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Review

Bronchiectasis-COPD Overlap Syndrome: A Comprehensive Review of its Pathophysiology and Potential Cardiovascular Implications

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Abstract

Bronchiectasis-Chronic Obstructive Pulmonary Disease Overlap Syndrome (BCOS) is a complex pulmonary condition that merges bronchiectasis and chronic obstructive pulmonary disease (COPD), presenting unique clinical challenges. Patients with BCOS typically exhibit a range of symptoms from both conditions, including a chronic productive cough, reduced lung function, frequent exacerbations, and diminished exercise tolerance. The etiology of BCOS involves multiple factors such as genetic predisposition, respiratory infections, tobacco smoke, air pollutants, and other inflammatory mediators. Accurate diagnosis requires a comprehensive approach, incorporating pulmonary function tests to evaluate airflow limitation, radiographic imaging to identify structural lung abnormalities, and blood eosinophil counts to detect underlying inflammation. Treatment strategies are tailored to individual symptom profiles and severity, potentially including bronchodilators, inhaled corticosteroids, and pulmonary therapy to improve lung function and quality of life. Patients with BCOS are also at an increased risk for cardiovascular complications, such as stroke, ischemic heart disease, and cor pulmonale. Additionally, medications like beta-agonists and muscarinic antagonists used in COPD treatment can further affect cardiac risk by altering heart rate. This paper aims to provide a thorough understanding of BCOS, addressing its development, diagnosis, treatment, and associated cardiovascular complications, to aid healthcare providers in managing this multifaceted condition and improving patient outcomes.

Keywords: chronic obstructive lung disease, bronchiectasis, aspergillus fumigatus, pseudomonas aeruginosa, tobacco exposure, alpha 1 antitrypsin, inflammatory mediators, pulmonary hypertension, vascular remodeling, hypoxic vasoconstriction

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Introduction

Chronic obstructive pulmonary disease (COPD) is a persistent, progressive, obstructive lung condition marked by abnormalities of the airway and/or alveoli, accelerated decline in lung function, and irreversible pulmonary damage, often due to an inflammatory response.[1] As the third leading cause of death worldwide, COPD is responsible for 3.23 million deaths in 2019 alone and the seventh leading cause of poor health globally, as measured by disability-adjusted life years (World Health Organization). Additionally, nearly 90% of COPD deaths among individuals under 70 years occur in low- and middle-income countries, especially in African and Eastern Mediterranean regions, with tobacco smoke exposure as the primary cause and other significant risk factors, including air pollution and occupational exposures.[1–3] Bronchiectasis is another type of obstructive lung disease (OLD) characterized by permanent enlargement of airways due to chronic inflammation and recurrent infections. This condition leads to symptoms such as chronic cough, sputum production, and respiratory infections.[4,5] High-resolution computed tomography

(HRCT) is the foremost tool for detecting irreversible airway dilation in bronchiectasis, distinguishing it from COPD, which is diagnosed based on spirometry readings and computed tomography (CT) scan findings.[6] While COPD typically presents with milder and more diffuse airway wall changes, both conditions share similar features, including dyspnea, chronic productive cough, airflow obstruction, and a predisposition to recurrent exacerbations due to persistent or new infections.[7]

Bronchiectasis-Chronic Obstructive Pulmonary Disease Overlap Syndrome (BCOS) is a clinical condition where features of both bronchiectasis and COPD coexist in a single patient, leading to poorer outcomes and increased mortality compared to either disease alone.[8] The overlap of bronchiectasis and COPD, first described by Barker in 2002, is now recognized as a distinct COPD phenotype.[7,9] COPD overlap syndromes, such as BCOS, are characterized by the existence of clinical and/or laboratory signs of multiple diseases in one patient, with COPD often central to these respiratory overlaps. The risk of developing bronchiectasis is significantly higher in COPD patients, with a 1.9-fold increase compared to non-COPD patients.[10] The prevalence of BCOS has risen, with radiological evidence of bronchiectasis found in up to 69% of COPD patients.[11,12] Patients with BCOS exhibit a 2.20-fold greater risk of pneumonia, a 3.88-fold greater risk of acute exacerbation, a 1.74-fold greater risk of acute respiratory failure (ARF), and a 1.99-fold greater risk of cardiopulmonary arrest compared to those with COPD alone.[13] A single-center study revealed that patients with BCOS had a 5-year mortality rate of 55%, nearly three times higher than the 20% mortality rate in those with bronchiectasis alone. BCOS results in symptoms from both bronchiectasis and COPD, such as chronic cough, large amounts of mucus production, shortness of breath, and frequent exacerbations.[14]

Factors contributing to BCOS include chronic microbial infections, comorbidities, and underlying causes such as respiratory infections, systemic diseases, and immunological disorders. BCOS is particularly common among adults over 60 years old and smokers and is often associated with other chronic airway diseases, chronic rhinosinusitis, gastroesophageal reflux disease, and mycobacterial infection.[15] Patients with BCOS tend to have higher levels of proinflammatory cytokines, lower airway bacterial colonization, and prolonged recovery times following exacerbations.[16] Host-microbe interactions are critical in driving respiratory disease progression, with pathogenic organisms often serving as prognostic markers.[17] Understanding these interactions and their impact on disease trajectory is essential for the development of effective management strategies. BCOS is associated with longer intensive care unit (ICU) and hospital stays, prolonged mechanical ventilation, and an increased risk of ventilator-associated pneumonia.[18] Recent studies report high mortality rates of 28.5% over 48 months in patients with BCOS, indicating a poor prognosis.[15,19]

Patients diagnosed with BCOS exhibit an increased predisposition to pulmonary hypertension (PH) and cardiovascular (CV) complications, including heart disease and stroke (HDS), even in the absence of concurrent comorbidities.[20] Recent utilization of short-acting beta-agonists (SABAs), historical use of inhaled corticosteroids (ICSs), and antiarrhythmic medications are linked to heightened risks of HDS in this patient cohort.[21]

This review provides an overview of BCOS, focusing on its pathophysiology, diagnostic modalities, treatment approaches, and CV complications. Enhancing the understanding of this condition is essential for improving clinical management and outcomes for patients suffering from BCOS.

