

# Managing comorbid conditions in severe asthma

Philip G Bardin, Jhanavi Rangaswamy, Shaun W Yo

**C**omorbidity is the presence of one or more diseases or disorders occurring concurrently with a primary disease or disorder. In asthma, comorbid conditions are frequently present, and they add to the burden of respiratory symptoms associated with the primary condition. They often contribute to a severe and difficult-to-treat asthma phenotype.<sup>1</sup>

The link between comorbidity and asthma is complex. Some comorbid conditions can both occur together with asthma and masquerade as asthma itself, as with vocal cord dysfunction (VCD). Other conditions or factors can affect the nature and severity of asthma, leading to a distinct phenotype. Teasing apart the different components of comorbidity in severe asthma can be difficult, and general practitioners are often confronted by complexity that may seem beyond the scope of everyday care.

As asthma care has increasingly focused on personalised management for severe asthma, recognition of the role and importance of comorbid conditions has increased. To improve overall management and care, doctors need to take these concurrent disorders into account, and one way to simplify this process is to consider comorbid conditions as a “bundle” of disease traits that may be amenable to treatment – so-called “treatable traits”.<sup>2</sup> Managing these traits can potentially improve asthma control, reduce or remove the need for some medications and improve overall quality of life for many patients considered to have severe asthma.<sup>3</sup> Additionally, the appropriate treatment of comorbid conditions is a critical step in distinguishing the subset of patients with biologically severe asthma from among the undifferentiated group of patients presenting with difficult-to-treat asthma.<sup>4</sup> This has important implications for therapy, as outlined elsewhere in this supplement in the article on the diagnosis of severe asthma.<sup>5</sup>

In this review, we provide a brief overview of key comorbid conditions that are likely to be encountered in general practice. We also outline a simplified, iterative approach to assessing and managing comorbid conditions in severe asthma.

In conducting this review, we searched English language literature in PubMed using the key words severe asthma, comorbidity, treatment and management.

## The spectrum of comorbid conditions in severe asthma

A broad spectrum of comorbid conditions has been noted in association with severe asthma. Using a simplified approach, comorbid conditions can be grouped as either airway-related or airway-unrelated. In this context, we briefly outline prevalence, putative mechanisms, evidence for intervention, diagnosis and management (Box 1).

## Summary

- Asthma care has increasingly focused on personalised management for severe asthma, and recognition of the role and importance of comorbid conditions has increased.
- Severe asthma can be crippling; associated comorbid conditions often play a key role in the significant disease morbidity and frequently contribute to a severe and difficult-to-treat asthma phenotype.
- Comorbid conditions can be broadly grouped as being either airway-related or airway-unrelated.
- Airway-related comorbid conditions with the greatest impact are allergic rhinitis, chronic rhinosinusitis, vocal cord dysfunction, lung fungal sensitisation and underlying structural lung disease.
- The most important airway-unrelated comorbid conditions are obesity, obstructive sleep apnoea, gastro-oesophageal reflux disease and anxiety and depression.
- A diagnostic and management algorithm for comorbid conditions in severe asthma is outlined. It concentrates initially on the group with common comorbid conditions that can be managed in primary care. If asthma remains troublesome, emphasis can shift to identifying uncommon and more complex factors. The algorithm allows for personalised diagnostic and management pathways to be implemented.
- Personalised diagnosis and management of comorbid conditions are essential to achieving effective and improved outcomes for patients with severe asthma.

## A practical approach to managing comorbid conditions in severe asthma

Grouping comorbid conditions into either airway-related or airway-unrelated factors may help to simplify diagnosis and management. However, application in everyday clinical practice can be problematic, and an iterative, algorithmic approach modelled on identification first of common comorbid conditions may help general practitioners to diagnose, refer appropriately and, where possible, manage comorbid conditions in severe asthma. If symptoms persist, less common comorbid conditions should be considered. Box 2 illustrates this proposed algorithm.

