Chronic Respiratory Disease

Subjects: Respiratory System

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Chronic respiratory diseases are major contributors to the global burden of disease. Chronic respiratory diseases are pathologies of the airways and respiratory tract, for example, asthma, chronic obstructive pulmonary disease (COPD), and bronchiectasis.

treatable trait chronic respiratory disease asthma COPD bronchiectasis individualised therapy

1. Introduction

While these approaches are largely effective in chronic-disease control, it is recognised that patients with heterogenous diseases consisting of multiple phenotypes, like asthma, do not respond equally to the same type of treatment and have differing risks of exacerbation and prognosis [1]. Hence, a relatively recent treatment strategy proposed to tackle these limitations is a “treatable traits” approach.

The “treatable traits” approach involves treating specific traits possessed by patients, defined by specific trait markers, which are subsequently targeted by specific therapies. This differs from the current broad, stepwise treatment of the disease entity, such as the Global Initiative for Asthma guidelines, which has been shown to be limited in its ability to predict exacerbations when used by itself [1]. Multidimensional assessment incorporating treatable traits has the potential to improve care and provide more individualised therapy, allowing management principles to be tailored to each patient’s characteristics or traits [2].

2. Treatable Traits in Chronic Respiratory Disease

2.1. Physiological Traits

For physiological treatable traits (**Table 1**), these were studied mostly in the setting of asthma, COPD, and bronchiectasis. These studies described traits including airflow limitation, hypoxemia/hypercapnia, lung hyperinflation, and ciliary dysfunction.

Table 1. Overview of physiological treatable traits.

Condition	Treatable Trait	Trait-Identification Marker	Average Prevalence	Treatment Description and Benefits	Prognostic Implications	Author (Year)
Asthma	Airway limitation	Post-bronchodilator FEV1/FVC < 0.7 FEV1 < 80% predicted	52.5% (45.5–54.5%)	LAMA: ↑ Lung function, exacerbations Bronchial Thermoplasty: ↑ control, ↑ QoL, ↓ exacerbations SABA Short-acting anticholinergics: ↓ risk of admission Magnesium: ↓ odds of admission	Patients with poor PEFR response to salbutamol: ↑ airway obstruction, symptom duration and healthcare utilisation ↑ exacerbation risk	Hiles (2020) [3] Cazzola (2020) [4] Connolly (2018) [5] Simpson (2018) [6] Papaioannou (2018) [7] Hinks (2020) [8] Martin (2020) [1] McDonald (2019) [9]
Asthma	Hypoxemia/hypercapnia	SpO2 < 90% at rest or during 6 min walk test	10.9%	Investigation and implementation of domiciliary oxygen therapy and nasal CPAP	-	Hiles (2020) [3]
Asthma	Lung hyperinflation	>10% reduction in in inspiratory capacity	-	Systemic Corticosteroids: ↓ of dynamic hyperinflation	Dynamic hyperinflation ↑ in placebo group	Meer (2019) [10]
Bronchiectasis	Airway limitation	Low nasal NO, electron microscopic abnormalities, abnormal ciliary beating pattern	-	Inhaled saline, airway clearance, ongoing trial of ENaC inhibition	-	Shteinberg (2020) [11]
Bronchiectasis	Ciliary dysfunction	Elevated sweat chloride, characteristic electrophysiological abnormalities, CFTR mutations on two alleles	-	CFTR modulators	-	Shteinberg (2020) [11]
Chronic airway disease	Airway limitation	FEV1/FVC < 0.7 and FEV1 < 80% predicted	-	LAMA LABA-ICS: Significant functional and	-	Llano (2020) [12]

Condition	Treatable Trait	Trait-Identification Marker	Average Prevalence	Treatment Description and Benefits	Prognostic Implications	Author (Year)
				symptomatic improvement, Pulmonary rehabilitation		
COPD	Airway limitation	Post-bronchodilator FER < 70% and FEV1 < 80% predicted	88.9%	LAMA, LABA-ICS, Pulmonary rehabilitation	-	Hiles (2020) [3] Llano (2020) [12]
COPD	Hypoxemia/hypercapnia	PO2/PCO2	38.9%	Oxygen, NIV	Marker of poor prognosis	Llano (2020) [12] Gonçalves (2018) [13] Hiles (2020) [3]
COPD	Lung hyperinflation	[5][3][6] RV > 175% predicted or RV/TLC ≥ 0.38 [3]	-	Endobronchial valves, coils: ↑ in lung function, ↓ dyspnoea, ↑ QoL, ↑ exercise tolerance, ↓ residual volume lung volume reduction surgery Bronchoscopic thermal vapour ablation: ↑ lung function and QoL in upper lobe prominent emphysema [1]	- [1] [4][8][7]	Dijk (2020) [14]