Pathophysiology

The development of COPD and bronchiectasis involves similar mechanisms, such as alpha 1 antitrypsin (A1AT) deficiency, inflammatory mediators, tobacco exposure, microbiome alterations, and exposure to air pollutants.[22]

Tobacco Exposure

Cigarette smoke (CS) contains over 7000 chemical compounds, many of which result from incomplete combustion and thermal degradation of tobacco.[23] Inhalation of tobacco induces pulmonary toxicity, contributing to OLDs such as COPD, bronchiectasis, chronic bronchitis, and asthma. Exposure to CS and the subsequent development of these conditions lead to the sustained release of cytokines such as interleukin (IL)-1 beta, IL-6, IL-8, leukotriene (LT)-B4, monocyte chemotactic peptide-1, and tumor necrosis factor-alpha (TNF-α), disrupting multiple intercellular signaling pathways and

causing barrier dysfunction.[24] IL-8 and LT-B4 attract neutrophils to the respiratory tract, causing submucosal glands and goblet cells to overproduce mucus, releasing significant amounts of reactive oxygen species (ROS).[25] Tobacco exposure also impairs the coordination, reduces the length, and lowers the frequency of ciliary beats, which are crucial for mucociliary clearance. This decline in ciliary function compromises the host's defense mechanisms.[26]

The bronchial epithelial barrier, crucial for respiratory defense, relies on apical junctional complexes of tight junctions (TJs) and adherens junctions (AJs). These complexes are formed by proteins such as the claudin family, zonula occludens (ZO) proteins, and epithelial cadherin (E-cadherin), which support the structural integrity of the epithelial barrier.[27] In individuals with COPD, there is a significant reduction in ZO-1, occludin, and E-cadherin levels in the bronchial epithelium and lung tissues compared to healthy individuals. Exposure to tobacco smoke exacerbates this damage by acutely increasing epithelial permeability and further downregulating these crucial TJ and AJ proteins, particularly impacting E-cadherin.[28,29] The widespread impairment of cellular adhesion mechanisms and mucociliary clearance resulting from CS results in diminished structural and functional integrity of the lungs, as illustrated in Figure 1.

A1AT Deficiency

A1AT deficiency is a rare hereditary condition (occurs in approximately 0.02%–0.03% of people) marked by low levels of the A1AT protein, an antiprotease coded by the signal regulatory protein alpha 1 gene, produced in the liver that is crucial for protecting the lungs from injury.[30–32] A1AT suppresses the activity of neutrophil elastase (NE), an inflammatory mediator in the airways of inflammatory lung disease patients that inhibits macrophage function and is activated by dipeptidyl peptidase 1 (DPP1) during neutrophil maturation in bone marrow. If left unchecked, this enzyme can break down numerous structural proteins in the lungs and proteins associated with the innate immune response.[33–35] Although OLD can occur in nonsmoking individuals with A1AT deficiency, the decline of lung function is accelerated in smokers.[36] This process is driven by increased protease activity and decreased antiprotease activity.[37] Proteases play a crucial role in the defense

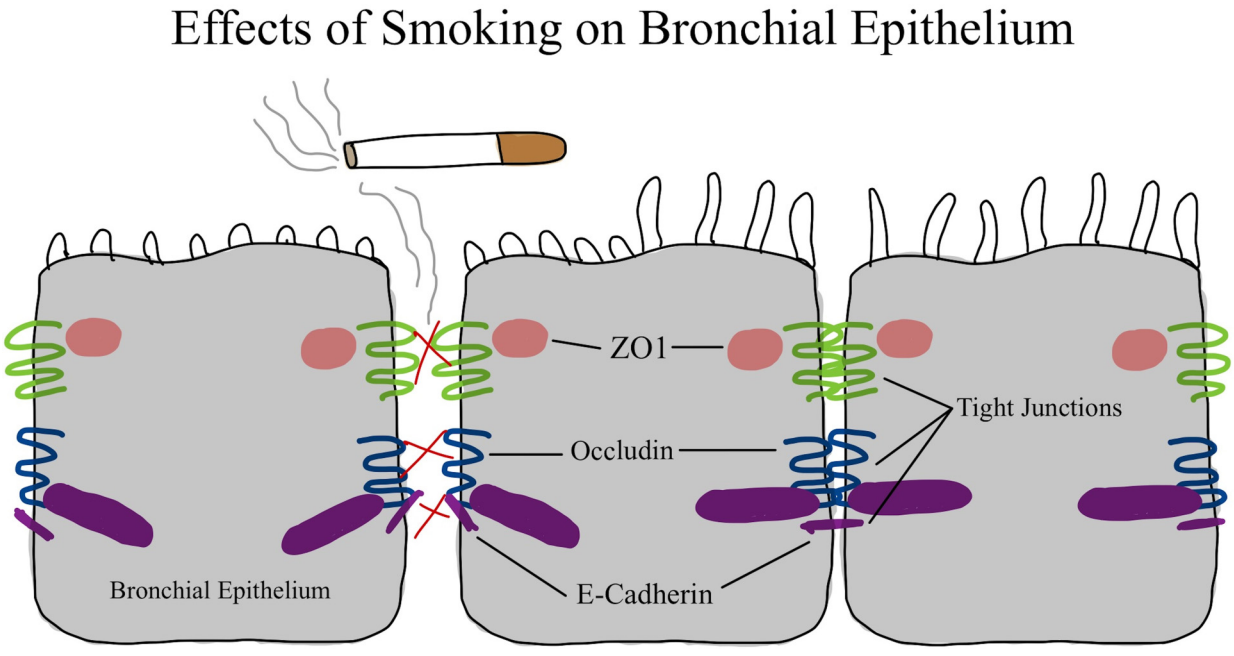

Figure 1. Effects of cigarette smoke on bronchial epithelium.
Note: This figure demonstrates how cigarette smoke disrupts tight junctions between lung cells and damages cilia, leading to lung tissue damage. The left side illustrates the effects of smoking, while the right side shows healthy lung cells with intact cilia and tight junctions.

system of the respiratory tract by maintaining tissue balance; antiproteases control their functions. An increase in overall protease activity, which targets Type I collagen and other extracellular matrix components like laminins and elastin, is linked to lung tissue destruction and the onset of OLD.[38] Lung proteases, including NE, matrix metalloproteinases, and cathepsins, degrade elastin and connective tissue as part of the standard tissue repair process. Their activity is typically balanced by antiproteases, such as A1AT, secretory leukoprotease inhibitors derived from airway epithelium, elafin, and tissue inhibitors of matrix metalloproteinase.[37] Patients with A1AT deficiency are more susceptible to an imbalance in leukocyte elastase activity due to bacterial colonization. One of the most harmful outcomes of this imbalance is the onset of BCOS, which results from the unrestricted activity of elastase on the structures within the airways, as shown in Figure 2.[39] Symptoms of lung conditions such as COPD and bronchiectasis usually appear in individuals with A1AT deficiency between 20 and 50 years old.[40]

Inflammatory Mediators

Neutrophils, macrophages, clusters of differentiation (CD)8+, and CD4+ T lymphocytes are the primary cells that cause the inflammatory processes in COPD and bronchiectasis, as evidenced by a rise of these inflammatory mediators in the lung sputum. This increase is attributed to the recruitment of monocytes and neutrophils from the bloodstream, triggered by chemotactic mediators released by airway epithelial cells and lung macrophages.[41,42] The decline in lung function in BCOS patients is also linked to a high proportion of CD4+ and CD8+ T lymphocytes that express