### Airway-related comorbid conditions

#### Allergic rhinitis

**Prevalence:** The prevalence of allergic rhinitis (AR) in severe asthma may be as high as 55–68%.<sup>6,7</sup> AR is also associated with early onset of severe asthma.<sup>8–10</sup>

**Pathophysiology:** The unified airway theory proposes that upper and lower airways function as a single unit and is supported by several observations. Patients with symptoms of AR often have reduced lung function on spirometry;<sup>11</sup> individuals with allergen sensitisation have a higher prevalence of both asthma and AR,<sup>10</sup> and the severity of AR often parallels that of asthma.<sup>12</sup>

# 1 Prevalence, associated asthma phenotypes and management options for common comorbid conditions in severe asthma

Comorbidity	Prevalence in severe asthma	Most commonly associated asthma phenotype	Management options
<b>Airway-related comorbid conditions</b>			
Allergic rhinitis	55–68%	Early onset allergic asthma	<ul style="list-style-type: none"> <li>• Nasal corticosteroids</li> <li>• Anti-leukotrienes</li> <li>• Allergen-specific immunotherapy (contraindicated in uncontrolled asthma)</li> </ul>
Chronic rhinosinusitis with or without nasal polyposis	45–50%	Late onset eosinophilic asthma (particularly associated with nasal polyposis)	<ul style="list-style-type: none"> <li>• Nasal corticosteroids</li> <li>• Nasal lavage</li> <li>• Low dose macrolide antibiotic</li> <li>• Endoscopic sinus surgery</li> </ul>
Vocal cord dysfunction	19–50%	Not associated with an asthma phenotype	<ul style="list-style-type: none"> <li>• Speech therapy</li> <li>• Treat coexistent gastro-oesophageal reflux disease and rhinosinusitis</li> <li>• Botulinum toxin injection of vocal cords</li> </ul>
Dysfunctional breathing	24–30%	Late onset non-eosinophilic asthma	<ul style="list-style-type: none"> <li>• Breathing exercises</li> <li>• Relaxation techniques</li> <li>• Thoracic muscle massage</li> </ul>
Allergic bronchopulmonary aspergillosis or severe asthma with fungal sensitisation	2.5%	Late onset allergic asthma	<ul style="list-style-type: none"> <li>• Oral corticosteroids</li> <li>• Itraconazole or voriconazole</li> <li>• Anti-IgE monoclonal antibody</li> </ul>
Bronchiectasis	24–40%	Not associated with an asthma phenotype	<ul style="list-style-type: none"> <li>• Airway clearance</li> <li>• Inhaled hyperosmolar agents</li> <li>• Exercise</li> <li>• Long term macrolide antibiotics</li> </ul>
Smoking and chronic obstructive pulmonary disease	Variable, up to 15–20%	Not associated with an asthma phenotype	<ul style="list-style-type: none"> <li>• Smoking cessation</li> <li>• Inhaled corticosteroids and bronchodilators for asthma and chronic obstructive pulmonary disease</li> </ul>
<b>Airway-unrelated comorbid conditions</b>			
Gastro-oesophageal reflux disease	46–63%	Not associated with an asthma phenotype	<ul style="list-style-type: none"> <li>• Twice-daily proton pump inhibitor</li> <li>• Referral to gastroenterologist if red flag symptoms</li> <li>• Anti-reflux surgery (limited evidence)</li> </ul>
Obesity	21–48%	Late onset non-eosinophilic asthma Also prevalent in other phenotypes	<ul style="list-style-type: none"> <li>• Dietitian referral</li> <li>• Exercise training</li> <li>• Bariatric clinic referral</li> </ul>
Obstructive sleep apnoea	Up to 88–96% on polysomnography	Not associated with an asthma phenotype	<ul style="list-style-type: none"> <li>• Sleep physician referral and polysomnography</li> <li>• Chronic obstructive pulmonary disease</li> </ul>
Anxiety and depression	Anxiety 81% Depression 31%	Not associated with an asthma phenotype	<ul style="list-style-type: none"> <li>• Psychologist referral</li> <li>• Pharmacotherapy</li> </ul>

**Evidence for intervention:** Patients with AR and severe asthma have poorer quality of life,<sup>12</sup> greater airway dysfunction and symptoms, and a greater number of hospital admissions.<sup>9</sup> They also have increased use of inhaled corticosteroids and bronchodilators.<sup>13</sup>

**Evaluation and impact of management:** Diagnosis of AR is symptom-based, and there are several validated questionnaires with high specificity and sensitivity such as the sinonasal questionnaire (SNQ).<sup>14</sup>

Treating comorbid AR in patients with asthma may reduce hospitalisation.<sup>15</sup> A few small-scale randomised controlled trials (RCTs) have shown that nasally administered corticosteroids in AR also improve asthma control,<sup>16,17</sup> although not in patients already using inhaled corticosteroids for asthma.<sup>18</sup> Anti-leukotriene compounds have been shown to reduce hospitalisation<sup>15</sup> and improve lung function in patients with asthma and AR, and also to reduce the corticosteroid dose.<sup>19</sup> To date, there are limited data in severe asthma. Allergen-specific immunotherapy has been shown to relieve symptoms and reduce the use of medications, and also to reduce bronchial hyper-reactivity in mild but not severe asthma.<sup>20</sup>

