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Pediatric Respirology and Critical Care Medicine

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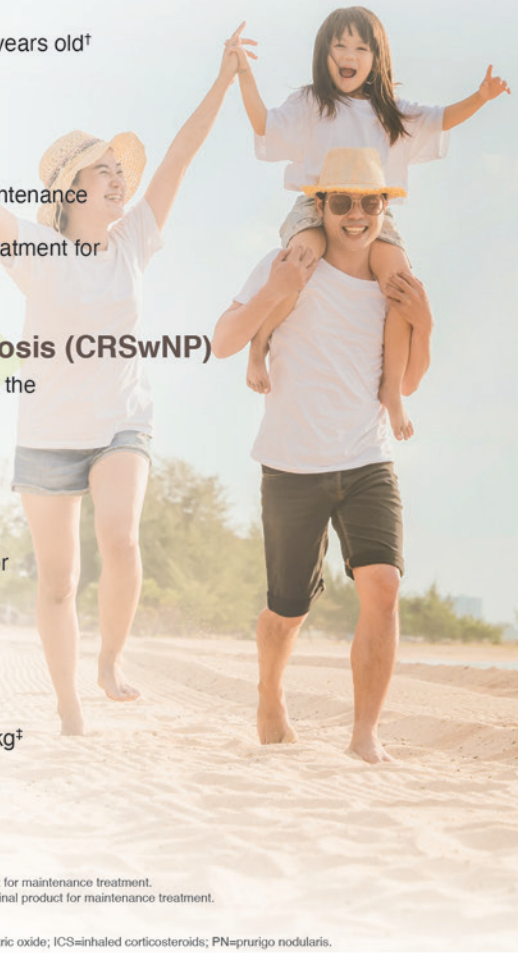

† Candidates for systemic therapy
* Characterised by raised blood eosinophils and/or raised FeNO, who are inadequately controlled with high dose ICS plus another medicinal product for maintenance treatment.
^ Characterised by raised blood eosinophils and/or raised FeNO, who are inadequately controlled with medium to high dose ICS plus another medicinal product for maintenance treatment.
# For whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control.
‡ Those who are inadequately controlled by, are intolerant to, or who are not candidates for conventional medicinal therapy.
Abbreviations: AD=atopic dermatitis; CRSwNP= chronic rhinosinusitis with nasal polyps; EoE= eosinophilic esophagitis; FeNO=fractional exhaled nitric oxide; ICS=inhaled corticosteroids; PN=prurigo nodularis.

References:
1. Guttman-Yassky E, et al. J Allergy Clin Immunol. 2019;143(1):155-172. 2. Gandhi NA, et al. Nat Rev Drug Discov. 2016;15(1):35-50 3.DUPIXENT® Hong Kong Prescribing Information

Presentation: Dupilumab solution for injection in a pre-filled syringe with needle shield. Indications: Atopic Dermatitis (AD): Moderate-to-severe AD in adults and adolescents ≥12 years who are candidates for systemic therapy; severe atopic dermatitis in children 6 months to 11 years old who are candidates for systemic therapy. Asthma: In adults and adolescents ≥12 years as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised FeNO, who are inadequately controlled with high dose ICS plus another medicinal product for maintenance treatment. In children 6 to 11 years old as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised FeNO, who are inadequately controlled with medium to high dose ICS plus another medicinal product for maintenance treatment. For 300 mg only – Chronic rhinosinusitis with nasal polyposis (CRSwNP): As an add-on therapy with intranasal corticosteroids for the treatment of adults with severe CRSwNP for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control. Prurigo Nodularis (PN): Moderate-to-severe PN in adults who are candidates for systemic therapy. Eosinophilic esophagitis (EoE): In adults and adolescents ≥12 years, weighing ≥40 kg, who are inadequately controlled by, are intolerant to, or who are not candidates for conventional medicinal therapy. **Dosage & Administration:** Subcutaneous injection. AD adults: Initial dose of 600 mg (two 300 mg injections), followed by 300 mg Q2W. AD adolescents (12-17y/o): Body weight <60 kg- initial dose of 400 mg (two 200 mg injections), followed by 200 mg Q2W. Body weight ≥60 kg- same dosage as adults. AD children (6-11y/o): Body weight 15kg~<60 kg- initial dose of 300 mg on Day 1 follow by 300 mg on Day 15, then 300mg Q4W. Body weight ≥60 kg- same dosage as adults. * The dose may be increased to 200 mg Q2W in patients with body weight of 15 kg~< 60 kg based on physician's assessment. AD children (6 months-5y/o): Body weight 5kg~<15 kg- initial dose of 200 mg, then 200 mg Q4W. Body weight 15kg~<30 kg- initial dose of 300 mg, then 300 mg Q4W. Dupilumab can be used with or without topical corticosteroids. Topical calcineurin inhibitors may be used, but should be reserved for problem areas only, e.g. face, neck, intertriginous and genital areas. Consider discontinuing treatment in patients who have shown no response after 16 weeks. Asthma adults and adolescents: Initial dose of 400 mg, followed by 200 mg Q2W. For patients with severe asthma and on oral corticosteroids or with severe asthma and co-morbid moderate-to-severe AD or adults with co-morbid severe CRSwNP- initial dose of 600 mg, followed by 300 mg Q2W. Asthma children (6-11y/o): Body weight 15kg~<30 kg- 300 mg Q4W. Body weight 30kg~<60 kg- 200 mg Q2W; or 300 mg Q4W. Body weight ≥60 kg- 200 mg Q2W. For paediatric patients (6-11y/o) with asthma and co-morbid severe atopic dermatitis, as per approved indication, the recommended dose should follow AD children (6-11y/o). Patients receiving concomitant oral corticosteroids may reduce steroid dose gradually once clinical improvement with dupilumab has occurred. The need for continued dupilumab therapy should be considered at least annually as determined by a physician. CRSwNP: Initial dose of 300 mg, followed by 300 mg Q2W. Consider discontinuing treatment in patients who have shown no response after 24 weeks. PN: Initial dose of 600 mg (two 300 mg injections), followed by 300 mg Q2W. Dupilumab can be used with or without topical corticosteroids. Consider discontinuing treatment in patients who have shown no response after 24 weeks. EoE: 300 mg QW. Dupilumab 300 mg QW has not been studied in patients with EoE weighing <40 kg. Dosing beyond 52 weeks has not been studied. For Missed dose instructions, please refer to the full prescribing information. **Contraindications:** Hypersensitivity to dupilumab or any of the excipients. **Precautions:** Not be used to treat acute asthma symptoms, acute exacerbations, acute bronchospasm or status asthmaticus. Do not discontinue corticosteroids abruptly upon start of dupilumab. Reduction should be gradual and performed under supervision of a physician; it may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy. Biomarkers of type 2 inflammation may be suppressed by systemic corticosteroid use. If systemic hypersensitivity reaction occurs, discontinue dupilumab and initiate appropriate therapy. Be alert to vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in patients with eosinophilia. Treat pre-existing helminth infections before initiating dupilumab. If patients become infected while receiving dupilumab and do not respond to anti-helminth treatment, discontinue dupilumab until infection resolves. Cases of enterobiasis were reported in children 6 to 11 years old in the paediatric asthma development program. Advise patients to promptly report new onset or worsening eye symptoms. Patients who develop conjunctivitis, dry eye and keratitis that does not resolve following standard treatment should undergo ophthalmological examination. Sudden changes in vision or significant eye pain that does not settle warrant urgent review. Patients with comorbid asthma should not adjust or stop asthma treatments without consultation with physicians. Carefully monitor patients after discontinuation of dupilumab. Avoid using live and live attenuated vaccines concurrently with dupilumab. Patients should be brought up to date with immunisations before starting dupilumab. **Drug Interactions:** Immune responses to TdaP vaccine and meningococcal polysaccharide vaccine were assessed. Patients receiving dupilumab may receive concurrent inactivated or non-live vaccinations. **Pregnancy and lactation:** Should be used during pregnancy only if potential benefit justifies potential risk to foetus. Unknown whether dupilumab is excreted in human milk or absorbed systemically after ingestion. Decision must be made whether to discontinue breast-feeding or dupilumab taking into account benefit of breast feeding for the child and benefit of therapy for the woman. **Undesirable effects:** Most common adverse reactions reported- injection site reactions, conjunctivitis, conjunctivitis allergic, arthralgia, oral herpes, eosinophilia and injection site bruising. Safety profile observed in adolescents and children 6 months to 11 years old consistent with that seen in adults. For other undesirable effects, please refer to the full prescribing information. **Preparation:** 2 x 300mg/2ml in pre-filled syringe with needle shield, 2 x 200mg/1.14ml in pre-filled syringe with needle shield. **Legal Classification:** Part 1, First & Third Schedules Poison **Full prescribing information is available upon request.**

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Contents

Update in Paediatric Asthma, Immunotherapy for Food Allergy, and High-Flow

In this issue of "Pediatric Respirology and Critical Care Medicine," Professor Andrew Bush has updated recent knowledge on paediatric asthma.[1] As we all know, he is a world-renowned paediatric respirologist. His research has made a significant impact and progress in paediatric asthma management globally. We are honoured to have him publish the article related to asthma in our journal first in 2017 and again in this issue.

Professor Andrew Bush has described the superiority of the combination therapy, beta-2 agonist combined with inhaled corticosteroids, in the same single inhaler device and being used for both controller and reliever, which is called the single maintenance and reliever therapy regime. He has used this term interchangeably with an anti-inflammatory reliever. Although there has been convincing evidence showing that this regime was helpful; however, the previous studies focussed on only the 12 years and over age group. Further studies in children younger than 12 years of age are needed to be done shortly.

Moreover, new treatments for asthma are mentioned in this study. Instead of using oral corticosteroids for difficult asthma, we now have more options to choose from, such as omalizumab, dupilumab, mepolizumab, dupilumab, and tazepelumab. These drugs are in the group of biologics that act at different steps in the allergic mechanisms of asthma. Unfortunately, the evidence base in children is much less compared with adults. Omalizumab has had relatively most evidence in paediatrics. It is, therefore, should be selected first. In adults, elevations of blood oeosinophil count and fractional exhaled nitric oxide were found to be independent predictors of future asthma attacks. However, in children, these parameters as well as spirometry failed to predict a bad outcome. As a result, we do not know for sure, which child will need to have such intensified treatment.

Another interesting review paper in this issue is about immunotherapy for food allergy, which consists of oral immunotherapy (OIT), sublingual immunotherapy (SLIT), epicutaneous immunotherapy, a combination of anti-immunoglobulin E into OIT or SLIT, and introduction of hypoallergenic allergens by modifying native food products, such as boiling or baking or using recombinant food proteins.[2] The author has nicely appraised the safety and efficacy of each immunotherapy technique, which differs from the others. More research studies are required to establish the most suitable approach to food allergy in children.

After the COVID-19 pandemic, a high-flow nasal cannula (HFNC) was recognised as a method of respiratory support before noninvasive and invasive ventilation. It delivers not only oxygen but also positive airway pressure and heated humidity. The authors conducted a study showing in detail that the arterial blood gas parameters obtained from the children with respiratory distress were noted to improve significantly within the first hour of initiation of HFNC.[3] Lactate levels were also decreased. This is another reason why HFNC has become more popular in everyday paediatric practice.

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Conflicts of interest

There are no conflicts of interest.

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References

1. Andrew B. Update in paediatric asthma 2024. Pediatr Respirol Crit Care Med 2024;8:3-10.

2. Wan WTC. Immunotherapy for food allergy: Current proposals to improve safety and efficacy. Pediatr Respirol Crit Care Med 2024;8:11-5.
3. Lokeswari B. To study the efficiency of high flow nasal cannula in improving the arterial blood gas parameters in children admitted to pediatric intensive care unit with respiratory distress. Pediatr Respirol Crit Care Med 2024;8:16-22.

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Update in Paediatric Asthma 2024

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The aim of this manuscript is to update a previous review article, published in 2017.[1] Many things have stayed the same: the need to determine what treatable traits underlie a diagnosis of asthma[2,3], and the need to get the basics right with a multidisciplinary approach.[4,5] This last is particularly important as more and more expensive biologicals become available; nothing is easier, and nothing is both more harmful and intellectually sloppy, than to add more treatment to a failing regime without seriously considering why the regime is failing; no-one in their right mind would add a single other medication to a failing tuberculosis regime; why do we do this so readily in children with asthma?

An important new concept, which is not captured by guidelines, is the distinction between disease activity and disease damage. The Rheumatologists have absolutely grasped this concept—an arthritis may be active, with no joint deformity, or inactive but with major chronic disability. The approach to the two categories should be totally different; if the disease is crippling, but burnt out then not much can be done except to palliate the destruction, but if active, irrespective of function, treatment should be aggressive, and the better preserved the function the more aggressive should be the treatment of active disease. The same paradigm should be used for asthma. Fixed impairment of spirometry is a sign of damage not disease activity; new tools are needed to measure the latter (below).

Getting Smart With Rescue Therapy

Conventionally, short-acting, rapid onset β-2 agonists (SABA) are used as needed to control symptoms and as acute treatment of asthma attacks. However, this approach is far from ideal. It is well known that over-use of SABA,[6] especially in association with under-use of inhaled corticosteroids (ICS)[7] is a major risk factor for severe asthma attacks.[8] Eformoterol is a rapid onset, long-acting β-2 agonist (LABA), unlike salmeterol which is a partial agonist with slow onset of action which exhibits tachyphylaxis. Combination therapy (eformoterol and budesonide) in the same inhaler (usually a Turbuhaler) has long been used as a regular once or twice-daily therapy and as needed to relieve symptoms in adults and children aged 12 years and over.[9] This approach is superior to using SABA as rescue therapy combined with regular combination therapy or increasing the dose of ICS. This is the SMART regime (Single maintenance and reliever therapy) and has the merit of simplicity (only one inhaler device), which may be particularly important in teenagers. The evidence for this regime is unequivocal in children aged 12 years and over.

Recently, GINA has recommended the use of combination therapy as reliever at all levels of asthma severity in those aged 12 years and over.[10] There is sound biological logic behind this recommendation. LABAs are never prescribed in asthma without concomitant ICS, because this approach may mask worsening underlying airway inflammation, and even contribute to inflammation worsening.[11-15] The asthma paradox in most if not all current National guidelines is that we allow the use of SABAs without concomitant ICS at Step 1! It is also the case that what is perceived as "mild" asthma is in fact no such thing. In the U-BIOPRED "mild" school-age cohort only around half had adequate symptom control, nearly 10% had been admitted to intensive care the group as a whole had a median of at least one asthma attack in the previous

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year.[16] Clearly, the expectations of many families about what can and should be achieved with asthma therapy are lower than we would want.

