



Hypersensitivity reactions to beta-lactams in children

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Purpose of review

To present the most recent evidence on beta-lactam hypersensitivity reactions in children.

Recent findings

Drug provocation tests (DPTs) are the gold standard when investigating beta-lactam allergy in children and evidence is increasingly supporting DPTs without skin tests as a safe approach when evaluating children with nonimmediate mild reactions to beta-lactams. Of note, data are limited in the adolescent population, and this attitude may not apply to this age group. Standardization of DPT protocols is required in nonimmediate reactions, as many protocols ranging from 1 to 10 days have been described. The optimal duration of DPT is still unknown, with extended protocols providing slightly more sensitivity and possible higher long-term compliance, at the expense of potential side effects associated with prolonged antibiotic use. On the other hand, 1-day DPTs will identify the vast majority of patients, and the rest will only develop a mild rash during a subsequent full treatment. The natural history of beta-lactam allergy in children is not well studied with recent evidence pointing to the resolution of most confirmed beta-lactam allergies after 3 years.

Summary

Further studies are needed for the standardization of DPT protocols and to confirm the favourable natural history of beta-lactam drug allergies in children. In addition, multicentric studies are required to confirm the increasingly accepted position of performing DPTs without skin tests in nonimmediate mild reactions to beta-lactams and to further evaluate the possibility of performing DPTs in benign immediate reactions to beta-lactams in children.

Keywords

antibiotic allergy, beta-lactam, children, drug allergy, hypersensitivity drug reaction, penicillin

INTRODUCTION

Beta-lactam allergy is among the most common drug allergies in children [1[•]]. The self-reported prevalence of beta-lactam allergy in children varies from 1.7 to 5.2%, the most frequent beta-lactam being amoxicillin [2]. Reactions to beta-lactams are generally classified as immediate and nonimmediate reactions. This classification originates from Terrados *et al.* [3] and was later adopted by the latest International Consensus (ICON) on Drug Allergy [4]. Immediate reactions occur within the 1st hour of drug administration and typically involve urticaria and/or other symptoms of anaphylaxis; non-immediate reactions occur more than 1 h after drug administration and symptoms can range from maculopapular cutaneous reactions or delayed urticaria to more severe systemic drug reactions such as Drug Reaction with Eosinophilia and Systemic Symptoms or Steven–Johnson Syndrome [2]. Most reactions in children are nonimmediate mild reactions, defined as uncomplicated exanthemas without danger signs

[1[•]]. Beta-lactam allergy is clearly overdiagnosed in the paediatric population, as the vast majority of children developing an exanthema during a beta-lactam treatment are labelled as allergic without a confirmatory allergic workup. This is mainly due to lack of access to an allergy specialist or fear of a more severe allergic reaction upon re-exposure [5]. However, most skin exanthemas occurring during beta-lactam treatment are likely due to underlying viral infections, which may mimic an allergic reaction

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KEY POINTS

- Most skin eruptions during beta-lactam treatment in children are likely due to viral infections, which can mimic an allergic reaction.
- DPTs without skin testing can be considered in children with mild nonimmediate beta-lactam hypersensitivity reactions.
- Some authors propose DPTs without skin testing in mild immediate reactions, although this approach is controversial and requires further multicentric studies.
- The optimal length of DPTs for nonimmediate reactions to beta-lactams still needs to be defined.

[5,6], and the majority of children do not react on subsequent exposure to the index drug [5]. Beta-lactam allergy diagnosis relies on a complete allergy workup [1[■]]. The optimal timing of the allergy workup is not well defined and remains controversial. According to international guidelines (ICON) [4], the allergy workup should be performed ideally 4–6 weeks after the complete resolution of symptoms, but this delay can be adapted depending on the type and severity of the initial reaction. Traditionally, the evaluation of drug allergy in paediatric patients consists of a complete clinical history, and depending on the type of reaction, skin tests, laboratory tests (if available and validated) and/or drug provocation tests (DPTs), which are considered the gold standard for both immediate and nonimmediate reactions [1[■]]. Recent evidence is increasingly supporting direct DPTs without skin tests in children with suspicion of mild nonimmediate reactions [1[■],2]. However, at present, there is no standardized DPT protocol in children [7]. This review aims to present the most recent evidence on beta-lactam hypersensitivity in children.

