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Emerging Issues in Pediatric Asthma: Gaps in EPR-3 Guidelines for Infants and Children

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Abstract

There are many complexities to the treatment of infants and children with recurrent wheezing and asthma. NHLBI's Expert Panel Report-3 (EPR3), published in 2007, provides guidance to clinicians who care for infants and children with asthma. Since that time, many important clinical trials have further informed the evidence base available to clinicians. In this manuscript, new approaches to long-term therapy, intermittent fixed-dose and dynamic dose therapies, and emerging therapies for asthma are reviewed. Further, additional gaps in guideline-based care and areas for future research are discussed.

Keywords

Asthma; Wheezing; Children; Guideline; Infants; Inhaled Corticosteroids; Long Acting Beta Agonists; Anticholinergics; Biologics; Action Plan; Yellow Zone; Dynamic dose; Fixed dose

Introduction

The National Heart, Lung and Blood Institute (NHLBI) published the Expert Panel Report-3 (EPR3) guidelines for the diagnosis and treatment of asthma across the ages in 2007(1). EPR3 divides its recommendations by age: 0–4 years, 5–11 years, and 12 years and above. These recommendations were based upon the best evidence available at the time, and many significant studies have been published in the interim that help guide therapy, particularly for infants and children. This review discusses how recent trials inform asthma management and identifies remaining gaps in our knowledge to guide asthma treatment in infants and children. \

Infants and children between 0–4 years of age most often have intermittent wheezing episodes associated with viral(2) and bacterial(3) infections, and are mostly or completely well in between infections. As a whole, this population has relatively low impairment, but high-risk disease, with intermittent wheezing episodes that can lead to significant morbidity(4). There are many different “wheezing phenotypes” in this age group(5–7), and the patterns of airway inflammation observed in many older patients with asthma are typically absent in wheezing infants(8, 9), but can develop during the preschool period(10).

All of these factors complicate treatment recommendations for children less than 5 years of age.

Children 5–11 years of age develop more persistent disease and have features of airway inflammation more typical of older children and adults with asthma(9, 11). However, when compared to adults, children 5–11 years of age have a significantly increased rate of severe exacerbations(4, 12). This potential high level of *both* risk and impairment must be considered in the treatment of this age group.

Long Term Therapy for Infants and Children

0–4 Years of Age

EPR-3 recommends that modifications in long-term controller therapy be made based upon assessments of both asthma severity and control. These take into account both the impairment and risk domains of the disease. While it is clear that the preferred step 2 daily controller therapy for children (5–11 years) and adults (12 years and above) is inhaled corticosteroids (ICS), the evidence is less clear for the 0–4 year age group. EPR-3 recommends low-dose ICS as the preferred step 2 therapy in this age group; however, treatment with either ICS(13, 14) or leukotriene receptor antagonists (LTRA)(15, 16) has been shown to reduce symptoms and exacerbations in preschool children. Further, there are limited head-to-head studies comparing ICS vs. LTRA in this age group, and published data suggest a less distinct differential response in favor of ICS(17) compared to that seen in older children and adults. An ongoing clinical trial, the Individualized Therapy for Asthma in Toddlers (INFANT) trial, performed by the NHLBI-funded AsthmaNet (ClinicalTrials.gov ID NCT01606306), is aimed at addressing this guideline gap, and perhaps most importantly, identifying predictors of improved responses to daily low-dose ICS, daily LTRA, and intermittent ICS/SABA therapy.

EPR-3 treatment recommendations at step 3 and above in children 0–4 years are based upon data extrapolated from older children and adults, and also on expert opinion(1). Studies are needed to address these large gaps in this population. Specifically, combination therapy with ICS + LABA has not been studied in children under 4 years of age. Furthermore, no comparator trials of add-on therapies have been completed to date. In part, this reflects the challenge of identifying a large cohort of patients in this age group with moderate to severe persistent asthma in order to adequately power such trials.

