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Clinical significance of decline in serum IgE levels in allergic bronchopulmonary aspergillosis

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Summary

Background and Aims: The total serum IgE level is a marker of immunological activity in allergic bronchopulmonary aspergillosis (ABPA), and a 35% decline beyond six weeks is traditionally taken as criteria for remission. The aim of this study was to evaluate the magnitude and clinical significance of decline in serum IgE levels at six weeks in patients with ABPA.

Methods: All consecutive patients with ABPA presenting to the Chest Clinic were followed up with clinical evaluation, total IgE levels and chest x-ray every six weeks for three months. We analyzed the percentage decline in IgE levels and correlated it with clinical outcomes of relapse and complete remission.

Results: Of the 242 asthmatics, 54 were diagnosed with ABPA (29 males, 25 females; mean age-34 years). There was clinical and radiological improvement at six weeks in all patients receiving glucocorticoid therapy. The IgE levels fell by a mean of 38.8%, and the decline was significantly higher in patients with baseline IgE levels >2500 IU/mL than with levels ≤2500 IU/mL (44% vs. 26%). Twenty-two patients did not attain a 35% decline in IgE levels,

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and this number was significantly higher in patients with IgE levels <2500 IU/mL. On multivariate analysis, the decline in IgE levels at six weeks did not predict clinical outcomes.

Conclusions: A 35% decline in serum IgE levels at six weeks is not seen in all patients with ABPA, and the decline is slower in patients with baseline IgE levels <2500 IU/mL. The quantum decline in serum IgE levels does not predict clinical outcomes.

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Introduction

Allergic bronchopulmonary aspergillosis (ABPA) is a pulmonary disorder caused by a complex hypersensitivity response to antigens released by the fungus *Aspergillus fumigatus*.¹ The clinical entity was first described by Hinson et al. in 1952,² and the clinical and immunologic significance of *A. fumigatus* in the sputum were reported by Pepys and coworkers in 1959.³ The prevalence of ABPA in bronchial asthma is fairly high and a recent meta-analysis suggested the prevalence of ABPA in asthma clinics to be as high as 13 percent.⁴ Diagnostic criteria for ABPA have been laid and generally include the following eight major criteria: (a) history of asthma; (b) transient or fixed pulmonary infiltrates; (c) immediate cutaneous hyperreactivity to *A. fumigatus* antigen; (d) absolute eosinophil count >1000/ μ L; (e) serum precipitins against *A. fumigatus*; (f) total IgE levels >1000 IU/mL; (g) central bronchiectasis on high-resolution computed tomography (HRCT); and, (h) raised *A. fumigatus* specific IgE or IgG levels.⁵ However, none of these are specific for ABPA,^{6–14} and there is still no consensus on the number of criteria needed for diagnosis, and patients in different stages of ABPA may not fulfill all these criteria.^{1,6}

Similarly, there is no established definition for remission of ABPA. The most widely followed criteria are clinical and radiological improvement with at least 35 percent decline in total serum IgE levels. However, this criterion for remission is based on the results of a single retrospective study.¹⁵ This criterion has not been further studied in detail. Moreover the clinical significance of decline in serum IgE levels is not known especially with regards to clinical outcome. There is a dramatic fall in the total serum IgE levels with institution of glucocorticoids in patients with ABPA with associated radiological and clinical improvement.¹⁶ The total serum IgE level is a marker of immunological activity in ABPA, and it is probable that the changes in total serum IgE levels especially the magnitude of fall be associated with clinical outcomes in terms of relapse and ability to achieve complete remission.

The disorder is highly prevalent in India. We have previously reported our experience with screening stable outpatients with bronchial asthma and acute severe asthma for ABPA.^{17,18} We have also recently reported the prognostic factors associated with clinical outcomes in patients with ABPA.¹⁹ The aim of this manuscript was to evaluate the magnitude of fall of total serum IgE levels at six weeks, and the clinical significance of the quantum decline in total serum IgE levels with regards to relapse and propensity to maintain sustained clinical remission.