## Chronic rhinosinusitis

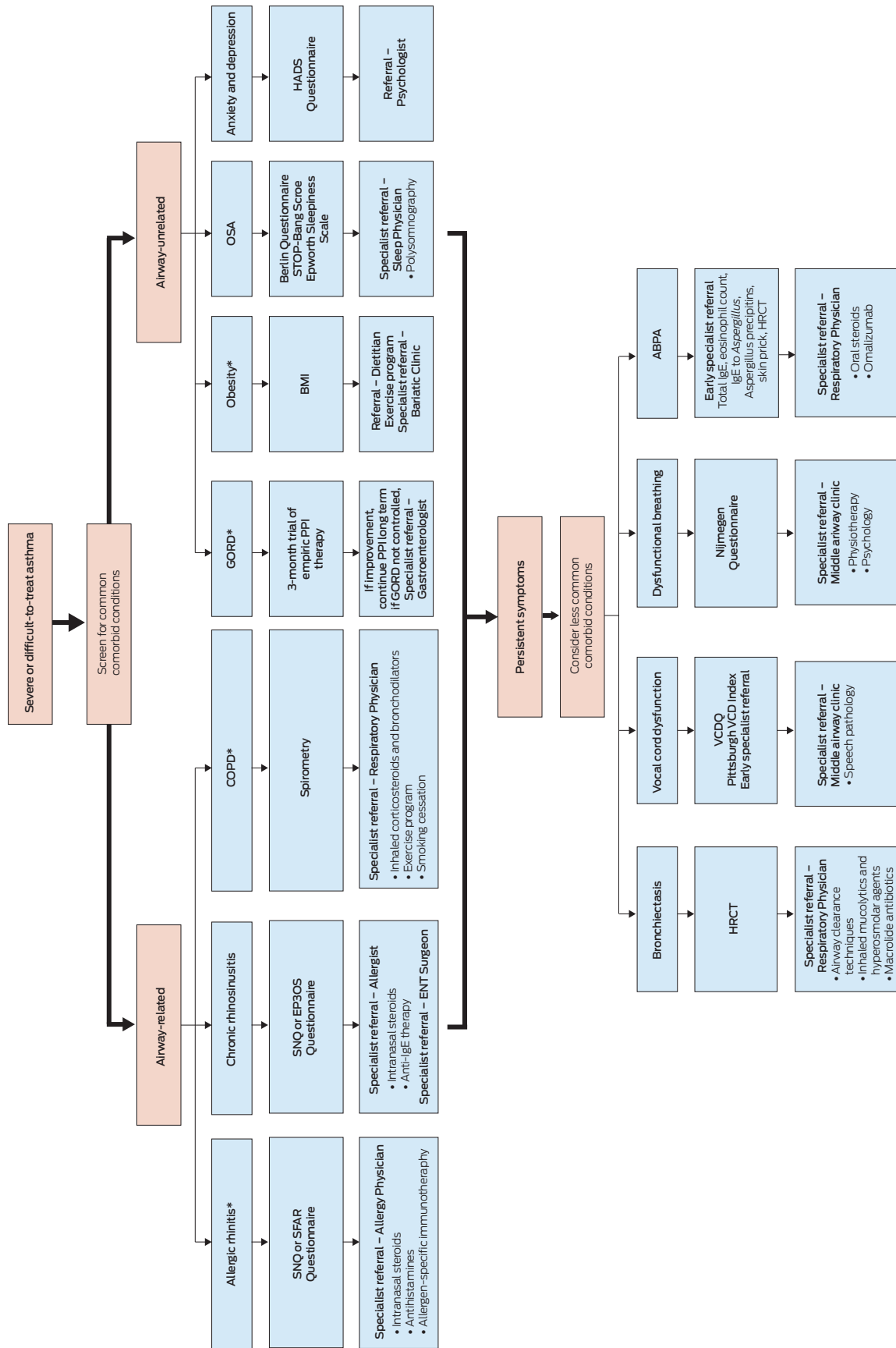
**Prevalence:** The prevalence of chronic rhinosinusitis (CRS) ranges from 45–50% in severe asthma.<sup>8,21</sup> CRS is an independent predictor of asthma exacerbations in severe asthma.<sup>22,23</sup> Nasal polyps are associated with a more severe asthma phenotype.<sup>24</sup>

