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<https://doi.org/10.1016/j.jaip.2021.03.019>

Current approach to the diagnosis of allergic bronchopulmonary aspergillosis



To the Editor:

We read the work of Saxena et al¹ with great interest. In this study, the authors aimed to compare the diagnostic performance of various criteria used for evaluating allergic bronchopulmonary aspergillosis (ABPA) and found that the International Society for Human and Animal Mycology (ISHAM) criteria were only marginally better than the Rosenberg-Patterson criteria to identify ABPA in patients diagnosed with asthma. They also improved the sensitivity of the ISHAM criteria by modifying it. We thank the authors for working on a subject for which data are lacking in the literature.

In this study, the authors reported that, of the 543 subjects, 338 (62.2%) were mild-to-moderate asthma and 205 (37.8%) were severe asthma cases. However, the data regarding the percentage of the severe asthma cases in patients with ABPA, diagnosed separately with the ISHAM and Rosenberg criteria, were missing. We believe that this information is important to answer the questions: (1) Is ABPA only seen in severe asthmatics? (2) In what proportion of patients with mild-to-moderate asthma should we expect ABPA? Providing the percentage of severe asthma cases in both diagnostic criteria separately might guide and alert clinicians to diagnose ABPA in their daily clinical practice.

Another important point we want to draw attention is that the low sensitivity of the ELISA method used to detect *Aspergillus fumigatus*-specific IgG and the lack of a consensus on the definite cutoff value lead to a discussion on the need for this parameter in ABPA diagnosis.² This is also valid for *Aspergillus* precipitating antibody tests. In-house precipitin assays with poorly defined antigens have been prepared by various specialist laboratories for this purpose, but their replication in other laboratories is inconsistent.³ It is therefore not possible to use them in resource-poor facilities, and specialist mycology laboratories are few.⁴ The results with precipitins were deficient in this study, similar to an earlier one.⁵ The technique is also manual

and time-consuming, the results are subjective, and reliable replication is difficult.⁶

We believe that it is necessary to discuss and re-evaluate the necessity of *A. fumigatus* precipitating antibodies and specific IgG positivity and be flexible with the current diagnostic criteria, especially in patients with radiological findings that are consistent with ABPA with elevated total IgE levels.

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No funding was received for this work.

Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication February 28, 2021; accepted for publication March 8, 2021.

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<https://doi.org/10.1016/j.jaip.2021.03.024>

Reply to "Current approach to the diagnosis of allergic bronchopulmonary aspergillosis"



To the Editor:

We thank Türk et al¹ for the interest shown in our article.² Regarding their first question, the prevalence of allergic bronchopulmonary aspergillosis (ABPA) in our study was 19.6% (106 of 542) as assessed by a multidisciplinary team (MDT). We classified our asthmatic subjects as mild-to-moderate (mild intermittent, mild persistent, and moderate persistent) and severe (comprising severe persistent), according to the 2004 Global Initiative for Asthma guidelines.³ The prevalence of ABPA was not statistically different in the 2 categories of asthma with either the Rosenberg-Patterson, International Society for Human and Animal Mycology (ISHAM) ABPA working group, modified ISHAM ABPA working group criteria, or ABPA diagnosed by an MDT evaluation (Table I). We have also previously shown

TABLE I. Prevalence of allergic bronchopulmonary aspergillosis (ABPA) in subjects with different severity of asthma

Various criteria	Mild-to-moderate asthma (n = 338)	Severe asthma (n = 205)	P value
Rosenberg-Patterson criteria	50 (14.8)	36 (17.6)	.40
ISHAM ABPA working group criteria	53 (15.7)	36 (17.6)	.63
Modified ISHAM ABPA working group criteria	59 (17.5)	43 (21.0)	.31
ABPA diagnosed by MDT	60 (17.8)	46 (22.4)	.18

Data are presented as n (%).

ISHAM, International Society for Human and Animal Mycology; MDT, multidisciplinary team.

TABLE II. Performance of diagnostic criteria for allergic bronchopulmonary aspergillosis (ABPA) using LCA, with and without *A. fumigatus*-specific IgG

Various criteria	Sensitivity (95% CI)	Specificity (95% CI)
Modified ISHAM ABPA working group criteria*	94.3 (88.1-100)	100 (92.5-100)
Modified ISHAM ABPA working group criteria without <i>A. fumigatus</i> IgG	68.8 (60.8-100)	100 (99.9-100)

The figures in parentheses correspond to 2.5%-97.5% bootstrap confidence intervals (CIs) obtained by bootstrapping 1000 samples.

ISHAM, International Society for Human and Animal Mycology; LCA, latent class analysis.