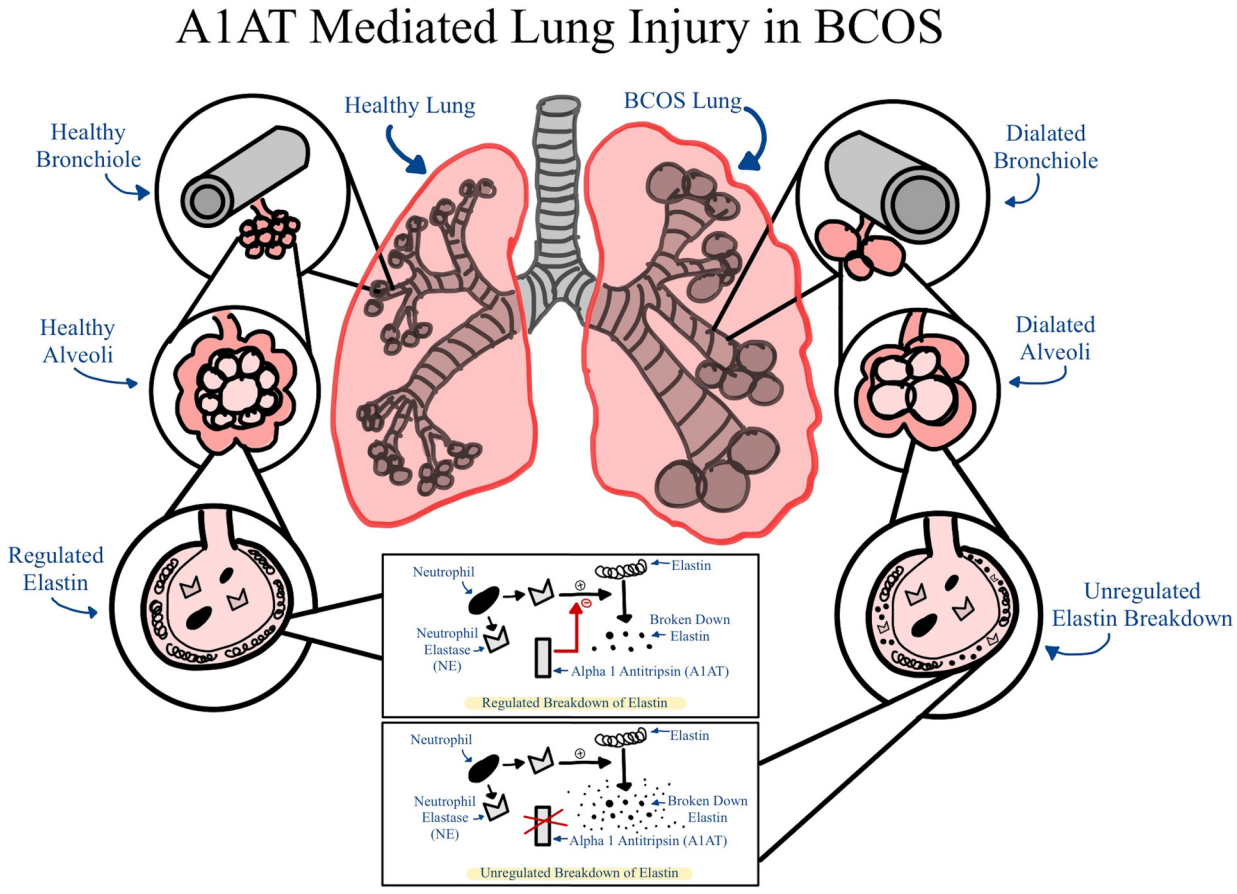

Figure 2. A1AT deficiency in BCOS.
A1AT: Alpha-1 antitrypsin; BCOS: Bronchiectasis-COPD Overlap Syndrome; NE: neutrophil elastase.
Note: This figure illustrates the role of A1AT in regulating the breakdown of elastin by NE in healthy lung tissue on the left. Conversely, the right side depicts the unregulated breakdown of elastin by NE in the lungs of patients with BCOS with A1AT deficiency, highlighting the resultant tissue damage.

C-C chemokine receptor type 5 (CCR5) and C-X-C chemokine receptor type 3 (CXCR3). CD8 + cells are usually elevated in airway infections, possibly due to the chronic or repeated colonization of the lower respiratory tract in BCOS patients by bacterial and viral pathogens contributing to this inflammatory response.[43] CD8 + cells and CCR5-mediated macrophage activation contribute to lung damage by releasing cytokines that harm junctional complexes in the lung epithelium and cause inflammation. At the same time, CXCR3 prompts macrophages to produce enzymes that degrade the extracellular matrix, reducing lung elasticity.[44–47] Bronchial epithelial overexpression of toll-like receptor 4 and nucleotide-binding oligomerization domain in OLD are also associated with increased bronchial inflammation.[48] Additionally, oxidative stress contributes to initiating several inflammatory processes in OLDs. The overproduction of mucus and the buildup of neutrophils result in the creation of a significant amount of ROS, which deactivate antiproteases and result in their loss of inhibitory function, leading to the destruction of lung tissue.[49]

Microbiome

Individuals with BCOS may experience adverse clinical outcomes due to the colonization of persistent pathogenic microorganisms and the simultaneous presence of proteolytic byproducts within their airways.[50]

A study conducted by Everaerts et al revealed Aspergillus fumigatus as the most common pathogen found in the sputum of BCOS patients.[51] Another study conducted by Patel et al found that 53.8% of BCOS patients tested positive for one or more potentially harmful microorganisms in their sputum including *Haemophilus influenzae*, *Branhamella catarrhalis*, *Haemophilus parainfluenzae*, *Pseudomonas aeruginosa*, *Streptococcus pneumoniae*, *Klebsiella species*, *Staphylococcus aureus*, and *Enterobacter* species.[52]

The use of ICS can result in several side effects, including a weakened immune response. In patients with COPD who are on ICS, this reduced immune function can increase their susceptibility to infections from Aspergillus fumigatus, a common pathogen associated with bronchiectasis. This weakened immune response allows the fungus to grow more quickly in the airways, potentially leading to sensitization and the worsening of bronchiectasis.[51] Studies indicate that COPD patients who test positive for Aspergillus fumigatus cultures often receive higher doses of ICSs, providing further evidence for this relationship. Aspergillus's proteases may exacerbate mucus production and contribute to airway remodeling, which are critical factors in developing bronchiectasis. These findings suggest the significant role of Aspergillus fumigatus in the onset and progression of bronchiectasis among COPD patients treated with ICSs.[51]

Pseudomonas aeruginosa, another prevalent pathogen detected in BCOS, alters the lung environment by adhering to the epithelium, leading to lung damage. It produces a toxic pigment called pyocyanin (PCN), which causes oxidative stress and damage in both the lung tissue and nearby immune cells, leading to fibrosis over time.[53] PCN induces oxidative stress by releasing ROS such as superoxide and hydrogen peroxide, which are driven by dismutase. Under aerobic conditions, a nonenzymatic reduction cycle creates superoxide and hydrogen peroxide, with nicotinamide adenine dinucleotide phosphate (NADPH) serving as the electron donor and PCN as the acceptor. As depicted in Figure 3, the interaction between PCN and mitochondria can inflict damage to lung epithelium through various processes such as the release of free radicals leading to oxidative injury to cell cycle components, direct deoxyribonucleic acid (DNA) damage, depletion of NADPH, and enzyme inhibition.[54]