There are now four large randomised controlled studies[17-20] and a meta-analysis[21] in the 12 years and over age group which demonstrated the superiority of combination therapy even in mild asthma at steps 1 and 2 in terms of reduction of all and severe asthma attacks. This was achieved in Step 2 patients using a *lower* dose of ICS; the fear that combination therapy would result in ICS overdose has not been realised. In this age group, AIR (anti-inflammatory reliever) therapy has such a substantial body of evidence that it should be standard therapy.

The SMART/AIR approach has been criticised as relying on symptom perception, but of course, all therapies rely on the patient or family perceiving a need. Indeed, one factor important in non-adherence to ICS is the perception that they are not needed. A further criticism has been that SMART/AIR is associated with less good symptom control, which has resulted in EMEA failing to endorse this approach.[21] However, the decrement in symptom control was below the minimal clinically important difference; patients preferred the SMART/AIR strategy; and the cause of death in asthmatic patients is asthma attacks, not poor day-to-day control. The combination strategy means that asthma deaths due to ICS neglect and SABA over-dosing cannot happen. Indeed, I have argued elsewhere that it is time for SABA to be regarded as a controlled drug, like opiates, in school-aged children, and reserved for in-hospital acute bronchodilator response testing and for acute attacks of asthma.[22] Implementing this approach requires a change in asthma plans, but this is readily achievable and proposals for how these would look have been published.[23]

The 6–11-year age group has been left behind. Shockingly, as yet there are no data in the under 12-year population at step 1.[24] There is a single SMART study in this age group, with similar results as in older children and adults. There are two published studies supporting the use of as needed ICS/SABA in children with mild asthma. In the first, the TREXA study,[25] a four-way comparison of as needed SABA vs. as needed SABA plus ICS, vs. regular ICS plus as needed SABA vs. regular ICS plus as needed SABA plus ICS, the outcomes were equivalent for all three ICS-containing regimes and worse for the as needed SABA group. Growth in height was reduced in both regular ICS groups compared with SABA only and as needed SABA plus ICS; the latter two showed equivalent gain in height. In another study of African-American children in which standard therapy was compared to as needed ICS plus SABA,[26] the attack frequency was the same in both groups, but with around one third less ICS administered in the as needed group. There were minimally worse asthma control test (ACT) scores in the six and over group, c-ACT was identical in the younger children. The families and children preferred the as-needed regime.

However, it is shameful that children have lagged behind adults in terms of AIR using eformoterol containing regimes. There are trials recruiting or being planned in New Zealand, the United Kingdom and South Africa to address this, and these results will be important. It will be important to ensure that the budesonide-eformoterol combination continues to be available in a metered dose inhaler for the younger children who may find dry powder devices difficult to use. In terms of pre-school children, the INFANT study showed that the as needed ICS plus SABA regime was inferior to regular ICS,[27] but this needs confirming, and indeed such a study is underway in New Zealand.

Overall, the use of ICS plus LABA or SABA makes biological sense; and takes away two major risk factors for asthma attacks. GINA has it right, and we need the studies in the 5–11-year-old age group.

Beyond Long-Term Oral Corticosteroids: The New Biologicals

Thankfully, the days of children stuck on oral corticosteroids have largely passed; new, powerful monoclonals have superseded oral steroid-based regimes. However, it cannot be over-stressed that children referred for consideration for biologics require a detailed investigation; most of such referrals in fact need to get the basics right.[28] It is always easier to add more treatment rather than ask why the existing treatment is not working, and the easy route must be avoided. Biologics are indicated in (a) true therapy resistant asthma, and (b) refractory difficult asthma due to persistently poor adherence.[29] This latter is controversial in some circles, because good adherence is seen as a pre-requisite for biologic therapy. However, as discussed elsewhere, it is virtually impossible to ensure adherence short of directly observed therapy; and in any case, a child should not be penalised for non-adherence; it is more important to keep the child alive despite non-adherence.

Understanding the role of biologics requires an appreciation of the biology of asthma. Crudely this is divided into T-helper (TH) Types 1 and 2. The mechanisms of Type 2 involve the pivotal cytokines interleukin (IL)-4, -5, and -13. The drivers of TH-1 (or perhaps better, TH2 low) asthma are poorly appreciated.[30] With one exception, biologics are directed at TH2 driven asthma. The available agents and their mechanisms are shown in Table 1 and Figure 1. What is depressing is that, with the exception of omalizumab, the evidence base in children is much less than in adults; monoclonals which are found to be inactive in adults are automatically assumed to be

inactive in children despite mounting evidence of age-related mechanistic differences (below); and the lack of evidence in children for biomarkers to predict response (also discussed in detail below).

The initial biologic: omalizumab

This is a humanised monoclonal antibody which binds to circulating IgE, thus preventing IgE binding to the high affinity receptor. Omalizumab also has effects boosting anti-viral immunity.[31] Since asthma attacks are mostly viral driven in children with uncontrolled allergic inflammation, the double ant-viral, anti-inflammatory effects of omalizumab are highly beneficial. The dose and frequency of injections (every 2 or 4 weeks) is determined by body weight and IgE level; international guidelines vary, but an IgE above 1300 IU/mL is generally taken as a contraindication, but with no evidence base. In adults, patients with high FeNO and blood eosinophil count responded best[32]; IgE level was not a biomarker of response. We do not have similar data to predict response in children; one small study suggested that an elevated FeNO which reduced in response to parenteral triamcinolone was a marker of a good outcome.[33] There are numerous randomised controlled trials, real life studies and systematic reviews documenting the efficacy of omalizumab in decreasing attack frequency and improving symptom control, while often allowing reduction in ICS dose.[34-36] The benefits may extend beyond 2 years.[37] Omalizumab is the biologic for which there is most evidence in children, and therefore is the one I use as first choice in eligible patients.

Table 1: Biologics licensed for paediatric asthma and their indications

Biologic	Mode of action	Age licensed
Omalizumab	Binds circulating IgE Downregulates high-affinity IgE receptor (FceRI)	≥6 years
Mepolizumab	Binds circulating IL5	≥6 years
Dupilumab	Binds to IL4-R alpha subunit, preventing binding of IL4 and IL13	≥6 years
Tezepelumab	Binds circulating TSLP	>12 years

IL = interleukin, IgE = immunoglobulin E, TSLP = thymic stromal lymphopoietin

Mepolizumab: anti-IL5

Mepolizumab binds circulating IL5, which has numerous effects promoting eosinophil survival and mobilisation from the bone marrow to the airway. The mepolizumab story is a salutary reminder of the need for precision medicine if valuable therapies are not to be discarded. The initial study failed to show benefit,[38] and it was only when mepolizumab was trialled in patients with eosinophilic asthma who were attack prone that the dramatic reduction in attacks was documented.[39,40] The pivotal DREAM study was in adults and children of 12 years and over and documented a reduction in asthma attacks of around one-third.[41] However, the vast majority of patients were in fact adults, and no attempt was made to look for developmental changes in response.

MUPPITS-2 was a superb double blind, placebo-controlled, year-long study of mepolizumab in children and young people aged 6–17 years.[42] Entry criteria

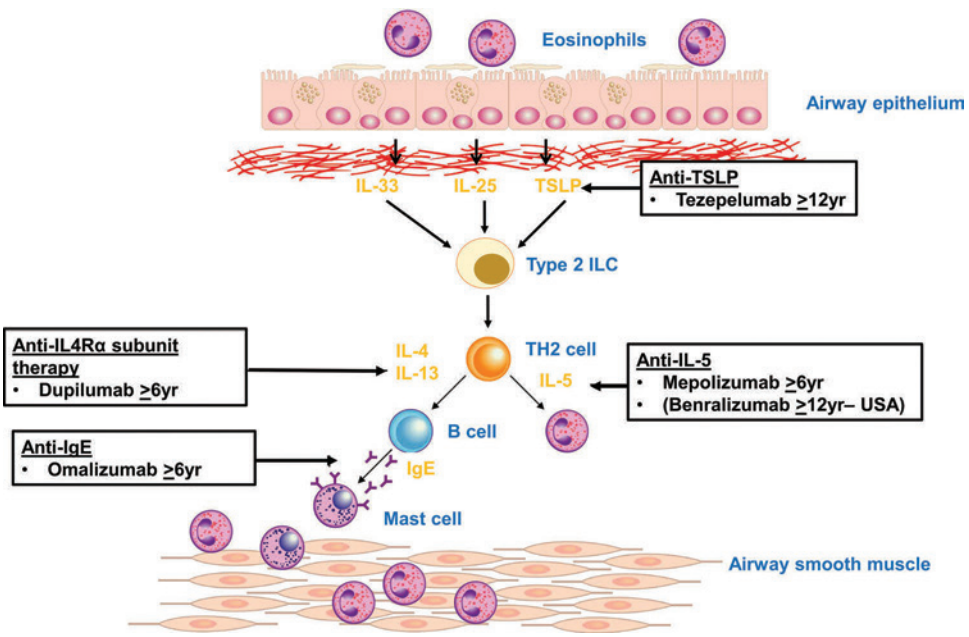

Figure 1: Summary of the pathways of TH2 inflammation and the modes of action of the new biologicals (modified from figures kindly provided by Prof Sejal Saglani). IL = interleukin, IgE = immunoglobulin E, ILC = innate lymphoid cell, TSLP = Thymic stromal lymphopoietin

included at least two asthma attacks in the preceding year and a blood eosinophil count set at the rather low level of ≥150 cells/μλ (see below). The primary outcome was the number of asthma attacks defined as treatment with oral corticosteroids. 290/390 were randomised to mepolizumab (n = 146) or placebo (n = 144). There was a small but statistically significant reduction in asthma attacks and mepolizumab was safe. However, inspection of the data shows the results were far less dramatic than for DREAM.[43] Despite this disappointing result, in the UK mepolizumab is recommended as the next-line biological after omalizumab.

Reslizumab binds to circulating IL5, and benralizumab binds to the IL5 receptor; the latter has the most dramatic effects in reducing airway and circulating eosinophils.[44] Neither has been trialled or licensed in young children; in the USA, Benralizumab is licensed in children aged 12 years and over.

Dupilumab: anti IL4/13

Dupilumab binds to the IL4-R alpha subunit, thus preventing the binding of IL4 and IL13. There is substantial evidence of benefit in children with eczema and adults with asthma.[45] The VOYAGE study was another superb double blind, placebo-controlled, year-long study of dupilumab in 408 children age 6–11 years.[46] The primary end point was the annualised rate of severe asthma attacks and were evaluated separately in the children who had either a type 2 inflammatory picture (≥150 eosinophils/μλ or FeNO ≥20 ppb at baseline) or a blood eosinophil count of at least 300 cells/ μλ at baseline. In both groups, compared with placebo, there were significant reductions in attack rates, improvement in FEV1,[46,47] and better asthma control. Interestingly, there was an increase in the number of viral infections in the dupilumab group, but the medication was very safe. Benefits were seen even in children with no evidence of allergic asthma.[48] Benefits were maintained during a year long, open label extension of VOYAGE, with no new safety concerns.[49] My opinion is that the VOYAGE and MUPPITs-2 data, in the absence of a head-to-head comparison, means that dupilumab is the biologic of choice in eligible children if omalizumab has either failed or the child is ineligible.

Tezepelumab: treatment for TH2 high and low asthma

Tezepelumab acts upstream from the classical TH2 signature cytokines IL4, IL5 and IL13. Thymic stromal lymphopoietin (TSLP) is an alarmin secreted by airway epithelial cells as an early step in the inflammatory cascade with pleiotropic effects and is blocked by Tezepelumab. In a Phase 3, double blind, placebo-controlled, year-long study of Tezepelumab versus placebo in more than 1000 patients age 12–80 years, again the primary end-point was asthma attacks, and this was assessed in those with baseline blood eosinophil counts <300/μλ cells per microliter. Annualised attack rate was approximately halved in the active group, and the results were similar in the low blood eosinophil group.[50] Spirometry and quality of life was also improved. These findings were confirmed in two other Phase 3 studies[51,52] and in a combined analysis.[53] The improvements were maintained in a 2 years follow up study, irrespective of blood eosinophil count, FeNO or atopic status.[54] Excitingly, Tezepelumab is the first monoclonal effective in TH2 low asthma.

The New Biologicals: Unanswered Questions

Biomarkers

There is a real scarcity of data in paediatrics about biomarkers predicting successful treatment with a biological. In particular, the blood eosinophil count has been used uncritically. In adults, 300 cells/μλ approximates to the upper limit of normal, but in young children, this figure may below the mean[55]! It is therefore unwise to extrapolate from adult data in setting thresholds for biologicals. There is also a lack of data about the variability of blood eosinophil count in children. The eosinophil count may be elevated by non-asthma atopic diseases such as atopic dermatitis (as is FeNO) and also elevated by parasitic infections. There is certainly a need for data in adults and children from areas with a high burden of parasitic disease. Defining predictors of response, thus avoiding empirical N-of-1 trials in children, is a major research priority.

Which biological first?

There are no head-to-head comparisons of biologics in children, although the results of the ongoing TREAT trial which compares omalizumab and mepolizumab will be of interest.[56] Since there are most paediatric data for omalizumab, this would be my first choice in eligible children. If the child is ineligible, then on the basis of MUPPITS-2 and VOYAGE, I would use dupilumab in eligible patients, especially if the child also has bad eczema, but this is not supported by UK guidelines, which reserve dupilumab for those who have failed a mepolizumab trial. Rather what is needed is an understanding of which child will respond best to which biological.

Are the eosinophils always the bad guys?

