Centre of Excellence- Treatable Traits

TREATABLE TRAITS LITERATURE SUMMARY

March- September 2021

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Search Strategy

Literature was reviewed between March 2021 and September 2021. Search Terms were:

“Treatable Traits AND asthma”
“Treatable Traits AND COPD”
“Treatable Traits AND bronchiectasis”
“Treatable Traits AND airways disease”

Acknowledgements

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Asthma and COPD

1. Agusti, A., et al. (2021). "Moving towards a Treatable Traits model of care for the management of obstructive airways diseases." Respir Med 187: 106572.

Abstract- Asthma and chronic obstructive pulmonary disease (COPD) are two prevalent chronic airways diseases. Both are complex and heterogeneous. Traditionally, clinical guidelines have advocated a stepwise approach to pharmacotherapy of asthma and COPD, but there is increasing realization that both require a more personalized and precise management approach. To this end, a management strategy based on the so-called Treatable Traits has been proposed. Emerging evidence suggests that this model improves relevant outcomes in patients with chronic airway diseases but further research is needed to guide implementation. This review discusses the challenges, opportunities, and hurdles that its implementation will have to face.

https://pubmed.ncbi.nlm.nih.gov/34478992/

Summary- This review shows that there is an increasing realisation in that personalised management is required in airway disease. The Treatable Traits strategy improves relevant outcomes in patients, but further research is needed into its implementation.

2. Blasi, F., et al. (2021). "Clinical Evolution and Quality of Life in Clinically Based COPD Chronic Bronchitic and Emphysematous Phenotypes: Results from the 1-Year Follow-Up of the STORICO Italian Observational Study." Int J Chron Obstruct Pulmon Dis **16**: 2133-2148.

Abstract- INTRODUCTION: Understanding clinical evolution of chronic obstructive pulmonary disease (COPD) is crucial for improving disease management. MATERIALS AND METHODS: STORICO (NCT03105999), an Italian, multicenter, non-interventional, observational study conducted in 40 pulmonology centers, aimed to describe the 1-year clinical evolution and health status of clinicallbased phenotypes. Baseline and follow-up data of COPD subjects with a chronic bronchitis (CB) or emphysema (EM) phenotype were collected. The frequency of COPD symptoms during the 24 hours (gathered via the night-time, morning and day-time symptoms of COPD questionnaire) and the anxiety and depression levels (via the HADS Scale) were recorded at each visit. RESULTS: A total of 261 CB and 159 EM patients were analyzed. CB patients with ≥1 night-time symptom seemed

to be more frequent (51.7%, 41.8% and 41.4% at baseline, 6-month and 12-month follow-up, respectively) than EM (37.7%, 32.1% and 30.2% at study visits) even if no statistical differences were observed at time points between phenotypes (chi-square test p-values presence/absence of night-time symptoms in CB vs EM at study visits >0.0007). In the first 6 months, the frequency of patients with ≥1 night-time symptom decreased of 9.9% in CB and of 5.6% in EM. A clinically relevant decline of DLCO % predicted over 1 year in EM was observed, the mean (SD) being 61.5 (20.8) % at baseline and 59.1 (17.4) % at 12-month follow-up. EM had higher levels of anxiety and depression than CB (median (25th-75th percentile) HADS total score in CB: 7.0 (4.0-13.0) and 7.0 (3.0-12.0), in EM: 9.0 (3.0-14.0) and 9.5 (3.0-14.0) both at baseline and at 6-month follow-up, respectively), considering 1.17 as minimally clinical important difference (MCID) for the total score. CONCLUSION: EM patients, evaluated in a real-world setting, seem to suffer from a worse clinical condition and health status compared to CB patients, appearing to have "more treatable" traits

https://pubmed.ncbi.nlm.nih.gov/34345170/

Summary- This study identifies that emphysema patients have a worse clinical condition and health status compared to chronic bronchitis. This helps identify treatable traits for the different COPD phenotypes, e.g. the emphysema group had a higher anxiety and depression symptoms when compared to chronic bronchitis.

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3. Couillard, S., et al. (2021). "How I Do It: Workup of Severe Asthma." Chest.

Abstract- A 56-year-old man has difficult-to-control asthma and a history of four exacerbations in the prior 12 months despite high-dose inhaled corticosteroids (ICS) and additional controller therapies. Is he suitable for more advanced therapeutic options? We review the clinical assessment of a patient with suspected severe asthma and discuss factors contributing to poor asthma control and how biomarkers assist in disease investigation and stratification. The key components of our multidisciplinary approach are to confirm an asthma diagnosis and adherence to treatment, to assess any contributing comorbidities or confounding factors, and to stratify what type of asthma the patient has. The combination of spirometry and repeated measures of key biomarkers of type 2 airway inflammation-the blood eosinophil count and fractional exhaled nitric oxide-identifies whether poor disease control is driven by uncontrolled, ICS-resistant type 2 airway inflammation or ongoing airflow obstruction. A failure to

elicit evidence of either suggests an alternative driver for the patient's symptoms, including chronic airway infection and non-asthma causes. Each phenotype represents a treatable trait that requires a specific targeted approach. Critically, steroids can cause harm, and their use should be guided by objective evidence of inflammation rather than symptoms alone. After assessment of treatment adherence and exclusion of relevant comorbidities, the patient was found to have severe asthma with ICS-resistant type 2 airway inflammation. We consider additional treatment options at our next appointment (Part 2/2 of this How I Do It series).

https://pubmed.ncbi.nlm.nih.gov/34265308/

Summary- This case study identifies a real-life assessment of treatable traits in a patient with difficult to control asthma. The paper proposes multidisciplinary team involvement, and a standard pathway for patients who are referred to a specialist airways clinic.

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4. Gibson, P. G., et al. (2021). "Asthma and Comorbid Conditions-Pulmonary Comorbidity." J Allergy Clin Immunol Pract.

Abstract- Pulmonary comorbidities can increase disease severity and health care costs associated with asthma management. Vocal cord dysfunction/inducible laryngeal obstruction is a common comorbidity that results from intermittent laryngeal obstruction. Patients describe distinct episodes of dyspnea that do not respond to bronchodilators. Inspiratory stridor is common. The gold standard diagnostic testing strategy is continuous laryngoscopy performed during exercise or irritant challenges. Dysfunctional breathing (DB) is an overarching term that describes conditions with a chronic change in the pattern of breathing that results in pulmonary and extrapulmonary symptoms. The prevalence of DB in asthma is up to 30%, and breathing retraining can improve symptoms and quality of life in people with DB and asthma. Asthma-chronic obstructive pulmonary disease overlap (ACO) refers to both asthmatics who develop fixed airflow obstruction after a history of exposure to smoke or biomass and patients with chronic obstructive pulmonary disease who have "asthmatic features" such as a large bronchodilator response, elevated levels of serum IgE, or peripheral eosinophil counts ≥300 per μL. Triple inhaler therapy with inhaled corticosteroid/long-acting beta-agonist/long-acting muscarinic should be considered in people with ACO and severe symptoms or frequent exacerbations. The clinical expression of bronchiectasis involves persistent mucus hypersecretion, recurrent exacerbations of infective bronchitis, incompletely reversible airflow obstruction, and lung fibrosis

and can occur in up to 30% of adults with longstanding asthma. The treatable traits strategy is a useful model of care to manage the complexity and heterogeneity of asthma with pulmonary comorbidity.

https://pubmed.ncbi.nlm.nih.gov/34492401/

Summary- This review looks at several comorbid pulmonary conditions and how they can influence asthma e.g., vocal cord dysfunction, dysfunctional breathing, COPD and bronchiectasis. Targeted treatment e.g., breath training for dysfunctional breathing may improve patient outcomes.