5–11 years of age

There is clear evidence to support ICS as the preferred step 2 therapy for children 5–11 years of age with asthma(1). EPR-3 recommendations at step 3 and above are primarily based upon data extrapolated from older children and adults. However, since that time, data has emerged that can help guide clinicians' selection of therapy at step 3 in 5–11 year old children. A recent trial in the Childhood Asthma Research and Education (CARE) Network examined the efficacy of three step-up approaches in children not well controlled on low-dose fluticasone: 2.5x ICS, 1x ICS + LABA, or 1x ICS + LTRA. This study demonstrated that LABA step-up was the most likely strategy to provide the best asthma control as reflected by a hierarchical primary outcome including both risk and impairment domains of

asthma control(18). However, many children did respond best to 2.5x ICS or 1x ICS + LTRA, so the authors concluded that if a clinician chooses one of these step-up options and the child does not become well controlled, it is advisable to select another step 3 therapy prior to moving to step 4. Additional recent studies have shown that ICS + LABA combination therapy is similar to,(19) or superior to,(20) doubling the dose of ICS in children in this age group. Collectively, these findings support the efficacy of ICS + LABA for step 3 therapy in 5–11 year old children. However, despite clear evidence of efficacy, recommending LABA in this group remains controversial due to concerns regarding potential risks associated with LABA therapy(21). Evidence to guide therapy at step 4 and above in 5–11 year old children is currently lacking and an important gap in guideline recommendations moving forward.

Intermittent and Adjustable Approaches to Therapy

EPR-3 recommendations at step 2 and above involve daily use of controller therapies in so-called “fixed-dose” regimens. However, many patients do not prefer to take daily therapy, and adherence to these regimens is often suboptimal, even in clinical trials(22). Fixed-dose daily therapy is also not responsive to the intrinsic variability of asthma. Furthermore, these approaches often do not adequately prevent asthma exacerbations. Finally, daily ICS therapy has small, but significant, effects on growth in children(23, 24). For all of these reasons, there have been a number of studies in both adults and children over the past decade that have examined alternative approaches to traditional fixed-dose regimens.

Intermittent High-Dose ICS

One alternative approach to daily controller therapy is a fixed-dose “yellow-zone” therapy, such as high-dose ICS for 7–10 days at the onset of symptoms associated with loss of asthma control. The Asthma Clinical Research Network (ACRN) IMPACT trial in adults compared intermittent high-dose ICS guided by a symptom based action plan to daily low-dose ICS in patients with mild persistent asthma(25). The trial found no significant difference in the primary outcome of AM peak flow between treatments, quality of life, or post-bronchodilator FEV1, but modest improvements in symptoms, prebronchodilator FEV1, and airway inflammation favoring daily therapy were observed (25). The authors concluded that additional studies were needed before this approach could be recommended.

High-dose ICS therapy in the yellow zone has been examined in children under 5 years of age with severe, intermittent wheezing episodes as well. The CARE Network performed two recent trials in the preschool age group. The AIMS study compared high-dose intermittent ICS vs. intermittent montelukast vs. usual care (scheduled albuterol) as yellow zone treatment during respiratory tract illnesses (RTIs), and found that both intermittent ICS and montelukast led to modest improvements in symptoms during yellow zone episodes, but did not significantly prevent severe exacerbations treated with systemic steroids(26). The MIST trial in modified Asthma Predictive Index (mAPI) positive children compared daily low-dose ICS to intermittent high-dose ICS during RTIs and found no difference in the rate of severe exacerbations treated with systemic corticosteroids(27). Ducharme and colleagues studied the efficacy of very high-dose fluticasone vs. placebo at the onset of RTIs for up to 10 days per episode and demonstrated significant reductions in the rate of systemic

corticosteroid use, but this was also associated with small, but significant, effects on growth(28). Taken together, intermittent high-dose ICS at the onset of the yellow zone appears to be an effective alternative to daily low-dose ICS in young children with severe, intermittent wheezing episodes. However, clinicians need to monitor the frequency and duration at which these regimens are used, and continue to monitor growth on a regular basis.

In patients treated with low-medium doses of ICS, EPR-3 suggests that doubling the dose of the ICS in the yellow zone is ineffective, but quadrupling (4x) the ICS dose may be an effective approach to exacerbation prevention(1). Since that time, Osborne and colleagues addressed this question in adults using a combination of symptoms and peak expiratory flow changes in order to identify the yellow zone(29). They identified a trend toward reductions in severe exacerbations in the patients in the 4x ICS group, and a significant, nearly 60%, reduction in exacerbations in the per-protocol analysis (ie patients who activated their symptom based action plan). This study suggests that at least quadrupling the dose of ICS may be an effective yellow zone strategy in adults, and the Step-up Yellow Zone Inhaled Corticosteroids to Prevent Exacerbations (STICS) trial, addressing this guideline gap in children 5–11 years of age is currently ongoing in AsthmaNet (ClinicalTrials.gov NCT02066129).