Nontuberculous mycobacteria (NTM), particularly the *Mycobacterium avium* complex (MAC), can significantly impact conditions like bronchiectasis and COPD. NTM can contribute to the development of bronchiectasis by damaging the bronchial walls, while the structural abnormalities and weakened local defenses in individuals with preexisting bronchiectasis or COPD can increase susceptibility to NTM colonization and infection.[55] NTM, commonly found in soil and water, is typically inhaled without causing illness due to the body's effective natural defenses. However, in those with compromised immune systems or preexisting lung conditions, NTM can lead to serious lung infections. MAC is responsible for approximately 80% of NTM-related lung disease cases in the US.[56] There are two forms of NTM: the benign nodular bronchiectasis and the progressive cavitary form.[57] Upon inhalation, NTM can form biofilms on the epithelial lining, which

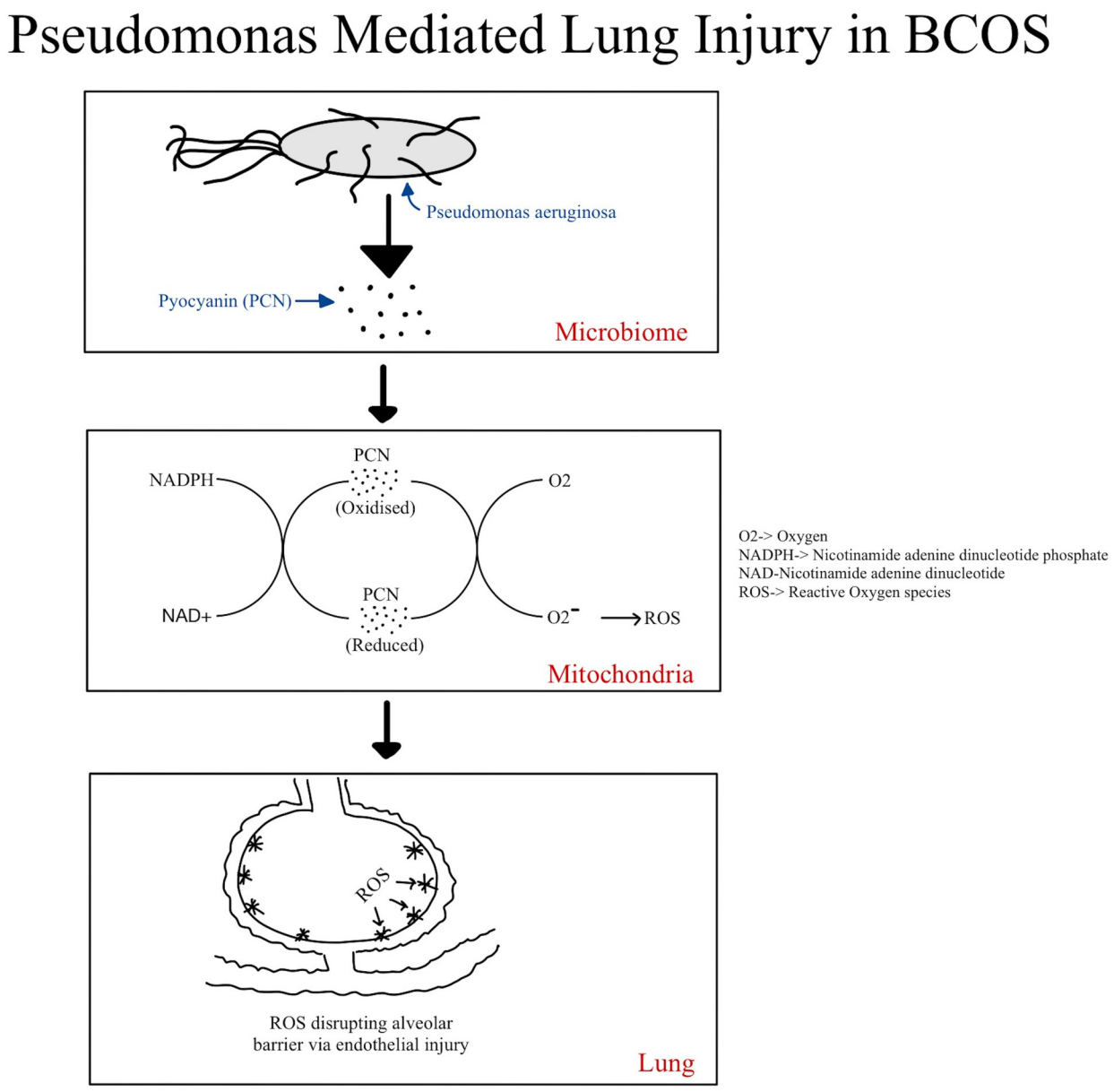

Figure 3. Pseudomonas in BCOS.
BCOS: Bronchiectasis-COPD Overlap Syndrome.
Note: This figure depicts how Pseudomonas, a pathogenic bacterium, releases pyocyanin, which disrupts mitochondrial function and ultimately leads to the production of reactive oxygen species that damages lung epithelium.

protect the bacteria from the immune response, promoting infection development.[58,59] Typically, NTM are engulfed by macrophages, forming phagosomes that fuse with lysosomes to destroy pathogens. However, MAC can disrupt this process by secreting the protein MAV_2941, which interferes with phagosome maturation and prevents the effective formation of phagolysosomes.[60] The resulting granulomas, composed of immune cells such as macrophages and lymphocytes, cause further damage to lung tissue, exacerbating preexisting conditions like COPD and bronchiectasis.[61]

Bronchiectasis Vicious Vortex

The concept of the "vicious vortex" in bronchiectasis illustrates the interconnected cycle of airway dysfunction, inflammation, infection, and structural damage.[62] In this cycle, inhaled harmful

particles are trapped by mucus, which is then expelled from the lungs through mucociliary clearance—a critical defense mechanism facilitated by cilia and coughing.[63,64] Epithelial ion channels, such as the epithelial sodium channel, regulate mucus hydration and thickness. Infections involving the release of NE and bacterial products from pathogens like nontypeable *H. influenzae* or *P. aeruginosa* can impair ciliary function, further compromising mucus clearance.[65] This compromised clearance leads to mucus accumulation in the bronchi, creating an environment conducive to bacterial growth. The persistent infection and inflammation resulting from this cycle progressively damage the lungs, leading to more severe bronchiectasis.[57]

Air Pollution

Air pollutants, such as particulate matter (PM), nitrogen dioxide (NO2), and ozone (O3), are known to damage lung epithelium and contribute to OLD, such as COPD and bronchiectasis.[66]

PM comprises microscopic particles that can be inhaled into the lungs, primarily emitted from motor vehicles and industrial processes. Some PM particles are small enough to penetrate the tracheobronchial tree and adhere to the small airways. These particles contain transition metals and organic aerosols that release ROS and suppress the lung's antioxidant defenses, increasing oxidative stress in the respiratory tract. The ROS released by PM can damage DNA strands and hinder DNA repair enzymes in epithelial cells, impairing mitochondria and leading to epithelial cell death.[67]