5. Heaney, L. G., et al. (2021). "Eosinophilic and Noneosinophilic Asthma: An Expert Consensus Framework to Characterize Phenotypes in a Global Real-Life Severe Asthma Cohort." Chest **160**(3): 814-830.

Abstract- BACKGROUND: Phenotypic characteristics of patients with eosinophilic and noneosinophilic asthma are not well characterized in global, real-life severe asthma cohorts. RESEARCH QUESTION: What is the prevalence of eosinophilic and noneosinophilic phenotypes in the population with severe asthma, and can these phenotypes be differentiated by clinical and biomarker variables? STUDY DESIGN AND METHODS: This was an historical registry study. Adult patients with severe asthma and available blood eosinophil count (BEC) from 11 countries enrolled in the International Severe Asthma Registry (January 1, 2015-September 30, 2019) were categorized according to likelihood of eosinophilic phenotype using a predefined gradient eosinophilic algorithm based on highest BEC, long-term oral corticosteroid use, elevated fractional exhaled nitric oxide, nasal polyps, and adult-onset asthma. Demographic and clinical characteristics were defined at baseline (ie, 1 year before or closest to date of BEC). RESULTS: One thousand seven hundred sixteen patients with prospective data were included; 83.8% were identified as most likely (grade 3), 8.3% were identified as likely (grade 2), and 6.3% identified as least likely (grade 1) to have an eosinophilic phenotype, and 1.6% of patients showed a noneosinophilic phenotype (grade 0). Eosinophilic phenotype patients (ie, grades 2 or 3) showed later asthma onset (29.1 years vs 6.7 years; P < .001) and worse lung function (postbronchodilator % predicted FEV(1), 76.1% vs 89.3%; P = .027) than those with a noneosinophilic phenotype. Patients with noneosinophilic phenotypes were more likely to be women (81.5% vs 62.9%; P = .047), to have eczema (20.8% vs 8.5%; P = .003), and to use anti-IgE (32.1% vs 13.4%; P = .004) and leukotriene receptor antagonists (50.0% vs 28.0%; P = .011) add-on therapy. INTERPRETATION: According to this multicomponent, consensus-driven, and evidence-based eosinophil gradient

algorithm (using variables readily accessible in real life), the severe asthma eosinophilic phenotype was more prevalent than previously identified and was phenotypically distinct. This pragmatic gradient algorithm uses variables readily accessible in primary and specialist care, addressing inherent issues of phenotype heterogeneity and phenotype instability. Identification of treatable traits across phenotypes should improve therapeutic precision.

https://pubmed.ncbi.nlm.nih.gov/33887242/

Summary- This study identifies that in the severe asthma population the eosinophilic phenotype was more prevalent (89.9%) than the noneosinophilic phenotype (10.1%). This prevalence is greater than what has been previously identified. The study also identified distinct eosinophilic and noneosinophilic severe asthma patterns based on a combination of clinical and biomarker variables e.g., age, time of asthma onset, IgE. This information helps physicians identify the type of asthma a patient has and its treatable traits. This should improve therapeutic precision.

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6. Hiles, SA et al., (2021). "Treatable Traits That Predict Health Status and Treatment Response in Airway Disease" J Allergy Clin Immunol Pract **9**(3): 1255-1264e2.

Abstract- Background: A strategy based on the assessment and management of treatable traits (TTs) has been proposed as a new paradigm in airway disease. There is a potentially long list of TTs with likely different clinical impact.
Objective: To identify TTs most strongly associated with poorer health-related quality of life (HRQOL) and treatments that most substantially improved HRQOL.
Methods: We pooled data from 2 parallel-group clinical trials of multidimensional assessment and individualized management targeted to TTs versus usual care in patients with chronic obstructive pulmonary disease or severe asthma (intervention N = 45; control N = 46). Following multidimensional assessment, 22 TTs were identified and the intervention group received treatments tailored to their identified TT. We used Bayesian Model Averaging to examine associations between TTs and HRQOL (St George's Respiratory Questionnaire) at baseline, as well as between each TT treatment and the observed change in HRQOL postintervention.

Results: TTs most substantially associated with poorer baseline HRQOL were frequent chest infections, breathing pattern disorder, inadequate inhaler technique, systemic inflammation (C-reactive protein >3 mg/L), and depression. In both trials, TT treatment led to a large, significant improvement in HRQOL compared with usual care (Cohen's d = 1.19; P < .001). Receiving a statin for

systemic inflammation and oral corticosteroid for eosinophilic airway inflammation was associated with the largest HRQOL improvements. Treatments for exercise intolerance, anxiety, and obesity were associated with smaller improvements in HRQOL.
Conclusions: This study contributes to identifying clinically impactful TTs by showing that TTs across pulmonary, extrapulmonary, and behavioral domains were associated with HRQOL impairment and treatment response.

https://doi.org/10.1016/j.jaip.2020.09.046

Summary- This study uses Bayesian Model Averaging to examine associations between treatable traits and health related quality of life as well as the association between each treatable trait treatment and change in health related quality of life post treatment. Traits that are associated with poor health related quality of life at baseline are frequent chest infections, breathing pattern disorder, inadequate inhaler technique, systemic inflammation and depression. Receiving treatment for systematic inflammation, eosinophilic airway inflammation, exercise intolerance, anxiety and obesity were associated with improvements in health related quality of life. This study provides starting point for a broader understanding around identifying the impact of individual treatable traits and their associated treatments.

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7. Hew, M. and E. Denton (2021). "Prioritizing Treatable Traits in Airways Disease." J Allergy Clin Immunol Pract **9**(3): 1265-1266.

https://pubmed.ncbi.nlm.nih.gov/33685609/

Summary- This editorial discusses the logistics of the Treatable Traits approach including proposed solutions. Hew and Denton discuss the paper by Hiles et a, who identify high yield traits. “With the exception of statins for systemic inflammation, most of the traits and treatments identified in this analysis are ready to be applied to or, regarding eosinophilic inflammation, modified for clinical practice.” The editorial concludes that this analysis is a welcome addition to the Treatable Traits approach however many remaining questions require larger, additional studies.

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8. Hizawa, N., et al. (2021). "A Prospective Cohort Study to Assess Obstructive Respiratory Disease Phenotypes and Endotypes in Japan: The TRAIT Study Design." Int J Chron Obstruct Pulmon Dis **16**: 1813-1822.

