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Validated questionnaires heighten detection of difficult asthma comorbidities

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ABSTRACT

Objective: Multiple extra-pulmonary comorbidities contribute to difficult asthma, but their diagnosis can be challenging and time consuming. Previous data on comorbidity detection have focused on clinical assessment, which may miss certain conditions. We aimed to locate relevant validated screening questionnaires to identify extra-pulmonary comorbidities that contribute to difficult asthma, and evaluate their performance during a difficult asthma evaluation. **Methods:** MEDLINE was searched to identify key extra-pulmonary comorbidities that contribute to difficult asthma. Screening questionnaires were chosen based on ease of use, presence of a cut-off score, and adequate validation to help systematically identify comorbidities. In a consecutive series of 86 patients referred for systematic evaluation of difficult asthma, questionnaires were administered prior to clinical consultation. **Results:** Six difficult asthma comorbidities and corresponding screening questionnaires were found: sinonasal disease (allergic rhinitis and chronic rhinosinusitis), vocal cord dysfunction, dysfunctional breathing, obstructive sleep apnea, anxiety and depression, and gastro-oesophageal reflux disease. When the questionnaires were added to the referring clinician's impression, the detection of all six comorbidities was significantly enhanced. The average time for questionnaire administration was approximately 40 minutes. **Conclusions:** The use of validated screening questionnaires heightens detection of comorbidities in difficult asthma. The availability of data from a battery of questionnaires prior to consultation can save time and allow clinicians to systematically assess difficult asthma patients and to focus on areas of particular concern. Such an approach would ensure that all contributing comorbidities have been addressed before significant treatment escalation is considered.

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Introduction

Asthma affects 300 million people across the globe [1]; 5–10% of them remain poorly controlled despite the use of high-dose inhaled corticosteroids and/or oral corticosteroids and are considered to have difficult-to-treat asthma. A variety of issues may cause difficulty, including limited adherence to medication, poor inhaler technique, psychosocial issues, persistent environmental triggers, and of note, uncontrolled extra-pulmonary comorbidities. Guidelines emphasise the need to identify and address these comorbid factors before escalating medication doses further, or employing novel and expensive therapies [2,3].

Previous reports have proposed different lists of extra-pulmonary comorbidities [4–6]. The approach to detecting these comorbidities has either been to rely on the clinical acumen of experts, to deploy an exhaustive battery of definitive investigations, or both [4,5].

We hypothesized that incorporating validated screening questionnaires into difficult asthma assessment would

increase detection of extra-pulmonary comorbidities, and so assist in identifying patients appropriate for further investigations or treatment. Our aims were to 1) identify extra-pulmonary comorbidities contributing to difficult asthma, 2) locate relevant validated screening questionnaires, 3) measure the detection rate of questionnaires for comorbidities when added to referring physician diagnoses, and 4) establish the feasibility of integrating these questionnaires into the workflow of a difficult asthma evaluation protocol.

Methods

To determine extra-pulmonary comorbidities relevant to difficult asthma, a MEDLINE search was performed using the search terms “difficult” OR “severe” asthma AND “comorbidities.” Guidelines, position papers, review articles and research papers were reviewed, from which major extra-pulmonary conditions were identified. The prevalence of each comorbidity and its association with asthma severity was determined.

For each comorbidity so identified, further searches were performed using the search terms ('assessment' OR 'questionnaire' OR 'diagnosis') AND 'comorbidity' restricted to the past 15 years. Candidate questionnaires were assessed and selected according to the following criteria: validated sensitivity and specificity, the presence of a quantitative cut-off score, and ease of use.

Our institution undertakes systematic outpatient assessment of difficult asthma patients. We accept referrals from respiratory and allergy specialists, from our institution's general asthma clinic as well as from other institutions. Patients were considered to have 'difficult asthma' if the managing respiratory or allergy specialists experienced difficulty managing the patients due to one or more of the following: a) diagnostic dilemma; b) poor symptom control; c) frequent or serious exacerbations; d) poor lung function; e) patient factors complicating management. We deliberately kept the inclusion criteria broad to reflect the real-life difficulties faced by asthma specialists.