Dynamic Dosing

A number of recent studies have also assessed the role of dynamic dosing with combinations of ICS/LABA or ICS/SABA. These approaches have been described by a number of terms, including single inhaler for maintenance and reliever (SMART)(30), as needed combination therapy(31), and rescue ICS(32). Each of these strategies are symptom driven, with the concept that co-administration of an anti-inflammatory therapy with a bronchodilator at the time of symptoms will provide more effective treatment than bronchodilator alone.

O'Byrne and colleagues studied the efficacy of the single inhaler for maintenance and reliever (SMART) approach with budesonide/formoterol compared to fixed-dose regimens of 4x budesonide or budesonide/formoterol, each with SABA for rescue, in patients from 4–80 years of age(30). They found that SMART therapy significantly reduced the rate of severe exacerbations, despite a dose of ICS that was significantly lower than the 4x budesonide group. Furthermore, in the 4–11 year old children, treatment with either SMART or fixed-dose budesonide/formoterol was associated with 1 cm greater growth than was observed in the 4x budesonide group during the yearlong trial(33).

Papi and colleagues studied ICS/SABA combination therapy in adults as a step-down approach for patients well controlled on low-dose ICS(31). When compared to fixed-dose beclomethasone, as needed beclomethasone/albuterol in a single inhaler was equally effective in preventing severe asthma exacerbations, and was more effective than albuterol alone. Similarly, the ACRN recently published the BASALT trial which demonstrated no significant difference in treatment failures among patients with mild-moderate persistent asthma treated with ICS + SABA (in separate inhalers) in a symptom-based fashion when compared to fixed-dosing based upon physician assessments or FeNO measurement at set

intervals(34). Similar outcomes were achieved in the symptom-based group despite lower cumulative doses of ICS.

The use of rescue ICS (ICS + SABA in separate inhalers) was studied in the CARE network TREXA trial in 5–18 year olds with mild asthma, well controlled on low-dose ICS as a potential step-down strategy(32). As needed beclomethasone + albuterol led to a reduction in severe exacerbations and treatment failures when compared to albuterol alone. These results with rescue ICS were similar to those achieved with daily ICS, but were associated with a 1.1 cm improvement in linear growth during the study.

In summary, dynamic dosing approaches using both ICS/LABA and ICS/SABA combination therapy have shown clear benefits in the treatment of children with asthma. They are appealing, as ICS is initiated very early following exposure to a trigger and the subsequent development of symptoms. Furthermore, these approaches have the potential to empower patients and potentially enhance adherence, while potentially decreasing side effects of higher doses of ICS used in fixed-dose regimens. While ICS/LABA SMART therapy was very effective for children 4–11 years of age, and this approach is used widely in Canada and Europe(35), current FDA concerns over LABA safety have limited its use in the United States(21). Additionally, there is currently no ICS/SABA combination inhaler available in the United States. Despite these issues, dynamic dosing is an important area for future study and use in clinical practice.

Step-Down of Therapy

An additional area of long-term therapy where guideline recommendations are limited is stepping-down treatment in patients who are well controlled. EPR-3 suggests that clinicians can *consider* stepping-down therapy in patients whose asthma is well controlled for at least 3 months(1). There is little guidance as to who, when, and how therapy should be stepped down. This question is particularly critical in the diverse pediatric population where disease expression can be highly variable with age. EPR-3 suggests reducing ICS doses gradually (by 25–50%). Two large recent meta-analyses support this recommendation(36, 37). Additionally, stepping-down to dynamic dosing as needed ICS/SABA is likely a good option for many children with mild asthma(32). The FDA has recommended that in patients well controlled on ICS/LABA combination therapy that the LABA should be discontinued prior to the ICS(21); however, there are a number of trials that suggest this may lead to greater likelihood of deterioration in asthma control(38–40). The majority of step-down trials have additionally focused on patients over 12 years of age. Taken together, it is clear that large gaps remain in guidelines for stepping-down therapy, particularly for infants and children.

Oral Corticosteroid Efficacy in Children 0–4

EPR-3 recommends short-courses of oral corticosteroids (OCS) for wheezing/asthma exacerbations not responsive to bronchodilators across all age groups. However, there is growing evidence to suggest that OCS may not be as efficacious in 0–4 year old children as they are in older children and adults. Several recent randomized trials in preschool children have not demonstrated benefit of OCS in children with acute wheezing(41, 42), and a recent

post-hoc analysis of two CARE network trials failed to show benefit in these children as well(43). Unfortunately, clinicians are left without other effective treatments for severe exacerbations, and OCS for these episodes remains the standard-of-care in the United States. This highlights a clear need for novel therapies for wheezing episodes in young children.

