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ORIGINAL ARTICLE

Evidence-Based Guidelines for the Management of Allergic Bronchopulmonary Aspergillosis (ABPA) in Children and Adolescents with Asthma

Joseph L. Mathew[1] · Ketan Kumar[1] · Sheetal Agrawal[2] · Sanjay Bafna[3] · Sonia Bhatt[4] · Pallab Chatterjee[5] · N. S. Chithambaram[6] · Rashmi Ranjan Das[7] · Hema Gupta[2] · Sarika Gupta[8] · Kana Ram Jat[9] · Pawan Kalyan[10] · Rashmi Kapoor[11] · Hardeep Kaur[9] · Jasmeet Kaur[12] · Satnam Kaur[13] · Suhas P. Kulkarni[14] · Amber Kumar[15] · Sanjiv Singh Rawat[16] · Vivek Saxena[17] · Anita Singh[18] · Somu Sivabalan[19] · Shetanshu Srivastava[20] · Anshula Tayal[9]

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Abstract

Background Allergic bronchopulmonary aspergillosis (ABPA) frequently complicates asthma. There is urgent need to develop evidence-based guidelines for the management of ABPA in children. The Evidence Based Guideline Development Group (EBGDG) of the Indian Academy of Pediatrics (IAP) National Respiratory Chapter (NRC) addressed this need.

Methods The EBGDG shortlisted clinical questions relevant to the management of ABPA in asthma. For each question, the EBGDG undertook a systematic, step-wise evidence search for existing guidelines, followed by systematic reviews, followed by primary research studies. The evidence was collated, critically appraised, and synthesized. The EBGDG worked through the Evidence to Decision (EtD) framework, to formulate recommendations, using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

Results Seven clinical questions were prioritized, and the following recommendations formulated. (1) Children with poorly controlled asthma should be investigated for ABPA (conditional recommendation, moderate certainty of evidence). (2) Low dose steroid therapy regimen (0.5 mg/kg/d for the first 2 wk, followed by a progressive tapering) is preferable to higher dose regimens (conditional recommendation, very low certainty of evidence). (3) Oral steroid regimens longer than 16 wk (including tapering), should not be used (conditional recommendation, very low certainty of evidence). (4) Antifungals may or may not be added to steroid therapy as the evidence was neither in favour nor against (conditional recommendation, low certainty of evidence). (5) For clinicians using antifungal agents, the EBGDG recommends against using voriconazole instead of itraconazole (conditional recommendation, very low certainty of evidence). (6) No evidence-based recommendation could be framed for using pulse steroid therapy in preference to conventional steroid therapy. (7) Immunotherapy with biologicals including omalizumab or dupilumab is not recommended (conditional recommendation, very low certainty of evidence).

Conclusions This evidence-based guideline can be used by healthcare providers in diverse clinical settings.

Keywords Asthma · Allergic bronchopulmonary aspergillosis (ABPA) · Evidence-based · Guideline

Introduction

Asthma is one of the commonest chronic childhood conditions, and accounts for a significant burden on healthcare systems [1]. In most children, asthma symptoms are controllable with appropriate therapy, and follow-up. However, a small subset may demonstrate poor control despite appropriate therapy.

Allergic bronchopulmonary aspergillosis (ABPA) is often associated with poor asthma control. It is considered to be an immunological reaction to antigens of the fungus *Aspergillus fumigatus* [2]. The broader term 'Allergic bronchopulmonary mycosis' (ABPM), reflects reaction to other fungi [3]. Patients with ABPA experience worsening asthma control, wheezing, production of viscid sputum and sometimes systemic symptoms. The diagnosis is based on the typical symptomatology, radiological changes and serological evidence of hypersensitivity to the fungus [4]. Treatment involves systemic

All authors after Ketan Kumar contributed equally, hence are arranged in alphabetical order by surname.

✉ Joseph L. Mathew
dr.joseph.l.mathew@gmail.com
Extended author information available on the last page of the article

corticosteroids with or without additional antifungal agents. It is well recognized that ABPA often complicates other underlying respiratory conditions, notably cystic fibrosis (CF) [5]. The broad principles of diagnosis and management of ABPA in CF patients, may overlap with asthmatic patients, however the two underlying conditions may behave differently.

There is growing evidence on ABPA in asthmatic adults, resulting in refinement of diagnostic criteria and management strategies [4]. However, there is limited evidence in the pediatric age group, and management is generally extrapolated from adults. There is urgent need to identify the magnitude of the problem in children, evolve evidence-based treatment plans, and explore the long-term consequences of ABPA in asthmatic children. This will facilitate the development of evidence-based guidelines for the pediatric age group.