The underlying assumption of biologics targeting Type 2 inflammation is that the eosinophil is dangerous and must be ruthlessly eradicated. However, the eosinophil has other functions, not merely being the cell that keeps asthma doctors busy. There are potential developmental roles in immune maturation and the development of the microbiota.[57] In the gut, eosinophils are important in IgA mediated gut immunity, and are antigen presenting cells.[58] Bone marrow eosinophils are needed for adjuvant-induced B-cell priming and maintenance of memory plasma cells.[59,60] Adipose tissue eosinophils have a role

in beige fat thermogenesis and glucose homeostasis via actions on alternatively activated macrophages.[61,62] There is also evidence for a role for the eosinophil in the response to infection. In an observational study of adult patients on one of the three anti-IL5 monoclonals mepolizumab, reslizumab and benralizumab, benralizumab was most effective in reducing sputum eosinophil counts, and indeed in most patients, esoinophils became undetectable in sputum.[44] However, benralizumab patients had more respiratory infections and more infection driven asthma attacks than patients in the other two therapy groups. Of note, there were also more infections in the dupilumab treated patients in VOYAGE (above). There is other evidence of an important anti-viral role for eosinophils.[63] Also, a retrospective study of COVID-19 infected adults showed that those with a blood eosinophil count ≥150/μλ were less likely to be admitted to hospital and less likely to die if admitted, than those with lower eosinophil counts.[64] On the other hand, biological therapy for asthma did not appear to be a risk factor for COVID-19 in severe asthma patients.[65,66] Of course, this does not mean that anti-TH2 strategies should be discarded, but just does sound a note of caution in their use.

Mechanisms of Severe Asthma

The assumption has always been made that adult and school age atopic allergic asthma are one and the same disease, and indeed for mild asthma, this may be the case. However, in severe asthma this may not be the case. The Brompton data challenged the TH2 paradigm as the cause of ongoing severe asthma.[67] In a bronchoscopic study, signature TH2 cytokines (IL4, IL5, IL13) were rarely found in bronchoalveolar lavage fluid (BALF) or induced sputum supernatant, and immunohistochemistry showed no increase in IL5 or IL13 positive cells. The SARP (Severe Asthma Research Program) were also unable to confirm a TH2 signature in severe paediatric asthma.[68] They studied 53 children with asthma children (31 with severe asthma) and 30 adults. IL-6 and IL-13 in BALF differentiated asthma from controls; CXCL1 (GRO), RANTES (CCL5), IL-12, IFN-γ, IL-10 differentiated severe from moderate asthma. They concluded that severe asthma was neither TH1 nor TH2 predominant. The complexities of really severe paediatric asthma were underscored in a study of 68 BALFs from 52 children with severe asthma.[69] Detection of viruses and bacteria was common, CCR5 +ve TH1 cells enriched in BALF, and there were a range of pro-inflammatory, TH1, TH17 and TH2 cytokines also detected in BALF. Importantly, there was no control group. Some children exhibited TH2 skewing which correlated with total serum IgE. Children who were multi-sensitised had increased IL5, IL33, IL28A/IFNλ2 which correlated with sIgE to House dust mite, ryegrass and fungi, but not cat, ragweed, or food sIgE. Interestingly, and perhaps accounting for the relatively disappointing results of MUPPITS-2 in younger children, BALF IL5 increased with age and correlated with BALF and blood eosinophil counts.

There are a number of areas for consideration from these studies. Firstly, all these patients were prescribed ICS and it was (rightly) deemed unethical to take them off treatment. So, it may be there was considerable TH2 inflammation underlying the disease which had been abolished by ICS. Secondly, it is clear that there are a spectrum of difficult asthma, ranging from a TH1/TH17 infection dominated group merging into the other extreme, a TH2 allergen driven group. One size will not fit all. Finally, there is clearly a group associated with infected BALF. It should be remembered that association does not prove causation. There are a number of hypotheses which need to be tested and cannot currently be distinguished. ICS are known to be immunosuppressive at the airway mucosal level,[70] so the first hypothesis is that infection is a consequence of treatment. It is also possible that infection is driving the airway disease in which case targeted antibiotics may be helpful, but this is unproven. Finally, asthma and infection may be a manifestation of an underlying mucosal immune issue unrelated to ICS.

There are practical consequences to these mechanistic findings. The lessons of the history of precision medicine is that unless pathology is understood in detail, there is a huge risk that inappropriate dispensing of specific medications to the wrong patient groups may lead to valuable therapies being discarded as inactive. We therefore cannot and must not assume that the child with severe asthma refractory to treatment will respond to a TH2 strategy. We need to be asking the question, what sort of difficult asthma does this child have, what is the endotype and thus what biological(s) is most likely to be efficacious. If this process demonstrates that a monoclonal discarded as inefficacious in adults might be beneficial, for example, the anti-IL13 monoclonal tralokinumab,[71] then I would be prepared to use it if I could source it.

A Need for a Paradigm Shift: Risk Prediction

Asthma is common, but not all asthmas are equal. Traditionally, children with asthma are assessed on present symptoms and spirometry, but these are poor predictors of the risk of a future attack. Spirometry in particular is a marker of airway damage (which may be reversible) but not risk or disease activity. Although poor symptom control and impaired spirometry are risk factors for an attack, both can be normal and the child having apparently good control but underlying uncontrolled Type 2 airway inflammation may pose a risk of a major asthma attack with an intercurrent viral infection. In adult data from secondary analyses of the placebo limbs of randomised controlled trials of biologics, elevations in blood eosinophil count and FeNO were independent

predictors of future asthma attacks.[72,73] We do not have corresponding data in children, but these are badly needed. We know that many children have relatively trivial symptoms without having acute attacks. If we could better predict risk, we would be able to focus scarce resources for asthma reviews on the high-risk group. We need more data to know whether intensifying treatment in those at high risk but who are well (a) reduces risk, and (b) is something families will buy into. The data on using FeNO to drive treatment is not convincing,[74] and in studies using biomarkers to try to reduce treatment safely, patients have been reluctant actually to take less treatment.[75,76] Nonetheless, it is important to try to establish a paradigm shift to consider disease activity and risk rather than being comfortable monitoring airway damage, which may have been the result of a long burnt-out process.

Summary and Conclusions

Although this update has focused on exciting new developments in asthma, it remains the case that getting the basics right is still the major goal of asthma management. Low dose treatment, taken efficiently and regularly, should be all the pharmacology that most children with asthma need. This should be combined with attention to asthma triggers in the environment. Step 1, as needed SABA should now be abolished in children aged 12 and over, in favour of combination as needed LABA/ICS. There are ongoing trials which should establish the evidence base for this approach in children aged 5–11. Thankfully, the days of children with asthma being on long term systemic corticosteroids should be over, as the new biologicals offer better outcomes for that small minority who are truly refractory to standard treatment. These biologicals are largely directed at TH2 high airway inflammation, which is the most common pathophysiology of childhood asthma. Although Tezepelumab offers options for TH2 low asthma in those age 12 and over, the options for younger children with this phenotype are limited. It should be noted TH2 low asthma is rare in children and should always prompt a re-evaluation of the diagnosis. Finally, we need to pay more attention to the concepts of risk of future attacks and disease activity when considering treatment.

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Conflicts of interest

There are no conflicts of interest.

References

1. Bush A. Asthma: What's new, and what should be old but is not! Pediatr Respirol Crit Care Med 2017;1:2-10.
2. Pavord ID, Beasley R, Agusti A, Anderson GP, Bel E, Brusselle G, *et al*. After asthma—Redefining airways diseases. A *Lancet* commission. Lancet 2018;391:350-40.
3. Agusti A, Bel E, Thomas M, Vogelmeier C, Brusselle G, Holgate S, *et al*. Treatable traits: Toward precision medicine of chronic airway diseases. Eur Respir J 2016;47:410-9.
4. Lødrup Carlsen KC, Hedlin G, Bush A, Wennergren G, de Benedictis FM, De Jongste JC, *et al*; PSACI (Problematic Severe Asthma in Childhood Initiative) group. Assessment of problematic severe asthma in children. Eur Respir J 2011;37:432-40.
5. Cook J, Beresford F, Fainardi V, Hall P, Housley G, Jamalzadeh A, *et al*. Managing the pediatric patient with refractory asthma: A multidisciplinary approach. J Asthma Allergy 2017;10:123-30.
6. Suissa S, Ernst P, Boivin JF, Horwitz RI, Habbick B, Cockroft D, *et al*. A cohort analysis of excess mortality in asthma and the use of inhaled beta-agonists. Am J Respir Crit Care Med 1994;149:604-10.
7. Suissa S, Ernst P, Benayoun S, Baltzan M, Cai B. Low-dose inhaled corticosteroids and the prevention of death from asthma. N Engl J Med 2000;343:332-6.
8. Buelo A, McLean S, Julious S, Flores-Kim J, Bush A, Henderson J, *et al*; ARC Group. At-risk children with asthma (ARC): A systematic review. Thorax 2018;73:813-24.
9. Jorup C, Lythgoe D, Bisgaard H. Budesonide/formoterol maintenance and reliever therapy in adolescent patients with asthma. Eur Respir J 2018;51:1701688.
10. Reddel HK, FitzGerald JM, Bateman ED, Bacharier LB, Becker A, Brusselle G, *et al*. GINA 2019: A fundamental change in asthma management: Treatment of asthma with short-acting bronchodilators alone is no longer recommended for adults and adolescents. Eur Respir J 2019;53:1901046.
11. Amrani Y, Bradding P. β_2-adrenoceptor function in asthma. Adv Immunol 2017;136:1-28.
12. Kersten ET, Koppelman GH, Thio BJ. Concerns with beta2-agonists in pediatric asthma—A clinical perspective. Paediatr Respir Rev 2017;21:80-5.
13. Sears MR, Taylor DR, Print CG, Lake DC, Li QQ, Flannery EM, *et al*. Regular inhaled beta-agonist treatment in bronchial asthma. Lancet 1990;336:1391-6.
14. Drazen JM, Israel E, Boushey HA, Chinchilli VM, Fahy JV, Fish JE, *et al*. Comparison of regularly scheduled with as-needed use of albuterol in mild asthma. Asthma Clinical Research Network. N Engl J Med 1996;335:841-7.
15. Aldridge RE, Hancox RJ, Cowant JO, Frampton CM, Town GI, Taylor DR. Eosinophils and eosinophilic cationic protein in induced sputum and blood: Effects of budesonide and terbutaline treatment. Ann Allergy Asthma Immunol 2002;89:492-7.
16. Fleming L, Murray C, Bansal AT, Hashimoto S, Bisgaard H, Bush A, *et al*; U-BIOPRED Study Group. The burden of severe asthma in childhood and adolescence: Results from the paediatric U-BIOPRED cohorts. Eur Respir J 2015;46:1322-33.
17. O'Byrne PM, FitzGerald JM, Bateman ED, Barnes PJ, Zhong N, Keen C, *et al*. Inhaled combined budesonide-formoterol as needed in mild asthma. N Engl J Med 2018;378:1865-76.
18. Beasley R, Holliday M, Reddel HK, Braithwaite I, Ebmeier S, Hancox RJ, *et al*; Novel START Study Team. Controlled trial of budesonide-formoterol as needed for mild asthma. N Engl J Med 2019;380:2020-30.
19. Bateman ED, Reddel HK, O'Byrne PM, Barnes PJ, Zhong N, Keen C, *et al*. As-needed budesonide-formoterol *versus* maintenance budesonide in mild asthma. N Engl J Med 2018;378:1877-87.
20. Hardy J, Baggott C, Fingleton J, Reddel HK, Hancox RJ, Harwood M, *et al*; PRACTICAL study team. Budesonide-formoterol reliever therapy *versus* maintenance budesonide plus terbutaline reliever therapy in adults with mild to moderate asthma (PRACTICAL): A 52-week, open-label, multicentre, superiority, randomised controlled trial. Lancet 2019;394:919-28.
21. Hatter L, Bruce P, Braithwaite I, Holliday M, Fingleton J, Weatherall M, *et al*. ICS-formoterol reliever *versus* ICS and short-acting β_2-agonist reliever in asthma: A systematic review and meta-analysis. ERJ Open Res 2021;7:00701-2020.
22. Bush A, Dalziel SR, Byrnes CA, Hatter L, Beasley R. Has the time come to end use of the blue inhaler? Lancet Respir Med 2021;9:e51.