Emerging Therapies for Asthma in Children

Biologics

The only biologic therapy currently FDA approved for the treatment of asthma is omalizumab, a monoclonal antibody directed against IgE. Omalizumab is most effective for the prevention of severe asthma exacerbations. EPR-3 recommended that omalizumab be considered for patients 12 years and above at step 5 or 6 with sensitization to a relevant perennial aeroallergen(1). Omalizumab is not currently FDA approved under 12 years of age, although it is approved for children 6 years of age and above in Europe. However, there is growing evidence for both the efficacy of omalizumab in patients 6 years and above (44, 45) and also the long-term safety of this medication(46, 47). If FDA approved, omalizumab for 5–11 year old children with severe asthma would be a welcome addition to guideline recommendations. Furthermore, there has been interest in the potential utility of omalizumab for the prevention of asthma in the preschool age group(48).

A number of other biologic therapies have recently emerged and are in various stages of development. While none of these therapies are currently FDA approved for the treatment of asthma in adults, there have been a number of promising studies demonstrating their efficacy, primarily in the risk domain of asthma control in patients with Type 2 inflammation. Mepolizumab, a monoclonal antibody directed at IL5, has shown efficacy in the prevention of severe asthma exacerbations in patients with evidence of elevated eosinophils in sputum or peripheral blood(49–51). Lebrikizumab, anti-IL13 antibody, has led to improvements in asthma control, particularly in patients with elevated periostin or exhaled nitric oxide (FeNO)(52). More recently, dupilumab, a monoclonal antibody against IL4R- α , which blocks signaling of both IL4 and IL13, was shown to reduce exacerbations and improve lung function in adults with elevated peripheral blood eosinophils and moderate-severe asthma(53). Finally, a phase 2 trial of inhaled interferon- β showed promise as a yellow zone therapy for the prevention and treatment of virus-induced asthma symptoms and exacerbations in adult patients with more severe disease(54). As these, and other biologic therapies aimed at the treatment and prevention of asthma emerge, it will be important to determine which patients are likely to benefit from these therapies. Targeted biomarker-based approaches show promise in this regard.

Long-acting Anticholinergics

Tiotropium, a long-acting anticholinergic, was first approved for use in patients with chronic obstructive pulmonary disease (COPD). However, there has been growing interest in its role in the treatment of asthma. Peters and colleagues compared tiotropium step-up therapy to LABA step-up and doubling the dose of ICS in patients who were not well controlled on low-dose ICS. They demonstrated that tiotropium led to significant improvement in symptoms and lung function compared to doubling the dose of ICS, and was non-inferior to

LABA step-up(55). Furthermore, several recent studies have demonstrated additional benefit of tiotropium added to ICS + LABA combination therapy in patients with more severe disease(56, 57). No placebo-controlled trials using tiotropium have been published in children to date; however, a recent case-series suggests that tiotropium may have efficacy in children(58). At least two tiotropium trials are ongoing in children under 12 years of age with moderate-severe asthma (ClinicalTrials.gov ID NCT01634139 & NCT01634152).

Conclusions

Many important findings have emerged in the interim since EPR-3 was published in 2007, but many knowledge gaps remain (Table 1). The role of intermittent therapy both in fixed-dose regimens and dynamic dosing of controller in combination with reliever therapies has been studied in children and adults. There are additionally many novel therapeutics for asthma in varying stages of development. It will be critical over time to fill these gaps in our knowledge base in order to optimally provide care to infants and children with asthma. Targeted and personalized approaches for therapy of children of varying phenotypes/endotypes are important goals to continue to pursue in the upcoming years.

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Table 1

Knowledge Gaps in Asthma Treatment in Children

Infants & Children 0–4 years	Children 5–11 years
<ul style="list-style-type: none"> • The role of intermittent therapy with high-dose ICS • The selection of daily controller therapy in children with persistent symptoms • Add-on therapies for children not controlled with Step 2 treatment • The role of dynamic dosing with ICS/LABA or ICS/SABA combinations • Strategies for step-down of therapy • Identification of novel therapies for exacerbations due to lack of OCS effectiveness in this age 	<ul style="list-style-type: none"> • The selection of daily controller therapies at Step 3 treatment and above • The role of 4x dosing in the yellow zone to prevent exacerbations • The role of dynamic dosing with ICS/LABA or ICS/SABA combinations • Effectiveness of tiotropium as add-on therapy in children • Strategies for step-down of therapy • Guidance for the use of omalizumab and other emerging biologics