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# Severe asthma and quality of life

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**Abstract:** Severe asthma has a great impact on the quality of life (QOL) of patients and their families. The magnitude of this morbidity is affected by several personal factors including age. Appropriate asthma control and modifications of social roles and activities are expected to improve QOL. Biologics, primarily monoclonal antibodies, have been developed to target specific pathways and molecules important in the pathogenesis of asthma. The use of biologics has shown some promising effects on the QOL of patients with severe recalcitrant asthma. Other potential measures involve targeting risk factors and comorbidities and improving the levels of adherence to therapy. This article briefly reviews the impact of severe asthma on QOL and the potential methods to combat this morbidity including the available therapeutic biologics.

**Keywords:** Severe asthma, Quality of life, Biologics, Adherence, Monoclonal antibodies

## Background

Severe and/or recalcitrant asthma is increasingly recognized as a major unmet need. Estimates vary worldwide, but generally 5 to 10% of patients are considered severe, that is, uncontrolled despite optimal pharmacologic therapy. Severe asthma has a great impact on the quality of life (QOL) of patients and their families. QOL is defined as the perception that individuals have of their position in life, in the context of the culture and system of values in which they live and in relation to their objectives, expectations, standards, and concerns [1].

QOL is an important construct for characterizing patient populations and evaluating therapeutic interventions, and this construct is not captured in other biological or clinical asthma outcome measures. None of the currently available QOL instruments is to be considered standard. Many instruments have been translated into languages other than English in order to address the global cultural differences. Some instruments do not adequately fit with age-related developmental capabilities. For instance, there are limited data on their value in the elderly, among whom there may be many confounding comorbidities. [2] In asthma, the conventional clinical outcomes address mortality and morbidity prevention and QOL assessment addresses the patients' well being. A factor analysis that addressed the relationship between quality of life and clinical status in asthma has shown clearly that patient well-being

cannot be imputed from clinical outcomes, and that it must be measured and interpreted independently [3].

An analysis of a large cohort of patients with severe or difficult-to treat asthma revealed that greater severity and numbers of asthma exacerbations were significantly associated with decreases in asthma-related QOL [4]. Symptoms and activity limitations are the two main domains that potentially affect the QOL in patients with severe asthma. Appropriate asthma control and modifications of other aspects of QOL, related to social roles and activities, are expected to improve QOL [5]. Also biological therapies are increasingly showing efficacy in terms of severe asthma control and hence living with better quality. We sought to briefly review the impact of severe asthma on QOL and the potential methods to combat this morbidity.

## The effects of severe asthma on QOL in relation to different age groups

The effect of asthma on QOL is expected to occur with different characteristics and magnitude according to several patient factors, including age. Moderate to severe asthma has led to a worse QOL as compared to mild persistent asthma; however, the personal burden of illness, as perceived by the patient, cannot be fully assessed by objective measures of disease severity; for asthma traditional clinical indices only moderately correlate with how patients feel and live daily [6].

The QOL concept represents the multidimensional perspective of asthma control. This is a better way to validate the impact of disease in the real life of patients. It may be directly assessed applying the QOL questionnaire (QOLQ)

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[7] or indirectly by the Asthma Control Test (ACT) [8]. The latter is not actually a QOL instrument but may give an idea about coping with the disease burden. Although correlation between these tools and GINA has been found, the QOLQ seems to be more appropriate for adjusting the treatment [9]. The asthma quality of life questionnaire (AQLQ) covers four health domains: activity limitation, symptoms, emotional function and environmental stimuli. A version adapted for children (Pediatric Asthma Quality of Life Questionnaire-Adapted, PAQLQ-A) is also available [10] and has been validated and translated to more than 40 languages. However, the application of this tool in daily practice is not easy, which has motivated several studies trying to detect those factors affecting more the QOL in children and adults. A study from Malaysia sought to determine clinical factors most related to QOL in adults with severe asthma. Symptom frequency, especially chest tightness and shortness of breath were strongly associated with impaired QOL scores. Among the domains measured, the ones most severely reduced were those relating to physical and emotional capabilities as well as general health status [11].

