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Comorbid ‘treatable traits’ in difficult asthma: Current evidence and clinical evaluation

Short title: Comorbid ‘treatable traits’ in difficult asthma

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ABSTRACT

The care of patients with difficult-to-control asthma ('difficult asthma') is challenging and costly. Despite high-intensity asthma treatment, these patients experience poor asthma control and face the greatest risk for asthma morbidity and mortality. Poor asthma control is often driven by severe asthma biology, which has appropriately been the focus of intense research and phenotype-driven therapies. However, it is increasingly apparent that extra-pulmonary comorbidities also contribute substantially to poor asthma control and a heightened disease burden. These comorbidities have been proposed as "treatable traits" in chronic airways disease, adding impetus to their evaluation and management in difficult asthma.

In this review, eight major asthma-related comorbidities are discussed; rhinitis, chronic rhinosinusitis, gastroesophageal reflux, obstructive sleep apnoea, vocal cord dysfunction, obesity, dysfunctional breathing, and anxiety/depression. We describe the prevalence, impact, and treatment-effects of these comorbidities in the difficult asthma population, emphasizing gaps in the current literature. We examine the associations between individual comorbidities, and highlight the potential for comorbidity clusters to exert combined effects on asthma outcomes. We conclude by outlining a pragmatic clinical approach to assess comorbidities in difficult asthma.

INTRODUCTION

Patients whose asthma remains difficult-to-control despite high intensity treatment have the greatest risk of asthma morbidity and mortality.(1, 2) Although patients with difficult-to-control asthma may have biologically severe disease, other factors are often at play. Severe asthma guidelines emphasise confirming the diagnosis of asthma, and addressing contributory factors and comorbidities, before phenotyping the pattern of inflammation.(3) Such an approach tacitly concedes the need to consider a range of issues before embarking on phenotype-driven biological treatment.

A number of extra-pulmonary comorbidities contribute to poor control in patients with difficult-to-control asthma, hereafter termed difficult asthma.(4) In such patients, these comorbidities may impact all three elements of difficult asthma assessment. Comorbidities may masquerade as asthma when a patient does not have asthma at all. They may add to the burden of symptoms, impaired quality of life, or exacerbation frequency. They may even constitute a distinct phenotype of severe asthma, as with obesity.(5)

There is a progressive move towards identifying and treating individual “treatable traits”. Comorbidities have been depicted as a distinct bundle of “treatable traits” in airway disease,(6) reinforcing the view that comorbidities play a significant role in chronic airway disease.

While guidelines recommend that comorbidities in difficult asthma should be addressed, a number of key questions remain.

1. How common are these comorbidities in difficult asthma?
2. To what degree do comorbidities contribute to difficult asthma?
3. Does treatment of comorbidities improve difficult asthma?
4. How should clinicians evaluate and address these comorbidities?

This review will address each question directly, and outline a pragmatic clinical approach to this challenging area. As many studies employ the term ‘severe asthma’ to describe asthma patients on high-intensity treatment, we have included such patients under the umbrella of ‘difficult asthma’. Comorbidities involving the lung (e.g. bronchiectasis) or resulting from asthma treatments (e.g. osteoporosis) fall outside the scope of this discussion.

HOW COMMON ARE COMORBIDITIES IN DIFFICULT ASTHMA?

Allergic and non-allergic rhinitis

Rhinitis is common in asthma and the prevalence is similar regardless of asthma severity. In the Unbiased BIOmarkers in PREDiction of respiratory disease outcomes (U-BIOPRED) cohort, allergic rhinitis was present in 55% of severe asthma patients and 60% of non-severe asthma patients, while *non*-allergic rhinitis was present in 15% of severe asthma patients, and 11% of non-severe asthma patients.(7)

Chronic rhinosinusitis

Among asthma patients, the prevalence of chronic rhinosinusitis ranges from 22-42%,(8, 9) and is higher in severe asthma, affecting 45% of patients in the Severe Asthma Research Program (SARP).(5) Similarly, the prevalence of nasal polyposis increases with asthma severity. In mild, moderate, and severe asthma patients, the prevalence of nasal polyposis was 4.8%, 9.6%, and 44.6% respectively.(10)