**Pathophysiology:** There is evidence that severe asthma and CRS have similar pathological abnormalities. Eosinophil inflammation and local IgE production may occur in both,<sup>25</sup> and innate lymphoid cells in sinus mucosal biopsies in CRS are associated with high tissue and blood eosinophilia.<sup>26</sup> The inflammatory profile of sinus mucosa and bronchial biopsies also correlate substantially in both mild and severe asthma.<sup>27</sup>

**Evidence for intervention:** The presence of CRS is associated with lower asthma-related quality of life.<sup>28,29</sup> CRS is also associated with poorer control and more exacerbations of asthma.<sup>28</sup>

**Evaluation and impact of management:** The European Position Paper on Rhinosinusitis and Nasal Polyps questionnaire is strongly associated with positive endoscopic findings in CRS.<sup>30</sup> The SNQ also has high sensitivity and specificity for CRS.<sup>14</sup>

## 2 Proposed iterative approach to assessing comorbid conditions in patients with severe asthma



\*Management may be appropriately initiated in primary care. Specialist referral is suggested at the discretion of the primary care physician or if treatment responses are unsatisfactory. Early specialist referral for diagnosis and management is generally indicated for less common co-morbid conditions.

ABPA = allergic bronchopulmonary aspergillosis; BMI = body mass index; COPD = chronic obstructive pulmonary disease; ENT = ear = nose and throat; EP3OS = European Position Paper on Rhinosinusitis and Nasal Polyps questionnaire; GORD = gastro-oesophageal reflux disease; HADS = Hospital Anxiety and Depression Scale; HRCT = high-resolution computed tomography; OSA = obstructive sleep apnoea; PPI = proton pump inhibitor; SFAR = score for allergic rhinitis; SNQ = Sino-Nasal Questionnaire; VCD = vocal cord dysfunction; VCDQ = vocal cord dysfunction questionnaire.♦

Nasal corticosteroids are considered first-line therapy in CRS treatment, with reduced asthma symptoms and improved control described in small RCTs.<sup>31</sup> There is limited evidence for nasal lavage and low dose macrolides.<sup>31</sup> Cohort studies have shown reduced asthma symptoms<sup>32</sup> and improved control<sup>33</sup> after sinus surgery. Anti-IgE therapy may yield improved outcomes,<sup>34</sup> but there is a need for further studies.

### Vocal cord dysfunction

**Prevalence:** The prevalence of VCD in asthma may range from 19% to 50% depending on severity. Our own data suggested that up to a third of patients with severe asthma have coexisting VCD.<sup>22,35,36</sup>

**Pathophysiology:** The causes of VCD are likely to be multifactorial. Dysfunctional breathing patterns may lead to laryngeal hyper-responsiveness followed by development of VCD. Several other conditions such as gastro-oesophageal reflux disease (GORD), anxiety and psychological disorders may contribute.<sup>37</sup>

**Evidence for intervention:** Due to symptom overlap, patients with VCD are often inaccurately diagnosed as having asthma, or as having severe asthma. This may lead to hospitalisation and inappropriate corticosteroid therapy.<sup>38</sup>

**Evaluation and impact of management:** Direct visualisation of paradoxical vocal cord movements (PVCN) is considered to be the gold standard for diagnosis. Our studies have used dynamic computed tomography of the larynx to diagnose VCD.<sup>36</sup> Surrogate measures of laryngeal dysfunction include attenuation of the inspiratory flow loop on spirometry, but changes may be non-specific.<sup>39</sup>

Several questionnaires can be used, but sensitivity and specificity are questionable.<sup>40-42</sup> The Vocal Cord Dysfunction Questionnaire (VCDQ) can be used to assess response to treatment.<sup>40</sup> In asthma, the Pittsburgh VCD Index has a reported sensitivity of 0.83 and specificity of 0.95 for diagnosing laryngoscopy-proven VCD,<sup>41</sup> but this has not been verified.

Treating VCD involves a multidisciplinary approach. Speech therapy is considered the mainstay of treatment<sup>43</sup> and can relieve symptoms and reduce PVCN.<sup>40,44</sup> Identifying and treating comorbid conditions (GORD, sinusitis, asthma) can yield improvement.<sup>43,45</sup> As yet no convincing data exist to support use of continuous positive airway pressure (CPAP) therapy, botulinum toxin<sup>46</sup> or psychotherapy.<sup>47</sup> Benefits of treating VCD itself and the impact on asthma outcomes have not been determined.