As a part of the TENOR study in the US, including adolescents and adults, Luskin et al. showed that asthma exacerbation frequency and severity and the number of triggers at baseline were strongly associated with patients' asthma-related QOL. They also identified specific asthma triggers that were strongly associated with QOL and risk of future exacerbations [4]. In a study from England, a mini Asthma Quality of Life Questionnaire (mAQLQ), and Asthma Symptom Utility (ASUI) measures were significantly worse for patients suffering exacerbations ($p < 0.001$) compared to those without, however, no data about the domains were measured in this work [12]. A study from Italy found that QOL (as evaluated by AQLQ) is significantly impaired in the group of patients with dyspnea, chest tightness, and asthmatic crisis [13]. It is noteworthy that many of these studies were not performed in severe asthma and more investigations are certainly needed to outline the exact alterations in QOL of severe asthma patients.

Some psychological aspects associated with asthma also lower QOL. After controlling for gender, age, negative affect, and number of co-morbid medical problems in adults, the physical concerns factor of anxiety sensitivity (AS-Physical Concerns) significantly predicted asthma control and influenced all domains of asthma-related QOL (symptoms, activity limitations, emotional functioning, and environmental stimuli) [14]. Asthma severity also affects QOL in adolescents, as has been reported in several studies from different countries [15–18]. Personality traits were significantly related to QOL of adolescents with asthma. These relations were fully mediated by coping and symptom reporting [19].

A study from Brazil revealed that the QOL was directly related to asthma control and asthma severity in children and adolescents [20]. The same was observed in German children [21]. The negative impact on QOL is not only on children but also on their caregivers [22] and family functioning [23, 24].

Finally, it can be said that the most important clinical parameter affecting the QOL of patients with bronchial asthma is disease severity, defined both in terms of objective spirometry results and quasiobjective variables such as the frequency of unscheduled clinic visits and hospitalizations due to exacerbations [25]. On the other hand, Stucky et al., studying 2032 adults with asthma, have found that other factors involving social roles and activities emerged as the strongest predictors of asthma-specific QOL [5]. It seems that the level and seriousness of negative mood and severity of disease in asthmatics significantly impair QOL [26].

## Biologics in severe asthma

Biologics, primarily monoclonal antibodies, have been developed to target specific pathways and molecules thought to be important in the pathogenesis of asthma. In order to justify their expense (typically 15,000 to 25,000 USD/year), these agents have been evaluated for their ability to reduce asthma exacerbations providing a pharmacoeconomic justification for their use.

Due to the heterogeneity of asthma, attempts have been made to optimize the likelihood of positive clinical responses associated with biologics by better characterizing the individual patient's phenotypic and endotypic characteristics, that is, the application of precision medicine. Two major endotypic categories of asthma have been proposed: T2-high (T2-hi) manifested by increased eosinophils in the sputum and airways of patients; and T2-low (T2-lo) manifested by increased neutrophils or a paucigranulocytic profile with normal eosinophil and neutrophil counts in the sputum and airways [27, 28].

Cytokines thought to be important in the pathogenesis of neutrophilic T2-lo asthma include interleukins (IL)-1, 8, 23 and 17 and TNF-alpha. A monoclonal antibody against IL-17 (brodalumab) has been studied in asthma, but did not show substantial benefits [29]. However, the patient population study was not enriched for the presence of airway neutrophilia. Due to adverse consequences, brodalumab clinical development for asthma has been stopped. Blocking TNF-alpha in severe asthma has been met with variable successes but an unacceptable risk-benefit ratio which has also led to a lack of further clinical development for asthma [28]. A CXC chemokine receptor 2 blocker (IL-8 antagonist) has shown no statistically significant improvements in pulmonary functions or symptom scores but a decrease in mild asthma exacerbations in a proof of concept study [30]. Overall, T2-lo asthma

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patients have few therapeutic options since the development of biologics for these patients lags behind those for T2-hi asthma and T2-lo asthma patients have greater resistance to steroids.