Based on a meta-analysis, the pooled prevalence of aspirin-exacerbated respiratory disease (AERD) is 7.2% in all asthmatics but 14.9% among severe asthmatics.(11)

Gastroesophageal reflux

Gastroesophageal reflux disease (GERD) symptoms are present in 40-80% of asthmatics,(12, 13) while objective evidence of gastroesophageal reflux (GER) on pH probe testing is found in 62-72% of asthmatics.(14, 15)

GERD is most frequent among severe asthma patients. In the SARP cohort, GERD symptoms were present in only 12-16% non-severe asthma patients but 41% of severe asthma patients.(16) Findings in U-BIOPRED showed similar results.(7)

Obstructive sleep apnoea

Studies using polysomnography to ascertain the prevalence of obstructive sleep apnoea (OSA) in the asthma population have not been reported although studies using symptoms are available. Snoring was present in 17.9% of patients with asthma(17) while 39.5% of patients seen at a general asthma clinic were thought to be at high risk of OSA based on the Berlin questionnaire.(18)

Among patients with difficult asthma, OSA was considered likely in 38.9% of patients based on a positive Berlin questionnaire or previous polysomnography (PSG).(19) Among unselected patients with severe asthma who underwent polysomnography, OSA was present in >80%.(20, 21)

Vocal cord dysfunction (VCD)

The diagnosis of VCD is challenging despite various investigation modalities. Direct visualisation of abnormal vocal fold movement at laryngoscopy is the gold standard, but false negatives occur during asymptomatic periods.(22) Exercise, odour, histamine, methacholine, and mannitol challenges have been used to increase the sensitivity of laryngoscopy.(22-27) Spirometry,(28) dynamic CT scanning(29) and questionnaires (30, 31) have also been used to diagnose VCD, with varying levels of diagnostic accuracy.

The prevalence of VCD is 19%(32) in asthma patients and 32% in difficult asthma patients.(19) One study directly comparing mild and severe asthma patients on dynamic CT confirmed a higher VCD prevalence among those with more severe asthma.(29)

Obesity

Obesity is epidemic in Western populations, with a prevalence of 36% among US adults.(33) The prevalence of obesity in asthma in one European study was 18% among non-severe asthma patients, but 39% among severe asthma patients.(7) A specific obese phenotype of severe asthma has been identified in UK and US cohorts,(5, 34) but not in Asian cohorts where obesity rates are much lower.(35)

Dysfunctional breathing

Dysfunctional breathing (DB) is a poorly defined syndrome with chemical (hypocapnia), mechanical (respiratory motion) and perceptual (patient symptom) components.(36)

Based on the Nijmegen Questionnaire (NQ)(37) and using a score ≥ 23 , the prevalence of DB in asthma was 29% in a primary care setting and 24.4% in a secondary care setting.(38, 39) Using the same definition, the prevalence of DB in difficult asthma was higher, at 30-64%.(19, 40)

Anxiety/Depression

Up to 18% of asthma patients have depression,(41, 42) while 11- 37% have anxiety.(41, 43) Patients with difficult asthma have even higher rates of depression and anxiety, at 31% and 81% for depression and anxiety respectively in one study.(44)

Summary and overview of comorbidity prevalence

The highest prevalence of extra-pulmonary comorbidities is observed in difficult asthmatics compared to the general asthma population. (Table 1). Not only are individual comorbidities common in difficult asthma, it is also common to find multiple comorbidities in each patient.(45)

Published cohorts vary widely when reporting the prevalence of rhinitis, CRS, DB and VCD, even when drawn from the same general population. Such differences in the reported prevalence of comorbidities in difficult asthma are partly due to inconsistent definitions and diagnostic criteria, as detailed above. However, another important factor may be under-diagnosis. Even among asthma specialists, a proportion of comorbidities was overlooked when these were not assessed systematically.(46) The sensitivity of clinical diagnosis for different comorbidities needs to be explored further across a range of clinical settings.

TO WHAT DEGREE DO COMORBIDITIES CONTRIBUTE TO DIFFICULT ASTHMA?

