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Pediatric Asthma: Guidelines-Based Care, Omalizumab, and Other Potential Biologic Agents

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Synopsis

Over the past several decades, the evidence supporting rational pediatric asthma management has grown exponentially. As more is learned about the various phenotypes of asthma, the complexity of management will continue to grow. This review focuses on the evidence supporting the current guidelines-based pediatric asthma management and explores the future of asthma management with respect to phenotypic heterogeneity and biologics.

Keywords

asthma; asthma management; pediatric asthma; biologics; omalizumab

Introduction

Asthma affects more than 6 million children, making it one of the most common chronic diseases of childhood, and the prevalence continues to increase.[1] Asthma accounts for over 14 million school absences each year and is the leading cause of hospitalizations among children.[2–4] Fortunately, advances in medical therapy have reduced the number of asthma-related deaths and improved overall quality of life for many asthmatics.[1, 2] Effective management guidelines now exist, with substantial supporting evidence from clinical trials in asthmatic children.[5] Over the past decade, however, there has been a rapid increase in novel therapies for asthma management and few of these have been studied in children.

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Further complicating pediatric asthma management is the diagnosis of asthma itself. There is significant heterogeneity amongst children who wheeze, and only a subset of all children who wheeze will go on to develop asthma.[6–8] Several studies have looked at both children who wheeze and those that subsequently develop asthma and have clustered children into distinct phenotypes.[6–9] This phenotypic variability is only the tip of the iceberg in the heterogeneity amongst asthmatics, as can be seen with range of responses to guidelines based therapy. Although this heterogeneity causes some difficulty in the diagnosis and management of asthma in children, it also poses the unique opportunity for targeted asthma therapy. In the era of biologics, targeted therapy may become increasingly important and fundamental to management.

This review will focus on (1) potential opportunities for prevention of pediatric asthma (2) the evidence supporting the current guidelines based therapies with an emphasis on phenotypic heterogeneity, and (3) promising novel therapeutics that have not yet been incorporated into standard care.

Prevention

Prevention is the holy grail of any chronic disease management, including for asthma. With tools such as the Asthma Predictive Index to predict which children will develop asthma, prevention may be a possibility for the future.[10] One phenotype that has been targeted for prevention already is the allergic atopic phenotype. There is a strong association between allergen sensitization and asthma, and early exposure to allergens in sensitized atopic children has been shown to reduce lung function.[11, 12] Prophylactic interventions have thus been aimed at reducing allergen exposure and inducing tolerance. The Inner City Asthma Study showed that reducing cockroach and dust mite allergen in the home significantly reduced asthma symptoms in inner-city asthmatic children.[13] Jacobsen et al showed that treatment with subcutaneous allergen immunotherapy prevents the development of asthma in atopic children.[14, 15] Subsequent trials have supported these findings, and similar results have been obtained using sublingual immunotherapy.[16–19]

There is also a strong association between RSV bronchiolitis and the development of asthma.[11, 20–24] Palivizumab, an anti-RSV monoclonal antibody, has been shown to reduce wheezing in premature infants, suggesting that perhaps it may prevent the development of asthma in this population.[25, 26] The impact of palivizumab on wheezing in term infants remains to be determined.

Lastly, given the growing evidence for the role of gut flora in the development of allergic and atopic disease, probiotics have become of interest in preventing not only asthma, but other allergic diseases as well. Unfortunately, the data have not supported the use of probiotics in the prevention of asthma thus far. Multiple studies have had limited if any positive results and a recent meta-analysis of trials of probiotic supplementation in pregnancy and infancy found no evidence that probiotics prevented the development of asthma.[27, 28] Some studies suggest that there may be a role for probiotics in preventing asthma in children that are otherwise atopic, although further work is needed in this area.[29]

Medication Adherence

Once the diagnosis of asthma is established, ensuring medication adherence becomes a fundamental component of asthma manegement.[5, 30, 31] Poor adherence leads to increased morbidity and unnecessary escalation of treatment regimens.[32, 33] In children with asthma, noncompliance with inhalers is a significant problem in all disease severity categories, with some studies citing rates of adherence below 60%.[31, 34–36]

The reasons for non-adherence are many and differ depending on the child and family.[30, 36–38] Cost, lack of knowledge about asthma, and patient motivation have been cited in multiple studies as the most critical barriers to adherence.[37, 38] In several analyses, education of the parent or caregiver on the importance of medication and impact on the underlying disease was found to be a major factor toward improving child medication adherence.[37, 38] Providers also play a key role, as appointment time constraints, changes in providers, and barriers to scheduling appointments have all been shown to worsen medication noncompliance.[37, 38] Implementation of the guidelines-based therapy and the development of novel therapies for the refractory asthmatic discussed below will only be of benefit if clinicians address adherence as a primary component of asthma management.

Inhaled Corticosteroids

Based on several large trials, inhaled corticosteroids have become the first-line agent in the management of asthma and remain the preferred treatment choice for all levels of persistent asthma in children.[39, 40] Unfortunately, in spite of improving asthma control, inhaled corticosteroids have not been shown to alter the progression of asthma. In a large randomized controlled trial from the CAMP Group, budesonide was not shown to preserve lung function when compared with placebo.[41, 42] The PEAK Trial demonstrated that inhaled corticosteroids decreased wheezing episodes and need for supplemental inhalers in young children with a positive modified Asthma Predictive Index, but this effect did not last once the inhaled corticosteroids were discontinued.[40] Similarly, inhaled corticosteroids have not been shown to alter the progression of intermittent to persistent wheezing in infants.[43] Additionally, there is evidence to suggest that well-controlled asthmatic children on inhaled corticosteroids with normal spirometry continue to have abnormalities in lung clearance indices, suggesting abnormalities persist despite not being detectable using standard office measurements.[44]

Interestingly, newer data suggest that inhaled corticosteroids may hold greater benefit in certain subpopulations. Numerous studies have shown heterogeneity in response to inhaled corticosteroids.[40, 45–47] For example, some studies have shown that treatment with fluticasone propionate has greatest benefit in children with frequent symptoms, family history asthma, and those with a positive asthma predictive index.[40, 45] Another study found better outcomes with inhaled corticosteroids in Caucasians, males, and those with aeroallergen sensitization.[47] More recently, benefit from fluticasone propionate has been associated with a specific CYP3A4 genetic polymorphism.[46]

Furthermore, the newer generation inhaled corticosteroids may improve control for the asthmatic population as a whole. Newer generation inhaled corticosteroids, ciclosenide and

mometasone, generate smaller particle size and thus better reach the peripheral airways at lower doses. Although there is evidence to suggest that children on traditional long-term inhaled corticosteroids may have increased risk for delayed growth, studies support that most children achieve their predicted adult heights when treated with recommended doses.[42, 48] Nevertheless, studies suggest that the newer generation inhaled corticosteroids have a smaller side-effect profile due to lower daily doses.[30, 49–54] A 2013 Cochrane Review, however, found no difference in control of asthma symptoms, exacerbations, or side effects between ciclosenide, budesonide, and fluticasone.[55] An additional potential benefit of these newer agents, however, is that both ciclosenide and mometasone are effective as once daily dosing, and thus may improve medication adherence.[30, 53, 56]

Alternatives to Inhaled Corticosteroids

Other agents, including cromolyn and leukotriene receptor antagonists, have also shown some benefit in children but largely have not performed as well as inhaled corticosteroids and thus are not considered first-line therapy.[5, 57–63] As with inhaled corticosteroids, there may be some phenotypic variability in response to leukotriene receptor antagonists. Evidence suggests that the differential response to inhaled corticosteroids and leukotriene receptor antagonists is greatest in children with lower lung function, allergic airway inflammation, and elevated FeNO, and children with higher ratios of urinary leukotriene E4 to FeNO may respond better to leukotriene receptor antagonists.[57, 61, 64–69] The data are somewhat inconsistent and thus these biomarkers have not yet made it into the guidelines for clinical practice.[5]

Theophylline, an agent with a long history in the mangement of asthma, has been shown to be inferior to inhaled corticosteroids and inferior to montelukast as add-on therapy.[70, 71] One small trial showed that the addition of theophylline to inhaled corticosteroids resulted in improvement in peak expiratory flow, but did not improve FEV1 or bronchial reactivity.[72] Given the lack of substantial supporting evidence, potential toxicity, and need for frequent monitoring, theophylline is not part of first-line therapy for children with asthma and is not recommended for children under 5.[5]