### Dysfunctional breathing

**Prevalence:** Dysfunctional breathing is a term describing breathing disorders where chronic changes in breathing pattern result in dyspnoea and other symptoms in the absence or in excess of the magnitude of physiological respiratory disease. As there is no established definition of dysfunctional breathing (DB), estimates of prevalence vary. In one study, DB was detected in up to 30% of patients with asthma; more so in those with difficult-to-treat asthma.<sup>22,48,49</sup>

**Pathophysiology:** Mechanisms are poorly understood but may be related to hypocapnia,<sup>50</sup> thoraco-abdominal breathing asynchrony,<sup>51</sup> or hyperventilation.<sup>52</sup> Asthma has been linked to panic disorders<sup>49</sup> which in turn are strongly associated with hyperventilation.<sup>53</sup>

**Evidence for intervention:** Patients with DB report a poorer asthma quality of life and asthma control, independent of airway hyper-responsiveness or airway inflammation.<sup>48</sup>

**Evaluation and impact of management:** The most widely used tool for assessing DB is the Nijmegen Questionnaire.<sup>54</sup>

Breathing techniques taught by a physiotherapist relieve respiratory symptoms without significant benefits on respiratory function.<sup>55,56</sup> Breathing exercises have been shown to reduce symptoms<sup>57</sup> and, in conjunction with thoracic muscle massage (Lotorp method), can relieve symptoms and improve peak expiratory flow (PEF), but not forced expiratory volume in 1 second (FEV<sub>1</sub>).<sup>58</sup> A meta-analysis was unable to provide definitive conclusions about asthma outcomes with breathing exercises (due to variations in study methods), but there was a trend towards a positive effect.<sup>59</sup> The benefits of psychological intervention on asthma outcomes have not been evaluated.

### Allergic bronchopulmonary aspergillosis and severe asthma with fungal sensitisation

**Prevalence:** The prevalence of allergic bronchopulmonary aspergillosis (ABPA) in severe asthma may be as high as 2.5%.<sup>60</sup> In patients with asthma who have significantly elevated IgE (> 1000 IU/mL), the prevalence of ABPA increases to 15%.<sup>61</sup> Isolation of fungus from the airway of patients with severe asthma and fungal sensitisation is common (up to 70%), suggestive of an association between fungal colonisation and both sensitisation and severity of asthma.<sup>62</sup> This has led to the use of the term "severe asthma with fungal sensitisation" (SAFS) to describe sensitisation to *Aspergillus* in severe asthma in the absence of other features of ABPA.

**Pathophysiology:** ABPA is considered to be an immune response acting via type-2 T-lymphocyte pathways (Th2 pathways) in lung disease. Th2 CD4+ cell responses to *Aspergillus* antigens are seen in bronchoalveolar lavage and systemically.<sup>63</sup> Sensitisation to *Aspergillus* increases the risk of adult-onset asthma.<sup>64</sup>

**Evidence for intervention:** ABPA is associated with persistent asthma, and there is a significant association between *Aspergillus fumigatus* IgE sensitisation, colonisation, and impaired post-bronchodilator FEV<sub>1</sub>.<sup>65</sup>

**Evaluation and impact of management:** Diagnostic criteria for SAFS have been proposed<sup>66</sup> and include: predisposing condition such as asthma or cystic fibrosis; *Aspergillus* skin test positivity or detectable IgE levels against *A. fumigatus*; elevated total serum IgE concentration (> 1000 IU/mL); and one of: precipitating serum antibodies to *A. fumigatus*; radiographic pulmonary opacities; or a total eosinophil count of > 500 cells/μL.

Although improvements in asthma outcomes have not been demonstrated in high-quality studies, treatment of ABPA is recommended in severe asthma.<sup>67</sup> The mainstay of ABPA treatment is oral corticosteroids.<sup>68</sup> Adjunctive antifungal agents have been shown to reduce oral corticosteroid requirements, with itraconazole recommended after meta-analysis of 12 trials. (Suggested treatment regimens vary but most suggest an itraconazole course of 4–6 months duration<sup>69</sup>). Voriconazole and posaconazole are also effective, even as second-line agents in patients who do not respond to itraconazole,<sup>70</sup> although there is a need for larger prospective studies. The impact of antifungal treatment in SAFS is uncertain, with mixed results in two RCTs.<sup>71</sup> International guidelines suggest no treatment in the absence of other characteristics of ABPA.<sup>4</sup> The anti-IgE monoclonal antibody treatment omalizumab may reduce exacerbations in ABPA.<sup>72</sup>