Additionally, PM exposure elevates inflammatory cytokines such as IL-6, IL-1 beta, and TNF-α, along with chemotactic molecules like IL-8 and monocyte chemoattractant protein produced by epithelial cells.[67] Specifically, IL-1 beta increases mucus production in airway epithelial cells, resulting in airway obstruction, compromised lung function, and persistent airway infections.[68]

NO2, a gaseous pollutant from combustion processes using air as an oxidant, is commonly found in automobile exhaust, refinery emissions, and fossil-fuel-powered power plants.[69] Inhaled NO2 interacts with moisture in the respiratory tract to form nitrous oxide and nitric acid, which can cause oxidative damage. Oxidative stress and inflammation correlate positively, leading to an inflammatory response that releases free radicals, exacerbating oxidative damage. NO2 also impairs the elimination of pathogens, reduces alveolar macrophage activity, and releases proinflammatory mediators, inducing lung inflammation.[70,71]

O3 is a highly reactive molecule composed of three oxygen atoms. Exposure to O3 can compromise the integrity of membranes and organelles in airway epithelial cells, causing stress and releasing mitochondrial ROS, DNA, and proteases. Mitochondrial DNA and ROS activate the neuronal apoptosis inhibitor protein, Class 2 transcription activator, heterokaryon incompatibility, Telomerase-associated protein, leucine-rich repeat, domains-containing protein 3 inflammasome and Cyclic Guanosine Monophosphate-Adenosine Monophosphate synthase (cGAS), which is a DNA sensor. cGAS activates the stimulator of interferon genes, accelerating the caspase-related pathway and leading to cell death and inflammation. This process damages the alveolar septa, causing remodeling and fibrosis. During inhalation, ozone directly interacts with airway cells, including macrophages and alveolar epithelial cells, causing oxidative damage as these cells release ROS and other inflammatory factors, such as cytokines and lipids. Moreover, ozone exposure can impair macrophages' phagocytic and efferocytosis functions, potentially leading to sustained lung epithelium damage and inflammation.[72,73]

Development of CV Complications in BCOS

The connection between BCOS and cardiovascular disease (CVD) is complex and not fully understood, but several interrelated factors contribute to this association. Key processes include lung hyperinflation, hypoxemia, PH, systemic inflammation, and oxidative stress.[74]

CS and other exposure factors in bronchiectasis and COPD can induce inflammatory changes that disrupt the pulmonary vascular endothelium. This disruption leads to chronic hypoxia, pulmonary artery remodeling, and vasoconstriction. These inflammatory changes alter intrinsic pulmonary vasodilator substances, reducing the production of prostacyclin synthase and endothelial nitric oxide synthase, while increasing endothelin levels.[75] Lung hyperinflation, a common characteristic of COPD, exacerbates these effects by impairing cardiac function through increased pressures within the cardiopulmonary system. Elevated

pressure impairs right ventricular function, restricts left ventricular filling, and ultimately reduces cardiac output. Additionally, hyperinflation and emphysema can cause ventilation/perfusion mismatches, resulting in hypoxemia.[74]

Hypoxemia triggers systemic vasodilation, or the widening of arteries, while simultaneously causing pulmonary vasoconstriction, which narrows the blood vessels in the lungs.[76,77] Chronic exposure to low oxygen levels can lead to persistent pulmonary vasoconstriction and structural alterations in the pulmonary blood vessels, such as thickening of vessel walls—a process known as myointimal hyperplasia. Factors such as hypoxia, lung hyperinflation, secondary erythrocytosis, and reduced pulmonary blood vessel surface area contribute to the development of PH.[77] In COPD patients, bronchiectasis worsens these complications by causing alveolar wall degeneration, reduced elastic recoil, and chronic hyperinflation, all of which further contribute to hypoxic pulmonary vasoconstriction (HPV) and loss of the vascular bed.[78] HPV helps maintain optimal ventilation and perfusion by diverting blood away from inadequately ventilated alveoli,[79] which can lead to altered respiratory mechanics, increased blood viscosity, and ultimately, PH. This progression from COPD and HPV to PH can result in right ventricular hypertrophy and dilation, often leading to right heart failure, known as cor pulmonale.[80]

Furthermore, bronchiectasis severity is linked to impaired flow-mediated dilation, largely due to chronic airway infections. These infections elevate the expression of vascular adhesion molecules and trigger systemic inflammation, marked by increased levels of IL-6, IL-8, and TNF-α. Oxidative stress, indicated by higher production of hydrogen peroxide, further exacerbates endothelial dysfunction, increasing the risk of CVD—a relationship also observed in COPD patients.[81]

The treatment of BCOS can also influence CV health. Beta-agonists, which stimulate β1-adrenoceptors in cardiac tissue, may lead to tachycardia, enhanced relaxation, and increased contractility.[82,83] Conversely, muscarinic agonists activate M2 muscarinic receptors, reducing heart rate by slowing firing rates in the sinoatrial (SA) node and delaying conduction in the atrioventricular (AV) node. This parasympathetic effect primarily affects the SA and AV nodes, altering action potential duration and contraction strength, especially when β-adrenergic receptors are also stimulated.[84]

The interplay between COPD, bronchiectasis, and CV complications is multifaceted, involving a cascade of physiological changes that adversely affect heart function and increase the risk of CVD.

Discussion

Bronchiectasis is increasingly recognized in individuals with COPD. It presents with a significant decline in functional and clinical status characterized by frequent exacerbations, reduced exercise tolerance, diminished quality of life, increased production of purulent sputum, airflow obstruction, dyspnea, and prolonged symptom duration. This condition also exerts a substantial impact on psychological well-being, contributing to a poorer prognosis.[22,85] Risk factors include advanced age (over 60 years), male gender, low body mass index, higher smoking rates, a history of tuberculosis, and recent hospitalizations.[86,87] Moreover, these patients frequently exhibit higher rates of bacterial colonization, particularly with *P. aeruginosa*, heightened local and systemic inflammation, and an increased risk of mortality.[88]

Chronic smokers above 40 years of age who have been smoking for a long time have built up mucus in their airways. Airways distal to this mucus build up become a common breeding ground for bacteria to build up leading to clinically significant destruction.

Diagnosis

COPD is typically identified through physiological assessments of spirometry findings that help establish the extent of irreversible airflow obstruction.[14] In contrast, bronchiectasis is diagnosed using structural observations from imaging methods that reveal enlarged airways and thickened airway walls, which contribute to recurrent infections and persistent symptoms.[89] Therefore, the diagnosis of BCOS benefits from integrating clinical assessment with radiological evidence to ensure accuracy.[90]

Depending on presenting symptoms and age, such as those with risk factors including smoking and age over 40, the diagnostic evaluation may encompass a sweat electrolyte test, electron microscopy of ciliated cells, serum immunoglobulin levels, or serum Aspergillus antibody and precipitin

assays, along with genetic testing as warranted. In cases of more diffuse bronchiectasis with acute exacerbations or sudden worsening of symptoms, bronchoscopy with lavage may be indicated. This procedure is particularly valuable in identifying acute airway infections when conventional sputum sampling proves inadequate for culture and antibiotic sensitivity determination.[91]