Step-Up Therapy

If inhaled corticosteroids do not adequately manage a child's asthma, the guidelines suggest that the next step in therapy be the addition of a long-acting beta agonist.[5] The addition of a long-acting beta agonist to inhaled corticosteroids has been shown to improve lung function for most children, but many studies have shown there is significant variability in response and resulting asthma control.[68, 73–78] The Best Add-On Giving Effective Response (BADGER) study showed that while the addition of long-acting beta agonists to low dose inhaled corticosteroids were the most likely to reduce exacerbations, and improve FEV_1 and the number of asthma control days when compared with medium dose inhaled corticosteroids or the addition of a leukotriene receptor antagonist, the study also demonstrated that there was significant variability amongst the children with regard to these results.[78] As many as 26.7% of children in the study responded better to a medium dose of inhaled corticosteroids and 29.2% to leutkotriene receptor antagonists.[78] In a recent study

post-hoc analysis of the BADGER study, Rabinovitch et al. identified phenotypic variables that would differentiate these populations of children.[68] The authors found that higher impulse oscillometry reactance area, suggesting peripheral airway obstruction, corresponded to better response to the addition of long-acting beta agonists to low dose inhaled corticosteroids than increasing the dose of inhaled corticosteroids or adding a leukotriene receptor antagonist.[68] Additionally, they found that higher urinary leukotriene E_4 levels predicted better response to the addition of leukotriene receptor antagonists.[68] Thus, just as with inhaled corticosteroids and leukotriene receptor antagonists as discussed before, there is likely phenotypic variability in response to long-acting beta agonists. Further work is needed to justify the use of these markers to differentiate asthma phenotypes in clinical practice.

Novel Uses for Old Therapies

Macrolides have been broadly studied in adult chronic pulmonary diseases as well as children with cystic fibrosis, and have shown significant benefits in some patients.[30, 79–82] The observed improvement is thought to be related to the immunomodulatory role of macrolides and resulting decrease in airway neutrophils.[30, 79–82] Initial optimism surrounding the benefit of macrolides in management of refractory asthma was humbled by the discovery that many macrolides decrease the clearance of steroids.[30, 83, 84] More recently, several small studies have suggested that the use of macrolides in children with asthma may reduce bronchial hyper-responsiveness, airway neutrophils, and shorten the duration of symptoms.[85, 86] There is also some evidence to suggest that asthmatics with colonization by *Chlamydia pneumonia* or *Mycoplasma pneumonia* may have more benefit from macrolides.[30, 87, 88] Some have argued that given the relatively low-risk of macrolides, a trial of therapy in refractory asthmatics is reasonable, although this recommendation has yet to become part of the US guidelines for pediatric asthma management.[5, 30] NHLBI AsthmaNet is currently investigating whether azithriymycin initiated at start of upper respiratory infection in preschool wheezers will alter the development of lower respiratory illness and exacerbation (NCT01272635).

Vitamin D is also known to have immunomodulatory effects and may play a role in the management of asthma.[30, 89, 90] Vitamin D has been shown in vitro to stimulate T-regulatory cells and the production of IL-10 in response to steroids, which then inhibits allergen-specific TH2 cells.[30, 89] Furthermore, a study from the Childhood Asthma Management Program found that children with vitamin D deficiency were more likely to have poorer lung function and less response to inhaled corticosteroids.[90] Whether supplementation of vitamin D impacts asthma outcomes remains to be determined and is currently being evaluated in adults in NHLBI AsthmaNet (NCT01248065).

The Era of Biologics

A subset of asthmatics remains severely symptomatic despite the above therapy, and prior to the introduction of biologics, these patients were relegated to long-term oral corticosteroids. With the advent of biologics, there is now hope that these severe steroid-dependent asthmatics may have alternative options for treatment.

Furthermore, biologics provide the perfect opportunity to selectively choose therapy based on asthma phenotype. The first of these agents to make it to the national guidelines is omalizumab. Omalizumab, an anti-IgE monoclonal antibody, is now recommended by the most recent guidelines from the National Asthma Education and Prevention Program for children 12 years of age and older with moderate-to-severe asthma. These recommendations are supported by over a decade of work showing that omalizumab reduces the frequency of asthma exacerbations, Emergency Department visits, hospitalizations, and decreases the need for rescue medications and steroids in children with asthma.[91–97] There is limited data at this point on the safety and efficacy of long-term use; some of the longest studies have shown that the medication was tolerated for at least 3 years with improvement in both symptoms and lung function.[98] Additionally, data is limited for children under 12 years of age.

Omalizumab has been further studied in specific patient populations and shown significant benefit for asthmatics of certain phenotypes. A major randomized controlled trial of omalizumab in inner city children with asthma of any severity demonstrated significant reduction in asthma exacerbations and symptoms.[99] Omalizumab had the greatest benefit in children with sensitization and exposure to cockroach and dust mites.[99] Post-hoc analysis further supported the concept that anti-IgE therapy may be of particular benefit in those with seasonal exacerbations.[99] Studies of omalizumab in other clinical phenotypes that are thought to be Th2 driven, including patients with chronic rhinosinusitis and those with nasal polyps, have shown promise as well.[100, 101] Given the substantial cost of omalizumab, many have argued for the importance of identifying populations that will have significant benefit and using the drug selectively in those groups.[99, 102, 103] Traditionally, the populations identified have been those with elevated IgE levels and more severe asthma, although recent work has begun to investigate the impact of anti-IgE on specific biomarkers in allergic asthmatics including FeNO, eosinophilia, periostin.[99, 104–107]

While omalizumab is the only biologic that has been approved for asthma in children, there are several others that have shown promise in clinical trials in adults and thus may eventually find their way into pediatric asthma management as well. Additionally, there are ongoing clinical trials for many of biologics in adolescents ages 12 and older. Many of these newer biologics target T cells or T cell cytokines. The role of T cells in asthma has been well-established and is discussed in detail elsewhere.[108] Here we discuss several of the newer biologics, but this list is only intended to be illustrative of the numerous and varied biologics in existence for asthma and is not meant to be a comprehensive list of all biologics trialed in asthma to date.

One such biologic is keliximab, a monoclonal antibody to the CD4 receptor. In phase II trails, keliximab seemed to improve peak expiratory flow, but resulted in diminished CD4 counts.[109, 110] Several of the other biologics under investigation target the cytokines involved in TH-2-mediated allergic and asthmatic inflammation, including IL-2, IL-5, IL-4, and IL-13. IL-2 leads to the activation of TH2 cells, and symptomatic asthmatics have long been known to have increased levels of the IL-2 receptor.[111] Daclizumab, a monoclonal antibody to the IL-2 receptor, has been shown in phase II trials to improve lung function in

adults with moderate to severe asthma on inhaled corticosteroids.[112] No trials have been done on daclizumab in children or adolescents with asthma.

IL-4 and IL-13 are directly involved in IgE-mediated mast cell degranulation and mucus hypersecretion and plays a role in airways remodeling in asthma.[113] Dupilumab, a human monoclonal antibody to IL-4, has been shown to reduce the frequency of asthma exacerbations and improve lung function in adults with persistent moderate-to-severe asthma and elevated sputum eosinophils.[114] No trials have been done on dupilumab in children or adolescents with asthma. Pitrakinra, a recombinant form of IL-4 that blocks the IL-4 receptor signaling, decreased asthma exacerbations and symptoms in patients with specific IL-4 receptor polymorphisms.[115] No trials have been done on pitrakinra in children or adolescents. Lebrikizumab, a monoclonal antibody to IL-13, has been shown in a phase II trial to improve lung function in adult asthmatics, particularly those with elevated serum periostin levels.[116] Periostin, a matricellular protein, is secreted by bronchial epithelial cells in response to IL-13 and results in airway remodeling.[117] Lebrikizumab is currently being studied in children under several different clinical trials, including adolescents age 12–17 on both an inhaled corticosteroid and a second controller agent, steroid-dependent children ages 12 and older, and steroid-dependent children ages 12 and older with a trial design focused on changes in biomarkers. Another anti-IL-13 antibody, tralokinumab, was found in phase IIa trials to also improve lung function, and most dramatically in those with high levels of airway eosinophils.[118] Tralokinumab is currently undergoing pharmokinectic studies in children ages 12–17.