Patients and methods

The present study is a retrospective analysis of prospectively collected data, and includes all consecutive treatment-naïve patients of ABPA diagnosed between July 2006 and June 2008. We have been prospectively screening all consecutive patients with asthma presenting to the Chest clinic of our institution with an aspergillus skin test. Patients who were found to demonstrate immediate cutaneous hyperreactivity to aspergillus antigen were further investigated. The patients were considered to have ABPA if they met both the following criteria: elevated total IgE levels (more than 1000 IU/mL) and elevated IgE levels against *A. fumigatus* (more than 0.35 kU per liter); and, two of the following criteria: presence of serum precipitating antibodies against *A. fumigatus*, radiographic pulmonary opacities (fixed/transient), absolute eosinophil count more than 1000/ μ L and central bronchiectasis on HRCT.¹⁷ Patients who had taken glucocorticoids for more than three weeks in the preceding six months were excluded from screening. None of the patients were screened for cystic fibrosis. All patients were screened with routine stool examination to exclude parasitic infestations. The study was cleared by the Institute Ethics Committee, and an informed consent was taken from all patients as per protocol.

Aspergillus skin test was performed using *A. fumigatus* antigen prepared in the Department of Medical Mycology. It was read every 15 min for 1 h, and then after 6–8 h. The reactions are classified as type I if wheal and erythema developed within a minute, reached a maximum after 10–20 min and resolved within one to two hours; and, type III reaction if any amount of subcutaneous edema was present after 6 h. **Levels of serum IgE (total) and IgE (for *A. fumigatus*)** were assayed with commercially available kits using the quantitative enzyme-linked immunosorbent assay (Demeditec diagnostics GmbH, Kiel, Germany) and the fluorescent enzyme immunoassay (UniCap Systems; Pharmacia Upjohn; Stockholm, Sweden). ***A. fumigatus* precipitins** were detected by the Ouchterlony's gel diffusion techniques according to the method of Longbottom and Pepys.¹⁰ **Spirometry** with bronchodilator reversibility was performed using commercial spirometer (Morgan RS-232 Spiro), and patients were categorized to have mild, moderate and severe obstruction as per the standardized practice in our laboratory.²⁰ Bronchodilator reversibility was considered to be significant if, after 200 μ g of inhaled salbutamol, the forced expiratory volume in the first second (FEV1) and/or forced vital capacity (FVC) increased by more than 12% and 200 mL.²¹ **Absolute eosinophil count** was performed manually by counting the cells on the peripheral smear. **High-resolution CT of the thorax** (IV

contrast was not administered) was performed on a 16-row, multiple detector, CT scanner (LightSpeed Plus; GE Medical Systems; Slough, UK) with a 512 matrix size. The scans (120 kV; 10 mA; window width, 1500 Hounsfield units [HU]; and window level, 600 HU) were obtained with a scan time of three seconds in the supine position at full end-inspiration from lung apex to base. The image acquisition was contiguous and the images (1.25 mm at 10-mm intervals) were reconstructed using the high-spatial-frequency algorithm. Gross localization of individual bronchopulmonary segments were identified by the anatomical division of the appropriate lobar and segmental bronchus, and their relationship with the major and minor fissures.^{22,23} The radiological abnormalities were categorized for the presence and extent of bronchiectasis with the criteria described by Reiff et al. used to classify bronchiectasis.²⁴ Bronchiectasis was classified as 'central' when confined to the medial half of the lung, at a point midway between the hilum and the chest wall.²⁵ The presence of high-attenuation mucus was considered if the mucus plugs were visually denser than the normal skeletal muscle.²⁶

The patients were treated with glucocorticoids with the following regimen: prednisolone 0.75 mg/kg for six weeks, 0.5 mg/kg for six weeks; then tapered by 5 mg every six weeks to continue for a total duration of at least six to twelve months. No patient received itraconazole or any other azole derivatives. The patients were followed up with history and physical examination, chest radiograph and IgE levels (total) every six weeks. A repeat CT scan was not done unless a complication was suspected. Patients were classified as having **remission** – if the IgE levels declined by more than 35 percent *and* there was clearance of chest radiographic lesions after three months of glucocorticoids, **relapse** – doubling of the baseline IgE levels irrespective of the patient's symptoms or appearance of radiologic infiltrates, **complete remission** – no ABPA exacerbations over the next 3 months after stopping therapy, **glucocorticoid-dependent ABPA** – patient required oral prednisolone for recurrent relapses of ABPA and **end-stage ABPA** – extensive bronchiectasis with either cor pulmonale and/or type 2 respiratory failure.⁸ For the purpose of this study, IgE levels were noted at baseline and six weeks after glucocorticoid therapy and percentage decline was calculated as: (baseline IgE levels minus IgE levels after six weeks of glucocorticoid therapy) divided by baseline IgE levels.