### Bronchiectasis

**Prevalence:** The prevalence of bronchiectasis is significantly higher in severe asthma (range 24–40%)<sup>73,74</sup> than in milder disease (3%).<sup>75</sup>



**Pathophysiology:** Impaired mucociliary clearance and increased bronchial secretions may lead to airway obstruction and airflow limitation. This in turn will predispose patients to exacerbations of their asthma.<sup>76</sup>

**Evidence for intervention:** Patients with asthma who have bronchiectasis have more exacerbations, hospitalisations,<sup>77</sup> and more chronic respiratory failure.<sup>75</sup>

**Evaluation and impact of management:** High resolution computed tomography is the diagnostic modality of choice in bronchiectasis.<sup>78</sup>

Treatment for bronchiectasis includes airway clearance,<sup>79</sup> exercise,<sup>80</sup> and inhaled hyperosmolar agents.<sup>81,82</sup> Regular macrolide use may reduce exacerbations in patients with bronchiectasis,<sup>83</sup> without benefits on lung function.<sup>84</sup> Despite the relatively high prevalence of bronchiectasis in severe asthma, to date, evidence to support specific treatments is lacking.

### Chronic obstructive pulmonary disease

**Prevalence:** Chronic obstructive pulmonary disease (COPD) prevalence in severe asthma may be as high as 15–20%,<sup>85</sup> but estimates are limited.

**Pathophysiology:** There is considerable overlap in the airway inflammation observed in severe asthma and COPD.<sup>86</sup> Moreover, patients with asthma who smoke have increased numbers of neutrophils in the airways and corticosteroid resistance, as is characteristic of COPD.<sup>87,88</sup>

**Evidence for intervention:** Patients with asthma and COPD are more often hospitalised,<sup>89</sup> have greater health impairment<sup>90</sup> and more frequent exacerbations<sup>91,92</sup> than for either condition alone.

**Evaluation and impact of management:** There is a limited body of evidence to inform management of patients with asthma and COPD. Smoking cessation is essential, and inhaled corticosteroids and bronchodilators remain the mainstay of treatment.<sup>93</sup> Due to the important role of corticosteroids in uncontrolled asthma, the Global Initiative for Asthma (GINA) guidelines<sup>3</sup> suggest treatment with inhaled corticosteroid (ICS) and adjunctive long-acting  $\beta$ -agonist (LABA) therapy, with avoidance of LABA monotherapy. Several large high-quality RCTs have shown improvement in lung function and reduced risk of exacerbations when a long-acting muscarinic antagonist (LAMA), tiotropium, is added to ICS/LABA combination therapy, with other LAMAs requiring further study.<sup>94</sup> A meta-analysis of eight studies (including four large RCTs) did not recommend LAMA over LABA add-on therapy to ICS.<sup>95</sup> It should be noted that these studies generally included patients with asthma of mild to moderate severity and not those with typical asthma-COPD overlap.

### Airway-unrelated comorbid conditions

#### Gastro-oesophageal reflux disease

**Prevalence:** GORD is common in patients with asthma, particularly severe asthma, with a reported prevalence of 46–63%.<sup>24,96,97</sup> A study of 24-hour oesophageal pH testing in patients with asthma found that 51% of patients had abnormal results.<sup>97</sup>

**Pathophysiology:** Acid in the oesophagus may produce bronchoconstriction through increased vagal tone,<sup>98,99</sup> and GORD increases bronchial hyper-responsiveness, with a dose-response relationship.<sup>100</sup>

The association between asthma and GORD may be bidirectional. Methacholine-induced bronchoconstriction has been found to increase the rate of transient lower oesophageal sphincter relaxation and reflux episodes.<sup>101</sup> Additionally, the use of oral corticosteroids may exacerbate GORD.<sup>102</sup>

**Evidence for intervention:** GORD is associated with poorer asthma control and asthma-related quality of life<sup>22,103,104</sup> and it is an independent predictor of asthma exacerbations.<sup>105,106</sup>

**Evaluation and impact of management:** Empiric therapy with a proton pump inhibitor (PPI) twice-daily is the recommended initial step in patients with symptoms of GORD.<sup>107</sup> Improvement of asthma and GORD during a 3-month trial of PPI therapy is considered diagnostic of GORD-triggered asthma.<sup>108</sup>