There are several new monoclonal antibodies targeting IL-5, a cytokine linked directly with sputum eosinophilia and airway hyper-responsiveness in asthma.[119] Mepolizumab, a monocloncal antibody to IL-5, has been shown to reduce exacerbations and improve quality of life scores in adults with eosinophilic asthma in phase III clinical trials.[120–122] Numerous studies have shown, however, that mepolizumab has no impact FeNO or FEV1.[120–124] There are numerous ongoing clinical trials of mepulizumab recruiting children ages 12 and older, designed to examine dosing, efficacy, safety, longterm safety, and steroid-sparing effect. Reslizumab, another monoclonal antibody to IL-5, has shown promise in phase II trials in improving asthma quality of life scores and lung function.[125, 126] Interestingly, the greatest benefit was seen in those patients with asthma and nasal polyps.[126] The efficacy and safety of reslizumab in children ages 12 and older with eosinophilic asthma is currently being examined in the several clinical trials.

Potential Therapeutic Targets

In addition to the above-mentioned cytokines, numerous other cytokines have been suggested as targets for biologics in the treatment of asthma (Table 1).[127, 128] Studies in mice suggest that IL-9 may play a role in airway hyperresponsivness, airway eosinohilia and mucus secretion.[129] Medi-528, a monoclonal antibody to IL-9, is under investigation, and has reached phase 2 trials with some promise.[130] Work is also ongoing to develop an anti-IL-25 antibody for use in allergic asthmatics, as IL-25 plays a role in the activation of TH2 lymphocytes, and the development of allergic asthmatic traits.[131] IL-33 was also recently identified as important potential target, as it was found to promote airway remodeling in

pediatric patients with steroid resistant asthma.[132] Pre-clinical studies have shown that anti-IL-33 can prevent the development of allergic asthma in mice.[133] TNF-α, which has shown great success in many chronic inflammatory diseases, is known to be up-regulated in the airways of severe asthmatics.[134, 135] Unfortunately, anti-TNF agents, such as infliximab and golimumab, have had not had much success in asthma secondary to significant risk with limited benefit.[136, 137]

Tyrosine kinase inhibitors, which have become part of the standard of care in the management of many malignancies, have recently come under investigation for use in asthma given their role in inflammatory gene expression.[30, 138] A preliminary study of masitinib, a c-kit/PDGF receptor tyrosine kinase inhibitor, showed promise in reducing asthma symptoms in severe steroid-dependent asthmatics.[138] Further work is needed to determine if the benefits outweigh the potential side effects of such therapy, and a phase III clinical trial of masitinib in severe steroid-dependent asthmatics is currently underway.

Chemokines involved in the homing of inflammatory cells have also attracted attention as being potential targets in the treatment of asthma.[127] CCR3 and eotaxin are involved eosinophil infiltration in the airways, and their presence and level in induced sputum correlates with asthma severity.[139, 140] Furthermore, additional work suggests the CCR3 may play a role in smooth muscle remodeling in asthmatic airways.[141] There has been some investigation into CCR3 and eotaxin antagonists, and results of a clinical trial of a CCR3 receptor antagonist in adults with mild-moderate asthma are currently pending publication.[142, 143] CCR4 is overexpressed in TH2 lymphocytes in asthma, and RS-1748, a CCR4 antagonist, has been shown to reduce airway inflammation in animal models.[127, 144] Another CCR4 antagonist, AMG 761, is currently undergoing phase I clinical trials in asthmatics. Other chemokines may eventually be targeted for asthma therapy as well.

There are many other potential targets under investigation including phospholipase A2, 5′-lipoxygensase, phosphodiesterase-4, thymic stromal lymphopoietin, OX40 ligand, and tissue kallikrein-1, and discussion of these targets is beyond the scope of this review and are discussed in more detail elsewhere.[30, 127]

Conclusions

The management of asthma is becoming much more patient-specific, as more and more is learned about biology behind the development and progression of asthma. The future of asthma management will likely involve phenotypic characterization and potentially even genotypic characterization in certain cases to determine appropriate therapy. Until that time, the therapies sufficient for the majority of pediatric asthmatic patients and the focus should remain on ensuring adherence to the guidelines through education of both patients and providers.

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References

1. Survey NHI. Current Asthma Prevalence. National Center for Health Statistics, Centers for Disease Control and Prevention; 2005.
2. Services DoHaH. Services HaH. Healthy People 2010 Midcourse Review. Washinton DC: US Government Printing Office; 2007.
3. Akinbami LJ, Schoendorf KC. Trends in childhood asthma: prevalence, health care utilization, and mortality. Pediatrics. 2002; 110(2 Pt 1):315–22. [PubMed: 12165584]
4. NCES. Education USDo. Condition of Education. 2001.
5. 3 EPR. Guidelines for the Diagnosis and Management of Asthma. 2007.
6. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. N Engl J Med. 1995; 332(3): 133–8. [PubMed: 7800004]
7. Henderson J, Granell R, Heron J, Sherriff A, Simpson A, Woodcock A, Strachan DP, Shaheen SO, Sterne JA. Associations of wheezing phenotypes in the first 6 years of life with atopy, lung function and airway responsiveness in mid-childhood. Thorax. 2008; 63(11):974–80. [PubMed: 18678704]
8. Spycher BD, Silverman M, Brooke AM, Minder CE, Kuehni CE. Distinguishing phenotypes of childhood wheeze and cough using latent class analysis. Eur Respir J. 2008; 31(5):974–81. [PubMed: 18216047]
9. Just J, Gouvis-Echraghi R, Rouve S, Wanin S, Moreau D, Annesi-Maesano I. Two novel, severe asthma phenotypes identified during childhood using a clustering approach. Eur Respir J. 40(1):55–60. [PubMed: 22267763]
10. Huffaker MF, Phipatanakul W. Utility of the Asthma Predictive Index in predicting childhood asthma and identifying disease-modifying interventions. Ann Allergy Asthma Immunol. 2014 (In Press).
11. Murray CS, Poletti G, Kebadze T, Morris J, Woodcock A, Johnston SL, Custovic A. Study of modifiable risk factors for asthma exacerbations: virus infection and allergen exposure increase the risk of asthma hospital admissions in children. Thorax. 2006; 61(5):376–82. [PubMed: 16384881]
12. Illi S, von Mutius E, Lau S, Niggemann B, Gruber C, Wahn U. Perennial allergen sensitisation early in life and chronic asthma in children: a birth cohort study. Lancet. 2006; 368(9537):763–70. [PubMed: 16935687]
13. Morgan WJ, Crain EF, Gruchalla RS, O'Connor GT, Kattan M, Evans R 3rd, Stout J, Malindzak G, Smartt E, Plaut M, Walter M, Vaughn B, Mitchell H. Results of a home-based environmental intervention among urban children with asthma. N Engl J Med. 2004; 351(11):1068–80. [PubMed: 15356304]
14. Jacobsen L, Niggemann B, Dreborg S, Ferdousi HA, Halken S, Host A, Koivikko A, Norberg LA, Valovirta E, Wahn U, Moller C. Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. Allergy. 2007; 62(8):943–8. [PubMed: 17620073]
15. Jacobsen L. Preventive aspects of immunotherapy: prevention for children at risk of developing asthma. Ann Allergy Asthma Immunol. 2001; 87(1 Suppl 1):43–6. [PubMed: 11476475]
16. Marogna M, Tomassetti D, Bernasconi A, Colombo F, Massolo A, Businco AD, Canonica GW, Passalacqua G, Tripodi S. Preventive effects of sublingual immunotherapy in childhood: an open randomized controlled study. Ann Allergy Asthma Immunol. 2008; 101(2):206–11. [PubMed: 18727478]
17. De Castro G, Zicari AM, Indinnimeo L, Tancredi G, di Coste A, Occasi F, Castagna G, Giancane G, Duse M. Efficacy of sublingual specific immunotherapy on allergic asthma and rhinitis in children's real life. Eur Rev Med Pharmacol Sci. 17(16):2225–31. [PubMed: 23893190]
18. Kim JM, Lin SY, Suarez-Cuervo C, Chelladurai Y, Ramanathan M, Segal JB, Erekosima N. Allergen-specific immunotherapy for pediatric asthma and rhinoconjunctivitis: a systematic review. Pediatrics. 131(6):1155–67. [PubMed: 23650298]
19. Lin SY, Erekosima N, Kim JM, Ramanathan M, Suarez-Cuervo C, Chelladurai Y, Ward D, Segal JB. Sublingual immunotherapy for the treatment of allergic rhinoconjunctivitis and asthma: a systematic review. JAMA. 309(12):1278–88. [PubMed: 23532243]