Statistical analysis

Statistical analysis was performed using the statistical package SPSS for MS-Windows (version 10; SPSS Inc; Chicago, IL) and StatsDirect (StatsDirect, version 2.7.2 for MS-Windows, England, StatsDirect Ltd, 2005. <http://www.statsdirect.com>). Data are presented in a descriptive fashion as mean (95% confidence intervals [CI]) or percentage (95% CI). Categorical variables were compared using the chi-square test while Mann-Whitney U test was used as applicable in case of continuous variables. To analyze the factors predicting poor outcome (i.e. relapses and failure to achieve complete remission), a multivariate logistic regression analysis was performed to derive adjusted odds ratio (AOR) and 95% confidence intervals (CI)

using the following variables: duration of asthma, lung function abnormality on spirometry, absolute eosinophil count, IgE levels (both total and *Af* specific), percentage decline in IgE levels after six weeks of glucocorticoids, extent of bronchiectasis based on the number of segments involved on HRCT and the presence of hyperattenuating mucus. Statistical significance was assumed at a *p*-value of less than 0.05.

Results

During the study period, 242 patients with bronchial asthma were screened for ABPA using aspergillus skin test; 87 (35.9%) patients were found to be positive and 54 (22.3%) patients were diagnosed to have ABPA. There were 29 males and 25 females with a mean age of 34.3 (95% CI, 30.6–38.0) years. The baseline characteristics of these patients with regards to clinical features, spirometry, serological findings and HRCT manifestations are shown in Table 1. The recognition of ABPA was generally delayed, and around 33 percent of patients had received antitubercular therapy in the past, median 1 (range, 1–2). Chest

Table 1 Baseline characteristics of the 54 patients with allergic bronchopulmonary aspergillosis.

Clinical characteristics	Results
Clinical findings	
Age in years	34.3 (30.6–38.0)
Male sex	29 (53.7; 40.6–66.3)
Duration of asthma in years	10.9 (8.0–13.9)
Hemoptysis	12 (22.2; 13.2–34.9)
Expectoration of brownish-black mucus plugs	15 (27.8; 17.6–40.9)
Intake of anti-tuberculous therapy	18 (33.3; 22.2–46.6)
Spirometry	
Normal	12 (22.2; 13.2–34.9)
Mild obstruction	14 (25.9; 16.1–38.9)
Moderate obstruction	21 (38.9; 27.0–52.2)
Severe obstruction	7 (12.9; 6.4–24.4)
Bronchodilator reversibility	24 (44.4; 32.0–57.6)
Immunological findings	
Aspergillus skin test	
Type 1	54 (100; 93.4–100)
Type 3	38 (70.4; 57.2–80.9)
Absolute eosinophil count per microliter	1145.8 (897.6–1393.9)
<i>A. fumigatus</i> precipitins No (%)	42 (77.8; 65.1–86.8)
IgE levels (total), IU/mL	7829.4 (5977.1–9681.7)
IgE levels (<i>A. fumigatus</i>), kUA/L	15.0 (9.41–20.59)
HRCT findings	
Normal HRCT	10 (18.5; 10.4–30.8)
Extent of bronchiectasis	
Lobes	2.7 (2.3–3.2)
Segments	6.8 (5.4–8.2)
High-attenuation mucus	12 (22.2; 13.2–34.9)

All the results are expressed as mean (95% confidence intervals) and number (percentage with 95% confidence intervals) unless otherwise stated.

radiograph showed fleeting pulmonary shadows in 19 (35.2%) patients. Ten (18.5%) patients had a normal HRCT (serologic ABPA [ABPA-S]) and 44 (81.5%) had bronchiectasis (ABPA-central bronchiectasis [ABPA-CB]). The mean (range) number of lobes and segments involved were 3 (0–5) and 6 (0–18) respectively. Twelve (22.2%) patients were identified to have high-attenuation mucus impaction on HRCT at presentation.