Allergic and non-allergic rhinitis

Mechanisms

Allergic rhinitis is often accompanied by lower airway dysfunction.(47) In addition, bi-directional cross-talk occurs between the upper and lower airways. Segmental bronchial challenge with grass pollen allergen induces allergic nasal inflammation.(48) Similarly, nasal provocation with grass pollen allergen induces bronchial inflammation.(49) This generalised airway response has been observed in non-allergic as well as allergic rhinitis.(50, 51)

Influence on asthma outcomes

Asthmatics with rhinitis have poorer symptom control (52, 53) and quality of life,(52-54) but not greater exacerbation frequency.(52, 55, 56) Furthermore, a longer duration of rhinitis, a greater severity of rhinitis, and sensitisation to perennial rather than seasonal allergens, were all associated with either greater airway dysfunction or more severe asthma.(47, 57-59)

Association with other comorbidities

Both allergic and non-allergic rhinitis are independent risk factors for obstructive sleep apnoea,(60, 61) likely related to nasal congestion and reduced upper airway patency (Figure 1).(62, 63)

Chronic rhinosinusitis

Mechanisms

The pathogenesis of chronic rhinosinusitis (CRS) parallels that of asthma in several ways. Firstly, nasal biopsies in CRS patients show epithelial damage and basement membrane thickening reminiscent of asthma.(64) Secondly, inflammatory subgroups in CRS mirror type 2 high and type 2 low inflammatory phenotypes observed in asthma.(34, 65) Thirdly, the pattern of inflammation within the upper and lower airways of individual patients is strongly concordant.(66) The presence or absence of nasal polyps can also give an indication of the type of airway inflammation.(67, 68)

Influence on asthma outcomes

Among asthma patients, the presence of CRS predicts more asthma symptoms,(8) more frequent exacerbations,(69, 70) and poorer quality of life.(8) In patients with difficult asthma, the presence of CRS increases the risk of frequent exacerbations by fourfold, even when adjusted for eosinophilic status.(19, 71) Sinusitis was independently associated with frequent exacerbations in the Severe Asthma Research Program (SARP) cohort (72) and the presence of CRS was incorporated into an asthma exacerbation risk prediction model.(73)

Association with other comorbidities

CRS frequently co-exists with obesity and depression in asthma.(74) CRS may also trigger VCD through the direct physical stimulus of post-nasal drip.(75)

Gastroesophageal reflux

Mechanisms

The relationship between GERD and asthma is bi-directional. Oesophageal irritation may cause bronchoconstriction. In patients with known asthma and endoscopy-diagnosed reflux, acid infusion into the oesophagus worsened peak flow rate (PEFR) and airway resistance.(76) The observed bronchoconstriction is likely vagally-mediated. (77) Acid infusion experiments also increased bronchial hyperresponsiveness in asthmatics.(78, 79)

On the other hand, asthma may predispose to GERD. Methacholine-induced bronchoconstriction increases the frequency of GER and transient lower oesophageal sphincter relaxation.(80) Oral corticosteroid (OCS) administration also increases oesophageal acid contact time and reflux risk.(81)

Influence on asthma outcomes

Among patients with asthma, the presence of GERD symptoms is associated with worse asthma symptoms and poorer quality of life(9, 12) although GER per se does not affect lung function.(82) In patients with difficult asthma, the presence of GERD symptoms is an independent risk factor for frequent exacerbations.(71, 72) GERD was also associated with worse asthma symptoms and poorer quality of life.(19)

Association with other comorbidities

Nocturnal GERD is associated with the development of rhinitis.(83) GER and its associated condition, laryngopharyngeal reflux, are common triggers for vocal cord dysfunction,(84) probably by direct laryngeal irritation or neural reflex.(85, 86) Asthma patients more often have anxiety and depression if also diagnosed with GERD.(12)