20. Stensballe LG, Simonsen JB, Thomsen SF, Larsen AM, Lysdal SH, Aaby P, Kyvik KO, Skytthe A, Backer V, Bisgaard H. The causal direction in the association between respiratory syncytial virus hospitalization and asthma. J Allergy Clin Immunol. 2009; 123(1):131–7. e1. [PubMed: 19130934]
21. Henderson J, Hilliard TN, Sherriff A, Stalker D, Al Shammari N, Thomas HM. Hospitalization for RSV bronchiolitis before 12 months of age and subsequent asthma, atopy and wheeze: a longitudinal birth cohort study. Pediatr Allergy Immunol. 2005; 16(5):386–92. [PubMed: 16101930]
22. Bacharier LB, Cohen R, Schweiger T, Yin-Declue H, Christie C, Zheng J, Schechtman KB, Strunk RC, Castro M. Determinants of asthma after severe respiratory syncytial virus bronchiolitis. J Allergy Clin Immunol. 2012; 130(1):91–100. e3. [PubMed: 22444510]
23. Stein RT, Sherrill D, Morgan WJ, Holberg CJ, Halonen M, Taussig LM, Wright AL, Martinez FD. Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 years. Lancet. 1999; 354(9178):541–5. [PubMed: 10470697]
24. Sigurs N, Aljassim F, Kjellman B, Robinson PD, Sigurbergsson F, Bjarnason R, Gustafsson PM. Asthma and allergy patterns over 18 years after severe RSV bronchiolitis in the first year of life. Thorax. 2010; 65(12):1045–52. [PubMed: 20581410]
25. Simoes EA, Groothuis JR, Carbonell-Estrany X, Rieger CH, Mitchell I, Fredrick LM, Kimpen JL. Palivizumab prophylaxis, respiratory syncytial virus, and subsequent recurrent wheezing. J Pediatr. 2007; 151(1):34–42. e1. [PubMed: 17586188]
26. Blanken MO, Rovers MM, Molenaar JM, Winkler-Seinstra PL, Meijer A, Kimpen JL, Bont L. Respiratory syncytial virus and recurrent wheeze in healthy preterm infants. N Engl J Med. 2013; 368(19):1791–9. [PubMed: 23656644]
27. Azad MB, Coneys JG, Kozyrskyj AL, Field CJ, Ramsey CD, Becker AB, Friesen C, Abou-Setta AM, Zarychanski R. Probiotic supplementation during pregnancy or infancy for the prevention of asthma and wheeze: systematic review and meta-analysis. BMJ. 2013; 347:f6471. [PubMed: 24304677]
28. Rose MA, Stieglitz F, Koksal A, Schubert R, Schulze J, Zielen S. Efficacy of probiotic Lactobacillus GG on allergic sensitization and asthma in infants at risk. Clin Exp Allergy. 2010; 40(9):1398–405. [PubMed: 20604800]
29. van der Aa LB, van Aalderen WM, Heymans HS, Henk Sillevis Smitt J, Nauta AJ, Knippels LM, Ben Amor K, Sprikkelman AB. Synbiotics prevent asthma-like symptoms in infants with atopic dermatitis. Allergy. 2011; 66(2):170–7. [PubMed: 20560907]
30. Robinson PD, Van Asperen P. Newer treatments in the management of pediatric asthma. Paediatr Drugs. 2013; 15(4):291–302. [PubMed: 23754138]
31. Sawicki GS, Strunk RC, Schuemann B, Annett R, Weiss S, Fuhlbrigge AL. Patterns of inhaled corticosteroid use and asthma control in the Childhood Asthma Management Program Continuation Study. Ann Allergy Asthma Immunol. 2010; 104(1):30–5. [PubMed: 20143642]
32. Halterman JS, Aligne CA, Auinger P, McBride JT, Szilagyi PG. Inadequate therapy for asthma among children in the United States. Pediatrics. 2000; 105(1 Pt 3):272–6. [PubMed: 10617735]
33. DiMatteo MR, Giordani PJ, Lepper HS, Croghan TW. Patient adherence and medical treatment outcomes: a meta-analysis. Med Care. 2002; 40(9):794–811. [PubMed: 12218770]
34. Milgrom H, Bender B, Ackerson L, Bowry P, Smith B, Rand C. Noncompliance and treatment failure in children with asthma. J Allergy Clin Immunol. 1996; 98(6 Pt 1):1051–7. [PubMed: 8977504]
35. Gamble J, Stevenson M, McClean E, Heaney LG. The prevalence of nonadherence in difficult asthma. Am J Respir Crit Care Med. 2009; 180(9):817–22. [PubMed: 19644048]
36. Bauman LJ, Wright E, Leickly FE, Crain E, Kruszon-Moran D, Wade SL, Visness CM. Relationship of adherence to pediatric asthma morbidity among inner-city children. Pediatrics. 2002; 110(1 Pt 1):e6. [PubMed: 12093987]
37. Bender BG. Overcoming barriers to nonadherence in asthma treatment. J Allergy Clin Immunol. 2002; 109(6 Suppl):S554–9. [PubMed: 12063512]
38. Grover C, Armour C, Asperen PP, Moles R, Saini B. Medication use in children with asthma: not a child size problem. J Asthma. 2011; 48(10):1085–103. [PubMed: 22013989]