There was clinical and radiological improvement in all the patients receiving glucocorticoid therapy at six weeks. The mean IgE levels at baseline were 7829 IU/mL, and fell by a mean of 38.8 (95% CI, 32.4–45.1) percent (Table 2). The percentage decline in IgE levels was significantly higher in patients with IgE levels more than 2500 IU/mL (Table 2). Twenty-two (40.7%) patients did not attain a 35 percent decline in IgE levels at six weeks although 100 percent could achieve this decline at three months. Also a higher proportion of patients with IgE levels of more than 2500 IU/mL were able to attain a 35% decline in IgE levels at six weeks (Table 2), and this difference was statistically significant ($p = 0.004$). There was no difference in the absolute or percentage decline of IgE levels in patients with central bronchiectasis (ABPA-CB) or those without.

The mean duration of follow-up was 20.1 months (95% CI, 16.9–23.2). All the patients went into remission at three months (Table 3). Twenty four (44%) patients had a relapse during the course of their treatment. All these patients were restarted on therapy with prednisolone and itraconazole. Of the 24 patients who relapsed, all could achieve remission; however therapy could be stopped only in 8 patients (i.e. complete remission). Thirty nine patients were classified to have undergone complete remission. The dosage of steroids was tapered, and therapy was stopped at a mean duration of 10.5 months (95% CI, 9.2–11.9 months) in these patients. Fifteen (27.8%) patients were maintained on long-term treatment with steroids and were classified as having glucocorticoid-dependent ABPA.

Multivariate logistic regression analysis was performed to identify the factors predicting relapse and failure to achieve complete remission. After adjustment for duration of asthma, abnormal lung function, absolute eosinophil count, IgE levels [total and Af specific], the severity of

Table 3 Outcome of allergic bronchopulmonary aspergillosis.

	Total (n = 54)
Duration of glucocorticoid therapy (months)	10.5 (9.2–11.9)
Remission	54 (100; 93.4–100)
Relapse	24 (44.4; 32.0–57.6)
Complete remission	39 (72.2; 59.1–82.4)
Glucocorticoid-dependent ABPA	15 (27.8; 17.6–40.9)
Follow-up (months)	20.1 (16.9–23.2)

All the results are expressed as mean (95% confidence intervals) and number (percentage) unless otherwise stated.

bronchiectasis (based on the number of segments involved) and the presence of high-attenuation mucus, the percentage decline in IgE levels at six weeks did not predict occurrence of relapse and failure to achieve complete remission (Table 4). The severity of bronchiectasis and presence of high-attenuation mucus predicted occurrence of relapses whereas only the severity of bronchiectasis predicted failure to achieve complete remission (Table 4).

Discussion

The results of this study suggest that not all patients achieve a 35 percent decline in total serum IgE levels beyond six weeks even with institution of high dose glucocorticoid therapy despite clinical and radiological improvement. The quantum fall in total serum IgE levels is smaller in patients with baseline IgE levels less than 2500 IU/mL, and this point should be kept in mind while managing patients with ABPA. The magnitude of decline in IgE levels did not predict the occurrence of clinical outcomes in patient with ABPA. This study also confirms our previous findings that only the extent of bronchiectasis on HRCT predicted relapses and the failure to undergo complete remission. The presence of hyperdense mucus predicted only the occurrence of relapse and a non-significant trend towards failure to achieve complete remission in patients with ABPA.

Table 2 Decline in IgE levels at six weeks.

Percentage decline		
Baseline IgE $\leq$ 2500 IU/mL (n = 11)		26.1% (19.9–32.3)
Baseline IgE $>$ 2500 IU/mL (n = 43)		44% (38.9–49.1)*
All patients (n = 54)		38.8% (32.4–45.1)
35% decline in IgE levels		
	IgE $\leq$ 2500 IU/mL (n = 11)	IgE $>$ 2500 IU/mL (n = 43)
IgE decline $<$ 35%	9 (81.8; 52.3–94.5)	13 (30.2; 18.6–45.1)
IgE decline $\geq$ 35%	2 (18.2; 51.4–47.7)	30 (69.8; 54.9–81.4)*
Decline in ABPA-s vs. ABPA-CB		
	ABPA-s (n = 10)	ABPA-CB (n = 44)
Absolute decline	2652 (399–4905)	4136 (2526–5745)
Percentage decline	35.8 (26.6–45.1)	41.4 (36.1–46.7)

All the results are expressed as mean (95% confidence intervals) and number (percentage with 95% confidence intervals) unless otherwise stated.