Abstract- BACKGROUND: Asthma, chronic obstructive pulmonary disease (COPD), and asthma-COPD overlap (ACO) are complex and heterogeneous diseases that share clinical characteristics (phenotypes) and molecular mechanisms (endotypes). Whilst physicians make clinical decisions on diagnostic groups, for some such as ACO there is no commonly accepted criteria. An alternative approach is to evaluate phenotypes and endotypes that are considered to respond well to a specific type of treatment ("treatable traits") rather than diagnostic labels. PURPOSE: The prospective, longitudinal, and observational TRAIT study will evaluate disease characteristics, including both phenotypes and endotypes, in relation to the presentation of obstructive respiratory disease characteristics in patients diagnosed with asthma, COPD, or ACO in Japan, with the aim of further understanding the clinical benefit of a treatable traits-based approach. PATIENTS AND METHODS: A total of 1500 participants will be enrolled into three cohorts according to their treating physician's diagnosis of asthma, COPD, or ACO at screening. Part 1 of the study will involve cross-sectional phenotyping and endotyping at study enrolment. Part 2 of the study will evaluate the progression of clinical characteristics, biomarker profiles, and treatment over a 3-year follow-up period. The follow-up will involve three annual study visits and three telephone calls scheduled at 6-month intervals. A substudy involving 50 participants from the asthma cohort (in which the ratio will be approximately 1:1 including 25 participants with a smoking history of ≥10 pack-years and 25 participants with no smoking history), 100 participants from the ACO cohort, and 100 participants from the COPD cohort will evaluate disease phenotypes using inspiratory and expiratory computed tomography scans. CONCLUSION: TRAIT will describe clinical characteristics of patients with obstructive respiratory diseases to better understand potential differences and similarities between clinical diagnoses, which will support the improvement of personalized treatment strategies.

https://pubmed.ncbi.nlm.nih.gov/34168442/

Summary- This study protocol aims to describe the clinical characteristics of patients with obstructive respiratory diseases so that we can understand the potential differences and similarities between clinical diagnoses of asthma, chronic obstructive pulmonary disease (COPD), and asthma-COPD overlap (ACO).

This will help provide evidence to evaluate the clinical benefit of a treatable traits-based approach in these groups.

9. Jacobsen, P. A., et al. (2021). "Characteristics and treatable traits of patients with chronic obstructive pulmonary disease (COPD) with and without paid employment." Respir Res **22**(1): 147.

Abstract- INTRODUCTION: Patients with COPD are vulnerable to workforce detachment. Better knowledge of features associated with paid work loss might be of help to design and select appropriate interventions. METHOD: This cross-sectional study aimed to explore the presence of treatable traits in COPD patients without paid work. Patients with COPD below 65 years at first referral to a hospital-based patient clinic were included. Using binary logistic regression analysis, the relationship between paid work and the following characteristics was explored: low daily physical activity, exercise, active smoking, Medical Research Council dyspnea scale (MRC), poor nutritional status, exacerbations, and fatigue (checklist individual strength (CIS)). Variables were adjusted for age, sex, forced expiratory volume in 1 s (FEV 1), and education level. RESULTS: In total, 191 patients (47.3%) were without paid work. The following treatable traits were related to not being in paid work: < 5000 steps/day (OR 2.36, 95% CI (1.52-3.68)), MRC ≥ 3 (OR 1.78, 95%CI (1.14-2.77)), CIS ≥ 36 points (OR 1.78, 95% CI (1.10-2.87)), six-minute walk distance (6MWD) < 70% of predicted (OR 2.62, 95% CI (1.69-4.06)), and ≥ 2 exacerbations per year (OR 1.80, 95% CI (1.12-2.92)). Significant differences were also seen in age (OR 1.06, 95% CI (1.02-1.10) per year), FEV 1% predicted (OR 0.98, 95% CI (0.97-1.00) per % predicted increase), and medium/high education level (OR 0.62, 95% CI (0.41-0.93)). When adjusting for all variables the only treatable trait that remained significant was 6MWD. CONCLUSION: Patients without paid work are more likely to have treatable traits with 6MWD revealing the most significant association.

https://pubmed.ncbi.nlm.nih.gov/33980226/

Summary- This study explored the presence of treatable traits in COPD patients without paid work. The treatable traits associated with not being in paid work included <5000 steps per day, MRC ≥ 3, checklist individual strength (CIS) ≥ 36 points, six-minute walk distance (6MWD) < 70% of predicted, ≥ 2 exacerbations per year, age, FEV1 % predicted and medium/high education level. Once all variables were adjusted the 6MWT remained significant.

10. Leong, P. and P. G. Bardin (2021). "The untreated treatable trait: Cardiovascular disease in COPD exacerbations." Respirology 26(5): 413-415.

https://pubmed.ncbi.nlm.nih.gov/33751741/

Summary- This commentary identifies that there is evidence that cardiovascular disease is a key treatable trait in COPD and is underdiagnosed and undertreated.

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11. Meteran, H., et al. (2021). "Treatment Response Biomarkers in Asthma and COPD." Diagnostics (Basel) **11**(9).

Abstract- Chronic obstructive pulmonary disease (COPD) and asthma are two of the most common chronic diseases worldwide. Both diseases are heterogenous and complex, and despite their similarities, they differ in terms of pathophysiological and immunological mechanisms. Mounting evidence supports the presence of several phenotypes with various responses to treatment. A systematic and thorough assessment concerning the diagnosis of both asthma and COPD is crucial to the clinical management of the disease. The identification of different biomarkers can facilitate targeted treatment and monitoring. Thanks to the presence of numerous immunological studies, our understanding of asthma phenotypes and mechanisms of disease has increased markedly in the last decade, and several treatments with monoclonal antibodies are available. There are compelling data that link eosinophilia with an increased risk of COPD exacerbations but a greater treatment response and lower all-cause mortality. Eosinophilia can be considered as a treatable trait, and the initiation of inhaled corticosteroid in COPD patients with eosinophilia is supported in many studies. In spite of advances in our understanding of both asthma and COPD in terms pathophysiology, disease mechanisms, biomarkers, and response to treatment, many uncertainties in the management of obstructive airways exist.

https://pubmed.ncbi.nlm.nih.gov/34574009/

Summary- This review identifies the importance of biomarkers in both asthma and COPD. Type 2 asthma is the most well described endotype but our understanding of non type 2 is increasing and if specific biomarkers can be identified it is possible better treatment options may be available for this group. Eosinophilia is a valuable

biomarker in some COPD patients but to date the benefits of monoclonal antibody therapies have not been overwhelming. The study suggests further research into biomarkers so that we can identify patients that may benefit from such treatments.

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12. Miravitlles, M., et al. (2021). "Spanish COPD Guidelines (GesEPOC) 2021: Updated Pharmacological treatment of stable COPD." Arch Bronconeumol (Engl Ed).