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PD. The tudies [5] cted, the , leading f airflow n shown rt-acting n LAMA, long-acting beta-agonists (LABA), inhaled corticosteroids (ICS), and pulmonary rehabilitation have been proposed to treat airflow limitation in COPD [3][12]. Airflow limitation was also described in bronchiectasis, with inhaled saline and airway clearance being the suggested treatment and with an ongoing trial on epithelial sodium channel inhibition [11].

Lung hyperinflation was also a trait targeted in the management of COPD patients, with endobronchial valves and bronchoscopic thermal vapour ablation showing improved lung function and quality of life [14].

Abbreviations: BMI, body mass index; CFTR, cystic fibrosis transmembrane conductance regulator; CPAP, continuous positive airway pressure; COPD, chronic obstructive pulmonary disease; EnaC, epithelial sodium channel; FER, forced expiratory ratio; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; ICS, inhaled corticosteroids; LABA, long-acting beta 2-agonists; LAMA, long-acting muscarinic antagonists; NIV, non-invasive ventilation; NO, nitric oxide; PCO2, partial pressure of carbon dioxide; PEFR, peak expiratory flow rate; QoL, quality of life; PO2, partial pressure of oxygen; RV, residual volume; SABA, short-acting beta-agonists; SpO2, peripheral capillary oxygen saturation; TLC, total lung capacity; ↑, increased/improved; ↓, decreased/reduced.

2.2. Biochemical Traits

Type-2 inflammation is widely documented as a treatable trait in chronic airway diseases like asthma and COPD (**Table 2**), with a prevalence of 42.0% in asthma patients [6]. Type-2 inflammation is characterised by T2-high expression, such as IL-13 induced genes or high eosinophil count. Chung et al. [15] reported that asthma patients with type-2 inflammation were predisposed to corticosteroid insensitivity and may be dependent on oral corticosteroids in severe cases. Treatment options include bronchodilators containing inhaled corticosteroids (ICS), which have been shown to be effective for asthma. ICS-LABA and ICS-LABA-LAMA combinations have similarly been effective for patients with COPD [12]. Anti-T2 biologics have also been shown to significantly reduce the risk of severe asthma exacerbation and improve lung function and quality of life of patients [15].

Table 2. Overview of biochemical treatable traits.

Condition	Treatable Trait	Trait-Identification Marker	Prevalence (Range)	Treatment Description	Prognostic Implications	Author (Year)
Asthma	Eosinophilia	Blood/Sputum Eosinophilia	54.3% (51.4–56.4%)	Corticosteroids: ↑ FEV1 Omalizumab: Significant ↓ in exacerbations and ↑ in CARAT and AQLQ. FEV1 ↑, RV ↓, mean BE ↓ Mepolizumab/Anti IL-5 Anti IL4/IL -13: High FeNO responds to anti-IL4/IL13 therapies	Associated with severe asthma, frequent exacerbations, ↓ lung function at baseline	Chung (2019) [15] Connolly (2018) [5] Dean (2017) [16] Feng (2019) [17] Santos (2018) [18] Pavord (2020) [19] Llano (2019) [20] Papaioannou (2018) [7] Hiles (2020) [3] Hinks (2020) [8]
Asthma	FeNO	FeNO levels	-	FeNO-guided ICS treatment: Improved symptoms, ↑ asthma control, ↓ exacerbations, ↑ QoL		Dean (2017) [16] Honkoop (2019) [21] Kuo (2019) [22]
Asthma	Neutrophil elastase/inflammation; CXCR2R2	Sputum neutrophilis ≥ 61%	36.5% (27.3–40%)	Macrolides: ↓ exacerbation. May result in antibiotic resistance Smoking cessation: ↓ of neutrophilic inflammation, lung-function improvement in asthmatics	↑ exacerbation risk	Connolly (2018) [5] Dean (2017) [16] Simpson (2018) [6] Papaioannou (2018) [7] Hiles (2020) [3] Hinks (2020) [8] McDonald (2019) [9]
Asthma	Paucigranulocytic phenotype	Neutrophil levels <61% and eosinophil levels <2%	-	Macrolides, bronchodilators,	↑ risk of moderate-severe acute	Papaioannou (2018) [7]

