disease: a single-center review. Am J Respir Crit Care Med. 2021;203:A1599. <https://doi.org/10.1164/ajrccm-conference.2021.203.1.MeetingAbstracts.A1599>

14. Gershon A, Mecredy G, Croxford R, To T, Stanbrook MB, et al. Outcomes of patients with chronic obstructive pulmonary disease diagnosed with or without pulmonary function testing. CMAJ. 2017;189(14):E530–E538. doi:10.1503/cmaj.151420

15. Pendharkar SR, Ospina MB, Southern DA, Hirani N, Graham J, Faris P, et al. Effectiveness of a standardized electronic admission order set for acute exacerbation of chronic obstructive pulmonary disease. BMC Pulm Med. 2018;18(1):93. doi:10.1186/s12890-018-0657-x

16. Atwood CE, Bhutani M, Ospina MB, Rowe BH, Leigh R, Deuchar L, et al. Optimizing COPD acute care patient outcomes using a standardized transition bundle and care coordinator: a randomized clinical trial. Chest. 2022;162(2):321–330. doi:10.1016/j.chest.2022.03.047

17. Bourbeau J, Bhutani M, Hernandez P, Aaron SD, Beauchesne MF, Kermelly SB, et al. 2023 Canadian Thoracic Society Guideline on pharmacotherapy in patients with stable COPD. Chest. 2023;164(5):1159–1183. doi:10.1016/j.chest.2023.08.014

18. Gage B, Lamb J, Dahri K. Evaluation of in-hospital management of inhaler therapy for chronic obstructive pulmonary disease. Can J Hosp Pharm. 2021;74(2):110–116.

19. Saint-Pierre MD. Adherence to the Canadian Thoracic Society Chronic Obstructive Pulmonary Disease Pharmacotherapy Guidelines in a real-world hospital setting. Canadian Journal of Respiratory, Critical Care, and Sleep Medicine. 2023;7(5):240–244. <https://doi.org/10.1080/24745332.2023.2255187>

20. Saint-Pierre MD. Evaluating Adherence to the 2023 Canadian Thoracic Society Chronic Obstructive Pulmonary Disease Pharmacotherapy Guidelines: a hospital-based study. Therapeutic

Advances in Pulmonary and Critical Care Medicine. 2025;20:29768675251336660. doi:10.1177/29768675251336660

21. Tkacz J, Evans KA, Touchette DR, et al. Prompt initiation of maintenance therapy in the us: a real-world analysis of clinical and economic outcomes among patients initiating triple therapy following a COPD exacerbation. *Int J Chron Obstruct Pulmon Dis*. 2022;17:329-342. doi:10.2147/COPD.S347735

22. Strange C, Tkacz J, Schinkel J, Lewing B, Agatep B, Swisher S, et al. Exacerbations and real-world outcomes after single-inhaler triple therapy of budesonide/glycopyrrrolate/formoterol fumarate, among patients with COPD: results from the EROS (US) Study. *Int J Chron Obstruct Pulmon Dis*. 2023;18:2245-2256. doi:10.2147/COPD.S432963. Erratum in: *Int J Chron Obstruct Pulmon Dis*. 2024;19:1799-1800. doi: 10.2147/COPD.S484253.

23. Tsai CL, Griswold SK, Clark S, Camargo CA Jr. Factors associated with frequency of emergency department visits for chronic obstructive pulmonary disease exacerbation. *J Gen Intern Med*. 2007;22(6):799-804. doi:10.1007/s11606-007-0191-7

24. Celli BR, Fabbri LM, Aaron SD, Agustí A, Brook R, Criner GJ, et al. An updated definition and severity classification of chronic obstructive pulmonary disease exacerbations: the Rome Proposal. *Am J Respir Crit Care Med*. 2021;204(11):1251-1258. doi:10.1164/rccm.202108-1819PP

