

Correspondence and Replies

Optimal asthma control in African American children with asthma



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To the Editor:

First, we congratulate Sumino et al¹ for taking on the challenge of conducting a difficult pragmatic trial in children with asthma.¹ Their study demonstrated no difference in asthma control or exacerbations between using maintenance and on-demand symptom-driven use of inhaled corticosteroid (ICS), albeit in children who had prior well-controlled asthma. In reality, few children or their caregivers are going to bother with having to take ICS and short-acting β -agonist (SABA) on demand via separate inhalers, especially via a holding chamber, which is cumbersome and difficult to use correctly. Moreover, using 2 such separate inhalers invites the possibility of becoming overreliant on SABA in conjunction with under-use of ICS.² The Best African American Response to Asthma Drugs (BARD) trial also in African American children with poor asthma control showed that 46% had a better response to an increased ICS dose while 46% had a superior response to increased ICS with the addition of a long-acting β -agonist (LABA).³ Aside from adherence issues, an inherent problem with using maintenance ICS or ICS/LABA is that the patient may end up taking unnecessarily higher doses of ICS whether they are well or ill. A further benefit of using LABA rather than SABA is the possibility of an airway-stabilizing effect with the former.⁴ In essence we believe this supports current Global Initiative for Asthma guidance advocating the use of low-dose ICS with formoterol combination on demand as the preferred reliever for adolescents aged 12 years and above. This so-called anti-inflammatory reliever regimen will always ensure perfect concordance between controller and reliever use to achieve optimal long-term control and lower ICS exposure.⁵ Also, such an anti-inflammatory reliever regimen is intuitive for patients to use and puts them in command of their own disease. Trials are now required to assess the use of anti-inflammatory reliever in younger children from age 6 years and above.

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Conflicts of interest: B. Lipworth reports nonfinancial support (equipment) from Glaxo-SmithKline; grants, personal fees (consulting, talks, and advisory board), and other support (attending American Thoracic Society and European Respiratory Society) from AstraZeneca; grants, personal fees (consulting, talks, and advisory board), and other support (attending European Respiratory Society) from Teva; personal fees (consulting) from Lupin, Glenmark, Vectura, Dr Reddy, and Sandoz, in relation to the submitted work; grants, personal fees (consulting, talks, and advisory board), other support (attending British Thoracic Society) from Boehringer Ingelheim; grants and personal fees (advisory board and talks) from Mylan; grants and personal fees (consulting) from Sanofi, outside of the submitted work; and that his son is presently an employee of AstraZeneca. R. Chan has nothing to disclose. C. R. Kuo reports personal fees (talks) from AstraZeneca and personal fees (talks) and other support (attending British Thoracic Society) from Chiesi, in relation to the submitted work.

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Reply



To the Editor:

We appreciate the correspondence from Lipworth et al¹ regarding our recent publication titled “A pragmatic trial of symptom-based inhaled steroid use in African American children with mild asthma,”² in which we evaluated the effectiveness of symptom-triggered, as-needed, inhaled corticosteroids (ICSs) for the treatment of mild asthma in African American children.² We agree that the requirement of 2 separate inhalers (short-acting β -agonist [SABA] and ICS) does create a potential challenge for the adherence of this regimen in real-life practices. The combined product (SABA/ICS) is not available in the United States and is currently undergoing clinical trial (NCT03769090, NCT03847896) and may become available in the United States soon. The combined product will likely be more convenient to the patients. Although the use of 2 inhalers can cause a potential burden to the patients, there is also a potential benefit. In our focus group study, we found that the primary care providers still frequently observe that the patients/families are confused with the role of each inhaler (rescue vs controller) in their practices³ and simple instruction for taking SABA and ICS both at the same time may benefit those with confusion. In addition, we do not believe that taking SABA and ICS at the same time will increase the risk of SABA overuse. In fact, it may decrease the ratio of SABA to ICS, which has been associated with poor asthma outcomes. We do recognize that there is more evidence available in regard to the use of as-needed ICS/long-acting β -agonist for mild asthma, but we believe that we do not have enough evidence at this time to draw a firm conclusion on whether as-needed ICS/long-acting β -agonist or ICS/SABA regimen is more effective in mild asthma. As needed use of ICS coupled with a β -agonist has potential benefit in adherence, increased sense of ownership of self-management and decreased overall use of ICS. In addition, a recent study has demonstrated a possible molecular mechanism by which the combination of

ICS and β_2 agonists may augment bronchodilation,⁴ which may further support its use in the management of asthma.