There have been a number of biologics developed to treat T2-hi asthma characterized by eosinophilic inflammation with or without antigen-specific IgE. Monoclonal antibodies directed against IgE, IL-4 and 13 and IL-5 have been extensively studied in asthma, and one anti-IgE and two anti-IL-5 monoclonal antibodies have been approved by the US FDA for the treatment of severe asthma [27, 28].

Omalizumab has been in clinical use for over 13 years. Numerous studies have shown that omalizumab reduces asthma exacerbation frequency, the need for corticosteroids, and asthma symptoms while improving QOL. However, omalizumab's effects on pulmonary functions are not insistently clinically important [27, 28]. Recent data suggest that patients with higher blood eosinophil levels may respond better to omalizumab [31–33].

Mepolizumab and reslizumab, anti-IL-5 monoclonal antibodies, have recently been approved for asthma therapy. Both of these monoclonal antibodies reduced asthma exacerbations in patients with higher blood eosinophil levels. Mepolizumab has also been shown to improve QOL and FEV1 in patients with higher blood eosinophil levels as well as reducing steroid need [34–36]. Reslizumab has consistently demonstrated ability to improve FEV1 and improve QOL in patients with asthma [37–39]. Mepolizumab is dosed monthly subcutaneously whereas reslizumab is dosed monthly intravenously.

Benralizumab has a different mechanism of action. It binds to the IL-5 receptor and causes antibody-dependent cell-mediated cytotoxicity of both eosinophils and basophils. It has been shown to decrease asthma exacerbation rates and improve FEV1 in severe asthma patients with elevated blood eosinophil levels [40, 41]. Benralizumab dosing has not been definitively established but will likely be subcutaneous monthly for the first three doses and then administered every eight weeks. None of the anti-IL-5 monoclonal antibodies has been shown to have clinical benefits in patients with low eosinophil counts in the peripheral blood.

Lebrikizumab and Tralokinumab are two anti-IL-13 monoclonal antibodies that have been studied for asthma. Although initially showing promise in patients with elevated blood periostin levels, replicating phase 3 studies of Lebrikizumab in severe asthma showed disparate results which has led to a lack of further clinical development for asthma [42]. Tralokinumab has been shown to have some positive results in reducing asthma exacerbations in patients with elevated levels of periostin or the dipeptidyl peptidase DPP-4 [43, 44].

Initial attempts to block IL-4 alone were unsuccessful for the management of asthma. Dupilumab is a monoclonal antibody directed against IL-4 alpha receptor, which is common to signaling for both IL-4 and IL-13. This monoclonal antibody is delivered subcutaneously every one to two weeks and has been shown to reduce asthma exacerbations and improve FEV1 and QOL in patients with severe asthma regardless of blood eosinophil levels [45, 46]. However, better effects are noted in patients with higher blood eosinophil levels.

Table 1 summarizes some of the most important characteristics of T2-hi biologics currently in clinical development or approved for the treatment of asthma and Table 2 displays data from clinical trials on the effect of some biologics on HRQOL in severe asthma patients.

## Other potential measures to improve QOL in severe asthma

Adherence to therapy is a determinant of improved asthma control and hence better QOL in severe asthma. A few adherence interventions have been studied closely in asthma. These include shared decision-making for