Blood Eosinophil Count

Blood eosinophil count (BEC) plays a significant role in assessing BCOS, serving as a critical diagnostic marker alongside other inflammatory indicators and diagnostic procedures. Patients exhibiting concomitant eosinophilia (>300 eosinophils/μL) demonstrate a markedly higher annual frequency of exacerbations due to Streptococcus and Pseudomonas microbiome profiles.[92,93] While individuals with decreased BEC (<100 eosinophils/μL) exhibit an elevated propensity for chronic bronchial infections resulting in higher bronchiectasis severity and increased mortality risk.[93]

Pulmonary Function Tests

The severity of airflow limitation correlates with the extent and severity of bronchiectasis in COPD and can be assessed through pulmonary function tests (PFTs).[91] Diagnostic criteria are based on irreversible airway obstruction, demonstrated by a postbronchodilator forced expiratory volume in the first second (FEV1)/forced vital capacity (FVC) ratio below the lower limit of normal (LLN) (lower fifth percentile), with preference given to Global Lung Function Initiative reference values.[94,95] Without these reference values, a fixed ratio of FEV1/FVC < 0.7 can be utilized. Whole-body plethysmography aids in evaluating static lung volumes and the degree of lung hyperinflation, while the diffusing capacity for inhaled carbon monoxide (DLCO) provides critical information regarding the severity of BCOS.[88]

Radiologic Imaging

Radiologic imaging, including CT, HRCT, and chest X-ray (CXR), is crucial for diagnosing OLDs like BCOS. HRCT acquires images with slices of 1.0–1.5 mm in thickness at 10 mm intervals, offering high diagnostic accuracy for BCOS by showing minimal false positive rates (1%) and false negative rates (2%), high sensitivity (93%–99%) and specificity (98%), and high positive predictive value (88%) and negative predictive value (81%). In contrast, CXR has comparatively lower sensitivity (87.8%) and specificity (74.4%) for diagnosing this condition.[96,97]

Imaging findings on CXR primarily reveal bronchial wall thickening, which is seen as poorly defined perihilar linear densities and obscured margins of the central pulmonary arteries (PAs). Additionally, mucus plugging may present as elongated opacities, occasionally exhibiting calcification. HRCT is currently regarded as the gold standard for diagnosing bronchiectasis in patients with COPD. It is identified in HRCT based on specific criteria, the most reliable being the measurement of the broncho-arterial ratio (BAR). This ratio compares a bronchus's internal diameter to its accompanying PA at the same branching level. A BAR greater than 1 in adults and greater than 0.8 in children, due to their smaller airway caliber, is indicative of bronchiectasis.[91]

Additional diagnostic features on imaging include the absence of normal bronchial tapering, the presence of a bronchus in contact with the mediastinal pleura, or the visualization of a bronchus within 1 cm of the pleura. Peribronchial thickening, where the bronchial wall thickness is more than twice that of a normal bronchus, is another key indicator. Characteristic signs such as the "signet ring" appearance, resulting from an eccentrically placed arteriole around a dilated bronchus, and the "tram track" appearance, indicating a lack of bronchial tapering at least 2 cm distal to the branching point, further support the diagnosis. These findings are optimally visualized in axial images, particularly in the middle lung zones, due to the horizontal orientation of the airways.[98]

Although COPD and bronchiectasis have different diagnostic approaches, both conditions can present with the same lung function abnormalities and symptoms. This similarity often leads to COPD misdiagnosis in patients with BCOS due to the broader availability of spirometry over CT scans.[87] However, with the increased use of CT scans for various lung evaluations, bronchiectasis is being more frequently recognized, explaining the rise in its diagnosis among COPD patients.[14] Therefore, using an integrated strategy based on clinical symptoms, environmental exposure, CT imaging, and spirometric criteria can be used to assist in establishing a diagnosis of both bronchiectasis and COPD, as depicted in Table 1.[99]

Table 1. Diagnostic criteria in BCOS.

Diagnostic criteria in BCOS	
Diagnostic procedure	Diagnostic features
Radiographic imaging	HRCT findings: • BA > 1 in adults & BA > 0.8 in children • Lack of tapering • Airway visibility within 1 cm of costal pleural surface or touching mediastinal pleura CXR findings: • Peribronchial wall thickening (bronchial wall thickness >2x to that of normal bronchus) • Poorly defined perihilar linear densities with mucus plugging presenting as elongated opacities exhibiting calcification Additional findings on CT or CXR: • Obscured margins of the central pulmonary arteries • "Signet ring" appearance - eccentrically placed arteriole around a dilated bronchus • "Tram track" appearance - lack of bronchial tapering at least 2 cm distal to the branching point
Pulmonary function tests	Spirometry (postbronchodilator response) • Fixed FEV1/FVC ratio of <0.7 • (FEV1)/ (FVC) ratio below the lower limit of normal (lower 5th percentile) • FEV1 may be improved by medical therapy Whole-body plethysmography • Indicates static lung volumes and lung hyperinflation DLCO • DLCO is decreased in COPD (destroyed alveoli cause loss of normal surface area of the lungs resulting in significantly decreased area for gas diffusion) • DLCO below the median 49% indicates poor prognosis and higher mortality • DLCO above the median 49% indicates good prognosis and lower mortality
88, 91,94-98, 100	

BA: beta-agonist; COPD: chronic obstructive pulmonary disease; CT: computed tomography; CXR: chest X-ray; DLCO: diffusion lung carbon monoxide; FEV1: forced expiratory volume in the first second; FVC: forced vital capacity; HRCT: high-resolution computed tomography.

Treatment/Management

BCOS commonly involves the use of bronchodilators, such as muscarinic antagonists and beta-2 agonists, which effectively relieve airflow obstruction and alleviate shortness of breath. Table 2 summarizes common medications used in the treatment of BCOS. Pulmonary rehabilitation also plays a crucial role by incorporating inspiratory muscle training alongside conventional oxygen therapy to optimize and maintain lung function. For individuals with localized disease, lung resection may be considered a therapeutic option. In more severe cases, lung transplant is recommended for bronchiectasis patients under 65 years of age with a FEV1 of less than 30% and significant clinical instability, including massive hemoptysis, severe secondary PH, recurrent ICU admissions, or respiratory failure despite optimal medical management.[97]

High-Frequency Chest Wall Oscillation

Older males, typically over the age of 40, with a history of long-term smoking often experience chronic inflammatory changes that lead to mucus accumulation in the airway linings, resulting in conditions involving airflow limitations such as COPD. A novel therapy known as High-Frequency Chest Wall Oscillation (HFCWO), or the inflatable vest, has been introduced to aid in chest physical therapy which can help improve symptoms in patients with COPD. This method uses high-frequency vibrations to thin the mucus and mobilize it toward larger airways. Typically, HFCWO

Table 2. Medications used in BCOS studies.