Obstructive sleep apnoea

Mechanisms

OSA may worsen asthma by driving airway inflammation.(87) OSA alters oxidative balance in the airways through repeated hypoxia and reoxygenation.(88) Exhaled breath condensate of inflammatory and oxidative stress markers, IL-6 and 8-isoprostane respectively, are increased in patients with OSA compared to obese controls and healthy controls.(88) These biomarkers can be suppressed by CPAP treatment.(89) Patients with OSA also have increased systemic inflammatory cytokines, endothelial T lymphocyte adherence,(90) increased sputum neutrophils,(91) and heightened bronchial hyperresponsiveness.(92)

Influence on asthma outcomes

Asthma patients with untreated OSA are more likely to have increased daytime and night-time asthma symptoms, even when controlled for other factors such as obesity, GERD and nasal disease.(93, 94) Patients also report a poorer asthma-related quality of life.(95)

In patients with difficult or severe asthma, OSA is a risk factor for worse asthma symptoms, poorer asthma-related quality of life, and more frequent exacerbations.(19, 71, 96)

Association with other comorbidities

GERD is more common in patients with OSA. (97) Increased GERD in OSA is likely due to more frequent transient lower oesophageal sphincter relaxations.(98, 99)

Vocal cord dysfunction

Mechanisms

VCD may arise from laryngeal hypersensitivity.(84, 100) Psychological factors also play an important role.(101) Importantly, vocal cord adduction has also been observed to occur in bronchoconstriction.(102) (103) This may therefore represent an adaptation akin to pursed lip breathing, which increases intrinsic positive end expiratory pressure and improves alveolar gas exchange. In patients with difficult asthma, it may be difficult to differentiate VCD occurring as a physiological response to airflow obstruction from a separate and symptomatic pathological entity.

Influence on asthma outcomes

Patients with VCD may be misdiagnosed as having asthma, while patients with both VCD and concomitant asthma may have misattribution of symptoms to asthma.(104-107) Patients with VCD misdiagnosed as asthma have higher medication use and healthcare utilisation.(108) High doses of inhaled corticosteroid and bronchodilator therapy can also result in laryngeal mucosal irritation, perpetuating further laryngeal dysfunction.(109) In difficult asthma, the presence of VCD is associated with a poorer quality of life.(19)

Association with other comorbidities

As discussed earlier, both rhinitis and GERD are common in patients with VCD.(110) VCD is also associated with anxiety and depression (Figure 1).(28, 101)

Obesity

Mechanisms

The link between obesity and asthma likely has multiple underlying mechanisms, including altered lung mechanics. Obese individuals have a lower functional residual capacity (FRC) and tidal volume. These changes can result in unloading of airway smooth muscle, which shortens more during bronchoconstriction.(111, 112) Dynamic changes in lung function after bronchoprovocation are also

different between obese and non-obese asthmatics.(113) With increasing BMI, FRC increases while inspiratory capacity decreases following bronchoprovocation, with correspondingly greater changes in dyspnoea scores.(113)

Another mechanism is cellular inflammation, although data regarding inflammatory profiles in obese asthma has been conflicting. Both increased and decreased sputum neutrophils have been described.(114, 115) Cluster analyses have identified a distinct obese, non-eosinophilic cluster with female preponderance (34, 116) but other studies described similar inflammatory profiles between obese and non-obese asthma.(117-119)

Corticosteroid insensitivity may be another cause of poor asthma control in obese asthmatics. Mitogen-activated protein kinase phosphatase 1 (MKP-1) is a key molecule by which corticosteroids inhibit proinflammatory gene expression,(120, 121) and increased BMI is associated with an attenuated *in-vitro* MKP-1 expression after dexamethasone induction.(121)

Other mechanisms include heightened adipokine levels which may act directly on airway epithelial cells,(122) and high fat meals and high trans fatty acid meals which increase airway neutrophilia and impair bronchodilator recovery.(123)

Influence on asthma outcomes

Obesity is also a risk factor for asthma misdiagnosis,(124) so objective tests to confirm variable airflow obstruction are particularly important. Obesity is associated with poorer asthma symptom control, asthma-related quality of life, and frequent exacerbations.(125-127) Waist circumference and waist-height ratio also predict worse symptoms, supporting a role for fat distribution.(126, 128)

Association with other comorbidities

Obesity increases the risk for GERD and OSA,(115) and the effects of these comorbidities on asthma control may be independent of each another.(129) Obesity is also associated with depression.(130)