23. Beasley R, Bruce P, Houghton C, Hatter L. The ICS/Formoterol Reliever Therapy Regimen in Asthma: A Review. J Allergy Clin Immunol Pract 2023;11:762-72.e1.
24. Bisgaard H, Le Roux P, Bjåmer D, Dymek A, Vermeulen JH, Hultquist C. Budesonide/formoterol maintenance plus reliever therapy: A new strategy in pediatric asthma. Chest 2006;130:1733-43.
25. Martinez FD, Chinchilli VM, Morgan WJ, Boehmer SJ, Lemanske RF, Jr, Mauger DT, *et al*. Use of beclomethasone dipropionate as rescue treatment for children with mild persistent asthma (TREXA): A randomised, double-blind, placebo-controlled trial. Lancet 2011;377:650-7.
26. Sumino K, Bacharier LB, Taylor J, Chadwick-Mansker K, Curtis V, Nash A, *et al*. A pragmatic trial of symptom-based inhaled corticosteroid use in African-American children with mild asthma. J Allergy Clin Immunol Pract 2020;8:176-85.e2.
27. Fitzpatrick AM, Jackson DJ, Mauger DT, Boehmer SJ, Phipatanakul W, Sheehan WJ, *et al*; NIH/NHLBI AsthmaNet. Individualized therapy for persistent asthma in young children. J Allergy Clin Immunol 2016;138:1608-18.e12.
28. Bracken MB, Fleming L, Hall P, Van Stiphout N, Bossley CJ, Biggart E, *et al*. The importance of nurse led home visits in the assessment of children with problematic asthma. Arch Dis Child 2009;94:780-4.
29. Bush A, Saglani S, Fleming L. Severe asthma: Looking beyond the amount of medication. Lancet Respir Med 2017;5:844-6.
30. Maspero J, Adir Y, Al-Ahmad M, Celis-Preciado CA, Colodenco FD, Giavina-Bianchi P, *et al*. Type 2 inflammation in asthma and other airway diseases. ERJ Open Res 2022;8:00576-2021.
31. Teach SJ, Gill MA, Togias A, Sorkness CA, Arbes SJ, Jr, Calatroni A, *et al*. Preseasonal treatment with either omalizumab or an inhaled corticosteroid boost to prevent fall asthma exacerbations. J Allergy Clin Immunol 2015;136:1476-85.
32. Hanania NA, Wenzel S, Rosén K, Hsieh HJ, Mosesova S, Choy DF, *et al*. Exploring the effects of omalizumab in allergic asthma: An analysis of biomarkers in the EXTRA study. Am J Respir Crit Care Med 2013;187:804-11.
33. Fleming L, Koo M, Bossley CJ, Nagakumar P, Bush A, Saglani S. The utility of a multidomain assessment of steroid response for predicting clinical response to omalizumab. J Allergy Clin Immunol 2016;138:292-4.
34. Normansell R, Walker S, Milan SJ, Walters EH, Nair P. Omalizumab for asthma in adults and children. Cochrane Database Syst Rev 2014;13:CD003559.
35. Corren J, Kavati A, Ortiz B, Colby JA, Ruiz K, Maiese BA, *et al*. Efficacy and safety of omalizumab in children and adolescents with moderate-to-severe asthma: A systematic literature review. Allergy Asthma Proc 2017;38:250-63.
36. Chipps BE, Lanier B, Milgrom H, Deschildre A, Hedlin G, Szefler SJ, *et al*. Omalizumab in children with uncontrolled allergic asthma: Review of clinical trial and real-world experience. J Allergy Clin Immunol 2017;139:1431-44.
37. Deschildre A, Marguet C, Langlois C, Pin I, Rittié J-L, Derelle J, *et al*. Real-life long-term omalizumab therapy in children with severe allergic asthma. Eur Respir J 2015;46:856-9.
38. Leckie MJ, ten Brinke A, Khan J, Diamant Z, O'Connor BJ, Walls CM, *et al*. Effects of an interleukin-5 blocking monoclonal antibody on eosinophils, airway hyper-responsiveness, and the late asthmatic response. Lancet 2000;356:2144-8.
39. Nair P, Pizzichini MM, Kjarsgaard M, Inman MD, Efthimiadis A, Pizzichini E, *et al*. Mepolizumab for prednisone-dependent asthma with sputum eosinophilia. N Engl J Med 2009;360:985-93.
40. Haldar P, Brightling CE, Hargadon B, Gupta S, Monteiro W, Sousa A, *et al*. Mepolizumab and exacerbations of refractory eosinophilic asthma. N Engl J Med 2009;360:973-84.
41. Pavord ID, Korn S, Howarth P, Bleecker ER, Buhl R, Keene ON, *et al*. Mepolizumab for severe eosinophilic asthma (DREAM): A multicentre, double-blind, placebo-controlled trial. Lancet 2012;380:651-9.
42. Jackson DJ, Bacharier LB, Gergen PJ, Gagalis L, Calatroni A, Wellford S, *et al*; US National Institute of Allergy and Infectious Disease's Inner City Asthma Consortium. Mepolizumab for urban children with exacerbation-prone eosinophilic asthma in the USA (MUPPITS-2): A randomised, double-blind, placebo-controlled, parallel-group trial. Lancet 2022;400:502-11.
43. Bush A. Differing effects of mepolizumab across the life course. Lancet Respir Med 2023;11:123-5.
44. Poznanski SM, Mukherjee M, Zhao N, Huang C, Radford K, Ashkar AA, *et al*. Asthma exacerbations on benralizumab are largely non-eosinophilic. Allergy 2021;76:375-9.
45. Holguin F, Cardet JC, Chung KF, Diver S, Ferreira DS, Fitzpatrick A, *et al*. Management of severe asthma: A European Respiratory Society/American Thoracic Society guideline. Eur Respir J 2020;55:1900588.
46. Bacharier LB, Maspero JF, Katelaris CH, Fiocchi AG, Gagnon R, de Mir I, *et al*; Liberty Asthma VOYAGE Investigators. Dupilumab in children with uncontrolled moderate-to-severe asthma. N Engl J Med 2021;385:2230-40.
47. Bacharier LB, Guilbert TW, Katelaris CH, Deschildre A, Phipatanakul W, Liu D, *et al*. Dupilumab improves lung function parameters in pediatric type 2 asthma: VOYAGE study. J Allergy Clin Immunol Pract 2023:S2213-2198(23)01352.
48. Papadopoulos NG, Szefler SJ, Bacharier LB, Maspero JF, Domingo C, Fiocchi A, *et al*. Assessment of dupilumab in children with moderate-to-severe type 2 asthma with or without evidence of allergic asthma. Allergy 2023;78:2157-67.
49. Bacharier LB, Maspero JF, Katelaris CH, Fiocchi AG, Gagnon R, de Mir I, *et al*; Liberty Asthma EXCURSION Investigators. Assessment of long-term safety and efficacy of dupilumab in children with asthma (LIBERTY ASTHMA EXCURSION): An open-label extension study. Lancet Respir Med 2024;12:45-54.
50. Menzies-Gow A, Corren J, Bourdin A, Chupp G, Israel E, Wechsler ME, *et al*. Tezepelumab in adults and adolescents with severe, uncontrolled asthma. N Engl J Med 2021;384:1800-9.
51. Menzies-Gow A, Colice G, Griffiths JM, Almqvist G, Ponnarambil S, Kaur P, *et al*. NAVIFATOR: A phase 3 multicentre, randomized, double-blind, placebo-controlled, parallel-group trial to evaluate the efficacy and safety of tezepelumab in adults and adolescents with severe, uncontrolled asthma. Respir Res 2020;21:266.
52. Menzies-Gow A, Ponnarambil S, Downie J, Bowen K, Hellqvist A, Colice G. DESTINATION: A phase 3, multicentre, randomized, double-blind, placebo-controlled, parallel-group trial to evaluate the long-term safety and tolerability of tezepelumab in adults and adolescents with severe, uncontrolled asthma. Respir Res 2020;21:279.
53. Corren J, Menzies-Gow A, Chupp G, Israel E, Korn S, Cook B, *et al*. Efficacy of tezepelumab in severe, uncontrolled asthma: Pooled analysis of the PATHWAY and NAVIGATOR clinical trials. Am J Respir Crit Care Med 2023;208:13-24.
54. Menzies-Gow A, Wechsler ME, Brightling CE, Korn S, Corren J, Israel E, *et al*; DESTINATION study investigators. Long-term safety and efficacy of tezepelumab in people with severe, uncontrolled asthma (DESTINATION): A randomised, placebo-controlled extension study. Lancet Respir Med 2023;11:425-38.
55. Hartl S, Breyer MK, Burghuber OC, Ofenheimer A, Schrott A, Urban MH, *et al*. Blood eosinophil count in the general population: Typical values and potential confounders. Eur Respir J 2020;55:1901874.
56. Saglani S, Bush A, Carroll W, Cunningham S, Fleming L, Gaillard E, *et al*. Biologics for paediatric severe asthma: Trick or TREAT? Lancet Respir Med 2019;7:294-6.
57. Chu VT, Beller A, Rausch S, Strandmark J, Zänker M, Arbach O, *et al*. Eosinophils promote generation and maintenance of immunoglobulin-A-expressing plasma cells and contribute to gut immune homeostasis. Immunity 2014;40:582-93.
58. Xenakis JJ, Howard ED, Smith KM, Olbrich CL, Huang Y, Anketell D, *et al*. Resident intestinal eosinophils constitutively express antigen presentation markers and include two phenotypically distinct subsets of eosinophils. Immunology 2018;154:298-308.
59. Wang HB, Weller PF. Pivotal advance: Eosinophils mediate early alum adjuvant-elicited B cell priming and IgM production. J Leukoc Biol 2008;83:817-21.

60. Chu VT, Fröhlich A, Steinhauser G, Scheel T, Roch T, Fillatreau S, *et al*. Eosinophils are required for the maintenance of plasma cells in the bone marrow. Nat Immunol 2011;12:151-9.
61. Wu D, Molofsky AB, Liang HE, Ricardo-Gonzalez RR, Jouihan HA, Bando JK, *et al*. Eosinophils sustain adipose alternatively activated macrophages associated with glucose homeostasis. Science 2011;332:243-7.
62. Qiu Y, Nguyen KD, Odegaard JI, Cui X, Tian X, Locksley RM, *et al*. Eosinophils and type 2 cytokine signaling in macrophages orchestrate development of functional beige fat. Cell 2014;157:1292-308.
63. Sabogal Piñeros YS, Bal SM, Dijkhuis A, Majoor CJ, Dierdorp BS, Dekker T, *et al*. Eosinophils capture viruses, a capacity that is defective in asthma. Allergy 2019;74:1898-909.
64. Ferastraoaru D, Hudes G, Jerschow E, Jariwala S, Karagic M, de Vos G, *et al*. Eosinophilia in asthma patients is protective against severe COVID-19 illness. J Allergy Clin Immunol Pract 2021;9:1152-62.e3.
65. Tuncay G, Cakmak, ME, Can Bostan, O, Kaya, SB, Damadoglu, E, Karakaya, G, *et al*. The course of COVID-19 in patients with severe asthma receiving biological treatment. J Asthma 2022;59:2174-80.
66. Rial MJ, Valverde M, Del Pozo V, González-Barcala FJ, Martínez-Rivera C, Muñoz X, *et al*. Clinical characteristics in 545 patients with severe asthma on biological treatment during the COVID-19 outbreak. J Allergy Clin Immunol Pract 2021;9:487-89.e1.
67. Bossley C, Fleming L, Gupta A, Regamey N, Frith J, Oates T, *et al*. Pediatric severe asthma is characterized by eosinophilia and remodeling without TH2 cytokines. J Allergy Clin Immunol 2012;129:974-82.
68. Fitzpatrick AM, Higgins M, Holguin F, Brown LAS, Teague WG; National Institutes of Health/National Heart, Lung, and Blood Institute's Severe Asthma Research Program. The molecular phenotype of severe asthma in children. J Allergy Clin Immunol 2010;125:851-57.e18.
69. Wisniewski JA, Muehling LM, Eccles JD, Capaldo BJ, Agrawal R, Shirley D-A, *et al*. T_H1 signatures are present in the lower airways of children with severe asthma, regardless of allergic status. J Allergy Clin Immunol 2018;141:2048-60.e13.
70. Sabroe I, Postma D, Heijink I, Dockrell DH. The yin and the yang of immunosuppression with inhaled corticosteroids. Thorax 2013;68:1085-7.
71. Russell RJ, Chachi L, FitzGerald JM, Backer V, Olivenstein R, Titlestad IL, *et al*; MESOS study investigators. Effect of tralokinumab, an interleukin-13 neutralising monoclonal antibody, on eosinophilic airway inflammation in uncontrolled moderate-to-severe asthma (MESOS): A multicentre, double-blind, randomised, placebo-controlled phase 2 trial. Lancet Respir Med 2018;6:499-510.
72. Couillard S, Laugerud A, Jabeen M, Ramakrishnan S, Melhorn J, Hinks T, *et al*. Derivation of a prototype asthma attack risk scale centred on blood eosinophils and exhaled nitric oxide. Thorax 2022;77:199-202.
73. Busse WW, Wenzel SE, Casale TB, FitzGerald JM, Rice MS, Daizadeh N, *et al*. Baseline FeNO as a prognostic biomarker for subsequent severe asthma exacerbations in patients with uncontrolled, moderate-to-severe asthma receiving placebo in the LIBERTY ASTHMA QUEST study: A post-hoc analysis. Lancet Respir Med 2021;9:1165-73.
74. Turner S, Cotton S, Wood J, Bell V, Raja EA, Scott NW, *et al*. Reducing asthma attacks in children using exhaled nitric oxide (RAACENO) as a biomarker to inform treatment strategy: A multicentre, parallel, randomised, controlled, phase 3 trial. Lancet Respir Med 2022;10:584-92.
75. Heaney LG, Busby J, Hanratty CE, Djukanovic R, Woodcock A, Walker SM, *et al*; investigators for the MRC Refractory Asthma Stratification Programme. Composite type-2 biomarker strategy versus a symptom-risk-based algorithm to adjust corticosteroid dose in patients with severe asthma: A multicentre, single-blind, parallel group, randomised controlled trial. Lancet Respir Med 2021;9:57-68.
76. Saglani S, Bingham Y, Balfour-Lynn I, Goldring S, Gupta A, Banya W, *et al*. Blood eosinophils in managing preschool wheeze: Lessons learnt from a proof-of-concept trial. Pediatr Allergy Immunol 2022;33:e13697.

Review Article

Immunotherapy for Food Allergy: Current Proposals to Improve Safety and Efficacy

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Abstract

This review mainly focuses on the novel approaches that improve the safety and efficacy of immunotherapies, namely SLIT [alone or as pre-treatment of oral immunotherapy (OIT)], epicutaneous immunotherapy (EPIT), combination of anti-IgE into OIT or sublingual immunotherapy (SLIT) and introduction of hypoallergenic allergens by modifying native food products (boiling, baking, etc.) or manufacturing recombinant proteins. Among these proposals, some are clinically proven safe such as the use of anti-IgE while some are still under preclinical trials such as the use of some newly developed recombinant food protein allergens. What is certain is that more preclinical and clinical reviews and trials would be required on all these proposals before they could be maturely, safely, and effectively promoted in the clinical settings for patients' use.

Keywords: Food allergy, immunotherapy, recombinant food protein

Introduction

Food allergy (FA) has been a crucial public health issue affecting children in many parts of the globe. In particular, rising prevalence is observed in the more urbanised worlds.[1] A meta-analysis done in 2023 has revealed the overall global FA prevalence to be 4.3% (Asia: 4.2%; Europe: 4.8%; America: 3.2%; Africa: 1.6%; Oceania: 7.5%).[2] While peanut and egg are found to be the two most common types of FA in Europe and America, fish and shellfish allergies are particularly common in Asia.[3] In Hong Kong, the incidence of FA among children is estimated at 5%–8%, with around 4.6% of parents ever seeking professional medical advice regarding suspected adverse reactions to food of their children.[4] The list of foods reported being allergenic in Hong Kong is ongoing, with common examples such as cow's milk, egg, peanuts, tree nuts, and shellfish. While some could outgrow the disease, depending on factors such as the type of FA, environmental factors leading to epigenetic changes, some childhood FA persists into adulthood.[5] Currently, the mainstay of management is food avoidance as well as patient and parent education on acute management in case of severe reaction such as anaphylaxis, coupled with early introduction of allergenic food as prevention.[6] Nonetheless, this is no cure and drawbacks including inconvenience and risk of accidental exposure point to the need of immunotherapy. It works by the delivery of food allergen in gradually increasing doses followed by a maintenance dose for months to years, to achieve desensitisation and subsequently, tolerance. It therefore provides a possibly definitive treatment for FA.