**Table 1** Biologics currently in development or approved for the treatment of asthma

| Drug | Target | Biomarkers | Effects | Route/Dose |
|------|--------|-----------|---------|-----------|
| Omalizumab | IgE | Ag-specific IgE  Better responses with higher FeNO and blood eosinophils >300 cells/ uL | Decreased asthma exacerbations | 150–375 mg SC q2-q4wks; frequency based on IgE and body weight |
| Mepolizumab | IL-5 | Blood eosinophil count >150 cells/uL at initiation or 300 cells/uL in past year | Decreased asthma exacerbations; Improvement in FEV1 | 100 mg SC q4wk. |
| Reslizumab | IL-5 | Blood eosinophil count >400 cells/uL | Decreased asthma exacerbations; Improvement in FEV1 | 3 mg/kg IV q4wks |
| Benralizumab | IL-5Rα | Blood eosinophil count >300 cells/ uL | Decreased asthma exacerbations; Improvement in FEV1. | 30 mg SC q4wks ×3 then q8wks |
| Tralokinumab | IL-13 | Elevated blood periostin and DDP-4 | Improvement in FEV1 | Not Defined |
| Dupilumab | IL-4Rα | Better responses with blood eosinophil count >300 cells/ uL | Decreased asthma exacerbations; Improvement in FEV1 | 200 or 300 mg SC q2wks; administered at home |

*DDP-4* dipeptidyl peptidase-4, *FeNo* fractional excretion of nitric oxide, *FEV1* forced expiratory volume in 1 s

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**Table 2** Data on impact of some biologic therapies on HRQOL of severe asthma patients

| Medication | Publication | Study design | Population | Results |
|---|---|---|---|---|
| Omalizumab | Holgate et al., 2004 [47] | RDBPC study | Patients ≥12 years with severe allergic asthma (n = 246) | Improved AQLQ scores through 32 weeks. |
| | Humbert et al., 2005 [48] | RDBPC study | Patients ≥12 years with uncontrolled severe persistent allergic asthma (n = 419) | Improved AQLQ scores after 28 weeks or discontinuation. |
| | Hanania et al., 2011 [49] | Prospective, MC, RDBPC, parallel-group, study | Patients ≥12 years with uncontrolled severe allergic asthma (n = 850) | Improved mean AQLQ scores (0.29 point [CI, 0.15 to 0.43]) after 48 weeks |
| | Brodlie et al., 2012 [50] | 16-week therapeutic study | Children with severe asthma (median age 12 years; 15 children <12 years and 19 ≥ 12 years). | Mini-AQLQ score increased from 3.5 to 5.9 (p < 0.0001). |
| | Barnes et al, 2013 [51] | MC retrospective observational study | Patients aged ≥12 years with severe persistent allergic asthma (n = 136) | Improved median AQLQ scores at 16 weeks and up to 12 months post-omalizumab initiation. |
| | Braunstahl et al., 2013 [52] | International, single-arm, open-label, observational registry | Uncontrolled persistent allergic asthma (n = 943). Two patients aged <12; the rest ≥12 years. | Clinically relevant (> 0.5 point) improvement from baseline in the AQLQ and mini-AQLQ scores in 67.2% of patients at month 12 and 60.7% at month 24. |
| | Odajima et al., 2015 [53] | multicenter, uncontrolled, open label study | Children (6–15 years) with uncontrolled severe allergic asthma (n = 38) | Improved scores of asthma-specific QOL questionnaire for pediatric patients after 24 weeks. |
| | Li et al., 2016 [54] | RDBPC, parallel-group, phase III study | Patients ≥18 years with uncontrolled moderate-to-severe persistent allergic asthma (n = 616) | Improved overall AQLQ scores and all individual domain scores after 24 weeks. |
| | Alhossan et al., 2017 [55] | Meta-analysis (24 observational studies across 32 countries) | Adults with Severe Allergic Asthma (n = 9213) | Improvements in quality of life at 4–6 months (Cohen's d = 1.05; 1.29 AQLQ points) and at 12 months of therapy (Cohen's d = 1.20; 1.51 AQLQ points). |
| Mepolizumab | Haldar et al., 2009 [56] | RDBPC, parallel group trial | Adults with refractory eosinophilic asthma (n = 61) | Improved AQLQ scores along one year (mean increase from baseline 0.55) |
| | Ortega et al., 2014 [33] | RDBPC, double dummy study | Adults with severe eosinophilic asthma (n = 576) | Improved SGRQ scores after 32 weeks |
| | Bel et al., 2014 [35] | RDBPC study | Adults with severe eosinophilic asthma (n = 135) | Improved SGRQ scores after 24 weeks |
| | Magnan et al., 2016 [57] | Post hoc analyses from two RDBPC, parallel group, studies | Adults with severe eosinophilic asthma previously treated with omalizumab (n = 711) | Improved SGRQ (after 24–32 weeks) vs placebo in both studies independent of prior omalizumab use. |
| | Chupp et al., 2017 [58] | RDBPC, MC, parallel-group, phase 3b study | Patients ≥12 years with severe eosinophilic asthma (n = 551) | A significant improvement in HRQOL from baseline (SGRQ total score at week 24) and a safety profile similar to that of placebo. |
| Lebrikizumab | Hanania et al., 2015 [59] | Pooled data from two MC, RDBPC studies | Patients ≥18 years with uncontrolled moderate-severe asthma (n = 463) | No placebo-corrected improvements in AQLQ scores at week 12 (wide confidence intervals) despite improvements in lung functions. |
| Tralokinumab | Piper et al., 2013 [42] | RDBPC, MC, parallel-group, phase 2a study | Patients >18 years with uncontrolled moderate-severe asthma (n = 194) | No differential effect was apparent in any of the patient reported outcomes at week 12 despite improved lung functions. |
| | Brightling et al., 2015 [43] | RDBPC, MC, parallel-group, phase 2b study | Patients >18 years with uncontrolled severe asthma (n = 383) | Improvement in AQLQ[S] (p = 0.019) in patients treated every 2 weeks (n = 33) compared with placebo (n = 48) |