Abstract- The Spanish COPD Guidelines (GesEPOC) were first published in 2012, and since then have undergone a series of updates incorporating new evidence on the diagnosis and treatment of COPD. GesEPOC was drawn up in partnership with scientific societies involved in the treatment of COPD and the Spanish Patients' Forum. Their recommendations are based on an evaluation of the evidence using GRADE methodology, and a narrative description of the evidence in areas in which GRADE cannot be applied. In this article, we summarize the recommendations on the pharmacological treatment of stable COPD based on 9 PICO questions. COPD treatment is a 4-step process: 1) diagnosis, 2) determination of the risk level, 3) initial and subsequent inhaled therapy, and 4) identification and management of treatable traits. For the selection of inhaled therapy, high-risk patients are divided into 3 phenotypes: non-exacerbator, eosinophilic exacerbator, and non-eosinophilic exacerbator. Some treatable traits are general and should be investigated in all patients, such as smoking or inhalation technique, while others affect severe patients in particular, such as chronic hypoxemia and chronic bronchial infection. COPD treatment is based on long-acting bronchodilators with single agents or in combination, depending on the patient's risk level. Eosinophilic exacerbators must receive inhaled corticosteroids, while non-eosinophilic exacerbators require a more detailed evaluation to choose the best therapeutic option. The new GesEPOC also includes recommendations on the withdrawal of inhaled corticosteroids and on indications for alpha-1 antitrypsin treatment. GesEPOC offers a more individualized approach to COPD treatment tailored according to the clinical characteristics of patients and their level of complexity.

https://pubmed.ncbi.nlm.nih.gov/33840553/

Summary – The Spanish COPD guidelines describe COPD treatment as a 4-step process. 1) diagnosis, 2) determination of the risk level, 3) initial and subsequent inhaled therapy, and 4) identification and management of treatable traits. The guidelines suggest some treatable traits are general and should be investigated in all patients e.g., smoking and inhaler technique

while others affect severe patients e.g. hypoxemia. The guidelines offer an individualised approach to COPD.

13. Morissette, M., et al. (2021). "Asthma COPD overlap: Insights into cellular and molecular mechanisms." Mol Aspects Med: 101021.

Abstract- Although there is still no consensus on the definition of Asthma-COPD Overlap (ACO), it is generally accepted that some patients with airway disease have features of both asthma and COPD. Just as its constituents, ACO consists of different phenotypes, possibly depending on the predominance of the underlying asthma or COPD-associated pathophysiological mechanisms. The clinical picture is influenced by the development of airway inflammatory processes either eosinophilic, neutrophilic or mixed, in addition to glandular changes leading to mucus hypersecretion and a variety of other airway structural changes. Although animal models have exposed how smoking-related changes can interact with those observed in asthma, much remains to be known about their interactions in humans and the additional modulating effects of environmental exposures. There is currently no solid evidence to establish the optimal treatment of ACO but it should understandably include an avoidance of environmental triggers such as smoking and relevant allergens. The recognition and targeting of "treatable traits" following phenotyping is a pragmatic approach to select the optimal pharmacological treatment for ACO, although an association of inhaled corticosteroids and bronchodilators is always required in these patients. This association acts both as an anti-inflammatory treatment for the asthma component and as a functional antagonist for the airway remodeling features. Research should be promoted on well phenotyped subgroups of ACO patients to determine their optimal management.

https://pubmed.ncbi.nlm.nih.gov/34521557/

Summary – This review identifies that there is no solid evidence to establish optimal treatment in ACO. It should include the avoidance of environmental triggers but the recognition of targeting treatable traits after phenotyping is a realistic approach in these patients.

Pham, J., et al. (2021). "Is ethnicity a 'treatable trait' in asthma?" Respirology **26**(6): 529-531.

https://pubmed.ncbi.nlm.nih.gov/33843109/

Summary- Commentary: Asthma is a global health problem, however certain ethnic groups experience poorer outcomes compared to others and research into ethnic minorities is limited. There is growing evidence that phenotypes and treatment responses vary between different ethnic populations. Understanding the cultural and genetic factors that influence asthma would help clinicians predict the clinical course of disease and treatment response. Further research into vulnerable ethnic groups is needed.

14. Sarwar, M. R., et al. (2021). "Treatable traits in an English cohort: prevalence and predictors of future decline in lung function and quality of life in COPD." ERJ Open Res **7**(2).

Abstract- BACKGROUND: "Treatable traits (TTs)" is a precision medicine approach for facilitating multidimensional assessment of every patient with chronic airway disease, in order to determine the core traits associated with disease outcomes where targeted treatments may be applied. OBJECTIVES: To determine the prevalence of TTs in chronic obstructive pulmonary disease (COPD) and which traits predict future decline in lung function and quality of life (QoL). METHODS: A 4-year longitudinal evaluation was conducted using data from 3726 participants in the English Longitudinal Study of Ageing (ELSA). TTs were identified based on published recommendations. Traits that predicted decline in lung function and QoL were analysed using generalised estimating equations. RESULTS: Overall, 21 TTs, including pulmonary (n=5), extra-pulmonary (n=13) and behavioural/lifestyle risk-factors (n=3) were identified. In multivariate analyses, the traits of chronic bronchitis (β -0.186, 95% CI -0.290 to -0.082), breathlessness (β -0.093, 95% CI -0.164 to -0.022), underweight (β -0.216, 95% CI -0.373 to -0.058), sarcopenia (β -0.162, 95% CI -0.262 to -0.061) and current smoking (β -0.228, 95% CI -0.304 to -0.153) predicted decline in forced expiratory volume in 1 s (FEV(1)). Of the seven traits that predicted decline in QoL, depression (β -7.19, 95% CI -8.81 to -5.57) and poor family and social support (β -5.12, 95% CI -6.65 to -3.59) were the strongest. CONCLUSION: The core TTs of COPD associated with a decline in lung function and QoL were identified. Targeting these impactful traits with individualised treatment using a precision medicine approach may improve outcomes in people with COPD.

https://pubmed.ncbi.nlm.nih.gov/34511973/

Summary – This study identifies the core treatable traits associated with a decline in lung function and quality of life in COPD. The treatable traits that predicted a decline in lung function (FEV1) were chronic bronchitis, breathlessness, underweight, sarcopenia and current smoking. The treatable traits that predicted a decline in quality of life were depression and poor family and social support. Targeting these traits may benefit patients with COPD.

15. Soler-Cataluña, J. J., et al. (2021). "Spanish COPD Guidelines (GesEPOC) 2021 Update Diagnosis and Treatment af COPD Exacerbation Syndrome." Arch Bronconeumol.

Abstract- This article details the GesEPOC 2021 recommendations on the diagnosis and treatment of COPD exacerbation syndrome (CES). The guidelines propose a definition-based syndromic approach, a new classification of severity, and the recognition of different treatable traits (TT), representing a new step toward personalized medicine. The evidence is evaluated using GRADE methodology, with the incorporation of 6 new PICO questions. The diagnostic process comprises four stages: 1) establish a diagnosis of CES, 2) assess the severity of the episode, 3) identify the trigger, and 4) address TTs. This diagnostic process differentiates an outpatient approach, that recommends the inclusion of a basic battery of tests, from a more comprehensive hospital approach, that includes the study of different biomarkers and imaging tests. Bronchodilator treatment for immediate relief of symptoms is considered essential for all patients, while the use of antibiotics, systemic corticosteroids, oxygen therapy, and assisted ventilation and the treatment of comorbidities will vary depending on severity and possible TTs. The use of antibiotics will be indicated particularly if sputum color changes, when ventilatory assistance is required, in cases involving pneumonia, and in patients with elevated C-reactive protein (≥ 20 mg/L). Systemic corticosteroids are recommended in CES that requires admission and are suggested in moderate CES. These drugs are more effective in patients with blood eosinophil counts ≥ 300 cells/mm(3). Acute-phase non-invasive mechanical ventilation is specified primarily for patients with CES who develop respiratory acidosis despite initial treatment.

https://pubmed.ncbi.nlm.nih.gov/34172340/

Summary- This article discusses the Spanish COPD guidelines. They propose a definition based syndromic approach, a new classification of severity and the recognition of different Treatable Traits.