For this study, we specifically asked each patient's referring physician whether any of the comorbidities identified in the literature was present in their patient, and this was documented prior to protocol evaluation (Online Supplement Appendix 1).

When the patient attended for assessment, a clinic coordinator administered all the screening questionnaires prior to clinical review. Scores were calculated for each questionnaire and the results were made available for the clinical consultation, as was the referring clinician's impression. The protocol clinicians provided a working clinical diagnosis for each extra-pulmonary comorbidity based on their clinical assessment. They were at liberty to disagree with either the questionnaire results or the referring clinician's impression.

Analysis

For each extra-pulmonary comorbidity, the primary outcome was its detection by the referring clinician alone compared to detection by the referring clinician supplemented by screening questionnaires (McNemar's test, $p < 0.05$ for statistical significance, data analysis by SPSS

version 19). The data collection and analysis was approved by the Alfred Hospital Research Ethics Committee as a low-risk audit project (Ref 285/15).

Results

Demographics

Eighty-six consecutively referred patients were included. The majority of patients were female (65%) with a mean age of 52 and a mean asthma duration of 30 years. At the time of initial assessment, patients were receiving inhaled corticosteroids (97%, mean dose 865 mcg of fluticasone equivalent), long-acting beta-agonist (90%), long-acting muscarinic antagonist (20%), oral corticosteroids (20%), montelukast (20%) and theophylline (7%). The mean pre-bronchodilator FEV₁ was $68 \pm 23\%$.

Extra-pulmonary comorbidities identified

Seven significant extra-pulmonary comorbidities were identified from the literature search: allergic rhinitis (AR), chronic rhinosinusitis (CRS), dysfunctional breathing (DB), vocal cord dysfunction (VCD), obstructive sleep apnoea (OSA), anxiety or depression (Anx/Dep), and gastro-oesophageal reflux disease (GORD). Obesity was also considered a significant and relevant comorbidity but excluded from this study because it is so easily detected.

The association of these extra-pulmonary comorbidities with asthma are shown in Table 1. The reported prevalence of these comorbidities varied from 20–95%. Treatment of each comorbidity has generally been shown to improve asthma control, although the data is inconsistent for GORD and VCD.

Questionnaires chosen

Specific questionnaires for AR, DB, VCD, OSA, Anx/Dep, and GORD were available (Table 2), but we were unable to find a questionnaire for CRS specifically. We therefore used the Sino-Nasal Questionnaire (SNQ) to detect undifferentiated sinonasal disease (including both AR and CRS). In our results, we have combined AR and CRS as a single comorbidity ('sinonasal disease'). Thus

Table 1. Association, prevalence and treatment outcomes of extra-pulmonary comorbidities in the difficult asthma patient.

Comorbidity		Associated with asthma?	Prevalence of comorbidity in asthma	Does treatment improve asthma?
Sino-nasal disease	AR	Yes [6]	80% [7] (all asthmatics)	Yes [8,9]
	CRS	Yes [10,11]	70–74% [12] (difficult asthma)	Yes [13]
GORD		Yes [14]	59% [14]	Inconsistent [15,16]
OSA		Yes [17]	75–95% [18–20] (difficult asthma)	Yes [17,21–23]
VCD		Yes [24]	19% [25] (all asthmatics) 75% (difficult asthma)	Inconsistent [26]
DB		Yes [28]	29% [27] (all asthma)	Yes [28]
Anx/Dep		Yes [29,30]	49% [29] (difficult asthma)	Yes [31]

Note. AR = allergic rhinitis; Anx/Dep = anxiety or depression; CRS = chronic rhinosinusitis; GORD = gastro-oesophageal reflux disease; DB = dysfunctional breathing; OSA = obstructive sleep apnoea; VCD = vocal cord dysfunction.

Table 2. Sensitivity and specificity of validated questionnaires used to screen for contributing comorbidity in the difficult asthma patient.