Medications Used in BCOS Studies				
Medications	Dosage	Advantages	MOA	Adverse effects
Inhaled corticosteroids (budesonide)	High-dose nebulized Budesonide	• Reduces bronchial inflammation -> opens airways • Reduce airway eosinophilia • Decreases bronchial hyperresponsiveness	• Anti-inflammatory • Immunosuppressive	• Bone metabolism • Adrenal insufficiency • Hypertension • Cataracts • Pneumonia
Mucolytics	30 mg orally- 3x/day for 3 weeks	• Decreases hypersecretion of mucus • Thins the mucus • Promotes sputum expectoration	• Alters crosslinks and molecular interactions within mucin polymers	• No significant side effects
PDE4 inhibitors: (roflumilast)	250 or 500 µg for 24 weeks	• Modulate systemic and airway inflammation • Inhibits cough reflex • Inhibits airway mucus secretion	• Inhibits inflammatory cytokine release • Inhibits neutrophil chemotaxis • Promotes apoptosis	• Diarrhea • Weight loss • Nausea
LAMA (Tiotropium) + LABA (Olodatero)	Fixed dose combination of 2.5/2.5 µg two puffs once daily	• Prevents bronchoconstriction • Improves lung function • ↓ exacerbations	• LAMA blocks muscarinic receptors preventing bronchoconstriction • LABA relaxes bronchial smooth muscles	• Olodatero : - QT interval prolongation • Tiotropium : - Pharyngitis - Bronchitis - Headaches
*Brensocatib	10 or 25 mg orally for 24 weeks	• Decreases exacerbation risk • Delayed time to first exacerbation	• Anti-inflammatory • Inhibits DPP1 • Activates neutrophil serine protease	• Periodontal disease • Skin hyperkeratosis
* Currently not approved by FDA[104, 117–122].				

BCOS: Bronchiectasis-COPD Overlap Syndrome; DPP1: dipeptidyl peptidase 1; FDA: food and drug administration; LABA: Long acting beta agonist; LAMA: Long acting muscarinic antagonist; MOA: Mechanism of action; PDE4: Phosphodiesterase 4.

sessions last for 15–20 min, after which the patient is encouraged to cough and huff to expel the loosened mucus from the lungs.[101]

Noninvasive Ventilation

Noninvasive ventilation (NIV) reduces the breathing effort required during acute exacerbations, leading to better partial pressure of carbon dioxide, enhanced lung function, improved quality of life, and lower mortality rates.[102] Notably, a study by Hill et al demonstrated significant benefits for bronchiectasis patients using nighttime NIV along with daily oxygen therapy, resulting in higher FEV1 values and shorter hospital stays.[97]

Although NIV is less commonly needed for bronchiectasis, it remains the standard treatment for COPD patients facing ARF. Indicators of ARF include breathlessness, worsening cough, and arterial blood gas levels below 60 mm Hg or above 45 mm Hg.[103] For administering NIV, an orofacial mask is used to apply inspiratory and expiratory pressures of 8–10 and 4–6 cm H2O, respectively. This setup helps manage the patient's respiratory rate and comfort based on their use of accessory muscles. NIV promotes increased daytime activity, better sleep quality, and improved respiratory health.[103]

DPP1 Inhibitor

Brensocatib, a therapeutic agent currently under study, has demonstrated significant efficacy in managing bronchiectasis in trials by inhibiting the enzyme DPP1, which activates neutrophil serine proteases. In a recent placebo-controlled clinical trial, Brensocatib was evaluated at oral doses of 10 and 25 mg over 24 weeks. The results demonstrated significant reductions in the frequency of exacerbations and hospitalizations among patients with bronchiectasis. Specifically, the 10 mg dose led to a 42% reduction in exacerbations and hospitalizations, while the 25-mg dose resulted in a 38% reduction in risk.[104,105]

The pharmaceutical company Insmed Inc. has announced plans to submit a New Drug Application to the U.S. Food and Drug Administration (FDA) by the end of 2024, with the aim of achieving regulatory approval and market availability by mid-2025. Despite its promising clinical benefits, Brensocatib is not without adverse effects which include periodontal disease, skin hyperkeratosis, and pneumonia, necessitating careful consideration and monitoring during its course.[33]

ICSs

ICSs, such as budesonide and ciclesonide, are essential in the treatment of BCOS, especially those with COPD predominance.[97,106] These medications are often combined with long-acting bronchodilators to effectively reduce the frequency of exacerbations, particularly in patients who continue to experience exacerbations despite bronchodilator therapy and have elevated BEC exceeding 100 cells/μL. The benefit is more pronounced and strongly recommended for patients with higher BEC (exceeding 300 cells/μL).[92] In fact, in a group of patients with BEC >300, the annual exacerbation risk of bronchiectasis was significantly decreased in patients taking ICSs.[107] However, finding the optimal balance between the therapeutic benefits of ICSs and the potential risks, such as increased susceptibility to infections, remains a contentious issue in clinical practice.[108]

ICSs can lead to side effects such as reduced bone density, oral candidiasis, insulin resistance, skin alterations, adrenal suppression, and increased susceptibility to pneumonia and mycobacterial infections by modifying the immune response.[109] For BCOS patients with bronchiectasis predominance, ICSs may not be suitable due to their potential to worsen bacterial colonization and increase the risk of recurrent lower respiratory infections.[85] Research has shown that ICSs can exacerbate the annual rate of exacerbations and hospitalizations in patients with less than 100 eosinophils/μL, a phenomenon not observed in those with eosinophil counts between 101 and 300/μL.[86] There is much disagreement regarding the usefulness of ICS due to their mechanism of inhibiting host-defense mechanisms and have been shown to dramatically increase the risk of bacterial infections such as pseudomonas and mycobacterium causing pneumonia and a higher mortality risk due to infections.[110]

Antibiotics

Antibiotics are essential for treating bacterial infections in BCOS, with treatment duration varying based on individual cases, as longer durations are recommended for bronchiectasis predominance. In comparison, shorter durations are

Table 3. Antibiotics used in BCOS.

Antibiotics used in BCOS				
Medications	Dosage	Advantages	MOA	Adverse effects
Fluoroquinolone: ciprofloxacin	Dual release liposomal ciprofloxacin 150/60 mg 28 days on, 28 days off **OR** Dry powder inhaled ciprofloxacin 32.5 mg twice daily for 28 days	• Reduced sputum bacterial density • Fewer bacterial exacerbations • Well tolerated	• Inhibits DNA gyrase and topoisomerase IV • Prevents supercoiling of bacterial DNA • Prevents DNA replication	**Most common:** • Nausea • Diarrhea • Headache **Rare:** • Neuropathy • Tendon rupture • Convulsions
Polymyxin: colistin	1 million IU twice daily	• Reduces exacerbations • Increases time to first exacerbation	• Cation polypeptides bind phospholipids on cell membrane • Disrupt cell membrane integrity	• Acute kidney failure • Acute respiratory failure (apnea)
Aminoglycoside: gentamicin	80 mg nebulized twice daily	• 30.8% *Pseudomonas* and 92.8% overall eradication in other pathogens • Fewer exacerbations • Increased time to first exacerbation	• Inhibits protein synthesis • Blocks translocation • Misreads mRNA	• Acute kidney failure • Hearing loss • Ataxia
Macrolides: azithromycin OR clarithromycin OR erythromycin	Azithromycin 1750 mg/week median dose for 15 months **OR** Clarithromycin 500 mg daily for 3 months **OR** Erythromycin 125 mg three times per day for 6 months	• Decreased exacerbation/ hospitalization frequency • Decreases neutrophils and neutrophil elastase in sputum • Mitigates neutrophil-mediated lung damage	• Inhibits protein synthesis • Binds to rRNA ribosomal subunit • Blocks translocation	• Upper GI discomfort (Abdominal pain) • Tinnitus • Risk for antibiotic resistance