39. Bisgaard H, Allen D, Milanowski J, Kalev I, Willits L, Davies P. Twelve-month safety and efficacy of inhaled fluticasone propionate in children aged 1 to 3 years with recurrent wheezing. Pediatrics. 2004; 113(2):e87–94. [PubMed: 14754977]
40. Guilbert TW, Morgan WJ, Zeiger RS, Mauger DT, Boehmer SJ, Szefler SJ, Bacharier LB, Lemanske RF Jr, Strunk RC, Allen DB, Bloomberg GR, Heldt G, Krawiec M, Larsen G, Liu AH, Chinchilli VM, Sorkness CA, Taussig LM, Martinez FD. Long-term inhaled corticosteroids in preschool children at high risk for asthma. N Engl J Med. 2006; 354(19):1985–97. [PubMed: 16687711]
41. CAMP. Long-term effects of budesonide or nedocromil in children with asthma. The Childhood Asthma Management Program Research Group. N Engl J Med. 2000; 343(15):1054–63. [PubMed: 11027739]
42. Covar RA, Spahn JD, Murphy JR, Szefler SJ. Progression of asthma measured by lung function in the childhood asthma management program. Am J Respir Crit Care Med. 2004; 170(3):234–41. [PubMed: 15028558]
43. Bisgaard H, Hermansen MN, Loland L, Halkjaer LB, Buchvald F. Intermittent inhaled corticosteroids in infants with episodic wheezing. N Engl J Med. 2006; 354(19):1998–2005. [PubMed: 16687712]
44. Macleod KA, Horsley AR, Bell NJ, Greening AP, Innes JA, Cunningham S. Ventilation heterogeneity in children with well controlled asthma with normal spirometry indicates residual airways disease. Thorax. 2009; 64(1):33–7. [PubMed: 18678703]
45. Roorda RJ, Mezei G, Bisgaard H, Maden C. Response of preschool children with asthma symptoms to fluticasone propionate. J Allergy Clin Immunol. 2001; 108(4):540–6. [PubMed: 11590379]
46. Stockmann C, Fassl B, Gaedigk R, Nkoy F, Uchida DA, Monson S, Reilly CA, Leeder JS, Yost GS, Ward RM. Fluticasone propionate pharmacogenetics: CYP3A4*22 polymorphism and pediatric asthma control. J Pediatr. 2013; 162(6):1222–7. 7 e1–2. [PubMed: 23290512]
47. Bacharier LB, Guilbert TW, Zeiger RS, Strunk RC, Morgan WJ, Lemanske RF Jr, Moss M, Szefler SJ, Krawiec M, Boehmer S, Mauger D, Taussig LM, Martinez FD. Patient characteristics associated with improved outcomes with use of an inhaled corticosteroid in preschool children at risk for asthma. J Allergy Clin Immunol. 2009; 123(5):1077–82. 82 e1–5. [PubMed: 19230959]
48. Agertoft L, Pedersen S. Effect of long-term treatment with inhaled budesonide on adult height in children with asthma. N Engl J Med. 2000; 343(15):1064–9. [PubMed: 11027740]
49. Robinson PD, Van Asperen P. Asthma in childhood. Pediatr Clin North Am. 2009; 56(1):191–226. xii. [PubMed: 19135588]
50. Milgrom H. Mometasone furoate in children with mild to moderate persistent asthma: a review of the evidence. Paediatr Drugs. 2010; 12(4):213–21. [PubMed: 20593906]
51. Skoner DP, Meltzer EO, Milgrom H, Stryszak P, Teper A, Staudinger H. Effects of inhaled mometasone furoate on growth velocity and adrenal function: a placebo-controlled trial in children 4–9 years old with mild persistent asthma. J Asthma. 2011; 48(8):848–59. [PubMed: 21854342]
52. Gelfand EW, Georgitis JW, Noonan M, Ruff ME. Once-daily ciclesonide in children: efficacy and safety in asthma. J Pediatr. 2006; 148(3):377–83. [PubMed: 16615971]
53. Pedersen S, Garcia Garcia ML, Manjra A, Theron I, Engelstatter R. A comparative study of inhaled ciclesonide 160 microg/day and fluticasone propionate 176 microg/day in children with asthma. Pediatr Pulmonol. 2006; 41(10):954–61. [PubMed: 16868976]
54. Skoner DP, Maspero J, Banerji D. Assessment of the long-term safety of inhaled ciclesonide on growth in children with asthma. Pediatrics. 2008; 121(1):e1–14. [PubMed: 18070931]
55. Kramer S, Rottier BL, Scholten RJ, Boluyt N. Ciclesonide versus other inhaled corticosteroids for chronic asthma in children. Cochrane Database Syst Rev. 2013; 2:CD010352. [PubMed: 23450613]
56. Friedman HS, Navaratnam P, McLaughlin J. Adherence and asthma control with mometasone furoate versus fluticasone propionate in adolescents and young adults with mild asthma. J Asthma. 2010; 47(9):994–1000. [PubMed: 20831468]

57. Chauhan BF, Ducharme FM. Anti-leukotriene agents compared to inhaled corticosteroids in the management of recurrent and/or chronic asthma in adults and children. Cochrane Database Syst Rev. 5:CD002314. [PubMed: 22592685]
58. Tasche MJ, Uijen JH, Bernsen RM, de Jongste JC, van der Wouden JC. Inhaled disodium cromoglycate (DSCG) as maintenance therapy in children with asthma: a systematic review. Thorax. 2000; 55(11):913–20. [PubMed: 11050259]
59. Knorr B, Franchi LM, Bisgaard H, Vermeulen JH, LeSouef P, Santanello N, Michele TM, Reiss TF, Nguyen HH, Bratton DL. Montelukast, a leukotriene receptor antagonist, for the treatment of persistent asthma in children aged 2 to 5 years. Pediatrics. 2001; 108(3):E48. [PubMed: 11533366]
60. Bisgaard H, Zielen S, Garcia-Garcia ML, Johnston SL, Gilles L, Menten J, Tozzi CA, Polos P. Montelukast reduces asthma exacerbations in 2- to 5-year-old children with intermittent asthma. Am J Respir Crit Care Med. 2005; 171(4):315–22. [PubMed: 15542792]
61. Sorkness CA, Lemanske RF Jr, Mauger DT, Boehmer SJ, Chinchilli VM, Martinez FD, Strunk RC, Szefler SJ, Zeiger RS, Bacharier LB, Bloomberg GR, Covar RA, Guilbert TW, Heldt G, Larsen G, Mellon MH, Morgan WJ, Moss MH, Spahn JD, Taussig LM. Long-term comparison of 3 controller regimens for mild-moderate persistent childhood asthma: the Pediatric Asthma Controller Trial. J Allergy Clin Immunol. 2007; 119(1):64–72. [PubMed: 17140647]
62. Ostrom NK, Decotiis BA, Lincourt WR, Edwards LD, Hanson KM, Carranza Rosenzweig JR, Crim C. Comparative efficacy and safety of low-dose fluticasone propionate and montelukast in children with persistent asthma. J Pediatr. 2005; 147(2):213–20. [PubMed: 16126052]
63. Garcia Garcia ML, Wahn U, Gilles L, Swern A, Tozzi CA, Polos P. Montelukast, compared with fluticasone, for control of asthma among 6- to 14-year-old patients with mild asthma: the MOSAIC study. Pediatrics. 2005; 116(2):360–9. [PubMed: 16061590]
64. Knuffman JE, Sorkness CA, Lemanske RF Jr, Mauger DT, Boehmer SJ, Martinez FD, Bacharier LB, Strunk RC, Szefler SJ, Zeiger RS, Taussig LM. Phenotypic predictors of long-term response to inhaled corticosteroid and leukotriene modifier therapies in pediatric asthma. J Allergy Clin Immunol. 2009; 123(2):411–6. [PubMed: 19121860]
65. Szefler SJ, Phillips BR, Martinez FD, Chinchilli VM, Lemanske RF, Strunk RC, Zeiger RS, Larsen G, Spahn JD, Bacharier LB, Bloomberg GR, Guilbert TW, Heldt G, Morgan WJ, Moss MH, Sorkness CA, Taussig LM. Characterization of within-subject responses to fluticasone and montelukast in childhood asthma. J Allergy Clin Immunol. 2005; 115(2):233–42. [PubMed: 15696076]
66. Zeiger RS, Szefler SJ, Phillips BR, Schatz M, Martinez FD, Chinchilli VM, Lemanske RF Jr, Strunk RC, Larsen G, Spahn JD, Bacharier LB, Bloomberg GR, Guilbert TW, Heldt G, Morgan WJ, Moss MH, Sorkness CA, Taussig LM. Response profiles to fluticasone and montelukast in mild-to-moderate persistent childhood asthma. J Allergy Clin Immunol. 2006; 117(1):45–52. [PubMed: 16387583]
67. Meyer KA, Arduino JM, Santanello NC, Knorr BA, Bisgaard H. Response to montelukast among subgroups of children aged 2 to 14 years with asthma. J Allergy Clin Immunol. 2003; 111(4):757–62. [PubMed: 12704354]
68. Rabinovitch N, Mauger DT, Reisdorph N, Covar R, Malka J, Lemanske RF Jr, Morgan WJ, Guilbert TW, Zeiger RS, Bacharier LB, Szefler SJ. Predictors of asthma control and lung function responsiveness to step 3 therapy in children with uncontrolled asthma. J Allergy Clin Immunol. 2013
69. Rabinovitch N, Graber NJ, Chinchilli VM, Sorkness CA, Zeiger RS, Strunk RC, Bacharier LB, Martinez FD, Szefler SJ. Urinary leukotriene E4/exhaled nitric oxide ratio and montelukast response in childhood asthma. J Allergy Clin Immunol. 2010; 126(3):545–51. e1–4. [PubMed: 20816189]
70. Seddon P, Bara A, Ducharme FM, Lasserson TJ. Oral xanthines as maintenance treatment for asthma in children. Cochrane Database Syst Rev. 2006; (1):CD002885. [PubMed: 16437447]
71. Kondo N, Katsunuma T, Odajima Y, Morikawa A. A randomized open-label comparative study of montelukast versus theophylline added to inhaled corticosteroid in asthmatic children. Allergol Int. 2006; 55(3):287–93. [PubMed: 17075269]