16. Sverrild, A., et al. (2021). "Airway Hyperresponsiveness to Inhaled Mannitol Identifies a Cluster of Noneosinophilic Asthma Patients with High Symptom Burden." J Allergy Clin Immunol Pract.

Abstract- BACKGROUND: Patients with asthma are heterogeneous in clinical presentation and in response to treatment. Despite this, tools to guide treatment are limited and include mainly measures of eosinophilic inflammation and symptoms. Airway hyperresponsiveness (AHR) to mannitol is present in patients across inflammatory phenotypes and improve with inhaled corticosteroids. OBJECTIVE: To investigate whether measuring AHR to mannitol in addition to eosinophilic inflammation and symptoms adds information to the phenotypic characterization of patients with asthma. METHODS: A total of 317 patients with asthma from 6 different cohorts were included in the analysis. All patients had measures of AHR to mannitol, blood eosinophils, and Asthma Control Questionnaire 5 available. A cluster analysis using Ward minimum variance method was performed. The distribution of fraction of exhaled nitric oxide, immunoglobulin E, lung function, induced sputum inflammatory cell count, age of onset, and severity of disease was compared between clusters. RESULTS: Four clusters were identified. Three of the clusters had proportionate levels of AHR, eosinophilic inflammation, and symptoms, but 1 cluster presented with low levels of eosinophilic inflammation and a significant symptom burden. Half of the subjects in this cluster presented with AHR to inhaled mannitol. Lung function, fraction of exhaled nitric oxide, body mass index, and immunoglobulin E were normal. CONCLUSIONS: Information on AHR to mannitol in addition to blood eosinophils and symptoms identifies a subgroup of asthma patients with symptomatic, noneosinophilic disease. Airway hyperresponsiveness to mannitol may provide a treatable trait in a subgroup of patients with noneosinophilic asthma.

https://pubmed.ncbi.nlm.nih.gov/34332175/

Summary- This study identifies that airway hyper responsiveness in response to mannitol, in addition with blood eosinophils and asthma symptoms identifies a subgroup of asthma patient with

non-eosinophilic disease. Airway hyperresponsiveness to mannitol may be a useful Treatable Trait in this group.

17. van Dijk, M., et al. (2021). "[COPD: working with treatable traits]." Ned Tijdschr Geneeskd **165**.

Abstract- COPD is the third most common chronic disease in the Netherlands and the number of patients is still rising. This article reviews causes of COPD, assesses the role of spirometry in diagnosing COPD, and considers ways to differentiate between COPD and heart failure, which can be difficult due to overlapping symptoms. To avoid a 'one size fits all' treatment, we elaborate on treatable traits - patient characteristics leading to specific treatment options- in order to optimize treatment for each individual patient. This applies both during stable disease and during exacerbations.

https://pubmed.ncbi.nlm.nih.gov/34346592/

Summary- This article discusses different ways to differentiate between COPD and heart failure, using a Treatable Traits approach.

18. Wang, G. and V. M. McDonald (2021). "Contemporary Concise Review 2020: Asthma." Respirology 26(8): 804-811.

Abstract- Bushfires and coronavirus 2019 (COVID-19) were dominate features of 2020. Patients with asthma were significantly affected by the 2019/2020 bushfire season with an increased burden compared to the general population. Patients with controlled asthma do not appear to be at higher risk of severe COVID-19 infection or death than the general population. Personalized medicine is proposed as the next era for asthma management, with treatable traits as a strategy to implement personalized medicine into practice. Patient engagement in personalized medicine strategies is important and needs to be further explored. Oral corticosteroid (OCS) use in asthma is common and contributes a major burden. OCS stewardship is recommended. Biologic therapies reduce exacerbations of severe asthma and biomarkers can be used to predict treatment responders. Epithelia at mucosal and cutaneous surfaces are components in asthma pathogenesis, through airway immunity and inflammation. Dysregulation of resident microbial communities in the lung, gut and skin microbiome is relevant to asthma pathogenesis, but there are still many unknowns in this field.

https://pubmed.ncbi.nlm.nih.gov/34164877/

Summary- This review looks at the 2020 asthma literature and highlights advances, identifies ongoing gaps in knowledge and provides an opportunity to reflect on the year that was.

19. Wu, W. W., et al. (2021). "Treatable Traits in Elderly Asthmatics from the Australasian Severe Asthma Network: A Prospective Cohort Study." J Allergy Clin Immunol Pract **9**(7): 2770-2782.

Abstract- BACKGROUND: Data on treatable traits (TTs) in different populations are limited. OBJECTIVE: To assess TTs in elderly patients with asthma and compare them to younger patients, to evaluate the association of TTs with future exacerbations, and to develop an exacerbation prediction model. METHODS: We consecutively recruited 521 participants at West China Hospital, Sichuan University based on the Australasian Severe Asthma Network, classified as elderly (n = 62) and nonelderly (n = 459). Participants underwent a multidimensional assessment to characterize the TTs and were then followed up for 12 months. TTs and their relationship with future exacerbations were described. Based on the TTs and asthma control levels, an exacerbation prediction model was developed, and the overall performance was externally validated in an independent cohort. RESULTS: A total of 38 TTs were assessed. Elderly patients with asthma had more chronic metabolic diseases, fixed airflow limitation, emphysema, and neutrophilic inflammation, whereas nonelderly patients with asthma exhibited more allergic characteristics and psychiatric diseases. Nine traits were associated with increased future exacerbations, of which exacerbation prone, upper respiratory infection-induced asthma attack, cardiovascular disease, diabetes, and depression were the strongest. A model including exacerbation prone, psychiatric disease, cardiovascular disease, upper respiratory infection-induced asthma attack, noneosinophilic inflammation, cachexia, food allergy, and asthma control was developed to predict exacerbation risk and showed good performance. CONCLUSIONS: TTs can be systematically assessed in elderly patients with asthma, some of which are associated with future exacerbations, proving their clinical utility of evaluating them. A model based on TTs can be used to predict exacerbation risk in people with asthma.

https://pubmed.ncbi.nlm.nih.gov/33831621/

Summary- This study looks at elderly patients with asthma and found 9 traits were associated with increased future exacerbation

in this group. These included upper respiratory tract induced asthma-attack, cardiovascular disease, diabetes and depression. This shows the Treatable Traits approach may be useful in this age group.

Paediatric Severe Asthma

1. Ramphul, M., et al. (2021). "Precision Medicine for Paediatric Severe Asthma: Current Status and Future Direction." J Asthma Allergy **14**: 525-538.