Immunotherapy for Food Allergies in Hong Kong

In the context of immunotherapy, various routes of administration have been practised or are under ongoing research in different parts of the world. They are, namely oral immunotherapy (OIT) being the commonest, sublingual immunotherapy (SLIT), and epicutaneous immunotherapy (EPIT).[7] While in Hong Kong, OIT is

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the major approach for children looking for definitive treatment for FA. Take peanut allergy, one of the more difficult types to outgrow, as an example. The Allergy Centre in the Hong Kong Sanatorium and Hospital practised the following protocol of OIT: 0-7 days of initial escalation phase or pre-immunotherapy oral peanut challenge to determine the starting dose of OIT;following by a build-up of doses over 0-22 months; lastly, regular intake of maintenance dose up to 3 years under half-yearly review by allergists.[8,9] A meta-analysis reviewing 39 RCTs has shown that OIT is probably safe and effective in treating peanut, milk, and egg allergy with a number-needed-to-treat = 2.[10] Examples of common adverse events (AEs) are gastrointestinal discomfort, angioedema, while rare but severe ones include eosinophilic esophagitis (EoE) and anaphylaxis etc.[11] Although most AEs could be resolved spontaneously or by injectable epinephrine, some led to dropout of studies or the therapeutic trials, leading to treatment failure.[12] Furthermore, while demonstrating a substantial benefit in terms of desensitisation, risk of experiencing systemic AEs increases in those receiving immunotherapy compared to not receiving.[13] With regard to this, various proposals are raised out to improve the safety of immunotherapy to allow treatment completion and thus maximise the efficacy to ultimately reach sustained unresponsiveness (defined as prolonged antigen hyporesponsiveness which persists after a period, typically 2–12 weeks of cessation of therapy and avoidance of allergen) that is, regarded as the practical endpoint of a successful treatment.[14] The following discussion shall review the safety, efficacy, and possible limitations of multiple recently emerged immunotherapeutic approaches.

Sublingual Immunotherapy (SLIT)

It is generally agreed that SLIT is a safer yet less effective approach when compared to OIT. However, there is limited research that directly compares the two approaches. A randomised, double-blind placebo-controlled (DBPC) study taken place in 2015 recruited participants aged 7 to 13 from the Johns Hopkins Paediatric Allergy Clinic aimed at comparing the efficacy, safety and mechanisms of sublingual and oral administration of allergenic extract of edible peanut.[15] In terms of efficacy, serological outcome (decrease in peanut-specific IgE and increase in peanut-specific IgG4) was more promising in OIT than SLIT. In terms of safety, the OIT group showed a significantly higher proportion of doses with adverse reactions compared to SLIT (43%>>9%), including oropharyngeal (commonest), GI, skin and respiratory symptoms. The OIT group reported reactions from mild severity to anaphylaxis that required the use of antihistamine, beta-agonist and even epinephrine for treatment, while the SLIT group reported no systemic reactions. Overall speaking, this study is the first that directly compared SLIT and OIT to prove SLIT has lower efficacy but higher safety than OIT. Other studies have also proven similar results in terms of the safety of SLIT—majority of participants only presented with mild AEs, mainly oropharyngeal symptoms and could be resolved by antihistamine alone.[16-19] The incidence of severe AEs such as anaphylaxis and the need of injectable epinephrine for symptom resolution was low.

With regard to the concern of compromised efficacy in SLIT compared to OIT, some studies of SLIT had successfully achieved clinical desensitisation, immunological changes (decrease in SPT wheal diameter, basophil reactivity) and humoral changes (decrease in peanut-specific IgE and increase in peanut-specific IgG4).[16,18] These are some promising evidence of the clinical potential of SLIT.

Nevertheless, most SLIT trials in the research field that yield more promising results targeted at treating allergic rhinitis (AR), atopic dermatitis and asthma while not a lot shed light on FA. Some SLIT trials targeting FA were able to demonstrate serological and immunological outcomes but it is uncertain whether they correlate well with clinical outcomes.

Pre-treatment by SLIT Followed by OIT

The DBPC study taken place in 2015 as aforementioned had another interesting finding that might be of clinical significance. After the double-blind phase, the study was modified such that participants continued with an unblinding phase that is, additional OIT/SLIT given on top of the prior active SLIT/OIT. Such pretreatment by SLIT before giving OIT was found to be able to significantly increase the challenge threshold and protect from adverse reactions.[15] Such pretreatment approach was also tested in another study with results showing its possibility in overcoming the limitations of SLIT dosing imposed by both volume and concentration while upholding OIT's more promising efficacy without a compromise of safety.[19]

Still, the major limitation observed in many trials involving OIT is a high drop rate due to AEs. Even with pretreatment by SLIT as a protective mechanism, a substantial proportion of participants reported persistently intolerable abdominal pain such that they have to discontinue from the study. Sample size is often small at the end, leading to a doubt on the practicability. Hence, this approach certainly warrants more future studies to discover its potential for clinical application.

Epicutaneous Immunotherapy (EPIT)

Another proposal to improve the safety profile of immunotherapy is via epicutaneous immunotherapy (EPIT), which is found effective to increase tolerance in terms of peanut allergy from a meta-analysis.[10] Most of the EPIT trials were done targeting peanut allergy hence as in the following discussion in this section. Because of

the minimal vascularity of epidermis, it is believed that EPIT is less likely to trigger systemic AEs as compared to OIT; while GI symptoms would be of lower incidence as well due to the route of administration. Majority of symptoms are mild patch-site reactions in which incidence likely decreases over time during the treatment course.[20,21] The dropout rate due to AEs was only 1.4% in a study of EPIT (using 250 µg-peanut protein patch) in children aged 4 to 11.[22] In the same study, none of the participants reported severe anaphylaxis while only 2.4% of participants required the use of epinephrine, in which symptoms were subsequently resolved without the need of dropping out. Generally speaking, high compliance to treatment is observed in peanut EPIT.

On the other hand, treatment efficacy is likely favourable. Another study of EPIT for peanut allergy has shown the following positive result: after the application of 250 µg-peanut protein patch for 12 months, there was a significant reduction in the predicted risk of unexpected allergic reactions after ingestion of peanut-contaminated packaged food.[23] In particular, as shown in a meta-analysis reviewing 10 randomised controlled trials (RCTs), substantial benefits of EPIT are more likely in peanut and cow's milk protein allergy with desensitisation significantly effective in peanut allergy.[24]

Limitations of current EPIT studies are worth-noting as well. Most of these studies targeted peanut allergy while data of EPIT for other FA such as shellfish remains limited. A pilot study on the efficacy of EPIT for children with milk-induced EoE revealed no significant difference between treatment (Viaskin milk) and placebo groups for the maximum eosinophil count at the end of the study.[25] In other words, successful and promising results of EPIT other than peanut allergy were uncommon at the current stage. Furthermore, the scope of study in some peanut EPIT was only limited to packaged food while the risk of allergic reaction to peanut exposure from unpackaged food such as those in restaurants, home was not evaluated. Despite seemingly promising results, it is worth pondering whether such reports would be clinically significant.

To summarise, EPIT might be another worth-promoted approach in treating FA in children due to its favourable results in terms of safety and efficacy in current studies but more research data is still required before wide clinical application.

Combining the Use of Anti-IgE Monoclonal Antibodies into OIT or SLIT

The use of anti-IgE monoclonal antibodies, most commonly omalizumab, is a rather well-established approach to improve the safety profile in currently available treatments of FA. For instance, the current protocol of OIT adopted by the Allergy Centre in the Hong Kong Sanatorium and Hospital also considered the use of anti-IgE.[8] The underlying goal is to increase the threshold of clinical reactivity to the allergen, hence facilitating subsequent treatment. Trials have proven that anti-IgE could speed up the desensitisation and, more importantly, sustained desensitisation after discontinuation of anti-IgE, likely due to the capability of a more rapid updosing in the build-up phase.[26] On the other hand, it was suggested that another benefit is additional immunomodulatory effect (induction of inhibitory IgG antibodies on top of reducing allergen-specific IgE), further enhancing the updosing speed.[27]

Some studies have done further to explore other benefits of the application of anti-IgE into the treatment regimen. A study conducted by the Stanford University aimed to test whether combining anti-IgE with multifood OIT could benefit multifood allergic patients.[26] In this study, the primary endpoint of success was defined as passing a DBPC food challenge at 36 weeks (i.e., no clinical reactivity to 2 g protein) for any 2 foods in that participant's OIT. Results showed that 83% of participants undergoing anti-IgE/OIT passed the primary endpoint successfully, significantly higher than the placebo group (33%). Meanwhile, this study was able to achieve zero dropout rate, a notable reduction in GI and respiratory symptoms as AE, highlighting the favourable safety profile of using anti-IgE. It is, hence, worth considering the expansion of anti-IgE into multifood OIT instead of single food OIT. In the era of individual-based therapies, it is also proposed to determine, adjust and monitor the dosage of anti-IgE via measuring the basophil allergen threshold sensitivity to ensure safe and effective treatment.[28]

Finally, in the context of anti-IgE, it is also worth mentioning that its application is currently extended to SLIT on top of OIT. However, most, if not all, anti-IgE applications on SLIT are limited to treating AR rather than FA.[29] They have proven to effectively reduce AEs in SLIT treating AR. Nevertheless, it is hoped that more of these recently emerged techniques could be trialled on FA in the not too distant future.

Adopting Recombinant and Other Forms of Hypoallergenic Proteins

To reduce the incidence of AE, especially systemic, another current approach is to use hypoallergenic food protein during immunotherapies.

One of the methods is to modify native food products. The use of roasted peanut flour in peanut OIT is found to be effective yet risky with a high rate of AE (≥45%), hence, doubtful for clinical application.[30] As an attempt to improve the safety profile, studies had attempted a biphasic OIT: starting with boiled peanuts, likely to have reduced allergenicity compared to roasted peanuts, as the

introductory step in OIT; followed by roasted peanuts as the second part of the OIT.[31,32] Paediatric participants in such trials could be desensitised to roasted peanuts after a biphasic OIT. Safety profile was favourable with low incidence of GI symptoms (<2% of doses) but occurrence of anaphylaxis and dropping out due to AE could not be completely avoided in one of the studies. Similar rationale had been applied on cow's milk OIT as well—the attempt of using baked milk to increase the reaction threshold for unbaked milk exposure.[33] However, results from the study gave uncertain conclusion on whether this approach could raise the maximum tolerated dose of unbaked milk and effectively promote the transition from baked to unbaked milk OIT. Comparatively, modifying native food products into hypoallergenic compounds as the initiating step of OIT has more promising trial results in peanut allergy than milk allergy at this stage.

To follow, another method is by using recombinant food proteins. Examples of study-proven hypoallergenicity in recombinant food protein included apples, fish, and peanuts. For apple allergy, radioallergosorbent test inhibition showed a 7.8-fold decrease in IgE-binding potency in mutant rMal d 1 mut (recombinant mutant of apple allergen) and hypo-allergenicity was confirmed by DBPCFC.[34] For fish allergy, preclinical development of recombinant fish allergen mutant Cyp c 1 has proven its hypoallergenicity with retained immunogenicity in forms of a subcutaneous vaccine that is, SCIT.[35]

Furthermore, one study has proposed rectal delivery of recombinant peanut allergen as it was hypothesised that this route of administration might, on top of the use of recombinant allergen, enhance the development of tolerance given the rich immunologic environment of the lower colon.[36] Yet, results showed high frequency of AE, including severe reaction in 20%. It is unclear whether the dosing of the recombinant allergen, the highly absorptive feature of this route of administration or other reasons account for such results.

To summarise, the major unsolved question in the context of hypoallergenic protein is that, it remains undetermined what level of hypoallergenicity in a recombinant food protein is safe for clinical immunotherapy. It requires more clinical trials with large sample size (patient number) in different FA since most of these newly developed techniques have not been proven clinically safe and effective.

Conclusion

To conclude, FA is a global public health issue that affects a substantial portion of the paediatric population. In most public and private clinical settings, including that in Hong Kong, the mainstay of management is by avoidance of the allergenic food in diet. Allergen avoidance brings inevitable risks and inconvenience to patients and their families, particularly for paediatric patients who are actively growing and in need of diversified nutrients from daily diets. The emergence and clinical adoption of immunotherapy aim to benefit these patients so that they could be exposed to these allergens safely. Yet, the major challenge faced in immunotherapies is to produce a favourable safety profile and reduce the incidence of AE while maintaining the efficacy of therapies.

This review mainly focuses on the novel approaches that improve the safety and efficacy of immunotherapies, namely SLIT (alone or as pretreatment of OIT), EPIT, combination of anti-IgE into OIT or SLIT and introduction of hypoallergenic allergens by modifying native food products (boiling, baking etc.) or manufacturing recombinant proteins. Among these proposals, some are clinically proven safe such as the use of anti-IgE while some are still under preclinical trials such as the use of some newly developed recombinant food protein allergens. What is certain is that more preclinical and clinical reviews and trials would be required on all these proposals before they could be maturely, safely, and effectively promoted in the clinical settings for patients' use.

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Conflicts of interest

There are no conflicts of interest.

References

1. Peters RL, Krawiec M, Koplin JJ, Santos AF. Update on food allergy. Pediatr Allergy Immunol 2021;32:647-57.
2. Feng H, Xiong X, Chen Z, Xu Q, Zhang Z, Luo N, *et al*. Prevalence and influencing factors of food allergy in global context: A meta-analysis. Int Arch Allergy Immunol 2023;184:320-52.
3. Dunlop JH, Keet CA. Epidemiology of food allergy. Immunol Allergy Clin North Am 2018;38:13-25.
4. Hong Kong Asthma Society. Pathology and Causes of Food Allergy [Internet] 2023. Available from: https://hkasthma.org.hk/en/about-allergies/pathology-and-causes-1. [Last accessed on 17th Dec 2023].
5. Kanikowska A, Janisz S, Mańkowska-Wierzbicka D, Gabryel M, Dobrowolska A, Eder P. Management of adult patients with gastrointestinal symptoms from food hypersensitivity-narrative review. J Clin Med 2022;11:7326.
6. Caffarelli C, Di Mauro D, Mastrorilli C, Bottau P, Cipriani F, Ricci G. Solid food introduction and the development of Food Allergies. Nutrients 2018;10:1790.
7. Gernez Y, Nowak-Węgrzyn A. Immunotherapy for food allergy: Are we there yet? J Allergy Clin Immunol 2017;5:250-72.
8. HKSH Lee Tak Hong Allergy Centre. Food Oral Immunotherapy (Desensitisation). Hong Kong: Hong Kong Sanatorium Hospital; 2023.
9. Lee T, Chan J, Lau VW, Lee W, Lau P, Lo M. Immunotherapy for peanut allergy. Hong Kong Med J 2014;20:325-30.
10. de Silva D, Rodríguez Del Río P, de Jong NW, Khaleva E, Singh C, Nowak-Wegrzyn A, *et al*.; GA2LEN Food Allergy Guidelines Group. Allergen immunotherapy and/or biologicals for IgE-mediated food allergy: A systematic review and meta-analysis. Allergy 2022;77:1852-62.