25. Saint-Pierre MD, Neder JA. Revisiting acute exacerbations of chronic obstructive pulmonary disease: insights from applying the Rome Proposal in a North American academic hospital. *Int J Chron Obstruct Pulmon Dis*. 2026;21:614290. doi:10.2147/COPD.S614290

26. Saint-Pierre MD. Severe acute exacerbations of chronic obstructive pulmonary disease: are there significant differences between hospitalized and emergency department patients? *Int J Chron Obstruct Pulmon Dis*. 2024;19:133-138. doi:10.2147/COPD.S447477

27. Saint-Pierre MD, Chagnon N, Neder JA. Just the facts: management of patients with an acute exacerbation of chronic obstructive pulmonary disease in the emergency department. *CJEM*. 2026;28(3):179-182. doi:10.1007/s43678-025-01050-w

28. Naderi N, Assayag D, Mostafavi-Pour-Manshadi SM, Kaddaha Z, Joubert A, Ouellet I, et al. Long-term azithromycin therapy to reduce acute exacerbations in patients with severe chronic obstructive pulmonary disease. *Respir Med*. 2018;138:129-136. doi:10.1016/j.rmed.2018.03.035

29. Pomares X, Montón C, Bullich M, Cuevas O, Oliva JC, Gallego M, et al. Clinical and safety outcomes of long-term azithromycin therapy in severe COPD beyond the first year of treatment. *Chest*. 2018;153(5):1125-1133. doi:10.1016/j.chest.2018.01.044

30. Albert RK, Connett J, Bailey WC, Casaburi R, Cooper JA Jr, Criner GJ, et al. Azithromycin for prevention of exacerbations of COPD. *N Engl J Med*. 2011;365(8):689-698. doi:10.1056/NEJMoa1104623

31. Uzun S, Djamin RS, Kluytmans JA, Mulder PG, van't Veer NE, Ermens AA, et al. Azithromycin maintenance treatment in patients with frequent exacerbations of chronic obstructive pulmonary disease (COLUMBUS): a randomised, double-blind, placebo-controlled trial. *Lancet Respir Med*. 2014;2(5):361-368. doi:10.1016/S2213-2600(14)70019-0

32. Saint-Pierre MD. Prophylactic azithromycin in preventing recurrent acute exacerbations of COPD and blood eosinophil counts: a hospital review. *Eur Respir J*. 2025;66 (suppl 69):PA2451. <https://doi.org/10.1183/13993003.congress-2025.PA2451>

33. Muñoz-Esquerre M, Díez-Ferrer M, Montón C, Pomares X, López-Sánchez M, Huertas D, et al. Roflumilast added to triple therapy in patients with severe COPD: a real life study. *Pulm Pharmacol Ther*. 2015;30:16-21. doi:10.1016/j.pupt.2014.10.002

34. Kiff C, Ruiz S, Varol N, Gibson D, Davies A, Purkayastha D. Cost-effectiveness of roflumilast as an add-on to triple inhaled therapy vs triple inhaled therapy in patients with severe and very severe COPD associated with chronic bronchitis in the UK. *Int J Chron Obstruct Pulmon Dis*. 2018;13:2707-2720. doi:10.2147/COPD.S167730

35. Cilli A, Bal H, Gunen H. Efficacy and safety profile of roflumilast in a real-world experience. *J Thorac Dis*. 2019;11(4):1100-1105. doi:10.21037/jtd.2019.04.49

36. Martínez FJ, Calverley PM, Goehring UM, Brose M, Fabbri LM, Rabe KF. Effect of roflumilast on exacerbations in patients with severe chronic obstructive pulmonary disease uncontrolled by combination therapy (REACT): a multicentre randomised controlled trial. *Lancet*. 2015;385(9971):857-866. doi:10.1016/S0140-6736(14)62410-7

37. Martínez FJ, Rabe KF, Sethi S, Pizzichini E, Mclvor A, Anzueto A, et al. Effect of roflumilast and inhaled corticosteroid/long-acting β 2-agonist on chronic obstructive pulmonary disease exacerbations (RE 2 SPOND). A randomized clinical trial. *Am J Respir Crit Care Med*. 2016;194(5):559-567. doi:10.1164/rccm.201607-1349OC