* p -value less than 0.05.

Table 4 Factors predicting relapse and complete remission in patients with allergic bronchopulmonary aspergillosis - multivariate analysis. All the results are expressed as mean (95% confidence intervals) and number (percentage, 95% confidence intervals) unless otherwise stated.

Variables	Relapse (n = 24)	No relapse (n = 30)	Adjusted OR (95% CI)
Duration of asthma (in years)	10 (6.5–13.4)	12.2 (6.8–17.6)	1.06 (0.99–1.13)
Lung function abnormality on spirometry	17 (70.8, 50.8–85.1)	23 (76.7, 59.1–88.2)	2.48 (0.37–16.83)
Absolute eosinophil count at presentation, cells/ μ L	1095.9 (773.1–1418.7)	1185.6 (804.3–1567)	0.99 (0.99–1)
Total IgE levels at presentation, IU/mL	8204.6 (5573.5–10835.7)	7529.3 (4808.6–10252)	1 (1–1)
Percentage decline in IgE levels at six weeks	42.8 (35.8–49.8)	38.4 (32.1–44.7)	1.02 (0.95–1.1)
<i>A. fumigatus</i> specific IgE levels at presentation, kUA/L	16.2 (8.7–23.7)	14.1 (5.6–22.5)	1.0 (0.96–1.04)
Lung segments involved by bronchiectasis on HRCT	9.0 (7.1–10.8)	5.0 (3.2–6.9)	1.22 (1.03–1.45)*
Presence of high-attenuation mucus	12 (50, 31.4–68.6)	2 (6.7, 1.8–21.3)	38.07 (1.96–740.24)*
Variables	Complete remission (n = 39)	No complete remission (n = 15)	Adjusted OR (95% CI)
Duration of asthma (in years)	9.6 (6.9–12.4)	14.3 (5.9–22.8)	1.06 (0.99–1.13)
Lung function abnormality on spirometry	29 (74.4, 58.9–85.4)	11 (73.3, 48.1–89.1)	1.64 (0.26–10.25)
Absolute eosinophil count at presentation, cells/ μ L	1158.1 (853.4–1462.8)	1113.7 (640.9–1586.6)	1 (0.99–1.0)
Total IgE levels at presentation, IU/mL	7242.3 (4990.3–9494.4)	9355.9 (5858.6–12853.2)	1 (1–1)
Percentage decline in IgE levels at six weeks	38.6 (33.1–43.9)	45.1 (35.9–54.2)	1.07 (0.99–1.15)
<i>A. fumigatus</i> specific IgE levels at presentation, kUA/L	16.2 (8.9–23.4)	12 (3.8–20.2)	0.96 (0.91–1.01)
Lung segments involved by bronchiectasis on HRCT	5.8 (4.2–7.3)	9.4 (6.6–12.2)	1.29 (1.06–1.57)*
Presence of high-attenuation mucus	6 (15.4, 7.2–29.7)	6 (40.0, 19.8–64.3)	2.79 (0.38–20.66)

* $p < 0.05$.

Very few studies have described the factors predicting outcome in patients with ABPA complicating bronchial asthma. In a study of 76 patients with ABPA, Greenberger et al. suggested that ABPA-S is less severe immunologically, however only the *A. fumigatus* specific IgG levels were higher in patients with ABPA-CB compared to ABPA-S. Other immunologic parameters were not significantly different between the two groups.²⁷ Kumar et al. had also classified the disease into three groups – ABPA-S (mild), ABPA-CB (moderate) and ABPA-CB-other radiologic findings (ORF). However, this was a single study and included only 18 patients.²⁸ In a large study of ABPA published from this center (126 patients), we have shown that the clinical, spirometric and immunologic findings were not significantly different when classifying ABPA into two groups (ABPA-S and ABPA-CB) or into the above mentioned three categories (ABPA-S, ABPA-CB and ABPA-CB-ORF).¹⁷ In a recently published multivariate analysis of 155 patients with ABPA, we had demonstrated that the severity of bronchiectasis and the presence of hyperattenuating mucoid impaction on HRCT predicted relapses of ABPA and the severity of bronchiectasis was an independent predictor of failure to

achieve long-term remission.¹⁹ Thus, it remains prudent to diagnose and treat ABPA early before bronchiectasis (which is irreversible lung damage) sets in.