Condition	Treatable Trait	Trait-Identification Marker	Prevalence (Range)	Treatment Description	Prognostic Implications	Author (Year)
				bronchial thermoplasty	exacerbations, ↑ all-cause mortality. Higher airflow limitation and dyspnoea present in these patients.	
Asthma	Proteins (periostin, galectin-3)	Sputum galectin-3	-	Anti-IgE therapy (omalizumab)	-	Dean (2017) [16]
Asthma	Type 2 inflammation	T2-high expression	42.0%	Salbutamol: Improved bronchodilator response Anti-T2 biologics: Major ↓ in severe exacerbations, small improvement in FEV1, improvement in asthma QoL scores	Corticosteroid insensitivity and oral corticosteroid dependence in severe patients	Chung (2019) [15] Simpson (2018) [6]
Bronchiectasis	Eosinophilia	IL-5, IL-13 and Gro-α in sputum	-	ICS, Bronchodilators, macrolides: Treatment showed little difference in clinical parameters between groups	-	Shteinburg (2020) [11] Shoemark (2019) [23]
Bronchiectasis	Neutrophil elastase/inflammation; CXCR2R2	Sputum neutrophils	-	Neutrophil elastase inhibitor: Significant ↑ in FEV1 and QoL. CXCR2 antagonist: ↓ sputum neutrophils, no difference in exacerbations. Macrolides Corticosteroids	↑ frequency of exacerbations and more rapid decline in FEV1 in some patients. Disease severity worse with ↑ BSI score, sputum volume, and ↓ predicted FEV1%	Chalmers (2018) [24] Shoemark (2019) [23]

Condition	Treatable Trait	Trait-Identification Marker	Prevalence (Range)	Treatment Description	Prognostic Implications	Author (Year)
Chronic airway disease	FeNO	Exhaled CO	-	Primary prevention	↑ acute exacerbations + major public health problem.	McDonald (2019) [25]
Chronic airway disease	T2-low inflammation	Eosinophil <100	-	Azithromycin, roflumilast, LABA-LAMA	-	Llano (2020) [12]
Chronic airway disease	Type 2 inflammation	Sputum/blood eosinophilia	-	ICS-LABA, ICS-LABA-LAMA, biologics	-	Llano (2020) [12] McDonald (2019) [25]
COPD	Eosinophilia	Sputum/blood eosinophilia	60.1% (22.2–60.1%)	Corticosteroids: Beneficial during exacerbations for patients with eosinophilia Anti-IL5	↑ number of moderate exacerbations, risk of future exacerbations. Exacerbations characterised by enhanced airway eosinophilic inflammation; generally milder, with ↓ mortality and ↓ hospital stay.	Garudadri (2018) [26] Gonçalves (2018) [13] Soriano (2018) [27] Müllerová (2018) [28] Müllerová (2018) [29] Hiles (2020) [3] Mathioudakis (2020) [30] Matsunaga (2020) [31] Matthes (2018) [32]
COPD	Neutrophil elastase/inflammation; CXCR2R2	Sputum neutrophils > 61%	44.4%	Macrolides	-	Hiles (2020) [3]
COPD	Proteins (periostin, galectin-3)	Specific marker	[3][32][28] -	Specific therapy	-	Llano (2020) [12]
COPD	T2-low inflammation	Eosinophil < 100	[17] -	Azithromycin, Roflumilast, LABA-LAMA	-	Llano (2020) [12]
COPD	Type 2 Inflammation	Eosinophil > 300/>100 if on OCS	-	ICS-LABA, ICS-LABA-LAMA, Biologics	-	Llano (2020) [12]

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been reported to reduce exacerbations in COPD [32]. Specifically for asthma, omalizumab has been shown to significantly reduce both eosinophilia and exacerbations, with improved lung function and quality of life [18].