72. Suessmuth S, Freihorst J, Gappa M. Low-dose theophylline in childhood asthma: a placebo-controlled, double-blind study. Pediatr Allergy Immunol. 2003; 14(5):394–400. [PubMed: 14641610]

73. Russell G, Williams DA, Weller P, Price JF. Salmeterol xinafoate in children on high dose inhaled steroids. Ann Allergy Asthma Immunol. 1995; 75(5):423–8. [PubMed: 7583864]

74. Zimmerman B, D'Urzo A, Berube D. Efficacy and safety of formoterol Turbuhaler when added to inhaled corticosteroid treatment in children with asthma. Pediatr Pulmonol. 2004; 37(2):122–7. [PubMed: 14730657]

75. Bisgaard H. Effect of long-acting beta2 agonists on exacerbation rates of asthma in children. Pediatr Pulmonol. 2003; 36(5):391–8. [PubMed: 14520721]

76. Van den Berg NJ, Ossip MS, Hederos CA, Anttila H, Ribeiro BL, Davies PI. Salmeterol/fluticasone propionate (50/100 microg) in combination in a Diskus inhaler (Seretide) is effective and safe in children with asthma. Pediatr Pulmonol. 2000; 30(2):97–105. [PubMed: 10922131]

77. Lenney W, McKay AJ, Tudur Smith C, Williamson PR, James M, Price D. Management of Asthma in School age Children On Therapy (MASCOT): a randomised, double-blind, placebo-controlled, parallel study of efficacy and safety. Health Technol Assess. 2013; 17(4):1–218. [PubMed: 23380178]

78. Lemanske RF Jr, Mauger DT, Sorkness CA, Jackson DJ, Boehmer SJ, Martinez FD, Strunk RC, Szefler SJ, Zeiger RS, Bacharier LB, Covar RA, Guilbert TW, Larsen G, Morgan WJ, Moss MH, Spahn JD, Taussig LM. Step-up therapy for children with uncontrolled asthma receiving inhaled corticosteroids. N Engl J Med. 2010; 362(11):975–85. [PubMed: 20197425]

79. Wong C, Jayaram L, Karalus N, Eaton T, Tong C, Hockey H, Milne D, Fergusson W, Tuffery C, Sexton P, Storey L, Ashton T. Azithromycin for prevention of exacerbations in non-cystic fibrosis bronchiectasis (EMBRACE): a randomised, double-blind, placebo-controlled trial. Lancet. 2012; 380(9842):660–7. [PubMed: 22901887]

80. Saiman L, Marshall BC, Mayer-Hamblett N, Burns JL, Quittner AL, Cibene DA, Coquillette S, Fieberg AY, Accurso FJ, Campbell PW 3rd. Azithromycin in patients with cystic fibrosis chronically infected with Pseudomonas aeruginosa: a randomized controlled trial. JAMA. 2003; 290(13):1749–56. [PubMed: 14519709]

81. Equi A, Balfour-Lynn IM, Bush A, Rosenthal M. Long term azithromycin in children with cystic fibrosis: a randomised, placebo-controlled crossover trial. Lancet. 2002; 360(9338):978–84. [PubMed: 12383667]

82. Clement A, Tamalet A, Leroux E, Ravilly S, Fauroux B, Jais JP. Long term effects of azithromycin in patients with cystic fibrosis: A double blind, placebo controlled trial. Thorax. 2006; 61(10):895–902. [PubMed: 16809416]

83. Flotte TR, Loughlin GM. Benefits and complications of troleandomycin (TAO) in young children with steroid-dependent asthma. Pediatr Pulmonol. 1991; 10(3):178–82. [PubMed: 1852515]

84. Ball BD, Hill MR, Brenner M, Sanks R, Szefler SJ. Effect of low-dose troleandomycin on glucocorticoid pharmacokinetics and airway hyperresponsiveness in severely asthmatic children. Ann Allergy. 1990; 65(1):37–45. [PubMed: 2195921]

85. Koutsoubari I, Papaevangelou V, Konstantinou GN, Makrinioti H, Xepapadaki P, Kafetzis D, Papadopoulos NG. Effect of clarithromycin on acute asthma exacerbations in children: an open randomized study. Pediatr Allergy Immunol. 2012; 23(4):385–90. [PubMed: 22433020]

86. Piacentini GL, Peroni DG, Bodini A, Pigozzi R, Costella S, Loiacono A, Boner AL. Azithromycin reduces bronchial hyperresponsiveness and neutrophilic airway inflammation in asthmatic children: a preliminary report. Allergy Asthma Proc. 2007; 28(2):194–8. [PubMed: 17479604]

87. Kraft M, Cassell GH, Pak J, Martin RJ. Mycoplasma pneumoniae and Chlamydia pneumoniae in asthma: effect of clarithromycin. Chest. 2002; 121(6):1782–8. [PubMed: 12065339]

88. Chu HW, Kraft M, Rex MD, Martin RJ. Evaluation of blood vessels and edema in the airways of asthma patients: regulation with clarithromycin treatment. Chest. 2001; 120(2):416–22. [PubMed: 11502638]

89. Xystrakis E, Kusumakar S, Boswell S, Peek E, Urry Z, Richards DF, Adikibi T, Pridgeon C, Dallman M, Loke TK, Robinson DS, Barrat FJ, O'Garra A, Lavender P, Lee TH, Corrigan C,

Hawrylowicz CM. Reversing the defective induction of IL-10-secreting regulatory T cells in glucocorticoid-resistant asthma patients. J Clin Invest. 2006; 116(1):146–55. [PubMed: 16341266]

90. Wu AC, Tantisira K, Li L, Fuhlbrigge AL, Weiss ST, Litonjua A. Effect of vitamin D and inhaled corticosteroid treatment on lung function in children. Am J Respir Crit Care Med. 2012; 186(6): 508–13. [PubMed: 22798322]
91. Busse W, Corren J, Lanier BQ, McAlary M, Fowler-Taylor A, Cioppa GD, van As A, Gupta N. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. J Allergy Clin Immunol. 2001; 108(2):184–90. [PubMed: 11496232]
92. Grimaldi-Bensouda L, Zureik M, Aubier M, Humbert M, Levy J, Benichou J, Molimard M, Abenhaim L. Does omalizumab make a difference to the real-life treatment of asthma exacerbations?: Results from a large cohort of patients with severe uncontrolled asthma. Chest. 143(2):398–405. [PubMed: 23505637]
93. Lafeuille MH, Dean J, Zhang J, Duh MS, Gorsh B, Lefebvre P. Impact of omalizumab on emergency-department visits, hospitalizations, and corticosteroid use among patients with uncontrolled asthma. Ann Allergy Asthma Immunol. 109(1):59–64. [PubMed: 22727159]
94. Brodlie M, McKean MC, Moss S, Spencer DA. The oral corticosteroid-sparing effect of omalizumab in children with severe asthma. Arch Dis Child. 97(7):604–9. [PubMed: 22685051]
95. Humbert M, Beasley R, Ayres J, Slavin R, Hebert J, Bousquet J, Beeh KM, Ramos S, Canonica GW, Hedgecock S, Fox H, Blogg M, Surrey K. Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. Allergy. 2005; 60(3):309–16. [PubMed: 15679715]
96. Lanier B, Bridges T, Kulus M, Taylor AF, Berhane I, Vidaurre CF. Omalizumab for the treatment of exacerbations in children with inadequately controlled allergic (IgE-mediated) asthma. J Allergy Clin Immunol. 2009; 124(6):1210–6. [PubMed: 19910033]
97. Soler M, Matz J, Townley R, Buhl R, O'Brien J, Fox H, Thirlwell J, Gupta N, Della Cioppa G. The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics. Eur Respir J. 2001; 18(2):254–61. [PubMed: 11529281]
98. Ozgur ES, Ozge C, Ilvan A, Nayci SA. Assessment of long-term omalizumab treatment in patients with severe allergic asthma long-term omalizumab treatment in severe asthma. J Asthma. 50(6): 687–94. [PubMed: 23557459]
99. Busse WW, Morgan WJ, Gergen PJ, Mitchell HE, Gern JE, Liu AH, Gruchalla RS, Kattan M, Teach SJ, Pongracic JA, Chmiel JF, Steinbach SF, Calatroni A, Togias A, Thompson KM, Szefler SJ, Sorkness CA. Randomized trial of omalizumab (anti-IgE) for asthma in inner-city children. N Engl J Med. 2011; 364(11):1005–15. [PubMed: 21410369]
100. Gevaert P, Calus L, Van Zele T, Blomme K, De Ruyck N, Bauters W, Hellings P, Brusselle G, De Bacquer D, van Cauwenberge P, Bachert C. Omalizumab is effective in allergic and nonallergic patients with nasal polyps and asthma. J Allergy Clin Immunol. 131(1):110–6. e1. [PubMed: 23021878]
101. Tajiri T, Matsumoto H, Hiraumi H, Ikeda H, Morita K, Izuhara K, Ono J, Ohta S, Ito I, Oguma T, Nakaji H, Inoue H, Iwata T, Nagasaki T, Kanemitsu Y, Ito J, Niimi A, Mishima M. Efficacy of omalizumab in eosinophilic chronic rhinosinusitis patients with asthma. Ann Allergy Asthma Immunol. 110(5):387–8. [PubMed: 23622013]
102. Oba Y, Salzman GA. Cost-effectiveness analysis of omalizumab in adults and adolescents with moderate-to-severe allergic asthma. J Allergy Clin Immunol. 2004; 114(2):265–9. [PubMed: 15316501]
103. Campbell JD, Spackman DE, Sullivan SD. The costs and consequences of omalizumab in uncontrolled asthma from a USA payer perspective. Allergy. 2010; 65(9):1141–8. [PubMed: 20148804]
104. Hanania NA, Wenzel S, Rosen K, Hsieh HJ, Mosesova S, Choy DF, Lal P, Arron JR, Harris JM, Busse W. Exploring the effects of omalizumab in allergic asthma: an analysis of biomarkers in the EXTRA study. Am J Respir Crit Care Med. 187(8):804–11. [PubMed: 23471469]