RCTs of twice-daily PPI in patients with moderate-to-severe asthma and symptomatic GORD have shown a benefit on asthma quality of life and exacerbations,<sup>109</sup> as well as minor improvements in PEF<sup>110</sup> and FEV<sub>1</sub>.<sup>111</sup> However, treatment of asymptomatic gastro-oesophageal reflux has not been shown to improve asthma control<sup>112</sup> or PEF.<sup>110</sup> Referral to a gastroenterologist is indicated if GORD is not controlled on twice-daily PPI or if the patient has red flag symptoms (dysphagia, odynophagia, involuntary weight loss or anaemia).<sup>113</sup>

There is insufficient evidence to guide the use of anti-reflux surgery in patients with GORD-related asthma and there are no RCTs comparing the effectiveness of anti-reflux surgery to therapy with PPIs.<sup>114</sup>

### Obesity

**Prevalence:** Obesity occurs frequently in patients with asthma. The rise in the prevalence of asthma has paralleled that of the obesity epidemic.<sup>115</sup> The prevalence of obesity, defined as body mass index  $\geq 30$ , is 21–48% in patients with severe asthma.<sup>24,116,117</sup>

Epidemiological studies have shown that obesity is a predictor of asthma prevalence and incidence,<sup>118,119</sup> and a meta-analysis found that the odds ratio of new-onset asthma is about 2.0 for obese compared with normal-weight subjects.<sup>118</sup> Finally, obesity-associated late-onset asthma appears to represent a distinct clinical phenotype of severe asthma, with a preponderance in women.<sup>116,120,121</sup>

**Pathophysiology:** Mechanistic links between obesity and asthma are not understood. Impaired thoracic and airway mechanics related to breathing at lower lung volumes and with smaller tidal volumes in obese patients appears to affect airway function.<sup>122</sup> Chronic systemic inflammation associated with obesity may be linked to airway inflammation.<sup>123</sup> Interestingly, the association between obesity and asthma is stronger in non-allergic adults,<sup>124</sup> suggesting that the association between obesity and severe asthma is not likely to be mediated by type-2 airway inflammation.

**Evidence for intervention:** Obesity is independently associated with asthma severity and poorer asthma outcomes.<sup>125,126</sup> Obese patients are less responsive to asthma treatments.<sup>127,128</sup> Obesity may also be an adverse consequence of systemic corticosteroid therapy. Obese patients with severe asthma are more likely to be on maintenance or frequent bursts of oral corticosteroid therapy.<sup>116,121</sup>

**Evaluation and impact of management:** Despite the association between obesity and asthma, there is a paucity of high-quality evidence to support the effectiveness of weight loss. A 2012 Cochrane review of trials of nonsurgical weight loss interventions concluded that the benefit on asthma control remains uncertain.<sup>115</sup>

More recently, however, a small randomised trial of dietary restriction and exercise found that a 5–10% weight loss resulted in small but clinically important improvements in asthma control and quality of life.<sup>129</sup> Another recent randomised trial demonstrated that exercise and dietary modification led to greater weight loss at 3 months than dietary modification alone.

This was associated with clinically significant improvements in asthma control, exacerbations and exercise capacity.<sup>130</sup> A referral to a dietitian is essential, ideally within a multidisciplinary severe asthma service.<sup>131</sup>

Exercise training is well tolerated in asthma and improves aerobic exercise capacity and health-related quality of life.<sup>132</sup> Exercise also appears to be directly beneficial to asthma control.<sup>129</sup>

Although bariatric surgery is the most effective method of achieving weight loss,<sup>133</sup> there are no randomised trials assessing its impact on asthma outcomes.

### Obstructive sleep apnoea

**Prevalence:** Cross-sectional studies of patients attending asthma clinics have reported that 39% have a high risk of obstructive sleep apnoea (OSA) based on the Berlin Questionnaire, a well validated screening tool.<sup>22,134</sup> A meta-analysis of studies using polysomnography noted an OSA prevalence of 49.5% in the adult asthma population.<sup>135</sup> Among patients with severe asthma, the prevalence is even higher, reported to be up to 88–96% in two small prospective studies.<sup>136,137</sup>

**Pathophysiology:** It is likely that OSA impacts on asthma through multiple mechanisms. Repetitive upper airway obstruction and hypoxia may induce airway inflammation, oxidative stress and systemic inflammation.<sup>138–141</sup> There may also be vagally-mediated airway hyper-responsiveness secondary to upper airway collapse.<sup>142</sup> Sleep apnoea may cause altered thoracic mechanics and intrathoracic pressures, which affect bronchial tone.<sup>140</sup>