*Presence of *A. fumigatus*-specific IgE >0.35 kUA/L and serum total IgE levels >500 IU/mL; and 2 of the following: (1) *A. fumigatus*-specific IgG >27 mgA/L; (2) bronchiectasis on computed tomography of the chest; (3) eosinophil count >500 cells/ μ L.

that the prevalence of ABPA does not vary according to the severity of asthma.⁴

We agree with Türk et al that the in-house ELISA and the precipitin assays have significant lab-to-lab variability and are inconvenient to perform. However, the availability of automated assays for measuring IgG against *Aspergillus fumigatus* has, to a large extent, solved these problems. To substantiate our point, we performed a systematic review of the PubMed database using the search term “(“allergic bronchopulmonary aspergillosis” OR “abpa” OR “allergic bronchopulmonary mycosis” OR “fungal sensitization” OR “fungal sensitisation” OR “fungal allergy” OR “mould allergy” OR “mold allergy” OR “fungal asthma”) AND IgG.” We included only studies published in the English language and reported at least 10 patients with ABPA complicating asthma. We found 10 studies (425 subjects) that measured *A. fumigatus*-specific IgG by automated assays in patients with ABPA.⁵⁻¹⁴ The pooled sensitivity (95% confidence interval [CI]) was 73% (95% CI, 59%-85%). On the contrary, the pooled positivity (95% CI) for detecting precipitating antibody by the double gel diffusion technique was 38% (95% CI, 18%-59%) from 5 studies (274 subjects).^{6-9,13} Interestingly, for every 4 (95% CI, 3-5) tests performed with the automated IgG assay, one would be missed by the precipitin test.

We also recalculated the diagnostic performance of the modified ISHAM ABPA working group criteria with and without *A. fumigatus*-specific IgG using latent class analysis on our original dataset of 543 asthmatics. On excluding *A. fumigatus* IgG from the criteria, the sensitivity dropped significantly (Table II). Although in a selected patient with typical imaging findings such as fleeting pulmonary opacities, finger-in-glove opacities, high-attenuation mucus, and the demonstration of a raised serum total IgE and *A. fumigatus*-specific IgE, the demonstration of an elevated *A. fumigatus*-specific IgG may not be required. Overall, *A. fumigatus*-specific IgG

appears to be a vital component of the composite diagnostic criteria of ABPA.

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No funding was received for this work.

Conflicts of interest: The authors declare that they have no relevant conflicts of interest. Received for publication March 6, 2021; accepted for publication March 8, 2021.

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<https://doi.org/10.1016/j.jaip.2021.03.023>

Delayed hypersensitivity reactions to piperacillin-tazobactam



To the Editor:

We read with great interest Gallardo et al's¹ article recently published in *The Journal of Allergy and Clinical Immunology: In Practice* regarding immediate hypersensitivity reactions to piperacillin-tazobactam (PipTaz) confirmed by either skin or drug provocation testing. Of interest are the key identification of different immediate-type hypersensitivity phenotypes and the systematic approach to clinical diagnostic as well as *in vivo* testing. The authors also performed drug provocation tests in the 2 patients with negative skin testing to confirm the drug allergy label. However, we note that a limitation of the article is the absence of an assessment of delayed PipTaz hypersensitivity reactions, which are frequently encountered in the hospital setting.

PipTaz is frequently used in cancer care and sepsis management for empirical gram-negative bacterial coverage.² In these cases, other confounding factors could be causal for skin eruptions such as graft versus host disease, fever as well as isolated eosinophilia, in the setting of infection in the critically ill.³ Although PipTaz is implicated in these scenarios, it may not be part of causality. When looking at allergy labels in our hospital over a 12-month period (October 2019 to September 2020), among the 42,643 patients admitted, 88 (0.2%) carried a PipTaz allergy label.

To contribute to the existing literature gap on PipTaz immune-mediated reactions as underlined in a recent journal editorial,⁴ we audited our prospective database of 1715 patients with antibiotic immune-mediated reactions (between April 2015 and October 2020 with some of the cases that might have been included in previous publications⁵⁻⁷).

Among the 44 identified (26; 59% immunosuppressed), 6 had presented an immediate reaction, 35 (80%) delayed, and for 3 patients the timing could not be determined from history. In terms of drug allergy causality association with PipTaz, 15 (34%) of patients had a Naranjo score of ≥ 5 (probable) and 29 (66%) a score of 4 (possible). After allergy investigations, 16 of 44 (36%) had positive beta-lactam intradermal testing (IDT)—4 (25%) immediate

and 12 (75%) delayed—11 of 44 (25%) had positive IDT to PipTaz (2 immediate and 9 delayed). Among these 11 patients, 8 had a positive IDT to amoxicillin/ampicillin (Amox/Amp). Among the patients with positive IDT to PipTaz, 6 had a positive IDT to penicillin G. A total of 6 patients had positive testing to PipTaz, penicillin G, and Amox/Amp. Among the patients with delayed positive IDT, 8 had interferon- γ enzyme-linked immunosorbent assay performed as per previously published method,^{6,7} with 4 (50%) having a positive assay. After allergy investigations, 3 (6.8%) patients were delabeled in the allergy clinic for their PipTaz drug allergy. Our data were limited by the absence of drug provocation tests after negative PipTaz testing due to the inability to give prolonged intravenous challenges in the setting of delayed hypersensitivity.

We need further data on delayed hypersensitivity reactions in the setting of PipTaz use, especially considering that they contribute to 75% of allergies encountered in a specialist drug allergy center. In particular, we need further studies that challenge immune-mediated hypersensitivity reactions with negative *in vivo* investigations, especially in PipTaz delayed hypersensitivity, and continue to enable the use of this life-saving antimicrobial therapy.

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No funding was received for this work.

Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication February 14, 2021; accepted for publication March 9, 2021.

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<https://doi.org/10.1016/j.jaip.2021.03.025>