Dysfunctional breathing

Mechanisms

The pathophysiology underlying DB in patients with asthma is not fully understood. In patients with asthma, voluntary hyperventilation that is sufficient to cause hypocapnia also increases airway resistance, a phenomenon not observed in normal controls.(131) However, even when asthma

patients have a similar minute ventilation to normal controls, hypocapnia can be present.(132) This implies that hypocapnia- and associated dysfunctional breathing- may be intrinsic to the pathophysiology of asthma, the underlying mechanism of which remains unclear.(132)

Patients with symptomatic asthma have increased tidal volumes and minute ventilation, and greater asynchrony between movements of the rib cage and abdomen.(133) It is uncertain, whether the abnormal breathing pattern leads to more intense symptoms, or whether the abnormal breathing pattern is driven by more severe asthma.

Influence on asthma outcomes

DB may be mistaken for asthma, as occurs in 1-2% of patients referred to difficult asthma clinics.(45, 134, 135) More commonly, DB may coexists with difficult asthma, where it is frequently under-recognised.(46) In asthma, the presence of DB is associated with increased ED visits, GP visits, limitation of activity, and reduced physical and mental health.(136, 137)

In patients with difficult asthma, DB is independently associated with poorer asthma control and asthma related quality of life, even when adjusted for other comorbidities and conventional lung function and inflammatory parameters.(19)

Association with other comorbidities

Dysfunctional breathing has been commonly described in patients with anxiety disorders such as panic disorders.(138, 139) One study also demonstrated an independent association between DB and VCD.(140)

Anxiety/Depression

Mechanisms

Depression and anxiety can impair a patient's ability to self-manage their asthma. There is an association between depression and poor medication adherence.(141, 142)

Influence on asthma outcomes

The presence of depression and anxiety affects a patient's self-management of asthma, and is associated with worse asthma symptom control, poorer quality of life, and a higher likelihood of asthma-related hospitalisations,(42, 143, 144) although this is not a universal finding.(145) The presence of anxiety also increases the risk of long-term work disability in asthma.(146)

Association with other comorbidities

The associations between anxiety and depression with other comorbidities of obesity, dysfunctional breathing and VCD have been discussed. Interestingly, a study examining the relationship between asthma, obesity and depression found that the effect of obesity on poor asthma control was completely mediated by depression.(147)

Summary of comorbidity contribution to difficult asthma

While direct causation is difficult to prove, overwhelming evidence from the literature demonstrates a close association between individual comorbidities and adverse asthma outcomes (Table 1). Multiple comorbidities commonly coexist in each difficult asthma patient. We observe that for each comorbidity discussed, associations have been described with two-to-five other comorbidities (Figure 1).

Further work is needed to examine the interplay between multiple comorbidities within a single individual with difficult asthma. Not only may comorbidities impact other comorbidities and asthma independently, it is also possible that specific clusters of comorbidities may develop in difficult asthma, which then exert an aggregate effect on the individual's asthma outcomes.

DOES TREATMENT OF COMORBIDITIES IMPROVE DIFFICULT ASTHMA?

Allergic and non-allergic rhinitis

In patients with rhinitis and mild intermittent asthma, the use of intranasal corticosteroids (INCS) compared to intranasal placebo improves asthma symptoms (148) and health-related quality of life.(149) However, in patients with persistent asthma on inhaled corticosteroids (ICS), the addition of INCS improves nasal symptoms but not asthma control.(150-152) There is no data on the effect of INCS on asthma control in patients with rhinitis and difficult asthma.

Allergen-specific immunotherapy for allergic rhinitis has durable effects.(153) Immunotherapy has also been shown to improve asthma symptoms and reduce bronchial hyperresponsiveness, regardless of the presence of allergic rhinitis.(154) However subcutaneous immunotherapy (SCIT) can be associated with systemic adverse reactions and uncontrolled asthma is considered an absolute contraindication for immunotherapy.(155) Immunotherapy via the sublingual route (SLIT) has fewer systemic adverse effects.(156) House dust mite (HDM) SLIT in asthma patients has been shown to prolong the time to asthma destabilisation following weaning of ICS treatment.(157) The role of either SCIT or SLIT in patients with rhinitis and difficult has not been extensively explored.