EVIDENCE FOR DRUG PROVOCATION TEST WITHOUT SKIN TESTING IN NONIMMEDIATE MILD REACTIONS TO BETA-LACTAMS

Based on adult guidelines, the investigation of non-immediate mild hypersensitivity drug reactions in children has traditionally involved delayed-reading intradermal tests (IDTs) and patch tests as a first step, followed by DPTs in cases when skin tests are negative. However, multiple studies have questioned the utility of IDTs in children, which have been shown to have a low sensitivity [5,8–10] and a low positive predictive value (PPV) [5,11[■]] in nonimmediate mild reactions. Caubet *et al.* [5,12] performed IDTs and

DPTs in 96 children with a history of mild nonimmediate reactions to beta-lactams, of which 14 were confirmed allergic. Seven had positive immediate reading-IDTs, and seven had positive DPTs with negative IDTs, giving a sensitivity of 50% [12]. Of note, none of the patients had positive delayed-reading IDTs or positive patch tests. Zambonino *et al.* [8] evaluated 783 children with a history of hypersensitivity reactions to beta-lactams, and 62 (7.92%) were confirmed allergic. In the 53 patients with nonimmediate reactions, two children had positive IDTs, whereas 51 were diagnosed by DPT with previously negative IDTs. Ponvert *et al.* [10] evaluated 1431 children and diagnosed nonimmediate beta-lactam allergy in 177 (12.4%). Nonimmediate beta-lactam allergy was confirmed by IDTs in 60 patients, whereas 104 children had positive DPTs with negative IDTs. Atanaskovic-Markovic *et al.* [9] evaluated 1026 children with a history of nonimmediate mild beta-lactam reactions. Seventy-six (7.4%) had confirmed nonimmediate reactions defined as positive skin tests or DPTs. Fifty-seven were confirmed by positive IDTs, whereas 19 had positive DPTs with previously negative IDTs [9]. The few studies that have examined the PPV of skin testing in mild nonimmediate drug reactions in children have shown that it is equally poor. In Caubet *et al.*'s [5] study, 11/88 children had a positive immediate-reading IDT, but only four of them had a mild exanthema when challenged, giving a PPV of 36% in that population. Vyles *et al.* [13] found that 3/100 children with a suspected beta-lactam allergy with positive skin tests had negative DPTs. More recently, Confino-Cohen *et al.* [14] performed IDTs followed by DPTs regardless of skin test results in 617 patients (of whom 66.6% were children) with nonimmediate reactions to beta-lactam. Again, there was no relationship between positive skin tests and DPT results, with 28 patients with positive IDTs having negative home DPTs. Hence, multiple studies have confirmed the poor diagnostic value of skin tests in children with nonimmediate mild reactions to beta-lactams and questioned their utility considering that they are painful and difficult to perform in children. The low diagnostic performance of skin tests in children might be explained by differences in interpretation of positive IDTs [15] and lack of standardization of those tests in the paediatric population. Skin thickness variability with age [16] may further complicate interpretation of tests.

Before proceeding to DPTs without skin test, one important question that needs to be considered is the safety of such an approach. Mill *et al.* [17[■]] performed direct graded DPTs without skin testing in children with a history of beta-lactam hypersensitivity. The majority of the 818 patients children evaluated in the study had nonimmediate benign

reactions to beta-lactams and only 48 (5.8%) had a positive DPT, of which 3.8% developed mild non-immediate reactions. No serious adverse reactions occurred. Other centres have recently performed DPTs without skin testing or without taking into account skin test results in children with mild non-immediate reactions and have had similar safe results, that is no severe reaction and 5–10% of positive DPTs with mild reactions [5,14,18[¶],19–21].

Based on the previous findings, evidence is increasingly supporting DPT without skin tests as a safe approach in nonimmediate mild reactions in children in a supervised setting, as reflected in new guidelines by the European Academy of Allergy and Clinical Immunology (EAACI) drug allergy interest group [1[¶]] and by the British Society for Allergy and Clinical Immunology [2]. However, this attitude still remains controversial and further prospective multicentric studies will help validate the safety of

such an approach and provide additional data to generate worldwide consensus. In addition, further studies are needed to assess whether DPTs without skin tests are safe in adolescents, as the number of adolescents in paediatric studies is too low to draw any conclusions.