11. Chinthrajah RS, Purington N, Andorf S, Long A, O'Laughlin KL, Lyu SC, *et al*. Sustained outcomes in oral immunotherapy for peanut allergy (POISED study):A large, randomised, double-blind, placebo-controlled, phase 2 study. Lancet 2019;394:1437-49.
12. Vickery BP, Scurlock AM, Kulis M, Steele PH, Kamilaris J, Berglund JP, *et al*. Sustained unresponsiveness to peanut in subjects who have completed peanut oral immunotherapy. J Allergy Clin Immunol 2014;133:468-75.
13. Nurmatov U, Dhami S, Arasi S, Pajno GB, Fernandez-Rivas M, Muraro A, *et al*. Allergen immunotherapy for IgE-mediated food allergy: A systematic review and meta-analysis. Allergy 2017;72:1133-47.
14. Feuille E, Nowak-Wegrzyn A. Allergen-specific immunotherapies for food allergy. Allergy Asthma Immunol Res 2018;10:189-206.
15. Narisety SD, Frischmeyer-Guerrerio PA, Keet CA, Gorelik M, Schroeder J, Hamilton RG, *et al*. A randomized, double-blind, placebo-controlled pilot study of sublingual versus oral immunotherapy for the treatment of peanut allergy. J Allergy Clin Immunol 2015;135:1275-82.e1.
16. Kim EH, Bird JA, Kulis M, Laubach S, Pons L, Shreffler W, *et al*. Sublingual immunotherapy for peanut allergy: Clinical and immunologic evidence of desensitization. J Allergy Clin Immunol 2011;127:640-6.e1.
17. Burks AW, Wood RA, Jones SM, Sicherer SH, Fleischer DM, Scurlock AM, *et al*; Consortium of Food Allergy Research. Consortium of Food Allergy Research. Sublingual immunotherapy for peanut allergy: Long-term follow-up of a randomized multicenter trial. J Allergy Clin Immunol 2015;135:1240-8.e1.
18. Kim EH, Yang L, Ye P, Guo R, Li Q, Kulis MD, *et al*. Long-term sublingual immunotherapy for peanut allergy in children: Clinical and immunologic evidence of desensitization. J Allergy Clin Immunol 2019;144:1320-1326.e1.
19. Keet CA, Frischmeyer-Guerrerio PA, Thyagarajan A, Schroeder JT, Hamilton RG, Boden S, *et al*. The safety and efficacy of sublingual and oral immunotherapy for milk allergy. J Allergy Clin Immunol 2012;129:448-55, 455.e1.
20. Jones SM, Sicherer SH, Burks AW, Leung DY, Lindblad RW, Dawson P, *et al*; Consortium of Food Allergy Research. Consortium of Food Allergy Research. Epicutaneous immunotherapy for the treatment of peanut allergy in children and young adults. J Allergy Clin Immunol 2017;139:1242-1252.e9.
21. Fleischer D, Sussman G, Beyer K, Hourihane J, Oriel R, Ford L, *et al*. Open-label follow-up of the Pepites Study (people) to evaluate the long-term efficacy and safety of epicutaneous peanut immunotherapy in peanut-allergic children. J Allergy Clin Immunol 2020;145:863-74.
22. Pongracic JA, Gagnon R, Sussman G, Siri D, Oriel RC, Brown-Whitehorn TF, *et al*. Safety of epicutaneous immunotherapy in peanut-allergic children: REALISE randomized clinical trial results. J Allergy Clin Immunol Pract 2022;10:1864-1873.e10.
23. Remington BC, Krone T, Kim EH, Bird JA, Green TD, Lack G, *et al*. Estimated risk reduction to packaged food reactions by Epicutaneous immunotherapy (EPIT) for peanut allergy. Annals Allergy Asthma Immunol 2019;123:488-493.e2.
24. Xiong L, Lin J, Luo Y, Chen W, Dai J. The efficacy and safety of epicutaneous immunotherapy for allergic diseases: A systematic review and meta-analysis. Int Arch Allergy Immunol 2019;181:170-82.
25. Spergel JM, Elci OU, Muir AB, Liacouras CA, Wilkins BJ, Burke D, *et al*. Efficacy of epicutaneous immunotherapy in children with milk-induced eosinophilic esophagitis. Clin Gastroenterol Hepatol 2020;18:328-336.e7.
26. Andorf S, Purington N, Block WM, Long AJ, Tupa D, Brittain E, *et al*. Anti-IgE treatment with oral immunotherapy in multifood allergic participants: A double-blind, randomised, controlled trial. Lancet Gastroenterol Hepatol 2018;3:85-94.
27. Stranks AJ, Minnicozzi SC, Miller SJ, Burton OT, Logsdon SL, Spergel JM, *et al*. Immunoglobulin E blockade during food allergen ingestion enhances the induction of inhibitory immunoglobulin G antibodies. Ann Allergy Asthma Immunol 2019;122:213-5.
28. Brandström J, Vetander M, Lilja G, Johansson SG, Sundqvist A-C, Kalm F, *et al*. Individually dosed omalizumab: An effective treatment for severe peanut allergy. Clin Exp Allergy 2017;47:540-50. doi:10.1111/cea.12862.
29. Kuehr J, Brauburger J, Zielen S, Schauer U, Kamin W, Von Berg A, *et al*. Efficacy of combination treatment with anti-IgE plus specific immunotherapy in polysensitized children and adolescents with seasonal allergic rhinitis. J Allergy Clin Immunol 2002;109:274-80.
30. Kopp MV, Brauburger J, Riedinger F, Beischer a D, Ihorst G, Kamin W, *et al*. The effect of anti-ige treatment on in vitro leukotriene release in children with seasonal allergic rhinitis. J Allergy Clin Immunol 2002;110:728-35.
31. Tao B, Morris S, Grzeskowiak L, Smith W, Forsyth K, Chataway T. Sequential hypoallergenic boiled peanut and roasted peanut oral immunotherapy. Clin Exp Allergy 2017;47:1501-4.
32. Grzeskowiak LE, Tao B, Aliakbari K, Chegeni N, Morris S, Chataway T. Oral immunotherapy using boiled peanuts for treating peanut allergy: An open-label, single-Arm trial. Clinical & Experimental Allergy. Clin Exp Allergy 2023;53:327-36.
33. Goldberg MR, Nachshon L, Appel MY, Elizur A, Levy MB, Eisenberg E, *et al*. Efficacy of baked milk oral immunotherapy in baked milk–reactive allergic patients. J Allergy Clin Immunol 2015;136:1601-6.
34. Bolhaar ST, Zuidmeer L, Ma Y, Ferreira F, Bruijnzeel-Koomen CA, Hoffmann-Sommergruber K, *et al*. A mutant of the major Apple Allergen, Mal D 1, demonstrating hypo-allergenicity in the target organ by double-blind placebo-controlled food challenge. Clin Exp Allergy 2005;35:1638-44.
35. Zuidmeer-Jongejan L, Huber H, Swoboda I, Rigby N, Versteeg SA, Jensen BM, *et al*. Development of a hypoallergenic recombinant parvalbumin for first-in-man subcutaneous immunotherapy of fish allergy. Int Arch Allergy Immunol 2015;166:41-51.
36. Wood RA, Sicherer SH, Burks AW, Grishin A, Henning AK, Lindblad R, *et al*. A phase 1 study of heat/phenol-killed, *E. coli*-encapsulated, recombinant modified peanut proteins Ara h 1, Ara h 2, and Ara h 3 (EMP-123) for the treatment of peanut allergy. Allergy 2013;68:803-8.

To Study the Efficiency of High-Flow Nasal Cannula in Improving the Arterial Blood Gas Parameters in Children Admitted to Pediatric Intensive Care Unit with Respiratory Distress

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Abstract

Background: In recent times, heated humidified high-flow nasal cannula has become increasingly popular and is now recognized as a standard respiratory support method for pediatric patients experiencing acute respiratory distress. **Aims and Objectives:** To study the correlation of high-flow nasal cannula (HFNC) with arterial blood gas (ABG) and clinical parameters. **Materials and Methods:** This prospective observational study included children aged 1 month to 14 years experiencing acute respiratory distress receiving HFNC support. Demographic information, vital signs, and ABG parameters were collected at four-time points: the first ABG at "0" h, indicating admission; the second ABG at "1" h, approximately 1 h after HFNC initiation; the third ABG at "12" h, as a follow-up after the initiation of respiratory support; and the fourth ABG at "24" h, representing daily monitoring for assessing the child's condition and outcomes. The collected data was subjected to analysis. **Results:** The study included 133 children, of which 64.66% were male and 35.34% were female, with a mean age of 0.9 years (ranging from 0.3 to 3 years) and a mean weight of 7.8 kg (ranging from 4.7 to 11.8 kg). Over time, there was a statistically significant decrease in heart rate, respiratory rate, and the need for FiO_2. Significant reductions in these parameters were observed within the first hour of initiating HFNC therapy, and improvements continued at 12 and 24 h compared to the baseline values (P value < 0.05). The study also revealed a decreasing trend in pCO_2 and lactate levels over time. Statistically significant reductions in these parameters were noted at the first hour of HFNC initiation, and improvements persisted at 12 and 24 h compared to the baseline (P value < 0.05). On the other hand, there was an increasing trend in SpO_2, pO_2, base excess, and HCO_3 over time. Significant increases in these parameters were observed at the first hour of HFNC initiation, and the positive trend continued at 12 and 24 h compared to the baseline (P value < 0.05). **Conclusion:** HFNC can serve as the primary noninvasive respiratory support for children facing respiratory distress. The majority of patients in our study demonstrated good tolerance to the HFNC. Notably, the utilization of HFNC resulted in a significant enhancement of the comfort scale among the participants. Positive changes were observed in vital parameters, comfort scale, and ABG parameters within just 1 h of initiating HFNC.

Keywords: Blood gas analysis, high-flow nasal cannula, respiratory distress

Introduction

High-flow nasal cannulas (HFNCs) are becoming more widely utilized as a noninvasive form of respiratory support, displaying promise in decreasing the necessity for intubation.[1-3] These devices allow the delivery of necessary oxygen concentrations with appropriate relative humidity and temperature. Studies have indicated that HFNCs can reduce airway resistance, enhance lung

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compliance, establish a certain level of continuous positive airway pressure, eliminate dead space, and reduce respiratory effort.[4-8] Numerous studies have highlighted the advantages of HFNC, including positive outcomes, enhanced physiological parameters, and reduced intubation rates.[9-11] Moreover, HFNC is generally better tolerated by pediatric patients compared to other respiratory support methods. Despite the existing body of research, there is a scarcity of studies specifically investigating the efficacy of HFNC in improving arterial blood gas (ABG) parameters. This study aims to fill this gap by assessing changes in ABG parameters with the use of HFNC in the Pediatric Intensive Care Unit (PICU), offering valuable insights into the safety and effectiveness of this treatment approach.

Aims and objectives

1) To study the correlation of HFNC with ABG and clinical parameters

Inclusion criteria

1) Children aged 1 month to 14 years.
2) Admitted with respiratory distress to PICU of any etiology.
3) Requiring HFNC.

Exclusion criteria

1) Age <1 month and >14 years.
2) Children with chronic conditions.
3) Children with surgical conditions.
4) Syndromic and CP children.

Materials and Methods

This prospective observational study was carried out at Sri Ramachandra Children's and Dental Hospital, Guntur, Andhra Pradesh, India, a tertiary care hospital from January 2022 to October 2022. Approval for the study was obtained from the Hospital Ethics Committee, and written informed consent was obtained from the parents or guardians of the patients before their inclusion in the study. The study included patients aged 1 month to 14 years experiencing respiratory distress from any cause and who underwent HFNC therapy. Demographic data was collected, and vital parameters such as heart rate, respiratory rate, and SPO_2 were recorded at four-time points: "0" h (admission), "1" h (approximately 1 h after HFNC initiation), "12" h (follow-up after respiratory support initiation), and "24" h (daily monitoring as part of the child's condition assessment). Serial comfort scores were also documented. ABG parameters were collected at four-time points: first ABG at "0" h (admission), second ABG at "1" h (approximately 1 h after HFNC initiation), third ABG at "12" h (follow-up after respiratory support initiation), and fourth ABG at "24" h (daily monitoring). Outcome parameters were recorded, and the collected data was compiled into a master sheet for subsequent statistical analysis.

Statistical analysis

The presentation of the Categorical variables was done in the form of number and percentage (%). On the other hand, the quantitative data with normal distribution were presented as the means ± SD and the data with non-normal distribution as median with 25th and 75th percentiles (interquartile range). The data normality was checked by using Kolmogorov–Smirnov test. The cases in which the data was not normal, we used nonparametric tests. The comparison of the variables which were quantitative and not normally distributed in nature were analyzed using Mann–Whitney *U* Test. The comparison of the variables which were qualitative in nature were analyzed using Chi-square test. Paired *t* test was used for comparison across follow-up. The data entry was done in the Microsoft EXCEL spreadsheet and the final analysis was done with the use of Statistical Package for Social Sciences (SPSS) software, IBM manufacturer, Chicago, USA, version 25.0. For statistical significance, *P* value of less than 0.05 was considered statistically significant.

Results

The study included a total of 133 children, with 86 (64.66%) being male and 47 (35.34%) being female. The mean age of the participants was 0.9 years, ranging from 0.3 to 3 years. Additionally, the mean weight was recorded as 7.8 kg, with a range of 4.7 to 11.8 kg [Table 1].

Vital parameters

The mean heart rate (per minute) values at 0, 1, 12, and 24 h were 175.19 ± 19.8, 153.85 ± 17.22, 136.84 ± 16.63, and 118.56 ± 14.61, respectively. Similarly, the mean respiratory rate (per minute) values at 0, 1, 12, and 24 h were 68.06 ± 8.79, 53.98 ± 7.42, 44.54 ± 6.64, and 36.37 ± 5.58, respectively. A discernible decreasing trend was observed in both heart rate and respiratory rate over time. Furthermore, a statistically significant reduction in heart rate and respiratory rate was noted at the first hour follow-up compared to the baseline values (*P* value < 0.05) [Table 2; Figure 1A and B].