The Evidence Based Guideline Development Group (EBGDG) of the Indian Academy of Pediatrics (IAP) National Respiratory Chapter (NRC) undertook the development of evidence-based guidelines for the management of ABPA in asthmatic children, using current scientific guideline development methodology. The details of the Evidence-based Guideline Development Group (EBGDG) composition, declaration and management of conflict of interest, and procedures adopted by the EBGDG, have been described elsewhere [6].

Scope of the Guideline

This evidence-based guideline focuses on ABPA in children and adolescents with asthma. The target users of the guideline are healthcare professionals managing such children. The EBGDG expects that patients and their families, healthcare advocacy groups, healthcare systems, and policymakers may also be users of this guideline. Although the authors primarily considered issues relevant to the Indian context, the guideline may be used in other settings as well.

Material and Methods

Formulating Clinical Questions

The EBGDG first prepared an extensive list of questions considered important in the management of ABPA in asthma. These questions were converted to the PICOTS format, describing the population (P), intervention (I), comparison (C), outcomes (O), timeframe for outcomes (T), and healthcare setting (S). EBGDG members independently scored each question on a scale from 1 to 9, based upon the perceived priority. The average score (and range) awarded to each question was tabulated, and circulated for a second round of scoring. This provided an opportunity to revise scores based on the perceived magnitude of the problem, variation in management practices, need for guideline recommendations, and risks of inappropriate management. Following the second round, the clinical questions with the highest total scores, and least variation, were shortlisted.

Evidence Retrieval, Evaluation and Synthesis

The EBGDG worked in five teams of 4–5 members; each team was primarily responsible for evidence synthesis on one or two clinical questions. Weekly online meetings were held for teams to present their work to the entire EBGDG. Decisions were taken by the whole group through consensus.

The team members first independently searched for existing evidence-based guidelines addressing the clinical question(s) allocated to them. The objective was to explore the scope of adoption, adaptation, or adolopment of existing recommendations to the local context. Searching was done through the websites of trustworthy international guideline agencies, professional scientific societies, and through Pubmed (Table 1). A broad search strategy was used to maximise sensitivity. The search output of each team member was verified by the entire

Table 1 Search strategy for pre-existing evidence-based guidelines addressing the shortlisted clinical questions

Websites/Databases	Search terms
Guidelines International Network (GIN) library World Health Organization (WHO) Global Initiative for Asthma (GINA) British Thoracic Society (BTS) Scottish Intercollegiate Guidelines Network (SIGN) American Thoracic Society (ATS) European Respiratory Society (ERS) National Institute for Health & Care Excellence (NICE) Australian Clinical Practice Guidelines International Society for Human & Animal Mycology (ISHAM) Cystic Fibrosis Foundation Cystic Fibrosis Trust MEDLINE through Pubmed	ABPA, allergic bronchopulmonary aspergillosis, aspergillosis, asthma, cystic fibrosis, bronchiectasis

ABPA Allergic bronchopulmonary aspergillosis

EBGDG, for consistency. Potentially relevant documents were searched for sections addressing the clinical questions.

If no relevant guideline applicable to the Indian context was identified, team members independently undertook searches for existing systematic reviews addressing their clinical question(s), in MEDLINE and the Cochrane Library. For this, a common broad search strategy was developed by the EBGDG. The search output citations were screened by title, followed by abstract. Citations with potentially relevant abstracts, and those lacking abstracts, were retrieved in full-text format. This step-wise screening was performed independently by each team member, and the results were presented individually to the entire EBGDG. Differences in search outputs or perception of relevance were resolved through discussion by the entire EBGDG, with the Chair guiding the final decision.

If no systematic review addressing the clinical question(s) was identified, teams conducted *de novo* systematic reviews under the supervision of the EBGDG Chair. The search strategy for each systematic review was finalized by the entire EBGDG. Within each team, members independently conducted searches in MEDLINE and the Cochrane Library, for primary studies addressing the question. For questions related to interventions, randomized controlled trials (RCT) were searched. Observational study designs were searched for the question related to ABPA prevalence. Search results from the two databases were pooled after removing duplicate publications. The citations were screened by title, followed by abstract. Citations with potentially relevant abstracts, and those lacking abstracts, were retrieved in full-text format. This step-wise screening was performed independently by each team member, and the results were presented individually to the entire EBGDG. Differences in search outputs or doubts about eligibility for inclusion were resolved through discussion by the entire EBGDG, with the Chair guiding the final decision. Eligible RCTs were critically appraised for methodological quality using the Cochrane Risk of Bias Tool [7].