38. Martínez FJ, Rabe KF, Calverley P, Fabbri M, Sethi S, Pizzichini E, et al. Effect of roflumilast on exacerbations in patients with severe COPD and a history of hospitalization receiving inhaled combination therapy: a pooled analysis of two randomized phase 4 studies [Conference proceedings]. *Am J Respir Crit Care Med*. 2017;195:A5724. doi:10.1164/ajrccm-conference.2017.195.1_meetingabstracts.a5724

39. Neder JA. Biologics in the management of chronic obstructive pulmonary disease: emerging perspectives. *Can Respir J Today*. 2025;1(1):12-19. <https://doi.org/10.58931/cret.2025.113>

40. Couillard S, Larivée P, Courteau J, Vanasse A. Eosinophils in COPD exacerbations are associated with increased readmissions. *Chest*. 2017;151(2):366-373. doi:10.1016/j.chest.2016.10.003

41. Bélanger M, Couillard S, Courteau J, Larivée P, Poder TG, Carrier N, et al. Eosinophil counts in first COPD hospitalizations: a comparison of health service utilization. *Int J Chron Obstruct Pulmon Dis*. 2018;13:3045-3054. doi:10.2147/COPD.S170743

42. Saint-Pierre MD, Abdulnour J. Oral add-on therapies and blood eosinophils in severe acute exacerbations of chronic obstructive pulmonary disease: a real-world hospital chart review. *Canadian Journal of*

Respiratory, Critical Care, and Sleep Medicine. 2024;8(6):254-259. <https://doi.org/10.1080/24745332.2024.2396463>

43. Tan WC, Bourbeau J, Nadeau G, Wang W, Barnes N, Landis SH, et al. High eosinophil counts predict decline in FEV1: results from the CanCOLD study. *Eur Respir J*. 2021;57(5):2000838. doi:10.1183/13993003.00838-2020

44. Bhatt SP, Rabe KF, Hanania NA, Vogelmeier CF, Cole J, Bafadhel M, et al. Dupilumab for COPD with type 2 inflammation indicated by eosinophil counts. *N Engl J Med*. 2023;389(3):205-214. doi:10.1056/NEJMoa2303951

45. Bhatt SP, Rabe KF, Hanania NA, Vogelmeier CF, Bafadhel M, Christenson SA, et al. Dupilumab for COPD with blood eosinophil evidence of type 2 inflammation. *N Engl J Med*. 2024;390(24):2274-2283. doi:10.1056/NEJMoa2401304

46. Sciurba FC, Criner GJ, Christenson SA, Martínez FJ, Papi A, Roche N, et al. Mepolizumab to prevent exacerbations of COPD with an eosinophilic phenotype. *N Engl J Med*. 2025;392(17):1710-1720. doi:10.1056/NEJMoa2413181

47. Tozorakimab met primary endpoint in both OBERON and TITANIA Phase III trials in patients with COPD [Internet]. 2026; [Published 2026 April 20, Accessed 2026 July 30] Available from: <https://www.astrazeneca.com/media-centre/press-releases/2026/tozorakimab-met-primary-endpoint-in-oberon-titania-phase-iii-trials-in-patients-with-copd.html>

48. Tozorakimab met primary endpoint in Phase III MIRANDA trial in patients with COPD [Internet]. 2026; [Published 2026 April 20, Accessed 2026 July 30]. Available from: <https://www.astrazeneca.com/media-centre/press-releases/2026/third-tozorakimab-positive-phase-iii-in-copd.html>



canadianrespirologytoday.com

Canadian Respirioly Today is published three times per year under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) license by Catalytic Health in Toronto, Ontario, Canada.
© 2026 Canadian Respirioly Today.

**Register for future digital and print issues by
visiting us at catalytichealth.com/crespt**

**Looking for more?
All back issues are available online at
canadianeespirologytoday.com**