The relationship between OSA and asthma could be bidirectional. Nocturnal asthma symptoms may exacerbate sleep apnoea and contribute to sleep disruption.<sup>140</sup> Another potential mechanism is the effect of corticosteroids on the upper airway.<sup>137,143</sup>

**Evidence for intervention:** OSA is associated with worse asthma symptoms, even after controlling for obesity, GORD and nasal disease.<sup>144,145</sup> Patients with severe or difficult-to-treat asthma and comorbid OSA have poorer asthma control and quality of life.<sup>22,146</sup> Moreover, 47% of patients with asthma have excessive daytime sleepiness, and OSA may have an additional impact on symptom burden and impaired quality of life, beyond its effects on asthma control.<sup>147</sup>

**Evaluation and impact of management:** Patients with severe asthma should be routinely screened for OSA.<sup>3</sup> The Berlin Questionnaire and STOP-Bang are validated tools.<sup>148,149</sup> Screening is particularly important for asthma patients with comorbid obesity or nasal disease, since these patients are at higher risk for OSA.<sup>150</sup> It is therefore recommended that patients at high risk for OSA be referred to a sleep physician for further assessment as appropriate.

An observational study of patients with asthma and moderate-to-severe OSA commenced on CPAP therapy showed small but clinically significant improvements in asthma control and quality of life at 6 months compared with baseline.<sup>151</sup> This has not been studied in RCTs.

### Anxiety and depression

**Prevalence:** Estimates of the prevalence of anxiety and depression in patients with asthma vary widely. In the general asthma population, the reported prevalence is 11–37% for

anxiety and 11–18% for depression.<sup>152–154</sup> Among patients with severe uncontrolled asthma, 81% had significant anxiety symptoms and 31% had symptoms of depression.<sup>155</sup>

**Pathophysiology:** Patients with severe asthma experience more psychological distress, worse cognitive dysfunction, and worse anxiety than those with moderate asthma. They also have more difficulty coping with their disease and have more problems with adherence to treatment.<sup>156</sup> Importantly, patients with severe prednisolone-dependent asthma are 3.5 times more likely to have depressive symptoms and 2.5 times more likely to have anxiety symptoms than patients with mild-to-moderate asthma.<sup>157</sup>

**Evidence for intervention:** Depression is associated with greater asthma severity, worse asthma control,<sup>112,158</sup> poorer asthma-specific quality of life, and an increased risk of hospitalisation for asthma.<sup>153</sup> Anxiety is associated with poor asthma control.<sup>152</sup> Depression is also an independent predictor of poor adherence to treatment with asthma medications.<sup>159</sup> A study of patients with difficult-to-treat asthma found that psychological dysfunction is associated with an almost 11-fold increase in the risk of frequent exacerbations. It was the strongest predictor out of 13 potential risk factors studied.<sup>23</sup> In addition, depression is associated with an increased risk of long-term or permanent work disability in patients with asthma.<sup>160</sup>

**Evaluation and impact of management:** Screening for anxiety and depression is recommended in all patients with severe asthma.<sup>3</sup> The Hospital Anxiety and Depression Scale (HADS) is a self-assessment questionnaire which is well validated and easily administered.<sup>161</sup> Patients with significant symptoms of anxiety and/or depression should be referred to a psychologist, ideally within a multidisciplinary severe asthma service.<sup>131</sup>

There is a paucity of data on the effectiveness of treatment for anxiety and depression on asthma outcomes. A systematic review of psycho-educational interventions in patients with difficult-to-treat asthma found weak evidence that it may reduce hospital admissions. However, the quality of the studies was poor and there was variability in the interventions used.<sup>162</sup> A randomised trial of cognitive behavioural therapy for asthma-specific anxiety found that this was effective in reducing anxiety, but other asthma-related outcomes were not studied.<sup>163</sup>

## Conclusion

Comorbid conditions are frequently a treatable component of severe asthma. This requires careful clinical assessment, special investigations where indicated and, sometimes, referral to specialists or specialised clinics. General practitioners have a crucial role to play in recognising the range of comorbid conditions, directing investigations and referrals and, ultimately, implementing optimised management. Coordinated, holistic care of patients with severe asthma and a spectrum of comorbidities is often not feasible within specialist respiratory practice; effective collaboration with general practitioners, who may be better placed to oversee optimal management across all domains, is essential.<sup>164</sup>

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