EVIDENCE FOR DRUG PROVOCATION TEST WITHOUT SKIN TESTING IN MILD IMMEDIATE REACTIONS TO BETA-LACTAMS

Both the European guidelines [1[¶]] and the US practice parameter [22] include skin testing (both SPTs and IDTs) as a first-line method for diagnosing immediate reactions to beta-lactam, before considering a DPT. Although it is relatively clear that skin tests are useful in patients with signs of anaphylaxis (Fig. 1), the necessity of skin tests has been put into

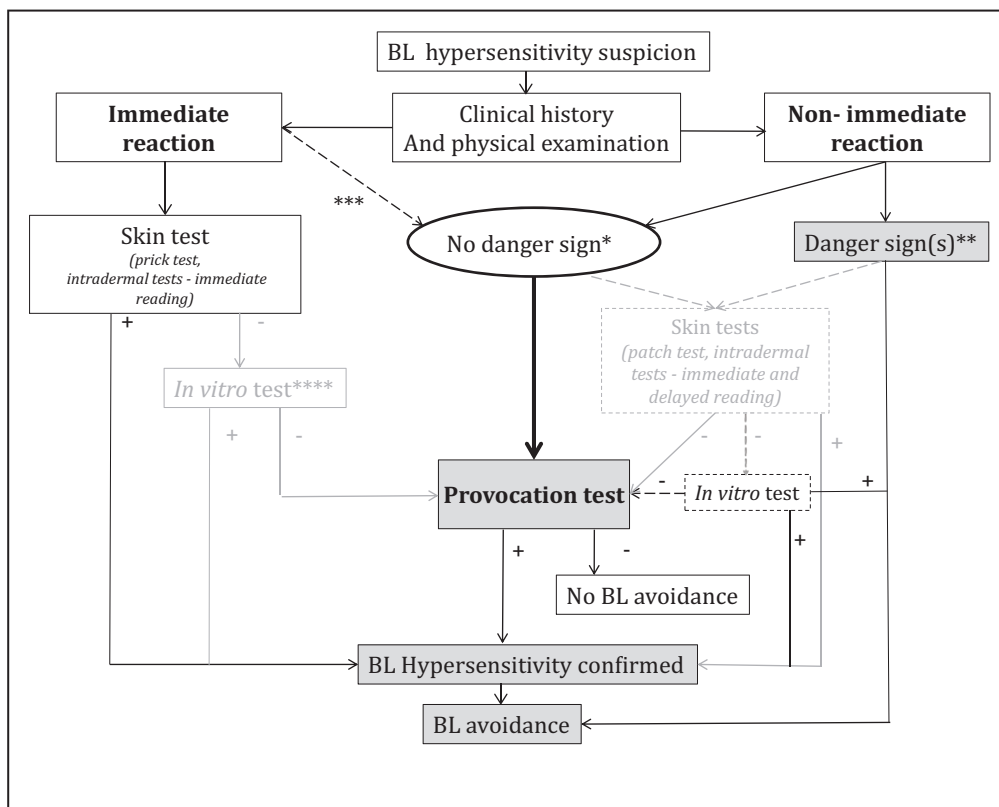


FIGURE 1. Algorithm for the management of children with suspicion of beta-lactam allergy. *Nonsevere uncomplicated exanthemas or urticaria. If there is any doubt, skin tests should be performed before drug provocation test. **This category includes more severe exanthemas, such as those with high extent and density of skin lesions and long duration, complication or danger signs. It includes also acute generalized exanthematous pustulosis, drug reaction with eosinophilia and systemic symptoms, Stevens–Johnson syndrome or toxic epidermal necrolysis. In specific cases, skin tests may be considered for identification of culprit among several used drugs. ***In case of isolated urticaria, some authors propose a direct drug provocation test, although this is still debated. ****Validated in-vitro tests recommended before skin tests if history of severe reaction or if skin tests are not possible or refused. They may confirm hypersensitivity only together with convincing history and/or other tests. BL, beta-lactam. Adapted with permission [1[¶]].