Each team presented the body of evidence addressing their clinical question(s), to the entire EBGDG. The group discussed the evidence, quality, and grading. The group then collectively worked through the Evidence to Decision (EtD) framework, to formulate recommendations [8, 9]. The evidence for each clinical question and the strength of the final recommendation was rated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [10].

Results

The seven shortlisted clinical questions based on a priori priority assignment criteria, are presented in Table 2. The searches for pre-existing guidelines did not identify relevant evidence-based guidelines addressing any of the clinical questions, hence a formal literature search was done for each question.

Clinical Question 1: Should All Children with Poorly Controlled Asthma be Investigated for ABPA?

Evidence Summary: There was no pre-existing systematic review addressing the question. Therefore, a fresh systematic review was conducted to determine the prevalence of ABPA in the target population. The pooled prevalence of Aspergillus sensitization (AS) and ABPA were calculated through meta-analysis, with subgroup analysis by age of participants, and asthma severity. The details of the systematic review are presented in the online Supplementary File 1, and the results are summarized in Tables 3 and 4.

Recommendation: Children with poorly controlled asthma (uncontrolled symptoms despite appropriate therapy with moderate to high dose of inhaled corticosteroids and long acting beta agonists, correct diagnosis, adequate adherence, correct inhalation technique, appropriate management of co-morbidity and appropriate environmental control) should be investigated for ABPA (conditional recommendation, moderate certainty of evidence).

Explanation: In this clinical question the EBGDG decided to compare data on prevalence of ABPA in children with poorly controlled asthma *vs.* those with well controlled asthma. The group decided *a priori* that if the prevalence was significantly higher in those with poorly controlled asthma, a recommendation in favor of investigating them would be made. The EBGDG also decided to examine the prevalence of AS in both groups as children with AS could later develop ABPA. However, there were only two studies that reported the prevalence of AS and ABPA in children with poorly controlled asthma [11, 12]. Both were conducted in India, but used variable definitions and methods, making direct comparison challenging. There were no studies in children comparing the prevalence of ABPA in poorly controlled asthma *vs.* well controlled asthma. There was also very limited data comparing ABPA prevalence in children with severe asthma *vs.* those where severity was not defined. However, the ABPA prevalence in adults was higher in those with severe asthma compared to those where severity was not defined (21% *vs.* 9%). There was only one study in adults, that reported prevalence by asthma severity [13]. Furthermore, the prevalence of AS was higher in children with severe asthma compared to those where severity was not defined (41% *vs.* 10%). While framing the recommendation, the EBGDG also considered that poorly controlled asthma is a major burden both to parents and healthcare facilities, and ABPA is a treatable condition.

Implementation Considerations: In order to rationalize the use of investigations and manage resources appropriately, the EBGDG advises that when children are investigated

Table 2 Clinical questions prioritized by the EBGDG

Population (P)	Intervention (I)	Comparator (C)	Outcome (O)	Timeframe for outcomes (T)	Setting (S)
1. Should all children with poorly controlled asthma be investigated for ABPA?					
Children with asthma	Investigations for ABPA, including combinations of: • Serum total IgE • Skin Prick Test (SPT) or Aspergillus specific IgE • Aspergillus specific IgG • Absolute Eosinophil Count (AEC) • Chest imaging	-	Prevalence of AS and ABPA in poorly controlled asthma* *vs.* well controlled asthma	Cross sectional	Inpatient or Outpatient
2. Which steroid regimen (low dose or high dose) should be used for the treatment of ABPA in children with asthma?					
Children with asthma and ABPA	Low dose oral steroid regimen (0.5 mg/kg/d for the first 2 wk, followed by progressive tapering over any duration)	High dose oral steroid regimen (0.75 mg/kg for 6 wk, followed by 0.5 mg/kg for next 6 wk, and then tapering over any duration)	• ABPA remission rate • No. of asthma and ABPA exacerbations • Spirometry parameters (FEV_1, FEV_1/FVC, FVC) • Side effects • Cost	3 mo, 6 mo, 12 mo, and >12 mo	Inpatient or Outpatient
3. What is the optimum duration of oral steroid therapy for ABPA in children with asthma?					
Children with asthma and ABPA	Duration of oral steroid therapy of more than 16 wk (including the phase of tapering)	Duration of oral steroid therapy (including tapering) upto 16 wk	• ABPA remission rate • No. of asthma/ABPA exacerbations • Spirometry parameters (FEV_1, FEV_1/FVC, FVC) • Side effects • Cost	12 mo, and >12 mo	Inpatient or Outpatient
4. Should antifungals be given to children with asthma and ABPA?					
Children with asthma and ABPA	Antifungal (any type, any duration) or antifungal plus steroids **Subgroup:** Type of antifungal: itraconazole, voriconazole, amphotericin B, any other	No antifungal, or placebo, or only steroids	• ABPA remission rate • No. of asthma and ABPA exacerbations • Spirometry parameters (FEV_1, FEV_1/FVC, FVC) • Side effects • Cost	3 mo, 6 mo, 12 mo, and >12 mo	Inpatient or Outpatient
5. Is voriconazole more efficacious than itraconazole in children with asthma and acute exacerbation of ABPA?					
Children with asthma and ABPA	Voriconazole plus steroids or other standard of care	Itraconazole plus steroids or other standard of care	• Reduction in total IgE • Exacerbation free period • No. of exacerbations during follow-up	3 mo, 6 mo, 12 mo and >12 mo	Inpatient or Outpatient