*AQLQ* Asthma Quality of Life Questionnaire, *HRQOL* health related quality of life, *MC* multicentre, *RDBPC* randomized double-blind placebo-controlled, *SGRQ* St George's Respiratory Questionnaire

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medication and dose choice, inhaler reminders for missed doses, reduced complexity of the regimen (once versus twice daily), comprehensive asthma education with home visits by asthma nurses and clinicians reviewing feedback on their patients' dispensing records [60].

Asthma education can lower risk of future emergency department visits and hospital admission [61]. Asthma education should highlight the importance of adherence to prescribed inhaled corticosteroids (ICS) even in the absence of symptoms [62]. This mandates that asthma education follow a repetitive pattern and involve literal explanation and physical demonstration of the optimal use of inhaler devices and should be tailored according to the socio-cultural background of the family. Inclusion of interactive components such as workshops, video games, internet programs [63], art therapy group sessions [64], and telephone asthma coaching [65] were reported to improve asthma control and hence QOL.

Targeted parenting skills were chosen to address treatment resistance in a prospective study. After the 6-month intervention, adherence with inhaled corticosteroids increased from 72.9 to 100.0%, ($p$ = 0.013). The percentage of children with controlled asthma increased from 0 to 62.5% ($p$ = 0.026) indicating a clinically meaningful change. Parents' ratings at 6 months suggested that asthma-related tasks and child behaviors were less problematic and their confidence to manage asthma increased [66]. Interventions designed to improve family functioning may actually reduce the extent to which children are distressed by their symptoms [67].

It was suggested that once-daily ICS therapy provides a practical therapeutic option that did not appear to jeopardize the clinical efficacy of asthma controller therapy. [68] Once-daily dosing strategy was associated with lower costs and higher level of quality-adjusted life-years (QALYs) [69].

Patients with asthma are encouraged to engage in sports and physical activities to achieve general well being, reduce cardiovascular risk, and improve QOL (evidence A). However, it does not confer specific benefit on lung functions or asthma symptoms per se with the exception of swimming in young patients (evidence B). Exercise-induced asthma can always be reduced by maintenance ICS and the use of SABA before or during exercise [60]. It was demonstrated that aerobic exercise reduces nuclear factor kappa light-chain enhancer of activated B cells (NF-κB) activation and increases release of the anti-inflammatory cytokine interleukin (IL)-10 [70]. Low- to moderate-intensity aerobic exercise was found to reduce asthmatic inflammation in clinical and experimental models [71].