Chronic rhinosinusitis

Some studies have shown improvements in asthma control following either surgery or medical CRS treatment.(158, 159) Among 17 steroid dependent patients with difficult asthma, surgery for CRS and nasal polyposis reduced airflow obstruction, and nine patients could be weaned off oral corticosteroids completely.(160) Another group of difficult asthma patients had improved quality of life and reduced asthma-related clinic visits following CRS surgery.(161)

Gastroesophageal reflux

A systematic review in 2003 found no consistent effect of medical treatment of GERD on asthma outcomes.(162) Most of the randomised controlled trials of proton-pump inhibition since the review was published also found either no, or clinically insignificant, effects on asthma symptoms, quality of life,(163) exacerbations (164) or lung function.(165) Only one study using lansoprazole in patients with GERD symptoms showed a reduction in asthma exacerbation rates.(166) The effect of medical GERD treatment in difficult or severe asthma is unclear.

Studies looking at surgical treatment of GERD are more promising. In a placebo controlled trial of 90 patients with wheezing and GERD, anti-reflux surgery reduced the need for asthma medication.(167) Another randomised controlled trial of patients with asthma and GERD found that Nissen fundoplication(168) significantly improved oesophageal erosions, oesophageal pH, and asthma symptoms compared to either placebo or medical treatment groups. The effect of surgical GERD treatment in difficult or severe asthma specifically is not known.

Obstructive sleep apnoea

Results from observational studies on the use of CPAP in patients with uncontrolled asthma with OSA have been promising. The application of nasal CPAP improves nocturnal symptoms,(169, 170) as well as asthma control and quality of life.(171) The effect of CPAP or other OSA treatments in the context of difficult or severe asthma is unknown.

Vocal cord dysfunction

Treatment modalities for VCD include non-pharmacological and pharmacological therapies. Speech retraining is the mainstay of treatment for VCD(172) and psychotherapy may be beneficial in some patients.(101) Pharmacological treatment such as gabapentin and pregabalin are effective for chronic refractory cough (173, 174) but little efficacy data exists for VCD. Inhaled ipratropium reduced exercise-induced VCD in a small case series.(175) In a small uncontrolled study, treatment

of GERD in patients with VCD with lansoprazole improved VCD symptoms in only a minority of patients.(176) The effect of the above-mentioned treatment on asthma control is unclear.

In patients with difficult asthma and VCD, botulinum toxin injection into laryngeal muscles reduced VCD and improved asthma control scores in an uncontrolled case series.(177)

Obesity

Randomised controlled trials on weight loss interventions for obese asthmatics showed promising results. A Cochrane systematic review found that weight loss was associated with improvement in asthma control.(178) A randomised controlled trial conducted in Brazil showed that a short-term weight-loss programme incorporating exercise improved asthma control, asthma-related quality of life and lung function.(179)

Observational studies demonstrated that bariatric surgery in obese asthmatics improved asthma symptom control, airway hyper-responsiveness, asthma quality of life and lung function parameters.(180-183) Non-surgical weight loss methods also showed similar improvements in asthma outcomes.(184) The beneficial effects on asthma were dependent on the magnitude of weight loss.(185, 186)

The effect of weight loss may be influenced by the Type 2 status of the individual, with improved airway hyper-responsiveness in 'Type 2 low, but not 'Type 2 high', patients.(181, 187) On the other hand, improvement in asthma outcomes may occur without changes in airway inflammation, suggesting that mechanisms unrelated to inflammation are also responsible.(188)

Dysfunctional breathing

A variety of breathing exercises have been used to control hyperventilation and anxiety symptoms in asthma, including the Papworth method, Buteyko breathing technique, yoga, and the Lowtorp method.(189, 190)

A Cochrane review evaluated 13 randomised controlled trials of breathing exercises in asthma.(189) Meta-analyses of breathing exercise versus usual care based on 2 studies, and breathing exercises versus nurse education based on 2 studies, showed improvement in AQLQ in patients who received breathing exercises. Heterogeneity among the other studies precluded meta-analysis for other asthma outcomes.