Table 2 (continued)

Population (P)	Intervention (I)	Comparator (C)	Outcome (O)	Timeframe for outcomes (T)	Setting (S)
6. Should pulse steroid therapy be used in children with asthma and ABPA?					
Children with asthma and ABPA	Pulse methylprednisolone or pulse dexamethasone	Conventional steroid therapy	• ABPA remission rate • No. of asthma and ABPA exacerbations • Spirometry parameters (FEV_1, FEV_1/FVC, FVC) • Side effects • Cost	3 mo, 6 mo, 12 mo and > 12 mo	Inpatient
7. What is the role of immunomodulators in children with asthma and ABPA?					
Children with asthma and ABPA	Immunomodulators (Omalizumab/ Dupilumab/ Other)	No immunomodulators (Placebo or nothing)	• ABPA remission rate • No. of asthma and ABPA exacerbations • Spirometry parameters (FEV_1, FEV_1/FVC, FVC) • Side effects • Cost	3 mo, 6 mo, 12 mo and > 12 mo	Inpatient

ABPA Allergic bronchopulmonary aspergillosis, *AS* Aspergillus sensitization, *EBGDG* Evidence based guideline development group, FEV_1 Forced expiratory volume in 1 s, *FVC* Forced vital capacity, *GINA* Global initiative for asthma

*The GINA 2021 guidelines do not have a category of "poorly controlled asthma" but define a group with "severe asthma"

for ABPA, serum total IgE and *Aspergillus* specific IgE [or skin prick test (SPT) for *Aspergillus*] should be performed first. Other investigations for minor diagnostic criteria of ABPA (eosinophil count, *Aspergillus* specific IgG, and CT chest) should be performed only if both total IgE and *Aspergillus* specific IgE (or SPT for *Aspergillus*) are suggestive of ABPA (total IgE > 1000 IU/ml and *Aspergillus* specific IgE > 0.35 mgA/L or positive SPT for *Aspergillus*).

Clinical Question 2: Which Steroid Regimen (Low Dose or High Dose) Should be Used for the Treatment of ABPA in Children with Asthma?

Evidence Summary: There was no pre-existing systematic review addressing the question. A fresh systematic review identified only one single-centre, non-blinded RCT [14]. The details of the systematic review are presented in the online Supplementary File 1.

Recommendation: The EBGDG recommends using low dose steroid therapy regimen (0.5 mg/kg/d for the first 2 wk, followed by a progressive tapering) for treatment of ABPA in children with asthma (conditional recommendation, very low certainty of evidence).

Explanation: Although there was no direct data addressing the clinical question, the single RCT (with high risk of bias) in adults, suggested that low-dose oral steroids could have comparable efficacy, but greater safety, compared to high-dose steroids (0.75 mg/kg for 6 wk, 0.5 mg/kg for another 6 wk, and then tapering) for preventing exacerbations and glucocorticoid dependence in ABPA. The EBGDG recognized that the dosage differences were also associated with differences in the duration of therapy; the impact of which could not be ascertained separately.

Implementation Considerations: This recommendation is applicable only to treatment naïve patients. The EBGDG also emphasizes that patients on steroid therapy should be monitored for adverse events using clinical examination and biochemical parameters, as per usual practice.

Clinical Question 3: What is the Optimum Duration of Oral Steroid Therapy for ABPA in Asthmatic Children?

