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Allergic Bronchopulmonary Aspergillosis (ABPA)

In this Issue...

In this issue, we focus on the problem of allergic bronchopulmonary aspergillosis (ABPA) as a major pulmonary complication in patients with cystic fibrosis (CF). The impact of ABPA on the course of CF lung disease poses special challenges, with chronic *Aspergillus* respiratory infection, even in the absence of ABPA, playing a significant role, according to data from 2 recent retrospective cohort studies. A summary of current diagnostic criteria is provided in this issue, along with a discussion on their limitations. Also included is an overview of recent papers highlighting newer serologic biomarkers and assays, such as immunoglobulin (Ig) E antibodies to recombinant *Aspergillus* allergens, quantitation of IgG antibodies to *Aspergillus*, and levels of the CC chemokine TARC (thymus and activation-regulated chemokine), that may improve diagnostic accuracy. A review of current treatments is presented as well, with particular attention paid to recent studies that can help optimize the use of antifungal agents, glucocorticosteroids, and possibly biologic therapy with monoclonal antibodies to IgE. In these patients, earlier and improved diagnosis and therapy are likely to lead to enhanced outcomes in terms of morbidity, quality of life, health care utilization, and possibly preservation of lung function.

**LEARNING OBJECTIVES**

At the conclusion of this activity, participants should be able to:

- Define the role of *Aspergillus* infection and allergic bronchopulmonary aspergillosis (ABPA) in the progression of cystic fibrosis (CF) pulmonary disease.
- Identify the essential criteria for diagnosing ABPA in patients with CF and potential new biomarkers.
- Describe the use of recommended treatments for ABPA in patients with CF, including limitations and potential alternatives.
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LAUNCH DATE

This program launched on December 8, 2009, and is published monthly; activities expire two years from the date of publication, ending in December 7, 2011.

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Unlabeled/Unapproved Uses

The author has indicated that none of the agents discussed are approved for ABPA.

Program Directors’ Disclosures
The diagnosis and treatment of ABPA in patients with CF differs from that in patients with asthma and remains problematic. CF shares several underlying features with ABPA, as originally described in patients with asthma, such as a high degree of allergic sensitivity to *Aspergillus* species (particularly *A. fumigatus*, responsible for >90% of all cases), episodic airway obstruction, pulmonary infiltrates, bronchiectasis, other atopic sensitivities or disease, and pronounced adaptive immune responses to *Aspergillus*. The constellation of findings and tests required for diagnosis of ABPA in patients with CF is complex and often not rigorously applied. In addition, some of the laboratory assays are not standardized or validated in terms of control populations. These difficulties have led to wide variations in estimates of the prevalence of ABPA in patients with CF, with a recent meta-analysis yielding an overall prevalence of 7.8% (95% confidence interval [CI], 5.8 to 10), thus rendering it one of the most common as well as troublesome complications of CF.¹

Recognizing these difficulties, the Cystic Fibrosis Foundation (CFF) convened a Consensus Conference on ABPA in June 2001. The resulting publication comprehensively reviewed the pathogenesis, diagnosis, and treatment of ABPA in patients with CF.² The Consensus Conference criteria for diagnosis of ABPA in patients with CF can be summarized as follows: (1) clinical deterioration (eg, increased cough, increased sputum, exercise intolerance, bronchospasm, reduced pulmonary function); (2) total serum IgE level >500 IU/mL; (3) specific IgE antibody to *Aspergillus*, as manifested by positive immediate prick skin test or blood antibody test (RAST [radioallergosorbent test] or CAP RAST [ImmunoCAP®; Phadia AB; Uppsala, Sweden]); (4) specific blood IgG antibodies to *Aspergillus* (precipitins or enzyme-linked immunosorbent assay [ELISA]); and/or (5) new or recent abnormalities on chest imaging radiography or computed tomography (CT) scan, such as infiltrates, mucus plugging, or bronchiectasis. The high prevalence of ABPA in persons with CF led to the recommendation to screen all patients annually, beginning at school age, using total serum IgE level. Treatment recommendations focused on the use of oral prednisone as first-line therapy and the addition of itraconazole as a preferred second-line agent. However, the toxicity of chronic dosing with systemic corticosteroids, difficulties encountered optimizing the use of itraconazole (discussed below), and inadequate clinical responses in some patients have led to exploration of a variety of other potential treatments, including inhaled amphotericin B, other triazole antifungal agents, high-dose pulse intravenous (IV) methylprednisolone, and omalizumab. Nevertheless, despite the widespread use of these agents, no controlled trials with these treatments have been conducted in individuals with ABPA.
ABPA EFFECTS ON LUNG FUNCTION AMONG PEDIATRIC PATIENTS WITH CF