Neutrophil-related inflammation was also prominent in patients with asthma, bronchiectasis, and COPD, and it is identified by high sputum neutrophil counts [3]. It was associated with increased exacerbation risk for each of the above conditions [9], and high sputum neutrophil counts predicted more rapid decline in FEV1 in patients with bronchiectasis. Macrolides were shown to reduce exacerbations in asthma and COPD, while smoking cessation was additionally recommended for asthma patients. Neutrophil elastase inhibitors were also shown to improve lung function and quality of life for patients with bronchiectasis [24].

Condition	Treatable Trait	Trait-Identification Marker	Prevalence (Range)	Treatment Description	Prognostic Implications	Author (Year)
[34] COPD	Vitamin D	Serum 25-hydroxycholecalciferol levels	-	Vitamin D supplementation: ↓ risk of respiratory tract infection.	VDD was associated with ↓ FEV1 at baseline and faster decline in FEV1	Llano (2020) [12]
Rhinitis/rhinosinusitis	Airway/nasal inflammation	Nasal cytology; nasal polyps biopsy	-	Corticosteroids, biologicals	-	Heffler (2019) [33]
United Airways Dz	Eosinophilia	Blood/sputum eosinophilia, blood periostin, high FeNO, absent specific IgE, non- reactive skin prick tests	-	Corticosteroids, anti-IL-5, IL-4, IL-13, anti-TSLP, CRTH2 antagonist	-	Yii (2018) [34]
United Airways Dz	Environmental	Total IgE, skin prick tests Peak flow monitoring Specific		Exposure avoidance, respiratory		Yii (2018) [34]

Condition	Treatable Trait	Trait-Identification Marker	Prevalence (Range)	Treatment Description	Prognostic Implications	Author (Year)
Asthma	Adherence and technique	Adherence check Adherence rating scales	44.0% (26.9–61.8%)	Self-management education and WAP Treatment changed when possible to minimise devices Inhaler technique skills Self-management education with adherence-aiding strategies	Inhaler-device polypharmacy is one of the best predictors of exacerbation risk ↑ exacerbation risk	Connolly (2018) [5] Simpson (2018) [6] Hiles (2020) [3] McDonald (2019) [9]
Asthma	Smoking/ex-smoker	Medical history of smoking or exhaled CO ≥ 10 ppm	14.3% (13.9–14.5%)	Counseling and NRT or varenicline, bupropion	-	Connolly (2018) [5] Simpson (2018) [6] Hiles (2020) [3] Milne (2020) [35]
Chronic airway disease	Adherence and technique	Adherence check Adherence rating scales	-	Understanding reason for non-adherence, directing education of adherence-	Suboptimal inhaler technique and inhaler device polypharmacy associated with ↑	Llano (2020) [12] McDonald (2019) [25]

Condition	Treatable Trait	Trait-Identification Marker	Prevalence (Range)	Treatment Description	Prognostic Implications	Author (Year)
				aiding strategies accordingly: Good adherence associated with ↓ severe exacerbations of asthma and COPD	healthcare utilisation	
Chronic airway disease	Smoking/ex-smoker	Medical history of smoking or exhaled CO ≥ 10 ppm	-	Counseling and NRT or varenicline, bupropion: Cessation ↓ lung function decline and future risk of exacerbations	Smoking is a risk factor for exacerbation	Llano (2020) [12] McDonald (2019) [25]
Chronic Airway Disease	Social issues	Interview	-	Activate support services	Poor family and social support and deprived socioeconomic status associated with ↑ symptom deterioration and exacerbation	McDonald (2019) [25]
COPD	Adherence and technique	Does not possess a WAP or does not use WAP during exacerbations Test of adherence to inhalers	55.6%	Self-management education and WAP Treatment changed when possible to minimise devices Inhaler technique skills Self-management education with adherence-aiding strategies	-	Hiles (2020) [3] Llano (2020) [12]
COPD	Smoking/ex-smoker	Medical history of smoking or [3]	19.4%	Counseling and NRT or	-	Hiles (2020) [3]

14.3% in f exhaled carbon monoxide and was shown to be a significant risk factor for exacerbation in chronic airway diseases [25]. Smoking cessation was shown to reduce lung-function decline and risk of recurrent exacerbations, highlighting the importance of opportunistic implementation of smoking cessation strategies during acute exacerbations [25].