Asthma is a heterogeneous disease, characterised by different phenotypes and endotypes. Precision medicine in asthma refers to the implementation of a targeted therapy for each individual child, based on the identification of treatable traits, including environmental, immunological and genetic factors. Severe asthma in children is associated with increased hospitalisation rates, a lower quality of life, increased healthcare costs and an increased mortality. In the era of new molecular biologics treatments, it is essential to improve deep phenotyping of children with severe asthma in order to deliver the most effective treatment to each individual child. In this review, we discuss the personalised approach to the assessment and management of severe asthma. We explore the indications and use of the currently licensed biologics, as well as the potential of other emerging treatments.

https://pubmed.ncbi.nlm.nih.gov/34045872/

Summary-This study discusses the importance of the Treatable Traits approach in children with severe asthma. This would need to consider minimally invasive or non-invasive tests and the recruitment of more children to phase 3 trials.

Bronchiectasis

1. Amati, F., et al. (2021). "Diagnosis and Initial Investigation of Bronchiectasis." Semin Respir Crit Care Med **42**(4): 513-524.

Abstract- Bronchiectasis refers to both the name of a disease and a single radiological appearance that may, or may not, be associated with disease. As chronic respiratory disease, bronchiectasis is characterized by a variable range of signs and symptoms that may overlap with other chronic respiratory conditions. The proper identification of bronchiectasis as a disease in both primary and secondary care is of paramount importance. However, a standardized definition of radiologically and clinically significant bronchiectasis is still missing. Disease heterogeneity is a hallmark of bronchiectasis and applies not only to radiological features and clinical manifestations but also to other aspects of the disease, including the etiological and microbiological diagnosis as well as the evaluation of pulmonary function. Although the guidelines suggest a "minimum bundle" of tests, the diagnostic approach to bronchiectasis is challenging and may be driven by the "treatable traits" approach based on endotypes and biological characteristics. A broad spectrum of diagnostic tests could be used to investigate the etiology of bronchiectasis as well as other pulmonary, extrapulmonary, and environmental traits. Individualizing bronchiectasis workup according to the site of care (e.g., primary, secondary, and tertiary care) could help optimize patients' management and reduce healthcare costs.

https://pubmed.ncbi.nlm.nih.gov/34261176/

Summary-This study demonstrates that the Treatable Traits approach may be useful in investigating aetiology, pulmonary, extrapulmonary and environment traits in bronchiectasis. This could help patients and reduce healthcare costs.

2. Detailleur, S., et al. (2021). "The Deteriorating Patient: Therapies Including Lung Transplantation." Semin Respir Crit Care Med **42**(4): 623-638.

Abstract- In this review paper, we discuss the characteristics that define severe bronchiectasis and which may lead to deterioration of noncystic fibrosis bronchiectasis. These characteristics were used to establish the current severity scores: bronchiectasis severity index (BSI), FACED, and E-FACED (exacerbation frequency, forced expiratory volume in 1 second, age, colonization, extension and dyspnea score). They can be used to predict mortality, exacerbation rate, hospital

admission, and quality of life. Furthermore, there are different treatable traits that contribute to severe bronchiectasis and clinical deterioration. When present, they can be a target of the treatment to stabilize bronchiectasis.One of the first steps in treatment management of bronchiectasis is evaluation of compliance to already prescribed therapy. Several factors can contribute to treatment adherence, but to date no real interventions have been published to ameliorate this phenomenon. In the second step, treatment in deteriorating patients with bronchiectasis should be guided by the predominant symptoms, for example, cough, sputum, difficulty expectoration, exacerbation rate, or physical impairment. In the third step, we evaluate treatable traits that could influence disease severity in the deteriorating patient. Finally, in patients who are difficult to treat despite maximum medical treatment, eligibility for surgery (when disease is localized), should be considered. In case of end-stage disease, the evaluation for lung transplantation should be performed. Noninvasive ventilation can serve as a bridge to lung transplantation in patients with respiratory failure.

https://pubmed.ncbi.nlm.nih.gov/34261186/

Summary- This review identifies that there are treatable traits that can contribute to severe bronchiectasis and clinical deterioration. When such traits are present, they can be the target of treatment to help stabilise bronchiectasis.

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3. Keir, H. R. and J. D. Chalmers (2021). "Pathophysiology of Bronchiectasis." Semin Respir Crit Care Med **42**(4): 499-512.

Abstract- Bronchiectasis is a complex, heterogeneous disorder defined by both a radiological abnormality of permanent bronchial dilatation and a clinical syndrome. There are multiple underlying causes including severe infections, mycobacterial disease, autoimmune conditions, hypersensitivity disorders, and genetic conditions. The pathophysiology of disease is understood in terms of interdependent concepts of chronic infection, inflammation, impaired mucociliary clearance, and structural lung damage. Neutrophilic inflammation is characteristic of the disease, with elevated levels of harmful proteases such as neutrophil elastase associated with worse outcomes. Recent data show that neutrophil extracellular trap formation may be the key mechanism leading to protease release and severe bronchiectasis. Despite the dominant of neutrophilic disease, eosinophilic subtypes are recognized and may require specific treatments. Neutrophilic inflammation is associated with elevated bacterial loads and chronic infection with organisms such as Pseudomonas aeruginosa. Loss of diversity of the normal lung microbiota and dominance of proteobacteria such as

Pseudomonas and Haemophilus are features of severe bronchiectasis and link to poor outcomes. Ciliary dysfunction is also a key feature, exemplified by the rare genetic syndrome of primary ciliary dyskinesia. Mucus symptoms arise through goblet cell hyperplasia and metaplasia and reduced ciliary function through dyskinesia and loss of ciliated cells. The contribution of chronic inflammation, infection, and mucus obstruction leads to progressive structural lung damage. The heterogeneity of the disease is the most challenging aspect of management. An understanding of the pathophysiology of disease and their biomarkers can help to guide personalized medicine approaches utilizing the concept of "treatable traits."

https://pubmed.ncbi.nlm.nih.gov/34261175/

Summary – This study identifies that an understanding of the pathophysiology and biomarkers of bronchiectasis may help guide personalised medicine using the Treatable Traits approach.

4. José, R. J. and M. R. Loebinger (2021). "Clinical and Radiological Phenotypes and Endotypes." Semin Respir Crit Care Med 42(4): 549-555.

Abstract- Bronchiectasis is a heterogenous disease with multiple etiologies and associated comorbidities. As bronchiectasis is a complex disease, it is unsound to think of it as a single disease particularly when the differing etiologies are likely to be driving bronchiectasis through initial divergent molecular pathways, known as endotypes, that phenotypically present as the same disease due to protracted airway inflammation, but revealing potential differing underlying mechanisms that may have disparity of drug responses. Improved understanding of the cellular immune, inflammatory, and microbiological milieu associated with clinical and radiological features of bronchiectasis has resulted in the recognition of important endotypes and phenotypes that will allow for personalized treatments to improve quality of life and outcomes of patients with bronchiectasis. Here we discuss clinical and radiological phenotypes, as well as emerging molecular endotypes that are possible treatable traits in bronchiectasis.

https://pubmed.ncbi.nlm.nih.gov/34261179/

Summary- This article highlights the complexity of bronchiectasis and discusses the endotypes, clinical and radiological phenotypes and outlines potential treatable traits.