Table 1: Demographic characteristics of high-flow nasal cannula (HFNC)

Demographic characteristics	HFNC (*n* = 133)
Female	47 (35.34%)
Male	86 (64.66%)
Age in years	0.9 (0.3–3)
Weight in kgs	7.8 (4.7–11.8)

Table 2: Descriptive statistics of vitals of HFNC group

Vitals	Mean ± SD	Median (25th–75th percentile)	Range	*P* value
Heart rate (per minute) at 0 h	175.19 ± 19.8	176 (164–188)	110–210	–
Heart rate (per minute) at 1 h	153.85 ± 17.22	156 (142–168)	102–188	<0.0001[a]
Heart rate (per minute) at 12 h	136.84 ± 16.63	140 (126–148)	94–188	<0.0001[a]
Heart rate (per minute) at 24 h	118.56 ± 14.61	120 (108–130)	88–156	<0.0001[a]
Respiratory rate (per minute) at 0 h	68.06 ± 8.79	68 (64–72)	44–96	–
Respiratory rate (per minute) at 1 h	53.98 ± 7.42	52 (50–58)	36–72	<0.0001[a]
Respiratory rate (per minute) at 12 h	44.54 ± 6.64	44 (40–48)	30–68	<0.0001[a]
Respiratory rate (per minute) at 24 h	36.37 ± 5.58	36 (32–38)	24–70	<0.0001[a]
SpO_2(%) at 0 h	89.93 ± 5.82	92 (88–94)	60–98	–
SpO_2(%) at 1 h	96.69 ± 1.49	97 (96–98)	92–100	<0.0001[a]
SpO_2(%) at 12 h	98.47 ± 0.9	99 (98–99)	92–100	<0.0001[a]
SpO_2(%) at 24 h	99.17 ± 0.58	99 (99–99)	96–100	<0.0001[a]
FiO_2 at 0 h	0.36 ± 0.05	0.35 (0.35–0.4)	0.29–0.55	–
FiO_2 at 1 h	0.34 ± 0.05	0.35 (0.3–0.35)	0.29–0.55	<0.0001[a]
FiO_2 at 12 h	0.32 ± 0.04	0.3 (0.3–0.35)	0.25–0.5	<0.0001[a]
FiO_2 at 24 h	0.29 ± 0.04	0.3 (0.25–0.3)	0.25–0.5	<0.0001[a]

[a]Paired *t* test

The mean SpO_2 (%) values at 0, 1, 12, and 24 h were 89.93 ± 5.82, 96.69 ± 1.49, 98.47 ± 0.9, and 99.17 ± 0.58, respectively. There was a noticeable increasing trend in SpO_2 (%) over time. Additionally, a statistically significant increase in SpO_2 (%) was observed at follow-up compared to the baseline value, with a *P* value less than 0.05 [Table 2; Figure 1C].

Most patients in the study demonstrated good tolerance to the HFNC. The use of HFNC significantly improved the COMFORT scale, indicating enhanced comfort for the patients. Notably, children experiencing severe agitation and discomfort due to respiratory distress showed a substantial calming effect after transitioning from nasal oxygen to HFNC. The observed improvement was significant within the first 30 to 60 min of HFNC initiation and continued to show significant enhancement over subsequent hours.

FiO_2 requirement

In our study, we utilized the bare minimum FiO_2 required to maintain SpO_2 levels above 92%. The mean FiO2 values at 0, 1, 12, and 24 h for the study subjects were 0.36 ± 0.05, 0.34 ± 0.05, 0.32 ± 0.04, and 0.29 ± 0.04, respectively. There was a clear declining trend observed in the requirement of FiO_2 over time. Additionally, a statistically significant reduction in the requirement of FiO_2 was noted at follow-up compared to the baseline value, with a *P* value <0.05 [Table 2; Figure 1D].

ABG parameters

The average pH values at different time points (0, 1, 12, and 24 h) for the study participants were 7.33 ± 0.08, 7.36 ± 0.07, 7.37 ± 0.06, and 7.39 ± 0.07, respectively. The mean pCO_2 levels at the corresponding time intervals were 37.83 ± 9.43, 36.37 ± 8.26, 35.17 ± 7.67, and 34.59 ± 8.79. Additionally, the mean pO_2 values at the specified time points were 70.23 ± 29.7, 90.85 ± 29.58, 90.92 ± 26.9, and 96.58 ± 25.6. Furthermore, the mean concentrations of Lactate (mmol/L) at 0, 1, 12, and 24 h were 1.98 ± 1.03, 1.35 ± 0.86, 1.25 ± 0.7, and 1.2 ± 0.66, respectively. The mean base excess (mmol/L) values at the specified time intervals were −5.54 ± 4.76, −4.48 ± 4.35, −4.16 ± 4.44, and −2.98 ± 4.46. Lastly, the mean HCO_3 (mmol/L) levels at 0, 1, 12, and 24 h were 19.79 ± 3.51, 20.77 ± 3.23, 21.09 ± 3.39, and 21.95 ± 3.41, respectively.

A decreasing pattern was observed in pCO_2 over time, revealing a significant reduction in pCO_2 levels during follow-up compared to the baseline value (*P* value < 0.05). A similar declining trend was noted in Lactate (mmol/L) over time, with a statistically significant reduction observed at follow-up compared to the baseline (*P* value < 0.05). Notably, a statistically significant reduction in both pCO_2 and Lactate levels was observed within 1 h of initiating HFNC.

Conversely, there was an increasing trend in pH, pO_2, base excess (mmol/L), and HCO_3 (mmol/L) over time. A significant improvement in these parameters was evident at follow-up compared to baseline values (*P* value < 0.05). Interestingly, statistically significant enhancements in pH, pO_2, base excess (mmol/L), and HCO_3 (mmol/L) were observed within 1 h of initiating HFNC [Table 3; Figure 2A–F].

Outcomes

All study subjects were successfully discharged, achieving a 100% discharge rate. The median (25th–75th percentile) duration of ICU stay in HFNC was 4 days (with an

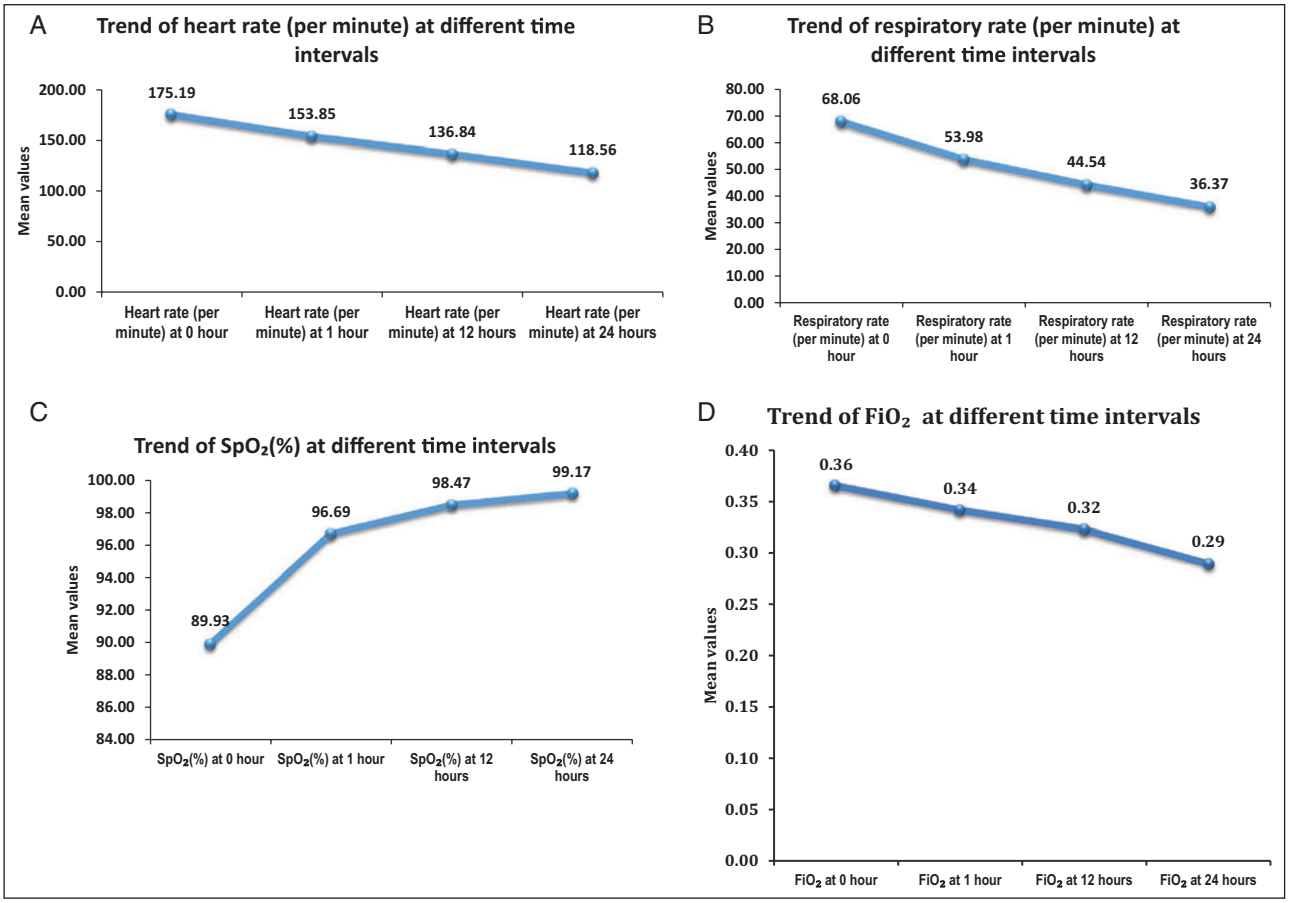

Figure 1: (A) Descriptive statistics of heart rate (per minute) at 0 h, heart rate (per minute) at 1 h, heart rate (per minute) at 12 h and heart rate (per minute) at 24 h. (B) Descriptive statistics of respiratory rate (per minute) at 0 h, respiratory rate (per minute) at 1 h, respiratory rate (per minute) at 12 h and respiratory rate (per minute) at 24 h. (C) Descriptive statistics of SpO_2(%) at 0 h, SpO_2(%) at 1 h, SpO_2(%) at 12 h and SpO_2(%) at 24 h. (D) Descriptive statistics of FiO_2 at 0 h, FiO_2 at 1 h, FiO_2 at 12 h and FiO_2 at 24 h

interquartile range of 3 to 5 days). Similarly, the median duration of hospital stay in HFNC was 6 days, with a range of 5 to 7 days (25th–75th percentile). These results are summarized in Table 4.

Discussion

In the 2014 Cochrane review, heated humidified high-flow nasal cannula for children was described as a method of delivering heated, humidified, and blended air/oxygen through nasal cannulas at flow rates equal to or greater than 2 L/min. This technique delivers both high concentrations of oxygen and potentially offers continuous distending pressure. HFNC has gained popularity for oxygen delivery due to its distinctive physiological advantages. It ensures a constant fraction of inspired oxygen (FiO_2), enhances mucociliary clearance, reduces the respiratory effort required, and decreases anatomical dead space.[12]

In a study conducted by Chang *et al.*[13] the initiation of HFNC therapy in the pediatric ICU resulted in initial FiO_2 and flow rates of 44.92 ± 16.71% and 29.13 ± 11.75 L/min, respectively. As the disease progressed, the maximum FiO_2 and flow rates recorded were 46.93 ± 18.82% and 30.05 ± 12.95 L/min, respectively, with a flow/body weight ratio of 1.73 ± 0.58 (L/kg). In our study, we observed a significant reduction in the FiO_2 required to maintain SpO_2 above 92% over time. Specifically, the FiO_2 values at 0, 1, 12, and 24 h for the study subjects were 0.36 ± 0.05, 0.34 ± 0.05, 0.32 ± 0.04, and 0.29 ± 0.04, respectively. This indicates a notable decrease in the need for FiO_2 to achieve the desired oxygen saturation level, and statistical significance was observed, particularly at the 1-h follow-up, compared to the baseline value (P value < 0.05).

In the study conducted by Chang *et al.*[13] notable improvements were observed in heart rate, breathing rate, and pulse oximetry (SpO_2) during both the early HFNC period (0.5–8 h) and the late HFNC period (8–24 h). Another study by Kallappa *et al.*[14] demonstrated a reduction in heart rate (median 171 to 136) and respiratory rate (median 79 to 53) within 4 h of initiating HFNC. In our study, the mean values of heart rate (per minute) at 0, 1, 12, and 24 h were 175.19 ± 19.8,

Table 3: Descriptive statistics of ABG parameters of HFNC group

ABG parameters	Mean ± SD	Median (25th–75th percentile)	Range	*P* value
pH at 0 h	7.33 ± 0.08	7.33 (7.29–7.38)	6.91–7.51	–
pH at 1 h	7.36 ± 0.07	7.36 (7.32–7.4)	7.06–7.52	<0.0001[a]
pH at 12 h	7.37 ± 0.06	7.38 (7.35–7.41)	7.14–7.52	<0.0001[a]
pH at 24 h	7.39 ± 0.07	7.4 (7.36–7.43)	6.84–7.54	<0.0001[a]
pCO_2 at 0 h	37.83 ± 9.43	37.1 (31.7–44.2)	14.7–61.7	–
pCO_2 at 1 h	36.37 ± 8.26	36.6 (31.9–41.1)	7.3–58.3	0.023[a]
pCO_2 at 12 h	35.17 ± 7.67	34.8 (30.5–38.6)	8.4–64.7	0.0004[a]
pCO_2 at 24 h	34.59 ± 8.79	34.8 (30.4–37.7)	14–98.9	0.0005[a]
pO_2 at 0 h	70.23 ± 29.7	61.7 (51–78)	34.3–176	–
pO_2 at 1 h	90.85 ± 29.58	86.4 (70–111)	32.2–202	<0.0001[a]
pO_2 at 12 h	90.92 ± 26.9	85.8 (73.6–106)	34.8–175	<0.0001[a]
pO_2 at 24 h	96.58 ± 25.6	94.7 (81.4–108)	38.5–160	<0.0001[a]
Lactate (mmol/L) at 0 h	1.98 ± 1.03	1.8 (1.2–2.5)	0.4–5.4	–
Lactate (mmol/L) at 1 h	1.35 ± 0.86	1.1 (0.8–1.5)	0.4–4.6	<0.0001[a]
Lactate (mmol/L) at 12 h	1.25 ± 0.7	1.1 (0.8–1.4)	0.4–4.6	<0.0001[a]
Lactate (mmol/L) at 24 h	1.2 ± 0.66	1 (0.8–1.4)	0.2–4.2	<0.0001[a]
Base excess (mmol/L) at 0 h	−5.54 ± 4.76	−5.2 (−8.1 to −2.5)	−27.2 to 5.1	–
Base excess (mmol/L) at 1 h	−4.48 ± 4.35	−4.3 (−5.9 to −1.7)	−27.3 to 4.4	<0.0001[a]
Base excess (mmol/L) at 12 h	−4.16 ± 4.44	−4.2 (−5.9 to −1.8)	−26.6 to 13	<0.0001[a]
Base excess (mmol/L) at 24 h	−2.98 ± 4.46	−2.6 (−4.4 to –0.7)	−22 to 12.7	<0.0001[a]
HCO_3(mmol/L) at 0 h	19.79 ± 3.51	20 (17.7–21.9)	5.4–28.2	–
HCO_3(mmol/L) at 1 h	20.77 ± 3.23	20.9 (19.5–22.6)	6.2–28.1	<0.0001[a]
HCO_3(mmol/L) at 12 h	21.09 ± 3.39	20.9 (19.7–22.9)	7.2–35.4	<0.0001[a]
HCO_3(mmol/L) at 24 h	21.95 ± 3.41	22.1 (20.6–23.8)	8.9–35.9	<0.0001[a]