105. Maselli DJ, Singh H, Diaz J, Peters JI. Efficacy of omalizumab in asthmatic patients with IgE levels above 700 IU/mL: a retrospective study. Ann Allergy Asthma Immunol. 110(6):457–61. [PubMed: 23706716]

106. Bousquet J, Wenzel S, Holgate S, Lumry W, Freeman P, Fox H. Predicting response to omalizumab, an anti-IgE antibody, in patients with allergic asthma. Chest. 2004; 125(4):1378–86. [PubMed: 15078749]

107. Wahn U, Martin C, Freeman P, Blogg M, Jimenez P. Relationship between pretreatment specific IgE and the response to omalizumab therapy. Allergy. 2009; 64(12):1780–7. [PubMed: 19627273]

108. Lloyd CM, Hessel EM. Functions of T cells in asthma: more than just T(H)2 cells. Nat Rev Immunol. 2010; 10(12):838–48. [PubMed: 21060320]

109. Kon OM, Sihra BS, Compton CH, Leonard TB, Kay AB, Barnes NC. Randomised, dose-ranging, placebo-controlled study of chimeric antibody to CD4 (keliximab) in chronic severe asthma. Lancet. 1998; 352(9134):1109–13. [PubMed: 9798587]

110. Kon OM, Sihra BS, Loh LC, Barkans J, Compton CH, Barnes NC, Larche M, Kay AB. The effects of an anti-CD4 monoclonal antibody, keliximab, on peripheral blood CD4+ T-cells in asthma. Eur Respir J. 2001; 18(1):45–52. [PubMed: 11510804]

111. Corrigan CJ, Hartnell A, Kay AB. T lymphocyte activation in acute severe asthma. Lancet. 1988; 1(8595):1129–32. [PubMed: 2896958]

112. Busse WW, Israel E, Nelson HS, Baker JW, Charous BL, Young DY, Vexler V, Shames RS. Daclizumab improves asthma control in patients with moderate to severe persistent asthma: a randomized, controlled trial. Am J Respir Crit Care Med. 2008; 178(10):1002–8. [PubMed: 18787222]

113. Steinke JW, Borish L. Th2 cytokines and asthma. Interleukin-4: its role in the pathogenesis of asthma, and targeting it for asthma treatment with interleukin-4 receptor antagonists. Respir Res. 2001; 2(2):66–70. [PubMed: 11686867]

114. Wenzel S, Ford L, Pearlman D, Spector S, Sher L, Skobieranda F, Wang L, Kirkesseli S, Rocklin R, Bock B, Hamilton J, Ming JE, Radin A, Stahl N, Yancopoulos GD, Graham N, Pirozzi G. Dupilumab in persistent asthma with elevated eosinophil levels. N Engl J Med. 2013; 368(26): 2455–66. [PubMed: 23688323]

115. Slager RE, Otulana BA, Hawkins GA, Yen YP, Peters SP, Wenzel SE, Meyers DA, Bleecker ER. IL-4 receptor polymorphisms predict reduction in asthma exacerbations during response to an anti-IL-4 receptor alpha antagonist. J Allergy Clin Immunol. 2012; 130(2):516–22. e4. [PubMed: 22541248]

116. Corren J, Lemanske RF, Hanania NA, Korenblat PE, Parsey MV, Arron JR, Harris JM, Scheerens H, Wu LC, Su Z, Mosesova S, Eisner MD, Bohen SP, Matthews JG. Lebrikizumab treatment in adults with asthma. N Engl J Med. 2011; 365(12):1088–98. [PubMed: 21812663]

117. Sidhu SS, Yuan S, Innes AL, Kerr S, Woodruff PG, Hou L, Muller SJ, Fahy JV. Roles of epithelial cell-derived periostin in TGF-beta activation, collagen production, and collagen gel elasticity in asthma. Proc Natl Acad Sci U S A. 2010; 107(32):14170–5. [PubMed: 20660732]

118. Piper E, Brightling C, Niven R, Oh C, Faggioni R, Poon K, She D, Kell C, May RD, Geba GP, Molfino NA. A phase II placebo-controlled study of tralokinumab in moderate-to-severe asthma. Eur Respir J. 2012; 41(2):330–8. [PubMed: 22743678]

119. Molfino NA, Gossage D, Kolbeck R, Parker JM, Geba GP. Molecular and clinical rationale for therapeutic targeting of interleukin-5 and its receptor. Clin Exp Allergy. 2012; 42(5):712–37. [PubMed: 22092535]

120. Haldar P, Brightling CE, Hargadon B, Gupta S, Monteiro W, Sousa A, Marshall RP, Bradding P, Green RH, Wardlaw AJ, Pavord ID. Mepolizumab and exacerbations of refractory eosinophilic asthma. N Engl J Med. 2009; 360(10):973–84. [PubMed: 19264686]

121. Nair P, Pizzichini MM, Kjarsgaard M, Inman MD, Efthimiadis A, Pizzichini E, Hargreave FE, O'Byrne PM. Mepolizumab for prednisone-dependent asthma with sputum eosinophilia. N Engl J Med. 2009; 360(10):985–93. [PubMed: 19264687]

122. Pavord ID, Korn S, Howarth P, Bleecker ER, Buhl R, Keene ON, Ortega H, Chanez P. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. Lancet. 2012; 380(9842):651–9. [PubMed: 22901886]

123. Leckie MJ, ten Brinke A, Khan J, Diamant Z, O'Connor BJ, Walls CM, Mathur AK, Cowley HC, Chung KF, Djukanovic R, Hansel TT, Holgate ST, Sterk PJ, Barnes PJ. Effects of an interleukin-5 blocking monoclonal antibody on eosinophils, airway hyper-responsiveness, and the late asthmatic response. Lancet. 2000; 356(9248):2144–8. [PubMed: 11191542]

124. Flood-Page P, Swenson C, Faiferman I, Matthews J, Williams M, Brannick L, Robinson D, Wenzel S, Busse W, Hansel TT, Barnes NC. A study to evaluate safety and efficacy of mepolizumab in patients with moderate persistent asthma. Am J Respir Crit Care Med. 2007; 176(11):1062–71. [PubMed: 17872493]

125. Kips JC, O'Connor BJ, Langley SJ, Woodcock A, Kerstjens HA, Postma DS, Danzig M, Cuss F, Pauwels RA. Effect of SCH55700, a humanized anti-human interleukin-5 antibody, in severe persistent asthma: a pilot study. Am J Respir Crit Care Med. 2003; 167(12):1655–9. [PubMed: 12649124]

126. Castro M, Mathur S, Hargreave F, Boulet LP, Xie F, Young J, Wilkins HJ, Henkel T, Nair P. Reslizumab for poorly controlled, eosinophilic asthma: a randomized, placebo-controlled study. Am J Respir Crit Care Med. 2011; 184(10):1125–32. [PubMed: 21852542]

127. Antoniu SA. Monoclonal antibodies for asthma and chronic obstructive pulmonary disease. Expert Opin Biol Ther. 13(2):257–68. [PubMed: 23282002]

128. Hansbro PM, Scott GV, Essilfie AT, Kim RY, Starkey MR, Nguyen DH, Allen PD, Kaiko GE, Yang M, Horvat JC, Foster PS. Th2 cytokine antagonists: potential treatments for severe asthma. Expert Opin Investig Drugs. 2012; 22(1):49–69.