113, 123–126

BCOS: Bronchiectasis-COPD Overlap Syndrome; MOA: Mechanism of action; IU: International units; mRNA: Messenger ribonucleic acid; rRNA: Ribosomal ribonucleic acid; GI: gastrointestinal.

advised for COPD predominance.[14] Macrolides (eg, azithromycin), fluoroquinolones (eg, ciprofloxacin), polymyxins (eg, colistin), and aminoglycosides (eg, gentamicin) play a crucial role in treating bacteria commonly found in BCOS such as Pseudomonas aeruginosa and Aspergillus fumigatus.[111] Long-term use of macrolides is also recommended for their anti-inflammatory and antimicrobial effects, which can reduce exacerbations of infectious bronchiectasis.[112] A study by Choi et al demonstrated that median weekly doses of azithromycin over 15 months significantly reduced moderate or severe exacerbations compared to COPD patients without bronchiectasis (46.5% vs 87.5%, $P = .005$).[113] BCOS management strategies should prioritize antibiotics, particularly in cases where *P. aeruginosa* infection is identified due to the heightened risks of pneumonia and hospitalizations within this subgroup of COPD patients.[114] Table 3 summarizes common antibiotic therapies that can be used in BCOS.

Mucolytics and Phosphodiesterase Inhibitors

Mucolytics and phosphodiesterase (PDE) inhibitors are crucial in the symptomatic management of patients with BCOS. Mucolytics enhance mucociliary clearance and aid sputum expectoration by modifying the viscoelastic properties of mucus. They achieve this by altering the crosslinks and molecular interactions within mucin polymers, thereby reducing mucus hypersecretion and viscosity, which is essential for managing both stable disease and acute exacerbations.[115] PDE4 inhibitors reduce systemic and airway inflammation, including cough reflex and mucus secretion. They inhibit eosinophilic and neutrophilic inflammation in the airways, effectively reducing COPD exacerbations, particularly in patients with bronchiectasis.[116]

Impact on CV System

COPD is associated with a threefold increased risk of sudden cardiac death, particularly in patients with frequent exacerbations.[127] The relationship between COPD and CVD indicates that COPD significantly raises the risk for 12 different CV conditions, including angina, myocardial infarction, heart failure, sudden cardiac arrest, atrial fibrillation, abdominal aortic aneurysm, peripheral arterial disease, pulmonary arterial hypertension, ischemic stroke, hemorrhagic stroke, and transient ischemic attacks.[128]

A study by Chung et al has revealed that patients diagnosed with BCOS exhibit an 18.2-fold increased risk of developing heart failure compared to those with COPD alone.[13] Among a cohort of 15 802 patients diagnosed solely with COPD, 1034 (6.54%) subsequently developed heart failure. In contrast, within the 3955 BCOS patients, 440 (11.1%) experienced heart failure. This marked difference in prevalence suggests that the heightened inflammatory response characteristic of BCOS significantly elevates the risk of CV complications, particularly heart failure.[13]

The population attributable risk of COPD for mortality related to ischemic heart disease is approximately 30%, independent of smoking. Studies suggest that COPD's risk for CVDs exceeds well-established CVD risk factors such as hypertension and hypercholesterolemia.[129] After a respiratory tract infection, patients with COPD exhibit a 56% increased rate of first CV events within the first 90 days.[130] A significant cause of mortality in COPD patients is ischemic heart disease, with CV mortality rates up to 28%. CVDs account for 20%–25% of deaths in advanced COPD due to left ventricular diastolic dysfunction, which leads to hypoxia, acidosis, ventricular interdependence, lung hyperinflation, and distension.[131]

PH is prevalent in COPD, affecting 33.33% of moderate and 66.66% of severe cases, comparable to other studies with 43% and 68%, respectively.[131] A reliable indicator for pulmonary vascular disease is the PA to aorta ratio, which calculates the main PA to aorta diameter. This ratio is elevated in BCOS, indicating that COPD and bronchiectasis may correlate with PA enlargement.[132] Patients with frequent BCOS exacerbations exhibit higher C-reactive protein levels, worsening arterial stiffness, and elevated troponin levels. There is a strong correlation between the bronchiectasis severity index and cardiac risk markers, even after adjusting for age.[133]

BCOS, being an immunocompromised condition, along with systemic side effects of oral steroids like hyperglycemia, hypertension, and hyperlipidemia, can significantly increase CV complications and lead to a poor prognosis.[19] Initiating long-acting beta-agonists or long-acting muscarinic antagonists in COPD patients has been linked to a 1.5-fold increase in severe CV risk.[134] SABA use is associated with an increased

risk of HDS, hypoxemia, and paradoxical reactions, leading to negative outcomes such as aggravated dyspnea and reduced walking distance.[135]

Conclusion

Individuals with COPD who exhibit preexisting airflow obstruction may overlap with bronchiectasis-associated airway dilation, culminating in a condition termed BCOS. This syndrome predominantly affects older male smokers, who exhibit a heightened incidence of BCOS and are consequently more susceptible to significant pulmonary function decline and parenchymal tissue destruction secondary to recurrent infections and chronic inflammation, thereby indicating a poor clinical prognosis. Exposure to tobacco smoke, reduced endogenous proteins in genetically sensitive individuals, chronic inflammation raising BECs, and notable changes in lung microbiomes can all cause lung injury in BCOS that contributes to airway dilatation and blockage. Inflammatory mediators such as IL-6, IL-8, LT-B4, and ROS are vital in causing chronic bronchial damage and respiratory compromise. Although HRCT remains the gold standard for diagnosing, other tests like PFTs, diffusion scans for carbon monoxide response, and CXR can also be useful in identifying the presence and severity of BCOS. ICSs, antibiotics, PDE4 inhibitors, mucolytics, and a combination of muscarinic antagonists and beta-agonist inhalers are used to treat BCOS. ICSs, antibiotics, PDE4 inhibitors, mucolytics, a combination of muscarinic antagonists and beta-agonist inhalers, and the newly anticipated drug Brensocatib are used to treat BCOS. Other supportive measures include pulmonary rehabilitation, oxygen therapy, lung transplantation, and NIV. The overall prognosis for Bronchiectasis in COPD patients is poor, and the need for early detection along with a strategized treatment plan remains the primary management approach. Even with significant advancements in our understanding of the relationship between bronchiectasis and COPD, poor outcomes like stroke, PH, and ischemic heart disease may still occur. By bridging the knowledge gap on the underlying causes of BCOS and identifying a causative link, we can enhance therapeutic strategies to prevent the onset of cardiopulmonary complications. Future research should prioritize uncovering the pathogenesis and early detection in BCOS patients to improve clinical outcomes.

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Supplemental Material

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