Pharmacological approaches

1. Calzetta, L., et al. (2021). "The Impact of Monoclonal Antibodies on Airway Smooth Muscle Contractility in Asthma: A Systematic Review." Biomedicines **9**(9).

Abstract- Airway hyperresponsiveness (AHR) represents a central pathophysiological hallmark of asthma, with airway smooth muscle (ASM) being the effector tissue implicated in the onset of AHR. ASM also exerts pro-inflammatory and immunomodulatory actions, by secreting a wide range of cytokines and chemokines. In asthma pathogenesis, the overexpression of several type 2 inflammatory mediators including IgE, IL-4, IL-5, IL-13, and TSLP has been associated with ASM hyperreactivity, all of which can be targeted by humanized monoclonal antibodies (mAbs). Therefore, the aim of this review was to systematically assess evidence across the literature on mAbs for the treatment of asthma with respect to their impact on the ASM contractile tone. Omalizumab, mepolizumab, benralizumab, dupilumab, and tezepelumab were found to be effective in modulating the contractility of the ASM and preventing the AHR, but no available studies concerning the impact of reslizumab on the ASM were identified from the literature search. Omalizumab, dupilumab, and tezepelumab can directly modulate the ASM in asthma, by specifically blocking the interaction between IgE, IL-4, and TSLP, and their receptors are located on the surface of ASM cells. Conversely, mepolizumab and benralizumab have prevalently indirect impacts against AHR by targeting eosinophils and other immunomodulatory effector cells promoting inflammatory processes. AHR has been suggested as the main treatable trait towards precision medicine in patients suffering from eosinophilic asthma, therefore, well-designed head-to-head trials are needed to compare the efficacy of those mAbs that directly target ASM contractility specifically against the AHR in severe asthma, namely omalizumab, dupilumab, and tezepelumab.

https://pubmed.ncbi.nlm.nih.gov/34572466/

Summary- This systematic review suggests that further studies are needed to compare the efficacy of monoclonal antibody therapies that directly target airway smooth muscle contractability against airway hyperresponsiveness. Airway hyperresponsiveness has been suggested as the main treatable trait in patients with eosinophilic asthma.

2. Cazzola, M., et al. (2021). "Step-up and step-down approaches in the treatment of asthma." Expert Rev Respir Med **15**(9): 1159-1168.

Abstract- Introduction: Significant intraindividual and temporal variability in symptom control is a feature of asthma that requires careful monitoring and the need to periodically review and adjust therapy. Both NHLBI/NAEPP and GINA offer helpful algorithms for a stepping approach to asthma.Areas covered: The problems arisen in applying the stepwise approach to the treatment of asthma proposed by NHLBI/NAEPP and GINA algorithms and their possible alternatives.Expert opinion: The current therapeutic stepping approach to asthma, which takes into account lung function, symptoms and quality of life, is certainly useful, but it does not consider the underlying mechanisms. Furthermore, patient's overestimation or underestimation of the severity of the disease and differences in the opinions on the level of asthma control required between patients and physicians and also between physicians in both primary care and specialist settings are common and may negatively affect asthma control and future risks. A reassessment of the conventional stepping approach to management of asthma is now needed. A pragmatic approach that sets therapeutic goals for each individual and associates them with the treatable traits of asthma which, when therapeutically targeted, will in many cases help to achieve the goals, seems more reasonable than the present stepping approach.

https://pubmed.ncbi.nlm.nih.gov/34032534/

Summary – This review discusses the importance of a therapeutic approach to asthma management. Both NHLBI/NAEPP and GINA offer helpful algorithms for a stepped approach to treatment however due to symptom variability (day to day, seasonally) a patient's drug treatment should be reviewed and adjusted periodically.

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3. Gibson, P. G., et al. (2021). "Mepolizumab improves clinical outcomes in patients with severe asthma and comorbid conditions." Respir Res **22**(1): 171.

Abstract- BACKGROUND: Comorbidities can complicate the management of severe asthma; therefore, the presence of comorbid conditions or traits often need to be considered when considering treatment options for patients with severe asthma. The aim of this analysis is to investigate the efficacy of mepolizumab in patients with severe eosinophilic asthma and comorbidities. METHODS: This was a post hoc analysis (GSK ID:209140) of data from the Phase IIb/III studies DREAM, MENSA, SIRIUS, and MUSCA. Patients aged ≥ 12 years with severe eosinophilic

asthma were randomized to: mepolizumab 750, 250, or 75 mg intravenously or placebo (DREAM); mepolizumab 75 mg intravenously or 100 mg subcutaneously or placebo (MENSA); or mepolizumab 100 mg subcutaneously or placebo (SIRIUS and MUSCA) every 4 weeks for 24 weeks in SIRIUS and MUSCA, 32 weeks in MENSA or 52 weeks in DREAM. In this analysis the primary endpoint was the annual rate of clinically significant exacerbations; secondary endpoints were Asthma Control Questionnaire-5 score, St George's Respiratory Questionnaire total score, and pre-bronchodilator forced expiratory volume in 1 s at study end. Subgroups were based on comorbidities at baseline. RESULTS: Overall, 1878 patients received placebo (n = 689) or mepolizumab (n = 1189). Across all comorbidity subgroups mepolizumab reduced the rate of clinically significant exacerbations by 44-68% versus placebo, improved Asthma Control Questionnaire-5 score by 0.27-0.59 points, and improved St George's Respiratory Questionnaire total score by 5.0-11.6 points. Pre-bronchodilator forced expiratory volume in 1 s was improved by 27.1-286.9 mL in all but one comorbidity subgroup, the diabetes mellitus subgroup. CONCLUSIONS: Mepolizumab reduces exacerbations, and improves asthma control, health-related quality of life, and lung function in patients with severe eosinophilic asthma despite comorbid conditions, including upper respiratory conditions, psychopathologies, cardiovascular conditions, gastroesophageal reflux disease, diabetes mellitus, and obesity. TRIAL REGISTRATION: https://clinicaltrials.gov/ DREAM, MEA112997/NCT01000506; MENSA, MEA115588/NCT01691521; SIRIUS, MEA115575/NCT01842607; MUSCA, 200862/NCT02281318.

https://pubmed.ncbi.nlm.nih.gov/34098955/

Summary- This study investigated the efficacy of mepolizumab in patients with severe eosinophilic asthma and comorbidities. Mepolizumab reduced exacerbations, improved asthma control, health-related quality of life, and lung function despite comorbid conditions e.g., CVD. This shows that mepolizumab is clinically beneficial as a targeted treatment to reduce disease burden in this population.

4. Rupani, H., et al. (2021). "Recent Insights into the Management of Inflammation in Asthma." J Inflamm Res **14**: 4371-4397.