Evidence Summary: There was no pre-existing systematic review addressing the question. A fresh systematic review identified only one single-centre, non-blinded RCT [14], which has been referred to in the preceding clinical question. Therein, the longer regimen continued for 8 to 10 mo, whereas the shorter regimen terminated between 3 to 5 mo. The outcomes reported in the study have been summarized under question 2. There was no statistically significant difference in any of the

Table 3 Meta-analysis of prevalence of aspergillus sensitization (AS) and ABPA

	Number of studies	Number of participants	Prevalence range (%)	Pooled prevalence (%) with 95% CI	I^2% (*p* value)
Aspergillus sensitization by age					
Adults	36	8018	5 to 51	26 (21, 30)	95.9 (0.00)
Children	9	3057	2 to 61	27 (18, 37)	98.4 (0.00)
Both	17	5865	4 to 87	29 (21, 37)	98.8 (0.00)
Overall	62	16940	2 to 87	27 (23, 30)	98.0 (0.00)
Aspergillus sensitization by asthma severity					
Mild to moderate asthma	0				
Severe asthma	17	3742	8 to 61	27 (21, 33)	95.2 (0.00)
Severity not defined	45	13198	2 to 87	27 (22, 31)	98.4 (0.00)
ABPA by age					
Adults	31	8199	1 to 70	11 (9, 14)	96.3 (0.00)
Children	4	334	11 to 33	19 (11, 27)	71.2 (0.02)
Both	10	2142	4 to 21	10 (6, 13)	87.7 (0.00)
Overall	45	10675	1 to 70	12 (10, 14)	95.7 (0.00)
ABPA by asthma severity					
Mild to moderate asthma	1	70	13	13 (7, 23)	
Severe asthma	13	1627	3 to 70	17 (12, 22)	93.4 (0.00)
Severity not defined	31	8793	1 to 33	10 (8, 12)	96.2 (0.00)

ABPA Allergic bronchopulmonary aspergillosis

clinically relevant efficacy outcomes between the two groups. The response rate and percentage decline in IgE (both at 6 wk) which were greater with the longer regimen, were attributable to the higher dose rather than longer duration. Participants receiving the longer regimen and higher cumulative steroid dose, had greater prevalence of adverse events also.

Recommendation: The authors recommend against using oral steroid regimens longer than 16 wk (including tapering), in children with asthma and ABPA (conditional recommendation, very low certainty of evidence).

Explanation: The cut-off of 16 wk was based on a review of treatment regimens in ABPA. For children weighing between 15 to 40 kg, the shorter regimen is completed before or at 16 wk, whereas the longer regimen continues beyond 16 wk (depending upon the body weight). In the single RCT in adults, the longer duration of therapy was also associated with higher initial dosage of steroid. Therefore, the EBGDG examined only long-term outcomes (at 12 mo and >12 mo), so that the effect of higher initial dose, would not be confused as the impact of greater duration. Similarly, as the timing when adverse events developed, was not mentioned

Table 4 Meta-analysis of prevalence of aspergillus sensitization (AS) and ABPA described by age and severity of asthma

	Number of studies	Number of participants	Prevalence range (%)	Pooled prevalence (%) with 95% CI	I^2% (*p* value)
Aspergillus sensitization					
Adults with severe asthma	10	1516	8 to 51	23 (16, 30)	92.1 (0.00)
Adults with asthma severity not-defined	26	6352	5 to 87	27 (21, 32)	95.9 (0.00)
Children with severe asthma	4	1308	27 to 61	41 (25, 56)	95.3 (0.00)
Children with asthma severity not-defined	5	1749	2 to 21	10 (3, 17)	97.4 (0.00)
Adults and children with severe asthma	3	918	9 to 43	18 (9, 26)	Not calculated
Adults and children with asthma severity not-defined	14	5097	4 to 53	31 (20, 41)	99.1 (0.00)
ABPA					
Adults with mild to moderate asthma	1	70	13	13 (7, 23)	
Adults with severe asthma	9	1083	3 to 70	21 (13, 28)	95.0 (0.00)
Adults with asthma severity not-defined	21	6861	1 to 28	9 (7, 12)	95.6 (0.00)
Children with severe asthma	2	206	11 to 26	16 (11, 21)	Not calculated
Children with asthma severity not-defined	2	128	15 to 33	17 (10, 23)	Not calculated
Adults and children with severe asthma	2	338	3 to 7	3 (1, 5)	Not calculated
Adults and children with asthma severity not-defined	8	1804	4 to 21	11 (8, 14)	78.4 (0.00)

ABPA Allergic bronchopulmonary aspergillosis

in the study, the EBGDG could not determine if the events were due to the longer duration, or higher dosage, or both. However, it is reasonable to assume that a longer steroid regimen (with greater total dosage) would be associated with greater frequency of adverse events [15].