[a]Paired *t* test

153.85 ± 17.22, 136.84 ± 16.63, and 118.56 ± 14.61, respectively. Additionally, the mean values of respiratory rate (per minute) at the corresponding time points were 68.06 ± 8.79, 53.98 ± 7.42, 44.54 ± 6.64, and 36.37 ± 5.58, respectively. The mean values of SpO_2 (%) at 0, 1, 12, and 24 h were 89.93 ± 5.82, 96.69 ± 1.49, 98.47 ± 0.9, and 99.17 ± 0.58, respectively. In our study, a declining trend was observed in heart rate and respiratory rate over time. There was a statistically significant reduction in both heart rate and respiratory rate at follow-up, particularly within the first hour after the initiation of HFNC. These improvements continued over the subsequent hours compared to the baseline values (*P* value < 0.05). Conversely, there was an increasing trend in SpO_2 (%) over time, and a statistically significant increase was noted at follow-up, especially within the first hour after initiating HFNC. This improvement persisted over the subsequent hours compared to the baseline values (*P* value < 0.05).

In the research conducted by Chang *et al.*[13] no notable differences in pH and PCO2 were observed following the initiation of HFNC during the early HFNC period. However, significant improvements in pH were documented in the late HFNC period (8–24 h). Similarly, a study by Kallappa *et al.*[14] reported enhancements in pH (median 7.32 to 7.38) and $PaCO_2$ (median 7.7 to 6.6 kPa) within 4 h of initiating HFNC. In our study, a statistically significant increase in pH was observed at follow-up, particularly within the first hour after initiating HFNC. This improvement continued over the subsequent hours as compared to baseline values (*P* value < 0.05). In our study, a progressive decline was observed in pCO_2 and Lactate (mmol/L) over time. There was a statistically significant reduction in both pCO_2 and Lactate (mmol/L) at follow-up, particularly within the first hour after the initiation of HFNC. This improvement persisted and continued to enhance over the subsequent hours compared to baseline values (*P* value < 0.05).

Conversely, an ascending trend was noted in pO_2, base excess (mmol/L), and HCO_3 (mmol/L) over time. Statistically significant increases were seen in pO_2, base excess (mmol/L), and HCO_3 (mmol/L) at follow-up, particularly within the first hour after initiating HFNC. These positive changes continued to improve over the subsequent hours as compared to baseline values (*P* value < 0.05).

In a study by Hilliard *et al.*[15] median SpO_2 was higher in the HFNC group at 8 and 12 h but similar at 24 h. Similarly, in our study, we observed an increasing trend in SpO_2 (%), and a significant increase was noted in SpO_2 at follow-up compared to baseline values, particularly within the first hour after initiating HFNC (*P* value < 0.05).

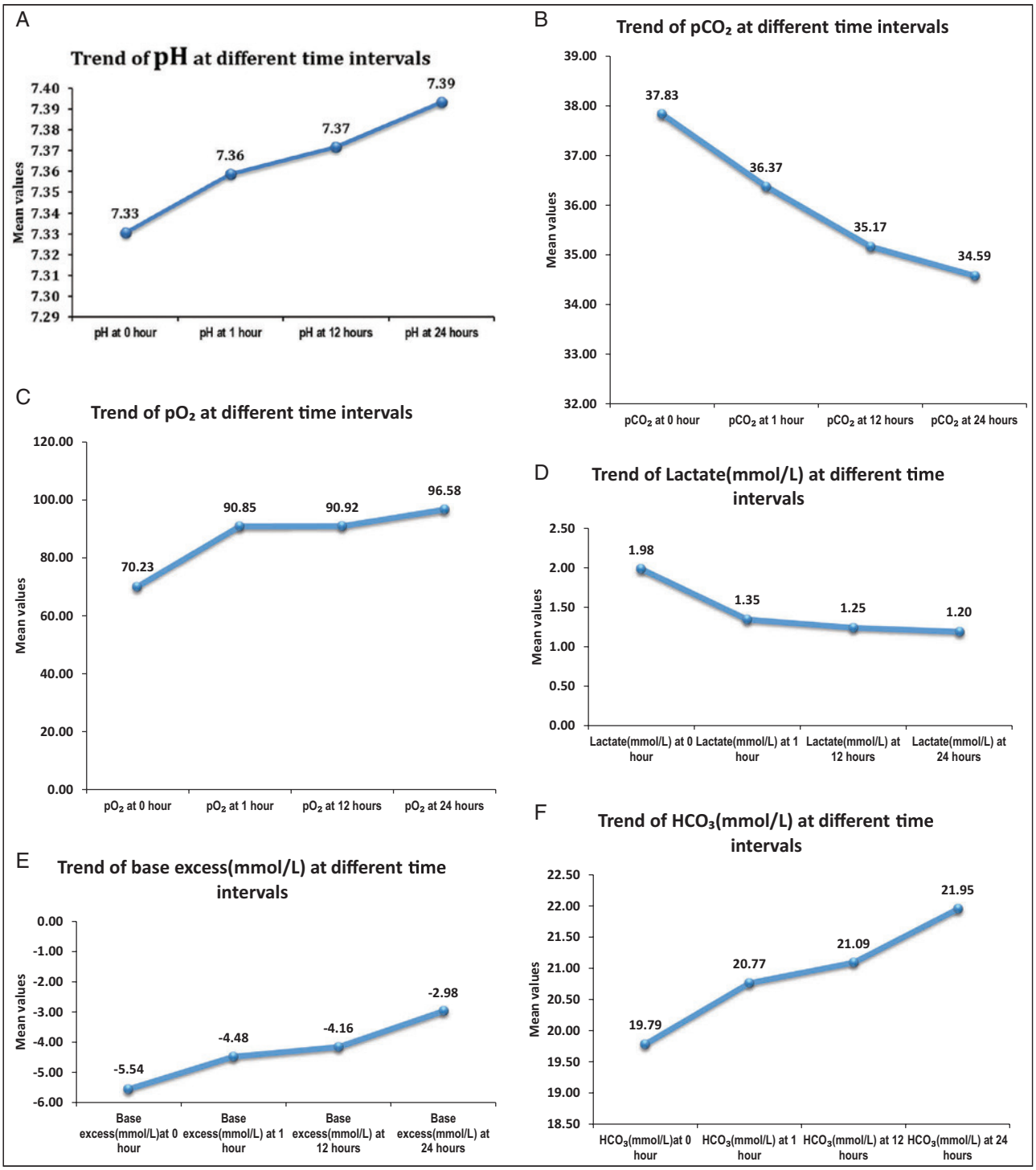

Figure 2: (A) Descriptive statistics of pH at 0 h, pH at 1 h, pH at 12 h and pH at 24 h. (B) Descriptive statistics of pCO_2 at 0 h, pCO_2 at 1 h, pCO_2 at 12 h and pCO_2 at 24 h. (C) Descriptive statistics of pO_2 at 0 h, pO_2 at 1 h, pO_2 at 12 h and pO_2 at 24 h. (D) Descriptive statistics of Lactate (mmol/L) at 0 h, Lactate (mmol/L) at 1 h, Lactate (mmol/L) at 12 h and Lactate (mmol/L) at 24 h. (E) Descriptive statistics of base excess (mmol/L) at 0 h, base excess (mmol/L) at 1 h, base excess (mmol/L) at 12 h and base excess (mmol/L) at 24 h. (F) Descriptive statistics of HCO_3(mmol/L) at 0 h, HCO_3(mmol/L) at 1 h, HCO_3(mmol/L) at 12 h and HCO_3(mmol/L) at 24 h

The majority of patients in our study tolerated the HFNC well. This aligns with findings from a study by Spentzas *et al.*[16] where the COMFORT scale was significantly improved with the use of HFNC. Switching from other oxygen delivery systems to HFNC resulted in enhanced COMFORT levels within the first 60 to 90 min (time 1 to

Table 4: Outcomes of HFNC

Outcomes	HFNC
Discharged	133 (100%)
Duration of ICU stay (days)	4 (3–5)
Duration of hospital stay (days)	6 (5–7)
Duration of HFNC requirement (days)	2 (2–3)

Mann–Whitney *U* test

time 2) and patients continued to experience significant improvement over the next 8 to 12 h (time 2 to time 3). In our study, we observed a significant improvement in the comfort level with the use of HFNC. Children experiencing severe agitation and discomfort with respiratory distress notably calmed within 30 to 60 min of initiating HFNC, and this improvement continued significantly over the subsequent hours.

Conclusion

HFNC emerges as a safe, well-tolerated, and feasible noninvasive respiratory therapy in the PICU. Our findings suggest that HFNC can be initiated as the primary oxygen therapy for children experiencing acute respiratory distress from various causes. Its simplicity in usage and high efficacy position it as the preferred first-line oxygen therapy. The remarkable improvement in vital parameters and comfort level within just 1 h of initiating HFNC underscores its suitability, particularly in resource-limited settings. The straightforward bedside monitoring of heart rate, respiratory rate, and SpO_2 proves adequate for assessing HFNC efficacy in such environments. Furthermore, the significant improvement in ABG parameters within the first hour of HFNC initiation supports its use in tertiary care settings. Notably, the statistically significant reduction in PCO_2 levels at 1 h may potentially lessen the necessity for invasive ventilation. ABG monitoring stands out as the optimal method for evaluating HFNC efficiency in emergency rooms and intensive care settings. These findings collectively emphasize the versatility and efficacy of HFNC, making it a valuable tool in different healthcare settings.

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Nil.

Conflicts of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

1. Zhao H, Wang H, Sun F, Lyu S, An Y. High-flow nasal cannula oxygen therapy is superior to conventional oxygen therapy but not to noninvasive mechanical ventilation on intubation rate: A systematic review and meta-analysis. Crit Care 2017;21:184.
2. Mikalsen IB, Davis P, Øymar K. High flow nasal cannula in children: A literature review. Scand J Trauma Resusc Emerg Med 2016;24:93.
3. Mile'si C, Boubal M, Jacquot A, Baleine J, Durand S, Odena MP, *et al*. High-flow nasal cannula: Recommendations for daily practice in pediatrics. Ann Intensive Care 2014;4:29.
4. Hutchings FA, Hilliard TN, Davis PJ. Heated humidified high flow nasal cannula therapy in children. Arch Dis Child 2015;100:571-5.
5. Mile'si C, Baleine J, Matecki S, Durand S, Combes C, Novais ARB, *et al*. Is treatment with a high flow nasal cannula effective in acute viral bronchiolitis? A physiologic study. Intensive Care Med 2013;39:1088-94.
6. Hough JL, Pham TMT, Schibler A. Physiologic effect of high-flow nasal cannula in infants with bronchiolitis. Pediatr Crit Care Med 2014;15:e214-9.
7. Dysart K, Miller TL, Wolfson MR, Shaffer TH. Research in high flow therapy: Mechanisms of action. Respir Med 2009;103:1400-5.
8. Maggiore SM, Idone FA, Vaschetto R, Festa R, Cataldo A, Antonicelli F, *et al*. Nasal high-flow versus Venturi mask oxygen therapy after extubation. Effects of oxygenation, comfort and clinical outcome. Am J Respir Crit Care Med 2014;190:282-8.
9. Kwon JW. High-flow nasal cannula oxygen therapy in children: A clinical review. Clin Exp Pediatr 2020;63:3-7.
10. Ergul AB, Calıskan E, Samsa H, Gokcek I, Kaya A, Zararsiz GE, *et al*. Using a high-flow nasal cannula provides superior results to OxyMask delivery in moderate to severe bronchiolitis: A randomized controlled study. Eur J Pediatr 2018;177:1299-307.
11. O'Brien S, Craig S, Babl FE, Borland ML, Oakley E, Dalziel SR, *et al*. "Rational use of high-flow therapy in infants with bronchiolitis. What do the latest trials tell us?" A Paediatric Research in Emergency Departments International Collaborative perspective. J Paediatr Child Health 2019;55:746-52.
12. Mayfield S, Jauncey-Cooke J, Hough JL, Schibler A, Gibbons K, Bogossian F. High-flow nasal cannula therapy for respiratory support in children. Cochrane Database Syst Rev 2014;3:CD009850.
13. Chang CC, Lin YC, Chen TC, Lin JJ, Hsia SH, Chan OW, *et al*. High-flow nasal cannula therapy in children with acute respiratory distress with Hypoxia in A Pediatric Intensive Care UnitA Single Center Experience. Front Pediatr 2021;9:664180.
14. Kallappa C, Hufton M, Millen G, Ninan TK. Use of high flow nasal cannula oxygen (HFNCO) in infants with bronchiolitis on a paediatric ward: A 3-year experience. Arch Dis Child 2014;99:790-1.
15. Hilliard TN, Archer N, Laura H, Heraghty J, Cottis H, Mills K, *et al*. Pilot study of vapotherm oxygen delivery in moderately severe bronchiolitis. Arch Dis Child 2012;97:182-3.
16. Spentzas T, Minarik M, Patters AB, Vinson B, Stidham G, Patters A, *et al*. Children with respiratory distress treated with high-flow nasal cannula. J Intensive Care Med 2009;24:323-8.