Questionnaires	Comorbidity	Items	Scored	Validated	Sensitivity (%)	Specificity (%)
SNQ [32,33]	Sino-nasal disease	5	✓	✓	90	94
SFAR [34]	AR	8	✓	✓	74	83
NIJMEGEN [3,5,26]	DB	16	✓	✓	91	95
PVCDI [37]	VCD	4	✓	✓	83	95
BERLIN [38,39]	OSA	10	✓	✓	86	77
HADS [40]	Anx/Dep	14	✓	✓	80	80
GERD-Q [41,42]	GORD	6	✓	✓	65	71

Note. AR = Allergic rhinitis; Anx/Dep = Anxiety or depression; Berlin = Berlin questionnaire; CRS = Chronic rhinosinusitis; GORD = Gastro-oesophageal reflux disease; GERDQ = GERDQ questionnaire; HADS = Hospital anxiety and depression scale; DB = Dysfunctional breathing; Nijmegen = Nijmegen questionnaire; OSA = Obstructive sleep apnoea; PVCDI = Pittsburgh vocal cord dysfunction index; SFAR = Score for allergic rhinitis questionnaire; SNQ = Sinonasal questionnaire; VCD = Vocal cord dysfunction.

seven questionnaires were used to detect six comorbidities (Table 2).

Detection of comorbidities by referring physicians versus referring clinicians supplemented by questionnaires

Eighty-six consecutively referred patients were included. Sixty-four were referred from within our institution's allergy, immunology and respiratory department; respiratory physicians or allergists at other hospitals referred the rest. If referred by a member of the difficult asthma protocol team, patients would be seen by a different protocol physician for maximum objectivity.

The approximate length of time to complete all questionnaires was 40 minutes. Only two patients had

difficulty completing the questionnaires: one had schizophrenia with thought disorder, and the other (non-English speaking) patient attended without a family member to translate. Thus 84 patients were included for final analysis.

Results showed that referring physicians only identified a certain number of contributing comorbidities based on their clinical impression. However, the use of questionnaires in addition to a referring clinician's impression significantly increased the detection of all six extrapulmonary comorbidities when compared to referring clinicians' impression alone (Figure 1). The same pattern was observed irrespective of whether the patient was referred from our own institution or another centre.

The use of questionnaires *alone* also detected more comorbidities than referring clinicians *alone* for most

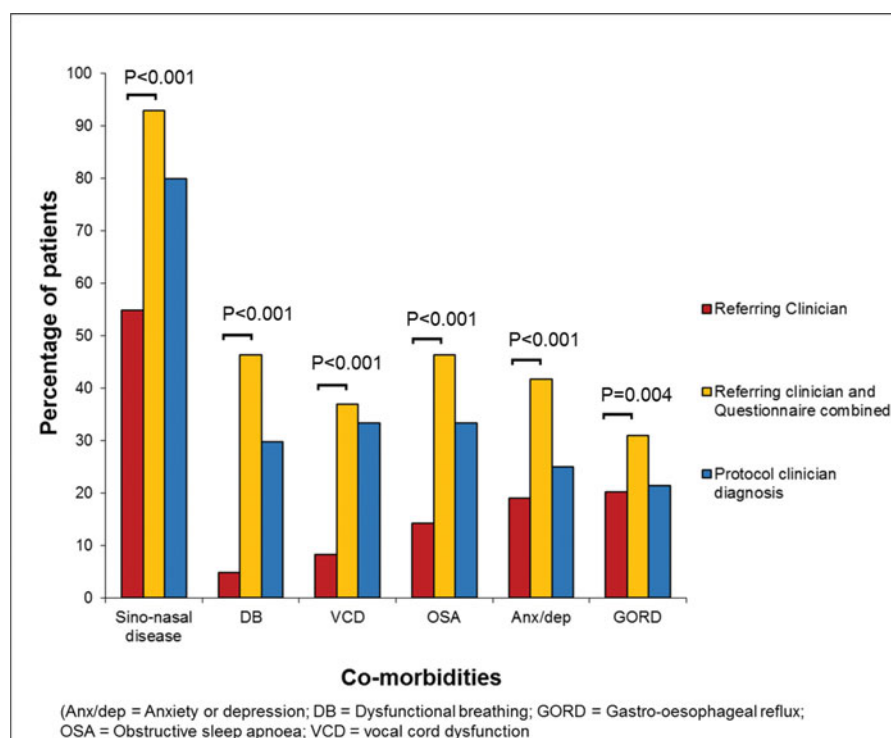


Figure 1. Proportion of patients with comorbidities detected by referring clinicians, by referring clinicians and questionnaires combined, and according to protocol clinician diagnosis.