question in benign cutaneous immediate reactions, defined as isolated urticaria (no severity signs, particularly signs of anaphylaxis) that appears within 1 h of drug administration. Indeed, the PPV of skin tests in immediate reactions is relatively unknown, as DPTs are usually not performed in children with positive skin tests for ethical reasons [23], in accordance with the latest ICON on drug allergy guidelines [4]. In addition, most immediate reactions in children are benign (i.e. without danger signs), and some authors hypothesized that the risk of severe reactions during DPTs without skin tests in benign immediate reactions is similar to the risk suggested for benign nonimmediate reactions. Thus, they propose to disregard the current classification and classify children in low risk (no danger signs) and high-risk reactions (presence of danger signs) irrespective of the delay of onset of symptoms [17²²,24–26]. Furthermore, the current classification of beta-lactam hypersensitivity reactions in immediate or non-immediate reactions is difficult to apply in clinical practice [27]. Parents often cannot provide a precise description of the time interval between the last culprit drug administration and the beginning of the hypersensitivity reaction. Moreover, it is not known if a child whose rash appears after a few days of antibiotics is due to the last given dose or previous dose.

In this context, Mill *et al.* [17²²] performed graded DPTs to amoxicillin without skin tests in 818 children with a suspected amoxicillin allergy, irrespective of the delay from the last dose received. Close to 100 of those patients had a history of mild immediate reactions occurring within 1 h of drug administration. Although patients with anaphylaxis were not excluded, none were present in the cohort. Out of the 17 immediate reactions on DPT (around one-fifth had a history of immediate reactions), all were mild and consisted of hives. These patients were later skin-tested with benzylpenicillin and benzylpenicilloyl polylysine, and only one was positive, giving a poor sensitivity for these tests. Unfortunately, amoxicillin IDTs were not performed as amoxicillin is not available in an injectable form in Canada. Thus, the diagnostic value of skin testing is difficult to evaluate in this study as one of the major components of skin tests is missing. Of note, this study mainly included children less than 10 years of age (median of 1.7 years). Recently, Vyles *et al.* [11²¹] evaluated 302 children presenting to the paediatric emergency department with low-risk symptoms of penicillin allergy, as reported by parents or guardians, including immediate reactions (precise number not specified). The authors characterized as ‘low-risk’ the reactions that were not likely to represent a severe IgE-mediated or

T-cell-driven process. A total of 100 children underwent penicillin allergy testing. An oral DPT was safely completed in every patient regardless of skin test findings, and all were negative. These previous studies go in line with a systematic review by Marrs *et al.* [25] concluding that nonserious beta-lactam allergies should be evaluated primarily with DPT-based clinical protocols. However, the evidence to support DPT without skin testing in benign immediate reactions remains limited and larger studies are still needed to confirm the safety of this approach. Indeed, considering that anaphylaxis is a very rare event in this population, multicentric studies will be needed to provide additional safety data pertaining to this approach.

STANDARDIZATION OF DRUG PROVOCATION TESTS

As previously discussed, DPTs are the gold standard when investigating hypersensitivity reactions to beta-lactams in children. However, there is no consensus on the optimal DPT protocol for investigating nonimmediate reactions, particularly regarding the length which ranges from 1 to 10 days [5,14,18²²,21,28–30]. Some groups personalize the length of DPTs depending on the delay of index reaction after initiation of the beta-lactam [10,31]. On one hand, shorter protocols are more convenient and have fewer side effects, whereas longer protocols may increase the sensitivity of the DPT. Analysis of different protocols is complicated by methodological differences in studies.

Data from studies with extended beta-lactam DPT protocols in children have shown that late reactions during home DPT after a negative 1st day DPT occur in between 0 and 6.2% of patients [5,8–10,17²²,18²²,21,29] (Table 1). Of note, reactions occurring on prolonged DPTs after the 1st day can still be linked to the first dose, which may result in an overestimation of delayed reactions with prolonged protocols. This concept was highlighted in a study by Chiriac *et al.* [32], in which a significant proportion of positive DPTs occurred 24 h after a single-day DPT. The same group and others [31–33] provide evidence that upon re-exposure, most patients react earlier or in a similar amount of time than the initial reaction; in addition, they argue that adequate cumulative dose is more important than reproducing the timing of exposure, and that the time required to eliminate the antibiotic (seven half-lives) is enough to activate an immune response by memory and effector T and B cells.