Condition	Treatable Trait	Trait-Identification Marker [3][25][12]	Prevalence (Range)	Treatment Description	Prognostic Implications	Author (Year)
		exhaled CO ≥ 10 ppm		varenicline, bupropion		Llano (2020) [12]

t therapy, increased symptomatic deterioration and exacerbations, with social support services proposed as a possible treatment option [25].

Abbreviations: CO, carbon monoxide; COPD, chronic obstructive pulmonary disease; NRT, nicotine replacement therapy; WAP, written action plan; ↑, increased/improved; ↓, decreased/reduced.

2.4. Microbiological Traits

Microbiological treatable traits were mostly found in asthma, bronchiectasis, COPD, and united (combined upper and lower) airway diseases. The most prevalent trait was chronic respiratory infection in both asthma and COPD, with an average prevalence of 45.0% and a prevalence range of 34.8–47.3% among the studies on asthma [3][36][6]. Various treatment options, such as antibiotics, mucolytics, roflumilast, education, and inhaled interferon-β treatment, were suggested [1][5][3]. However, evidence was lacking regarding their efficacy. In patients with COPD, chronic respiratory infection was present in 55.6% of the patients [3], with prognostic implications on their quality of life and dyspnoea severity [31]. Macrolides have been shown to decrease hospital admissions resulting from exacerbations, but their usage must be balanced against the risk of colonisation with macrolide-resistant organisms [31].

Another prominent microbiological trait is microbial colonisation, present in an average of 18.9% of asthmatics, with a range varying from 12.7 to 55.6% [5][3]. Microbial colonisation was present in an average of 44.8% of COPD patients, with prevalence ranging from 38.9 to 45% [3][30]. This is a separate trait from infection, as colonisation refers to the presence of organisms, while infection refers to the presence of signs and symptoms due to these organisms. Microbial colonisation nonetheless had prognostic significance, demonstrated particularly in COPD patients, with implications on quality of life and increment in dyspnoea [30]. Treatment options for this trait in patients with asthma include education and antibiotic-based written action plans (e.g., using macrolides) [3][8]. However, information regarding treatment options for this trait was inadequate in COPD. Interestingly, patients with microbial colonisation had lower mortality for exacerbations associated with viral infections compared to bacterial infections, though the clinical significance of this is uncertain [30].

2.5. Comorbidity Traits

Impaired physical function is a comorbidity seen in almost all chronic respiratory conditions, with a prevalence of 36.1% in COPD and 10.9% in asthma [3]. Impaired physical function can present in different forms, such as low appendicular skeletal muscle mass, limitations in mobility, and low muscle strength and has been shown to be an independent predictor of hospital admission and mortality in COPD. Patients with lower 6 min walking distance were also reported to have higher readmission risk [25]. Various management measures targeted at physical function can be implemented. For instance, Hiles et al. [3] recommended a high-protein diet, strength training, and regular pulmonary rehabilitation for patients with low appendicular skeletal muscle mass.

Another prevalent comorbidity trait is the presence of psychiatric conditions, particularly depression and anxiety in asthma and COPD. Treatments included counselling, cognitive behavioural therapy, and paroxetine [3][31].

Nutrition (underweight) is another common comorbidity, with a prevalence of 52.8% in COPD [3] and 38.1% in asthma, with a range of 35.1–58.2% [3]. These traits had similar prognostic implications, with decreased quality of life, increased severity of symptoms, and increased exacerbations [31][9][7][37]. Treatments to normalise body mass index, such as supplementation and weight loss, have also been shown to decrease asthma severity [7]. However, treatment benefits for COPD were not described in the literature.

Some of the other comorbidity traits with high prevalence include systemic inflammation, which was present in 56.4% of asthmatics and 63.9% of COPD patients, and sleep disorders, with a prevalence of 60.0% and 30.6% in patients with asthma and COPD, respectively [3]. For the mitigation of systemic inflammation, McDonald et al. showed that statin therapy improved C-reactive protein levels in COPD patients [2]. Separately, positive airway pressure has been shown to reduce overall mortality and exacerbation risk in COPD patients with sleep disorders, though its efficacy may be limited by patient adherence [31].

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