The IgE is the antibody associated with allergy and type I hypersensitivity. Although IgE is the least abundant immunoglobulin isotype (normal serum IgG levels are almost 270 times that of serum IgE levels), it can trigger powerful immunological responses, as in patients with ABPA. The total serum IgE level is a sensitive marker of the immunological process in patients with ABPA, and is thus the most useful test for diagnosis and follow-up of these patients. The cutoff for total IgE serum level in patients with ABPA is 1000 IU/mL, and often may reach levels in tens of thousands as noted in our study. In fact, a normal total serum IgE level almost excludes active ABPA as the cause of patient's current symptoms (in a patient currently not on glucocorticoid therapy). It is important to remember that the level may not reach normal even after therapy with glucocorticoids. Therefore, repeated measurements of IgE levels need to be ascertained over time to determine the baseline value for an individual patient during remission. The serum IgE determination also represents an important

clinical tool with which to follow patients over time. A doubling of the patient's baseline IgE levels signifies relapse of the disease. It was therefore logical to assume that the magnitude of decline in serum IgE levels would predict the clinical outcomes. But, the results of this study that the quanta of decline in serum IgE levels are not correlated with the clinical outcome. It is not only the immunological activity, but also the treatment response to glucocorticoid therapy in ABPA which is highly variable, and the glucocorticoid therapy controls the immunologic activity, albeit only temporarily.

The present study suggests that the presence of bronchiectasis is a marker associated with frequent relapses and failure to achieve complete remission. The presence of bronchiectasis identifies a group of patient with prolonged immunological responses against *A. fumigatus* antigens. It may also be probable that it defines a subgroup of patients with more severe inflammation. Recently, numerous genetic abnormalities including interleukin-10 promoter and surfactant protein polymorphisms have been identified in patients with ABPA and certain genetic abnormalities may predispose a patient to develop bronchiectasis.¹ The occurrence of bronchiectasis also makes the patient more susceptible to a persistent *A. fumigatus* colonization state with resultant recurrent relapses. Thus, it is of paramount importance to diagnose ABPA before bronchiectasis sets in i.e. in the ABPA-S stage. The exact reason why hyperattenuating mucus is associated with poorer outcomes remains unclear, possibly the higher attenuation points to a more inspissated and impacted type of mucus. It may also be hypothesized that patients with hyperattenuating mucus have specific genetic alterations which lead to formation of hyperdense mucus, and the genetic abnormalities dictate a disease with more severe inflammation and poorer outcomes. More research is needed to investigate the exact reasons for this association.

What are the clinical implications of our study? The results of this study suggest that a 35 percent decline in IgE levels at six weeks is not an absolute criterion for remission in patients with ABPA. The levels may vary from patient to patient (32–45 percent) and the fall may be less brisk in patients with total serum IgE levels less than 2500 IU/mL (20–32 percent). Thus the results of follow-up IgE levels need to be interpreted in the light of clinical findings. If there is a clinical and radiological improvement and the IgE levels fall by less than 35 percent at six weeks, one can safely follow the patient with a repeat serum IgE levels at three months. But, if the IgE levels decline by less than 35 percent and are associated with lack of clinical and radiological response, then further scrutiny is required to investigate the cause of a lack of decline. If no obvious cause is found, the dose of glucocorticoids needs to be increased to control the immunological activity, although this study was not designed to make this assumption.

Conclusions

In conclusion, the results of this study suggest that a 35% decline in total serum IgE levels at six weeks is not seen in all patients after institution of glucocorticoid therapy despite clinical and radiological improvement. The fall in

serum IgE levels is slower in patients with baseline IgE levels less than 2500 IU/mL. These points should be kept in mind while evaluating a patient with ABPA for remission. Finally, the quantum of decline in serum IgE levels does not predict clinical outcomes.

Conflict of interest

The authors have no conflict of interest to disclose

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