A few studies have evaluated the negative predictive value (NPV) of beta-lactam DPT protocols after re-exposure to the index drug 1 [17²²] to 3 years

Table 1. Comparison of single-day and extended drug provocation test protocols in exclusively pediatric studies

Reference	Year	Age (years)	Length of DPT (no. of days) ^a	Reactions on first day of DPT; number of reactions/total DPTs (%)	Reactions during home DPT after day 1; number of reactions/total DPTs (%)	NPV after rechallenge (1 to more than 3 years)
Caubet <i>et al.</i> [5]	2011	Median: 3.5 Range: 0.5–14.5	3	6/88 (6.8%)	0/88 (0%)	96.7% [34 ^{***}]
Zambonino <i>et al.</i> ^b [8]	2014	NHR: Median: 4, IQR: 2–6 HR: Median: 6, IQR: 3–9	3	50/777 (6.4%)	6/777 (0.77%)	NA
Atanaskovic-Markovic <i>et al.</i> [9]	2016	Mean: 7.7 Range: 1–18	3–4	6/969 (0.62%)	13/969 (1.3%)	NA
Ponvert <i>et al.</i> [10]	2011	Mean: 5.5 Range: 0.3–18	3–10	42/1431 (2.9%)	88/1431 (6.1%)	92.5% ^{c,d} [28]
Mill <i>et al.</i> [17 ^{***}]	2016	Median 1.7 IQR: 1–3.9	1	48/818 (5.9%)	NA	89.1%
Labrosse <i>et al.</i> [18 [■]]	2018	Mean: 5.1 Range: 0.7–17	5	3/130 (2.3%)	3/130 (2.3%)	97.6% ^d
Vezir <i>et al.</i> [21]	2016	Median: 4.3 IQR: 2–7.5	6	3/119 (2.5%)	1/119 (0.84%)	NA
Mori <i>et al.</i> [29]	2015	Mean: 8.5 Range: 1–17	6	6/177 (3.4%)	11/177 (6.2%)	NA

HR, hypersensitivity reactions; IQR, interquartile range; NA, not applicable; NHR, nonhypersensitivity reactions; NPV, negative predictive value.

^aA single-day drug provocation test (DPT) consists of either a graded or single-dose DPT at the hospital with a surveillance of symptoms appearing in the next 48–72 h. Prolonged DPTs consist of a similar single-dose or graded DPT, followed by the medication continued at home for a defined number of days. When discussing length of DPTs, the number of days includes the 1st day DPT performed at the hospital.

^bMedian age of total population not defined.

^cEarlier study by the same authors.

^dNPV was calculated based on data in studies.

[18[■], 34^{***}] or more [28] after a negative DPT in children. One-day DPTs were shown to have a NPV of 89.1% [17^{***}], compared with 96.7% [34^{***}] for 3-day DPTs, 97.6% [18[■]] for 5-day DPTs and 92.5% [28] for 5 to 7-day DPTs. Of note, Caubet *et al.*'s [5, 34^{***}] study with a NPV of 96.7% for the 3-day DPT better reflects a 1-day DPT, because all patients reacted within 24 h. Other data from adult centres have shown a NPV of 94.1 [35] and 96% [32] for the 1-day DPT. Ultimately, the NPVs after a 1 day and an extended DPT seem comparable.

Furthermore, the percentage of patients that react on retreatment with culprit antibiotic after prolonged DPTs is generally not much greater than the incidence of skin rashes after a treatment with antibiotics in the paediatric population, which is estimated around 1–5% per prescription [36]. An interesting concept is the number needed to harm (NNH) when performing prolonged DPTs [32]. When looking at the percentage of patients who react on prolonged challenges, if we estimate that around 5% of patients react on extended DPTs, one can consider that around 95 healthy children are exposed to a prolonged course of antibiotics to screen only five patients with mild delayed reactions. Taking into account the previous statements

and the fact that 1-day and extended DPTs have similar NPVs, a single-day DPT seems sufficient for the diagnosis of beta-lactam allergy in children and can help minimize the length of antibiotic exposure.