Among patients with difficult asthma, an uncontrolled study showed that breathing exercises in those with dysfunctional breathing improved Nijmegen scores, occurring in parallel with improvements in asthma control and exacerbation frequency.(191)

Anxiety/depression

A randomised trial demonstrated that in asthma patients with anxiety, education combined with cognitive behavioural therapy significantly improved asthma-specific fear, compared to usual clinical management,(192) but asthma-specific outcomes were not examined.

The impact of treatment for anxiety and depression in difficult or severe asthma is unclear.

Summary for comorbidity treatment-effects on difficult asthma outcomes

The current literature suggests that treatment of most extra-pulmonary comorbidities improves asthma outcomes, but this is based mainly on observational studies (Table 1).

For obesity, gastroesophageal reflux and allergic rhinitis, randomised controlled trials showed positive, conflicting, and negative asthma outcomes respectively following comorbidity treatment. For other comorbidities, high quality studies showing comorbidity treatment improving asthma outcomes are lacking.

It remains to be seen whether effective treatment of specific comorbidities can obviate the need for escalating asthma treatment in difficult asthma. More randomised controlled trials are needed to confirm favourable treatment effects on asthma outcomes, especially in patients with difficult asthma.

HOW SHOULD CLINICIANS EVALUATE AND TREAT THESE COMORBIDITIES?

Given the significant impact of extra-pulmonary comorbidities on asthma outcomes, it is critical to identify and manage these comorbidities in patients with difficult asthma.(19) Broadly speaking, there are three approaches to comorbidity assessment.

Unstructured assessment

Individual respiratory specialists typically assess each comorbidity during the clinical consultation based on history and physical examination. This approach is time consuming, especially when patients have multiple comorbidities.(45) Furthermore, clinicians are liable to miss important comorbidities.(46) Dysfunctional breathing and vocal cord dysfunction are particularly prone to be overlooked.

Exhaustive assessment

In contrast to an unstructured approach, some difficult asthma centres put all patients through an extensive battery of investigations and specialist review, including ear, nose and throat (ENT) surgeons, psychiatrists, and allied health professionals.(134, 193) This exhaustive approach is unlikely to overlook important comorbidities but is highly resource intensive, often necessitating multi-day admissions. Such methods are not be feasible in most health care settings and systems.

Targeted assessment

Our centre has developed a stratified approach to overcome the inherent insensitivity of unstructured comorbidity assessments, as well as to optimise the use of healthcare resources. This approach involves three stages (Figure 2):

1) *Questionnaire screening.* Validated questionnaires identify patients at high risk for each comorbidity. Questionnaires with high diagnostic sensitivities are available for the detection of sinonasal disease,(55) dysfunctional breathing,(37) vocal cord dysfunction,(194) gastroesophageal reflux,(195) obstructive sleep apnoea,(196) anxiety and depression (197) (Table 2). The obvious exception is obesity where measurement of height and weight are sufficient. Some questionnaires are copyrighted and permission should be sought ahead of use.

2) *Specialist assessment.* During the consultation, the questionnaire results assist the clinician in focusing the history on areas of particular interest. The asthma specialist then integrates the results of the screening questionnaires, clinical history, and examination to estimate the clinical probability of each comorbidity. This approach heightens the detection rate of almost all the comorbidities under discussion when compared to unstructured assessment.(46)

3) *Tailored referrals*. Only patients with a high clinical likelihood for a comorbidity are referred for further evaluation or treatment.

CONCLUSION

Extra-pulmonary comorbidities are important treatable traits to address in all patients with asthma, but particularly in patients with difficult asthma. These comorbidities are highly prevalent in difficult asthma, and multiple comorbidities often co-exist in the same patient. Better definitions and diagnostic methods for some comorbidities, such as vocal cord dysfunction and dysfunctional breathing, are essential for progress in these areas.

Comorbidities substantially influence outcomes in patients with difficult asthma. Available literature demonstrates the adverse impact of these comorbidities on asthma symptom control, asthma quality of life, and exacerbation rates.