Some risk factors contribute to severe asthma and alter the QOL including the presence of GERD, chronic rhinosinusitis, obesity, and confirmed food allergy. Weight reduction of even 5–10% can lead to better asthma control and QOL (Evidence B) [60]. Risk ratio analysis showed that obese children had a higher likelihood of going to the emergency department and of hospitalization than the overweight and normal-weight groups [72]. Older male children with more severe asthma who had at least one smoking parent reported lower asthma-specific QOL according to self- and proxy reports. [73]. Symptoms of gastroesophageal dysmotility are an independent predictor of cough-specific QOL of patients with cough variant asthma [74].

Panic disorder is a common anxiety disorder among asthmatic patients with overlapping symptoms (e.g., hyperventilation). It is associated with poor asthma control and QOL and may thus be an important target for treatment [75]. Sleep disturbances, such as difficulty initiating and maintaining sleep and early morning awakenings, are commonly reported by patients with asthma [76]. Sleep quality, independent of gastroesophageal reflux disease and obstructive sleep apnea has been associated with worse asthma control and QOL in patients with asthma, even after controlling for relevant covariates. Future research is warranted to determine if behavioral and/or medical treatment of sleep problems can improve asthma control and QOL [77].

A multicenter observational study suggested that temperature-controlled laminar airflow as a non-pharmacological management approach significantly reduced allergen exposure and airway inflammation and improved the QOL of patients with poorly controlled allergic asthma [78]. Another treatment option that was suggested for patients with severe therapy-refractory asthma is bronchial thermoplasty. It is said to down-regulate selectively structural abnormalities involved in airway narrowing and bronchial reactivity, particularly airway smooth muscles, neuroendocrine epithelial cells, and bronchial nerve endings [79]. The overall quality of evidence regarding this procedure is moderate and it leads to a modest clinical benefit in QOL [80].

## Conclusions

In conclusion, severe asthma is detrimental to the quality of life of patients. Therapies targeted to improve QOL include the approved and emerging biologics as well as combating risk factors and comorbidities, and improving the levels of disease control.

## Key Notes

- The most important clinical parameter affecting the QOL of patients with bronchial asthma is disease severity.

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- A number of biologics have been developed to treat asthma characterized by eosinophilic inflammation with or without antigen-specific IgE.
- An anti-IgE and two anti-IL-5 monoclonal antibodies are approved for the treatment of severe asthma and were correlated with better QOL in several trials.
- QOL in severe asthma could also be improved by achieving better adherence to therapy, potentiating health education, addressing risk factors, and targeting social and psychological domains

**Abbreviations**
ACT: Asthma control test; AQLQ: Asthma quality of life questionnaire; ASUI: Asthma symptom utility; DDP-4: Dipeptidyl peptidase-4; FeNo: Fractional excretion of nitric oxide; FEV1: Forced expiratory volume in 1 s; GERD: Gastroesophageal regurgitation disease; GINA: Global initiative for asthma; HRQOL: Health related quality of life; ICS: Inhaled corticosteroids; mAQLQ: Mini asthma quality of life questionnaire; MC: Multicenter; PAQLQ-A: Pediatric asthma quality of life questionnaire-adapted; QALYs: Quality-adjusted life-years; QOLQ: Quality of life questionnaire; RDBPC: Randomized double-blind placebo-controlled; SGRQ: St George's respiratory questionnaire; TENOR: The epidemiology and natural history of asthma: outcomes and treatment regimens

**Availability of data and materials**
This is a review article.

**Authors' contributions**
EH led the development of the document and contributed to "Abstract; Introduction; Table 2; Conclusion; Key Points". LC contributed to "The effects of severe asthma on QOL in relation to different age groups". TC contributed to "Biologics in severe asthma". YE and EH contributed to "Other potential measures to improve QOL in severe asthma". LR initiated the concept and reviewed the manuscript. All authors reviewed and approved the final manuscript.

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