FUTURE COMPLIANCE AFTER DRUG PROVOCATION TEST

Some studies with extended antibiotic DPTs suggest that these may increase future compliance in patients and healthcare professionals. Ratzon *et al.* [37] compared 26 children who underwent 7-day DPTs to 23 children who underwent a conventional 1-day DPT. They found that patients with longer DPT were more likely to use the antibiotic in the future when compared with the shorter DPT (78 vs. 61%, respectively). Another recent study by Labrosse *et al.* [18[■]] compared a 5-day amoxicillin DPT cohort of 114 children, to a previous similar cohort of 170 children published by the same authors who had undergone a single dose DPT. Twenty-five percentage of parents or physicians refused to give the antibiotic by fear of reaction after a single-day graded DPT compared with 1.3% after a 5-day DPT.

RISKS OF PROLONGED DRUG PROVOCATION TESTS AND LONG-TERM EFFECTS

Use of antibiotics in children comes with side effects including disturbances of the intestinal microbiota, risk of microbial resistance [38] and obesity [39]. A 7-day treatment with amoxicillin was shown to significantly alter the gut microbiota in children (30% reduction of total faecal bacteria), which may favour the growth of pathogenic organisms and cause changes in the colonic microenvironment [40]. No studies have studied the effect of 1-day DPTs compared with prolonged protocols on the gut microbiota, although longer DPTs may presumably have a higher impact on gut flora and increase gastrointestinal side effects. In addition, there may be a risk of developing new beta-lactam sensitizations with extended DPTs.

IN-VITRO DIAGNOSTIC TESTS

Although not fully validated in the paediatric population, specific IgE are generally recommended during the workup of children with a suspicion of immediate reactions (Fig. 1) [1[■]]. In patients with a history of severe anaphylaxis, some authors suggest that specific IgE be performed before skin testing, when available, as skin tests might be associated with a risk of systemic reaction [1[■],4,41].

Basophil activation tests (BAT) have also been proposed for the diagnosis of immediate reactions in adults, although not validated in children and not part of international guidelines. Barni *et al.* [42] recently evaluated 18 children with a clinical suspicion of immediate reactions to amoxicillin or amoxicillin-clavulanate. Reaction severity on DPT and skin tests did not correlate with BAT results in these children, although studies in adult populations seem promising for high-risk patients [43]. Altogether, data do not yet support the use of BAT during workup of penicillin allergic children.

Lymphocyte activation tests have shown promising results in adults with severe nonimmediate hypersensitivity reactions to beta-lactams [6]. However, they were shown to have a poor diagnostic value for mild nonimmediate reactions in children [12], and further studies are required to determine their validity in this population.

NATURAL HISTORY OF BETA LACTAM ALLERGY

There are few prospective studies on the natural history of beta-lactam allergy in children. Blanca *et al.* [44] performed a prospective study in adults

and found that a majority of patients with immediate reactions to penicillins and positive skin tests will lose their beta-lactam sensitivity to amoxicillin or benzyl penicillin determinants over a 5-year period. However, this does not necessarily imply tolerance acquisition as DPT was not performed. Tonson La Tour *et al.* [34[■]] recently performed a follow-up DPT after 3 years in children with a positive DPT to beta-lactams. In the study, 5/18 had immediate reactions, and 12/18 had nonimmediate reactions. Sixteen out of 18 (89%) had a negative DPT, and among these patients, 11 tolerated a subsequent treatment with the incriminated beta-lactam. These data support the fact that the majority of children with confirmed beta-lactam allergy (with both immediate and nonimmediate reactions) become tolerant after 3 years, although this is one study based on a limited number of patients. Further studies are still required to confirm these findings and to assess whether tolerance acquisition happens earlier.

CONCLUSION

A change in paradigm has recently occurred with recent studies supporting DPTs without skin testing for mild nonimmediate reactions to beta-lactams in children [24]. However, data are limited in the adolescent population, and this attitude may not apply to this age group. In addition, this approach cannot be recommended in mild immediate reactions due to limited data and the rarity of severe anaphylactic reactions. The optimal duration of DPT is still unknown, with extended protocols providing slightly more sensitivity and possible higher long-term compliance, at the expense of potential side effects linked with alteration of the gut microbiota and a high NNH. On the other hand, one dose will identify the vast majority of patients (NPV of 89.1–96.7%), and the rest will only develop a mild rash during a subsequent full treatment. Head-to-head studies are still needed to determine the optimal length taking into account the risk–benefit balance. Finally, additional prospective studies on the natural history of beta-lactam allergy in children are required.

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Conflicts of interest

There are no conflicts of interest.

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- of outstanding interest

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