Abstract- The present prevailing inflammatory paradigm in asthma is of T2-high inflammation orchestrated by key inflammatory cells like Type 2 helper lymphocytes, innate lymphoid cells group 2 and associated cytokines. Eosinophils

are key components of this T2 inflammatory pathway and have become key therapeutic targets. Real-world evidence on the predominant T2-high nature of severe asthma is emerging. Various inflammatory biomarkers have been adopted in clinical practice to aid asthma characterization including airway measures such as bronchoscopic biopsy and lavage, induced sputum analysis, and fractional exhaled nitric oxide. Blood measures like eosinophil counts have also gained widespread usage and multicomponent algorithms combining different parameters are now appearing. There is also growing interest in potential future biomarkers including exhaled volatile organic compounds, micro RNAs and urinary biomarkers. Additionally, there is a growing realisation that asthma is a heterogeneous state with numerous phenotypes and associated treatable traits. These may show particular inflammatory patterns and merit-specific management approaches that could improve asthma patient outcomes. Inhaled corticosteroids (ICS) remain the mainstay of asthma management but their use earlier in the course of disease is being advocated. Recent evidence suggests potential roles for ICS in combination with long-acting beta-agonists (LABA) for as needed use in mild asthma whilst maintenance and reliever therapy regimes have gained widespread acceptance. Other anti-inflammatory strategies including ultra-fine particle ICS, leukotriene receptor antagonists and macrolide antibiotics may show efficacy in particular phenotypes too. Monoclonal antibody biologic therapies have recently entered clinical practice with significant impacts on asthma outcomes. Understanding of the efficacy and use of those agents is becoming clearer with a growing body of real-world evidence as is their potential applicability to other treatable comorbid traits. In conclusion, the evolving understanding of T2 driven inflammation alongside a treatable traits disease model is enhancing therapeutic approaches to address inflammation in asthma.

https://pubmed.ncbi.nlm.nih.gov/34511973/

Summary- This study looks at the novel therapeutic approaches in asthma. Conventional asthma treatment is effective however recognising treatable traits and using biomarkers to identify inflammatory phenotypes helps personal treatment. mAbs have seen benefits for many patients however current mAbs fail to prevent all exacerbations. This identifies the need to treat other traits ad explore other inflammatory pathways.

Non-pharmacological management

1. Cecins, E., et al. (2021). "Feasibility, tolerance and effects of adding impact loading exercise to pulmonary rehabilitation in people with chronic obstructive pulmonary disease: study protocol for a pilot randomised controlled trial." Pilot Feasibility Stud **7**(1): 151.

Abstract- BACKGROUND: Chronic obstructive pulmonary disease (COPD) is a disorder linked with a multitude of extra pulmonary manifestations (also known as treatable traits), including low bone mineral density (BMD). To date, no specific guidelines exist for the management of BMD in this population. Impact loading exercise has been identified as an intervention that improves or maintains BMD in other populations. However, the feasibility of and tolerance to impact loading exercise has not been tested in people with COPD. The aim of the proposed study will be to investigate the feasibility and tolerance of adding impact loading exercise to a standard pulmonary rehabilitation programme (PRP) in people with COPD and report its effects on bone health, balance and falls risk. METHODS: This is a protocol for a pilot feasibility and tolerance randomised controlled trial (RCT). Fifty-eight people with COPD will be randomly allocated, on a 1:1 ratio, to either the experimental or control group. Initially, participants in both groups will complete a standard 8-week (twice-weekly) PRP followed by a 32-week period of maintenance exercises. Over the initial 8-week period, participants allocated to the experimental group will also undertake targeted lower limb resistance exercises and commence a programme of impact loading exercises (e.g. bounding and drop jumps). On completion of the initial 8-week PRP, in addition to the standard maintenance exercises, participants in the experimental group will continue with home-based impact loading exercises, four times a week, for the extra 32 weeks. The primary outcome of this study is feasibility of and tolerance to impact loading exercises. Feasibility will be measured using data collected pertaining to recruitment, withdrawal and completion. Adherence to the exercises will be collected using exercise logs. Tolerance to the exercises will be determined using outcomes to assess pain, recording any adverse effects such as a fall and feedback from the participants in semi-structured interviews on completing of the trial. The effects of the 40-week experimental intervention on bone health, balance and falls risk will be reported. DISCUSSION: This pilot RCT will test the feasibility and tolerance of an intervention that has never been trialed in people with COPD. It will also provide initial information regarding the size of the effect this intervention has on outcomes such as BMD, balance and falls risk. These data will be critical when designing a definitive RCT to advance this area of research. TRIAL REGISTRATION: Australian and New Zealand Clinical Trials Registry (ANZCTR): 12620001085965 (20/10/2020).

https://pubmed.ncbi.nlm.nih.gov/34344482/

Summary- This feasibility study is yet to be completed however may provide novel information regarding the non-pharmacological management bone mineral density in COPD. The study will investigate whether impact loading exercise is feasible and well-tolerated by this population when added to a standard pulmonary rehabilitation program.

2. Urban, M. H., et al. (2021). "Effects of Dynamic Hyperinflation on Left Ventricular Diastolic Function in Healthy Subjects - A Randomized Controlled Crossover Trial." Front Med (Lausanne) **8**: 659108.

Abstract- Objective: Diastolic dysfunction of the left ventricle is common in patients with chronic obstructive pulmonary disease (COPD). Dynamic hyperinflation has been suggested as a key determinant of reduced diastolic function in COPD. We aimed to investigate the effects of induced dynamic hyperinflation on left ventricular diastolic function in healthy subjects to exclude other confounding mechanisms associated with COPD. Design: In this randomized controlled crossover trial (NCT03500822, https://www.clinicaltrials.gov/), we induced dynamic hyperinflation using the validated method of expiratory resistance breathing (ERB), which combines tachypnea with expiratory resistance, and compared the results to those of tachypnea alone. Healthy male subjects (n = 14) were randomly assigned to the ERB or control group with subsequent crossover. Mild, moderate, and severe hyperinflation (i.e., ERB1, ERB2, ERB3) were confirmed by intrinsic positive end-expiratory pressure (PEEP(i)) using an esophageal balloon catheter. The effects on diastolic function of the left ventricle were measured by transthoracic echocardiographic assessment of the heart rate-adjusted transmitral E/A-ratio and E/e'-ratio. Results: We randomly assigned seven participants to the ERB group and seven to the control group (age 26 [24-26] vs. 24 [24-34], p = 0.81). Severe hyperinflation decreased the E/A-ratio compared to the control condition (1.63 [1.49-1.77] vs. 1.85 [0.95-2.75], p = 0.039), and moderate and severe ERB significantly increased the septal E/e'-ratio. No changes in diastolic function were found during mild hyperinflation. PEEPi levels during ERB were inversely correlated with the E/A ratio (regression coefficient = -0.007, p = 0.001). Conclusions: Our data indicate dynamic hyperinflation as a determinant of left ventricular diastolic dysfunction in healthy subjects. Therapeutic reduction of hyperinflation might be a treatable trait to improve diastolic function in patients with COPD.

https://pubmed.ncbi.nlm.nih.gov/34017848/

Summary- This study identifies that a therapeutic reduction in hyperventilation might be a TT to improve diastolic function in COPD.