Implementation Considerations: This recommendation is applicable only to treatment naïve patients. Children receiving steroid therapy should be monitored for adverse events using clinical and biochemical parameters, as per usual practice.

Clinical Question 4: Should Antifungals be Given to Children with Asthma and ABPA?

Evidence Summary: There was no pre-existing systematic review addressing the question. A new systematic review identified five RCTs [16–20]. The details of the systematic review are presented in the online Supplementary File 1. The data from the five trials could not be pooled through meta-analysis, as they compared different interventions.

Recommendation: The authors recommend using either the intervention (addition of antifungals) or comparison (no antifungals) in children with asthma and ABPA (conditional recommendation, low certainty of evidence).

Explanation: The evidence from the five trials described above [16–20] was judged to be of low, low, very low, very low and moderate quality respectively. All were conducted in adults; only one was blinded [19]. In the trial by Agarwal et al., comparing oral itraconazole *vs.* prednisolone [18], 8 participants in the intervention arm, who failed to respond at 6 wk, were excluded from further analysis. This created a serious concern with regard to data reporting of all randomized participants.

Antifungal therapy is expected to be associated with greater cost (compared to oral steroid therapy), and drug level monitoring further increases the cost.

Owing to the limited quantity and quality of available RCT evidence (with the additional concerns highlighted) in adult patients, the EBGDG was unable to formulate an evidence based recommendation, either in favour of, or against, the intervention. Therefore, the EBGDG recommends that individual clinicians, need not consider a change in their existing practice, *i.e.,* those using antifungals may continue to do so, and vice versa (until additional evidence becomes available). For those using antifungals, no particular agent is recommended based on the current evidence.

Implementation Considerations: Clinicians using antifungals need to be aware that preparations of antifungal agents may have variable bioavailability [21]. Hence some experts advocate measurement of serum levels to confirm bioavailability. This may not be readily available, hence the EBGDG does not recommend it for routine practice.

Clinical Question 5: Is Voriconazole More Efficacious Than Itraconazole in Children with Asthma and Acute Exacerbation of ABPA?

Evidence Summary: There was no pre-existing systematic review addressing the question. A new systematic review did not identify any RCTs in acute exacerbation of ABPA. Two trials comparing antifungal *vs.* oral prednisolone monotherapy in acute-stage ABPA were considered for indirect evidence synthesis. The details of the evidence summary are presented in the online Supplementary File 1.

Recommendation: For clinicians using antifungal agents, the EBGDG recommends against using voriconazole instead of itraconazole, in children with asthma and acute exacerbation of ABPA (conditional recommendation, very low certainty of evidence).

Explanation: There was no trial comparing voriconazole *vs.* itraconazole in children with ABPA exacerbations. The limited indirect evidence suggested that although voriconazole was not superior in efficacy to itraconazole, it appeared to be associated with higher frequency of adverse events (although it is unclear whether this is statistically or clinically significant). Currently, voriconazole therapy is more expensive than itraconazole therapy. Based on these considerations, the EBGDG recommended that for clinicians using antifungal agents, there is no justification to shift from using itraconazole to voriconazole.

Clinical Question 6: Should Pulse Steroids be Used in Children with Asthma and ABPA?

Evidence Summary: There was no pre-existing systematic review addressing the question. A new systematic review did not identify any RCTs, although there were 44 studies with other designs.

Recommendation: No recommendation.

Explanation: There are multiple reports describing the use of high dose intravenous steroids to treat ABPA exacerbations, especially in patients not responding to conventional treatment [22–24]. However, in the absence of robust evidence from formal clinical trials, the EBGDG did not consider it feasible to develop an evidence-based recommendation.

Clinical Question 7: Should Immunomodulators be Used in Children with Asthma and ABPA?

Evidence Summary: The literature search identified two systematic reviews addressing the question. One of them included

two very small trials and some case reports [25]. The other systematic review included a single RCT evaluating omalizumab [26]. The trial had been terminated prematurely due to inability to recruit participants [27]. Limited data on adverse events was available, but were likely due to the underlying disease. Hence, the EBGDG was unable to use either systematic review.