129. Temann UA, Geba GP, Rankin JA, Flavell RA. Expression of interleukin 9 in the lungs of transgenic mice causes airway inflammation, mast cell hyperplasia, and bronchial hyperresponsiveness. J Exp Med. 1998; 188(7):1307–20. [PubMed: 9763610]

130. Parker JM, Oh CK, LaForce C, Miller SD, Pearlman DS, Le C, Robbie GJ, White WI, White B, Molfino NA. Safety profile and clinical activity of multiple subcutaneous doses of MEDI-528, a humanized anti-interleukin-9 monoclonal antibody, in two randomized phase 2a studies in subjects with asthma. BMC Pulm Med. 2011; 11:14. [PubMed: 21356110]

131. Suzukawa M, Morita H, Nambu A, Arae K, Shimura E, Shibui A, Yamaguchi S, Suzukawa K, Nakanishi W, Oboki K, Kajiwara N, Ohno T, Ishii A, Korner H, Cua DJ, Suto H, Yoshimoto T, Iwakura Y, Yamasoba T, Ohta K, Sudo K, Saito H, Okumura K, Broide DH, Matsumoto K, Nakae S. Epithelial cell-derived IL-25, but not Th17 cellderived IL-17 or IL-17F, is crucial for murine asthma. J Immunol. 2012; 189(7):3641–52. [PubMed: 22942422]

132. Saglani S, Lui S, Ullmann N, Campbell GA, Sherburn RT, Mathie SA, Denney L, Bossley CJ, Oates T, Walker SA, Bush A, Lloyd CM. IL-33 promotes airway remodeling in pediatric patients with severe steroid-resistant asthma. J Allergy Clin Immunol. 2013; 132(3):676–85. e13. [PubMed: 23759184]

133. Liu X, Li M, Wu Y, Zhou Y, Zeng L, Huang T. Anti-IL-33 antibody treatment inhibits airway inflammation in a murine model of allergic asthma. Biochem Biophys Res Commun. 2009; 386(1):181–5. [PubMed: 19508862]

134. Howarth PH, Babu KS, Arshad HS, Lau L, Buckley M, McConnell W, Beckett P, Al Ali M, Chauhan A, Wilson SJ, Reynolds A, Davies DE, Holgate ST. Tumour necrosis factor (TNFalpha) as a novel therapeutic target in symptomatic corticosteroid dependent asthma. Thorax. 2005; 60(12):1012–8. [PubMed: 16166100]

135. Berry MA, Hargadon B, Shelley M, Parker D, Shaw DE, Green RH, Bradding P, Brightling CE, Wardlaw AJ, Pavord ID. Evidence of a role of tumor necrosis factor alpha in refractory asthma. N Engl J Med. 2006; 354(7):697–708. [PubMed: 16481637]

136. Erin EM, Leaker BR, Nicholson GC, Tan AJ, Green LM, Neighbour H, Zacharasiewicz AS, Turner J, Barnathan ES, Kon OM, Barnes PJ, Hansel TT. The effects of a monoclonal antibody directed against tumor necrosis factor-alpha in asthma. Am J Respir Crit Care Med. 2006; 174(7):753–62. [PubMed: 16840747]

137. Wenzel SE, Barnes PJ, Bleecker ER, Bousquet J, Busse W, Dahlen SE, Holgate ST, Meyers DA, Rabe KF, Antczak A, Baker J, Horvath I, Mark Z, Bernstein D, Kerwin E, Schlenker-Herceg R,

Lo KH, Watt R, Barnathan ES, Chanez P. A randomized, double-blind, placebo-controlled study of tumor necrosis factor-alpha blockade in severe persistent asthma. Am J Respir Crit Care Med. 2009; 179(7):549–58. [PubMed: 19136369]

138. Humbert M, de Blay F, Garcia G, Prud'homme A, Leroyer C, Magnan A, Tunon-de-Lara JM, Pison C, Aubier M, Charpin D, Vachier I, Purohit A, Gineste P, Bader T, Moussy A, Hermine O, Chanez P. Masitinib, a c-kit/PDGF receptor tyrosine kinase inhibitor, improves disease control in severe corticosteroid-dependent asthmatics. Allergy. 2009; 64(8):1194–201. [PubMed: 19614621]
139. Taha RA, Laberge S, Hamid Q, Olivenstein R. Increased expression of the chemoattractant cytokines eotaxin, monocyte chemotactic protein-4, and interleukin-16 in induced sputum in asthmatic patients. Chest. 2001; 120(2):595–601. [PubMed: 11502664]
140. Fulkerson PC, Fischetti CA, McBride ML, Hassman LM, Hogan SP, Rothenberg ME. A central regulatory role for eosinophils and the eotaxin/CCR3 axis in chronic experimental allergic airway inflammation. Proc Natl Acad Sci U S A. 2006; 103(44):16418–23. [PubMed: 17060636]
141. Joubert P, Lajoie-Kadoch S, Labonte I, Gounni AS, Maghni K, Wellemans V, Chakir J, Laviolette M, Hamid Q, Lamkhioued B. CCR3 expression and function in asthmatic airway smooth muscle cells. J Immunol. 2005; 175(4):2702–8. [PubMed: 16081847]
142. Dent G, Hadjicharalambous C, Yoshikawa T, Handy RL, Powell J, Anderson IK, Louis R, Davies DE, Djukanovic R. Contribution of eotaxin-1 to eosinophil chemotactic activity of moderate and severe asthmatic sputum. Am J Respir Crit Care Med. 2004; 169(10):1110–7. [PubMed: 15001461]
143. Erin EM, Williams TJ, Barnes PJ, Hansel TT. Eotaxin receptor (CCR3) antagonism in asthma and allergic disease. Curr Drug Targets Inflamm Allergy. 2002; 1(2):201–14. [PubMed: 14561201]
144. Nakagami Y, Kawase Y, Yonekubo K, Nosaka E, Etori M, Takahashi S, Takagi N, Fukuda T, Kuribayashi T, Nara F, Yamashita M. RS-1748, a novel CC chemokine receptor 4 antagonist, inhibits ovalbumin-induced airway inflammation in guinea pigs. Biol Pharm Bull. 2010; 33(6): 1067–9. [PubMed: 20522980]

Table 1

Potential therapeutic targets and ongoing studies to establish their role in asthma.

Therapeutic Target	Role in Asthma	Current Investigation
IL-9	AHR, airway eosinophilia, mucus secretion[129]	Medi-528, phase II trials[130]
IL-25	Activation of TH2 cells, allergic asthma[131]	Pre-clinical studies[131], development of anti-IL-25 antibody
IL-33	Airway remodeling[132]	Pre-clinical studies[133]
Tyrosine Kinase Inhibitors	Inflammatory gene expression[30, 138]	Masitinib[138], phase III clinical trial currently recruiting (NCT01449162)
CCR3	Airway eosinophilia, airway remodeling[142, 143]	GW766994, phase II clinical trial (NCT01160224)
CCR4	Airway inflammation[127, 144]	AMG 761, phase I clinical trial (NCT01514981)

AHR: airway hyperresponsiveness.