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Excipient allergy and importance of complete allergy histories



We read with great interest Sompornrattanaphan et al's¹ report on a case of fatal anaphylaxis from an amoxicillin-clavulanic acid (AMX-CL) drug provocation test (DPT) after a prior negative DPT. The authors postulate that the positive DPT with AMX-CL 300-21.45 mg was compatible with CL resensitization, as the patient previously tolerated a prior DPT with AMX-CL 1520-216.6 mg without reaction. We agree that the initial DPT dose was enough to confirm a negative result but question the seemingly rare possibility of resensitization.

Conversely, we caution the potential diagnosis of excipient allergy and wish to highlight the importance of reporting a complete drug allergy history. We had previously reported the importance of excipient testing in steroid allergy, but we believe that it needs to be considered in other drug allergies also.^{2,3}

In their report, the authors did not disclose the exact formulation of AMX-CL used in the DPTs. However, the different

ratios of AMX:CL suggest that the formulations in both DPTs were different. For example, if hypothetically, 19 mL of AUGMENTIN SUSPENSION (AMX:CL 400:57 mg/5 mL; GlaxoSmithKline, London, UK) was used for the initial negative DPT, whereas 2.5 mL of AUGMENTIN ES (AMX:CL 600:42.9 mg/5 mL; GlaxoSmithKline) was used for the positive DPT, then excipients only present in the latter formulation may have been the causative allergen instead (Table I). In this hypothesized scenario, carboxymethylcellulose (CMC) may have been the true allergen and CMC-containing eye drops for skin testing may have been useful.²

Excipient allergies can be easily missed or overlooked if the excipient list of each formulation is not examined. This is especially a concern in countries where excipient lists are not mandated by law or local regulatory bodies. We also encountered a case of anaphylaxis after administration of AMX-CL and suspected an excipient allergy. A 38-year-old woman suffered from life-threatening anaphylaxis minutes after administration of a single dose of intravenous 1.2 g AMX-CL preoperatively for oocyte retrieval. No colloids or other medications were given, and there was a significant acute tryptase rise to 38.0 ng/mL from a baseline of 2.0 ng/mL. Skin and basophil activation tests were all negative to penicillin allergenic determinants, AMX and CL. Other potential culprits such as chlorhexidine and latex were also excluded. A graded oral DPT with 10 mL of AUGMENTIN SUSPENSION (GlaxoSmithKline) was also negative. Six months later, she tolerated a subsequent 1.2 g dose of intravenous AUGMENTIN (GlaxoSmithKline) without reaction. We discovered that the formulation of intravenous AMX-CL in her index reaction was produced by a different pharmaceutical company, but no excipient list was available. In Hong Kong, drugs are not required by law to include excipient lists in product inserts, and we have been unable to retrieve an excipient list despite extensive efforts. This particular formulation has also been out of stock in Hong Kong, and there is no remaining supply for analysis or skin testing.

We hope that these unfortunate and challenging cases can remind physicians of the importance of taking a complete drug allergy history and to consider possible excipient allergy especially when faced with seemingly discrepant investigation results.

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TABLE I. Example of differences in excipients among different formulations of amoxicillin-clavulanic acid

Trade name	AUGMENTIN SUSPENSION	
	457 mg/5 mL—mixed fruit flavor	AUGMENTIN ES
Amoxicillin:clavulanic acid ratio	400 mg:57 mg	600 mg:42.9 mg
Manufacturer	GlaxoSmithKline, UK	GlaxoSmithKline, UK
Product reference	GlaxoSmithKline ⁴	GlaxoSmithKline ⁵
Excipient list	Xanthan gum, hydroxypropylmethylcellulose, colloidal silica, succinic acid, silicon dioxide, raspberry, orange “1,” orange “2,” golden syrup dry flavors, aspartame	Colloidal silicon dioxide, sodium carboxymethylcellulose-12, strawberry cream flavor, xanthan gum, aspartame, silicon dioxide