A fresh systematic review identified two RCTs, one evaluating omalizumab [28] and the other examining dupilumab [29, 30] in ABPA with asthma. The details of the systematic review are presented in the online Supplementary File 1.

Recommendation: The authors recommend against immunotherapy with biologicals including omalizumab or dupilumab in children with asthma and ABPA (conditional recommendation, very low certainty of evidence).

Explanation: The limited evidence described above was of very low quality due to small sample size, indirectness of evidence, and the fact that the baseline treatment for ABPA was not uniform in the intervention and comparison arms. In the trial on omalizumab, there was no separate reporting of outcomes after the two treatment phases. Although both RCTs showed some beneficial effects with omalizumab and dupilumab, with no significant adverse event observed in either, in the absence of clarity regarding whether the patients had received oral steroids and/or antifungals, it is difficult to ascertain the exact role of these biologicals for ABPA treatment. The cost of therapy is also expected to be large. Therefore, the EBGDG gave a conditional recommendation against the intervention, until more evidence about efficacy, and the criteria for using these agents become available.

Discussion

To the best of the authors' knowledge, this is the first evidence-based guideline related to ABPA in children with asthma. The EBGDG followed a robust scientific methodology for the selection of the topic, development of clinical questions, prioritization of the questions, and evidence synthesis [6]. They followed the current scientific methodology for the development of evidence-based guidelines, making this guideline trustworthy.

The EBGDG encountered several challenges in developing this guideline. First, there was no robust (direct) evidence available for six of the seven clinical questions. Even studies conducted in adults had serious methodological limitations, resulting in high risk of bias. Therefore, the EBGDG had to downgrade most of the limited available evidence, making it difficult to provide strong recommendations. On the other hand, there were multiple studies reporting prevalence of AS or ABPA (mostly in adults), but these had variable methodological rigour, diverse definitions, and variations in the procedures applied, making it difficult to compare data across studies. The EBGDG focused on prevalence in children with 'poorly controlled' asthma; however this term itself has variable definitions [11, 12] with some authors referring to it as uncontrolled asthma. Further, the term is not synonymous with severe asthma. Additionally, knowledge on ABPA itself is evolving; the diagnostic criteria have undergone modifications from the earliest Rosenberg Patterson criteria [31], to the current ISHAM criteria [32]. This further challenged comparison and collation of data. Last but not the least, the bulk of currently available RCT data originates from a single centre in Chandigarh, India. As these studies have serious methodological limitations, external validation would have helped, but is unavailable.

Despite these challenges, the EBGDG developed a scientifically robust guideline. Although it would be relatively easy to avoid providing recommendations on account of the limitations in evidence quantity and quality, the EBGDG consciously avoided this, so that guidance could be provided to the target audience. In fact, the EBGDG was unable to formulate a recommendation for only one of the clinical questions.

This guideline has several strengths in addition to methodological rigour. The EBGDG focused on multiple patient-centric outcomes, that too at multiple time points. They included cost considerations also, although there were no supporting data. During the process of working through the EtD tables, they considered additional evidence not directly related to the clinical questions. The EBGDG believes that these measures make this guideline trustworthy, and applicable in diverse clinical settings.

However, the EBGDG acknowledges some limitations. The group was unable to include representation of stakeholders such as patients/families or hospital administrators/policy makers in the EBGDG. However, they considered their perspective when working through the EtD framework. They did not have access to a large team of experts familiar with guideline methodology; in fact none of the EBGDG have undergone formal training such as the GIN INGUIDE programme [33].

The EBGDG intends to update this guideline within two years of its publication, as (hopefully) more (robust) evidence in children becomes available. Meanwhile, they also believe that the paucity of evidence identified will stimulate well-designed research studies in children with ABPA.

Although this evidence-based guideline was developed keeping the needs of clinicians managing ABPA in mind, it has several implications for research also. First, it has highlighted the paucity of high-quality research data for the management of ABPA, not only in children, but adults as well. Second, issues as fundamental as determining the burden of AS and ABPA, utilizing currently accepted diagnostic criteria, need to be urgently addressed. Even the underlying condition 'asthma' requires an

appropriate definition, in order to compare data across studies. Third, in children, the paucity of evidence on diverse issues related to management, call for well-designed clinical trials to understand which interventions are efficacious as well as safe. This can pave the way for studies on clinical effectiveness (outside research settings), economic analysis (to determine cost-effectiveness), and health technology assessment (to determine the real-world issues in implementing the evidence).