The presence of a symptomatic comorbidity warrants treatment, regardless of baseline asthma status or asthma control. However, randomised control data supporting the efficacy of comorbidity treatment to improve asthma outcomes are only available for a few comorbidities and, even then, not all the data are positive. This area therefore requires further rigorous research.

Finally, extra-pulmonary comorbidities appear to be under-recognised in the difficult asthma population, even by specialists. On occasion, comorbidity symptoms, in patients without asthma, may even be mistaken for asthma. Therefore, the evaluation of difficult asthma should always incorporate a meticulous search for these comorbidities. We suggest a stratified diagnostic approach which balances comprehensiveness against feasibility and cost.

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Table 1: Prevalence, impact, and treatment effects of comorbidities in asthma and difficult asthma

	Prevalence	Impact		Treatment effect	
	In difficult asthma compared to asthma	On asthma	On difficult asthma	On asthma	On difficult asthma
Allergic rhinitis	Similar	Symptoms ↑ QOL ↓	Not studied specifically	Immunotherapy improves symptoms. Nasal steroids improve symptoms	Uncertain
Non allergic rhinitis	Similar			Uncertain	Uncertain
Chronic rhinosinusitis	↑	Symptoms ↑ Exacerbations ↑ QOL ↓	Exacerbations ↑	Surgery or medication improves symptoms	Improved airflow obstruction and oral steroid dose
Gastroesophageal reflux	↑	Symptoms ↑ QOL ↓	Exacerbations ↑	Mainly no effect	Uncertain
Obstructive sleep apnoea	↑	Symptoms ↑ QOL ↓	Symptoms ↑ Exacerbations ↑ QOL ↓	CPAP improves symptoms and QOL	Uncertain
Vocal cord dysfunction	↑	Not studied specifically	QOL ↓	Uncertain	Botulinum injection improved symptoms
Dysfunctional breathing	↑	Exacerbations ↑	Symptoms ↑ QOL ↓	Improves QOL	Improved symptoms and exacerbation frequency
Obesity	↑	Symptoms ↑ QOL ↓ Exacerbations ↑	Symptoms ↑ Exacerbations ↑ QOL ↓	Surgical and medical treatment improves symptoms and QOL	Uncertain
Anxiety/Depression	↑	Symptoms ↑ QOL ↓ Exacerbations ↑	Not studied specifically	Improves symptoms and QOL	Uncertain

CPAP = continuous positive airway pressure, QOL = quality of life, ↑ = increased, ↓ = decreased

Table 2: Examples of validated questionnaires available to screen for extra-pulmonary comorbidities

Comorbidity	Questionnaires	Sensitivity (%)	Specificity (%)
Sinonasal disease (includes rhinosinusitis and allergic rhinitis)	*Sinonasal Questionnaire (SNQ) (55)	90	94
Gastroesophageal reflux	*Gastroesophageal reflux disease questionnaire (GERDQ) (195)	65	71
Obstructive sleep apnoea	*Berlin questionnaire (196)	86	77
Vocal cord dysfunction	*Pittsburgh vocal cord dysfunction index (PVCDI) (31)	83	95
Dysfunctional breathing	Nijmegen (37)	91	95
Anxiety and depression	*Hospital anxiety and depression score (HADS)(197)	80	80

*Permission required before use. SNQ: Professor Anne Dixon (Anne.Dixon@uvmhealth.org); GERDQ: AstraZeneca; Berlin Questionnaire: Professor Nikolaus Netzer (Nikolaus.Netzer@uibk.ac.at); PVCDI: Dr Andrei Petrov (petrovaa@upmc.edu); HADS: GL Assessment Ltd (registration@gl-assessment.co.uk)

Figure 1: Interaction of various comorbidities in asthma

Solid lines indicate significant associations between comorbidities.

CRS = chronic rhinosinusitis, DB = dysfunctional breathing, GERD = gastroesophageal reflux, OSA = obstructive sleep apnoea, VCD = vocal cord dysfunction

Figure 2: A stratified approach to comorbidity assessment

CT = computed tomography, ENT = ear, nose and throat specialist

*See Table 2 and reference 46 for examples of questionnaires that can be used