comorbidities except for GORD and anxiety and depression (Online supplement, Appendix 2). Incorporating questionnaire results into clinical assessment enabled protocol physicians to identify certain comorbidities better than referring physicians. These comorbidities were sinonasal disease (79.8% vs 54.8%, $p < 0.01$), OSA (33.3% vs 14.3%, $p = 0.005$), VCD (33.3% vs 8.3%, $p < 0.001$), and DB (29.8% vs 4.8%, $p < 0.001$). The detection of GORD and anx/dep were not significantly different between protocol physicians and referring physicians.

Comparison of two nasal questionnaires

The SNQ had a similar sensitivity and specificity to the SFAR (Score For Allergic Rhinitis) questionnaire for sinonasal disease (online supplement Appendix 3).

Discussion

Extra-pulmonary comorbidity assessment in difficult asthma has typically relied on expert clinician impression, or else an exhaustive battery of tests [4,5]. We report on the systematic use of validated questionnaires to screen for contributing comorbidities. This allowed the selective referral of patients for more intensive investigation.

Our results show that screening questionnaires significantly heighten detection of six extra-pulmonary comorbidities in difficult asthma when added to the referring specialist's clinical assessment. This applied to sinonasal disease (allergic rhinitis or chronic rhinosinusitis), dysfunctional breathing (DB), vocal cord dysfunction (VCD), obstructive sleep apnoea (OSA), anxiety/depression (anx/dep), and gastro-oesophageal reflux (GORD).

Our results were consistent regardless of whether patients were referred from within our institution or from another hospital. The majority of patients referred from within our institution were referred by specialists who also staffed the difficult asthma service. This suggests that screening questionnaires are of value in this setting even when added to expert evaluation.

With the assistance of these questionnaires, more contributing comorbidities were detected than by referring physicians alone. However, the protocol physicians were more discriminating than the questionnaires in their detection of comorbidities, as a proportion of positive questionnaire results for each comorbidity were discounted. This suggests that questionnaires were useful to increase the 'sensitivity' of comorbidity detection, while the protocol physicians enhanced the 'specificity' of the d process.

Among the six comorbidities, the questionnaires appear to have greatest utility in detecting sinonasal

disease, vocal cord dysfunction, dysfunctional breathing, and obstructive sleep apnea. The use of questionnaires for each of these conditions suggested their presence in an additional 30% of the overall cohort, which might otherwise have been missed.

We used two questionnaires for nasal disease. The SNQ is validated to detect undifferentiated sinonasal disease (CRS + AR), whereas the SFAR detects AR only. In our clinic setting, the SNQ was effective in screening for both AR and CRS. We found no additional benefit for using the SFAR when the SNQ was employed. In future, we will be removing SFAR from our questionnaire battery.

Our study has several limitations. Firstly, not all questionnaires used in our protocol were developed or validated for asthma patients. Secondly, there was no gold standard diagnosis for each comorbidity. Instead, we adopted a pragmatic approach. The majority of the questionnaires employed had high sensitivity—we therefore utilised them to identify high-risk patients suitable for further investigation. Thirdly, the use of questionnaires may be difficult to apply in non-English settings. Fourthly, we did not compare the performance of protocol physicians in detecting comorbidities with and without the assistance of the questionnaires, but the primary aim of the study was to examine the questionnaires rather than the clinicians. Finally, this study has not determined whether the increased detection of comorbidities using questionnaires translates into increased interventions or better patient outcomes.

Conclusion

Validated questionnaires heighten detection of extra-pulmonary comorbidities in difficult asthma. They are feasible to implement in an outpatient setting prior to the clinical consultation. Their results can rapidly direct the clinician to areas requiring further evaluation. They allow a more systematic approach to a complex patient cohort where contributing comorbidities can be missed and appropriate management of these conditions may avert inappropriate escalation of asthma treatment.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

Author contributions

All authors have been involved in the setup of the difficult asthma service as well as patient management. All authors read and approved the final manuscript. No funding was provided for this study.

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