Conclusions

This guideline provides evidence-based guidance to healthcare providers working in diverse settings, who manage children with asthma having ABPA. The key recommendations are that children with poorly controlled asthma should be investigated for ABPA (conditional recommendation, moderate certainty of evidence). Low(er) dose steroid therapy regimen (0.5 mg/kg/d for the first 2 wk, followed by a progressive tapering) is preferable to higher dose regimens (conditional recommendation, very low certainty of evidence). Oral steroid regimens longer than 16 wk (including the period of tapering), should not be used (conditional recommendation, very low certainty of evidence). Antifungal agents may or may not be added to steroid therapy as the evidence was neither in favour nor against (conditional recommendation, low certainty of evidence). For those clinicians who routinely use antifungal agents, the EBGDG recommends against using voriconazole instead of itraconazole. (conditional recommendation, very low certainty of evidence). There is no evidence to suggest whether pulse steroid therapy may be used in preference to conventional steroid therapy. At the present time, immunotherapy with biologicals is not recommended (conditional recommendation, very low certainty of evidence).

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Authors' Contributions JLM conceptualized the work, devised the methodology, reviewed and finalized the manuscript; KK prepared the draft manuscript. All authors contributed to the development of the guideline (framing questions, literature review, critical appraisal, evidence synthesis, translating evidence to decisions, framing recommendations, preparing the manuscript). JLM will act as the guarantor for this manuscript.

Declarations

Declarations of Interest All EBGDG members submitted written, formal, Declarations of interest (DoI) to the steering group, before undertaking the guideline development work. The steering group examined each submission, and judged that there were no conflicts of interest, precluding the participation of any member in the EBGDG.

Conflict of Interest None.

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Authors and Affiliations

Joseph L. Mathew[1] · Ketan Kumar[1] · Sheetal Agrawal[2] · Sanjay Bafna[3] · Sonia Bhatt[4] · Pallab Chatterjee[5] · N. S. Chithambaram[6] · Rashmi Ranjan Das[7] · Hema Gupta[2] · Sarika Gupta[8] · Kana Ram Jat[9] · Pawan Kalyan[10] · Rashmi Kapoor[11] · Hardeep Kaur[9] · Jasmeet Kaur[12] · Satnam Kaur[13] · Suhas P. Kulkarni[14] · Amber Kumar[15] · Sanjiv Singh Rawat[16] · Vivek Saxena[17] · Anita Singh[18] · Somu Sivabalan[19] · Shetanshu Srivastava[20] · Anshula Tayal[9]

1 Department of Pediatrics, Advanced Pediatrics Centre, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh 160012, India

2 Department of Pediatrics, ABVIMS and Dr. Ram Manohar Lohia Hospital, New Delhi, India

3 Department of Pediatrics, Bharati Vidyapeeth Medical College Hospital & Jehangir Hospital, Pune, India

4 Department of Pediatrics, F H Medical College, Etmaadpur, Agra, India

5 Department of Pediatrics, Apollo Multispeciality Hospital, Kolkata, India

6 Department of Pediatrics, Teerthanker Mahaveer Medical College and Research Centre, Moradabad, Uttar Pradesh, India

7 Department of Pediatrics, All India Institute of Medical Sciences, Bhubaneswar, India

8 Department of Pediatrics, King George's Medical University, Lucknow, India

9 Department of Pediatrics, All India Institute of Medical Sciences, New Delhi, India

10 Department of Pediatrics, Dr Pinnamaneni Siddhartha Institute of Medical Sciences and Research Foundation, Chinaoutapally, India

11 Department of Pediatrics, Regency Hospital Ltd., Kanpur, India

12 Department of Pediatrics, Sri Balaji Action Medical Institute, New Delhi, India

13 Department of Pediatrics, VMMC & Safdarjung Hospital, New Delhi, India

14 Department of Pediatrics, D. Y. Patil Medical College, D. Y, Patil Education Society (Deemed to be University), Kolhapur, Maharashtra, India

15 Department of Pediatrics, All India Institute of Medical Sciences, Bhopal, India

16 Department of Pediatrics, Child Care Clinic, Indore, India

17 Department of Pediatrics, Vatsalya Hospital, Kanpur, India

18 Department of Pediatrics, Sanjay Gandhi Postgraduate Institute of Medical Sciences (SGPGIMS), Lucknow, India

19 Department of Pediatrics, Dr Rela Institute & Medical Centre (RIMC), Chrompet, Chennai; and Sundaram Medical Foundation (SMF), Chennai, India

20 Department of Pediatrics, Dr Ram Manohar Lohia Institute of Medical Sciences, Lucknow, India