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A retrospective cohort study was conducted using the CF Center database from the Children’s Hospital in Bern, Switzerland. Patients with CF born between 1978 and 1999, and reviewed regularly between 1983 and 2005 (N=122), were enrolled in the study. Inclusion criteria were ≥3 annual lung function tests (spirometry and flow volume loop, lung volumes by whole body plethysmography and multibreath nitrogen washout, lung clearance index, specific airway resistance) between 6 and 20 years of age (median, 10 tests per subject). The treatment regimen, which was relatively uniform for the study cohort, is described extensively in the article’s online supplement. The study is unique in the availability of extensive longitudinal immunologic data pertaining to Aspergillus sensitization and ABPA in the same database as extensive longitudinal pulmonary physiologic measurements. ABPA was diagnosed in 16 of the 122 patients (13.1%), while 36 (29.5%) did not develop sensitization to Aspergillus. With regard to the development of Aspergillus sensitization and ABPA, time-event relationship analysis showed that the earliest selected event was onset of chronic P. aeruginosa infection (mean, 11.6 years of age), followed by development of IgE antibodies against certain Aspergillus recombinant allergens (mean, 13.1 years), then development of total IgE >1000 IU/mL (mean, 19.9 years), and finally diagnosis of ABPA (mean, 20.5 years).

In addition to extensive data on the evolution of adaptive immune responses to Aspergillus, the study examined the effect of these events on lung function in 5 selected “etiologic” groups: (1) CF patients neither colonized with P. aeruginosa nor sensitized to Aspergillus (n=16; “CF-controls”); (2) those sensitized to Aspergillus without having developed ABPA (n=45); (3) those who developed ABPA (n=16); (4) those intermittently colonized by Pseudomonas (n=21); and (5) those chronically infected with P. aeruginosa (n=24). As shown in Figure 1, for forced expiratory volume in 1 second (FEV₁) and forced expiratory flow after 50% of vital capacity has been expelled (FEF50), lung disease progression, as represented by z score change, was most severe with ABPA and worse than with chronic Pseudomonas infection. The data further suggest that Aspergillus sensitization without ABPA (group 2) is also a risk factor for pulmonary decline, as progression in this group of patients was greater than that in those either intermittently colonized with Pseudomonas (group 4) or those neither colonized with P. aeruginosa nor sensitized to Aspergillus (group 1).
In addition to the most severe progression of airflow limitation, patients with ABPA also showed the most severe progression of all other measured pulmonary functions—that is, hyperinflation and trapped gas, ventilation inhomogeneity, and airway resistance.

This study is limited by a number of important drawbacks. First, the retrospective cohort design is prone to bias. Changes were not adjusted for multiple confounding variables, and even if this had been done, unanticipated confounders can still fatally bias the results of any cohort study. Second, treatment of ABPA may have affected the changes in lung function. Separately, this group reported that 1 year of treatment for ABPA did not significantly affect spirometric lung function.¹ Nevertheless, the data do suggest that sensitization to *Aspergillus* and especially development of full-blown ABPA accelerate the decline in lung function reported in patients with CF, thus warranting vigilance in early detection and aggressive treatment.

References

Since ABPA represents an immune–mediated hypersensitivity lung disease, it is reasonable to hope that the appropriate immunologic test might provide a sufficient degree of sensitivity and specificity to offer an enhancement of diagnostic accuracy, if not replacement of the cumbersome current schema of multicomponent diagnostic criteria. Although total serum IgE levels fluctuate dramatically and often in concordance with clinical activity (and treatment) in persons with ABPA, they are not sufficiently specific to play such a defining role. And although *Aspergillus*-specific IgE antibodies levels are somewhat more specific, they also lack sufficient specificity for ABPA (as opposed to simple atopic sensitization) to be diagnostically useful and do not demonstrate a similar degree of correlation with disease activity. At any rate, total and specific IgE tests are standardized, with the ImmunoCAP assay preferred worldwide and providing results in mass units. The same cannot be said for *Aspergillus*-specific IgG tests. The traditional precipitin test using double diffusion in agar is, at best, semiquantitative, not sensitive, and dependent on unstandardized fungal extracts; the alternative ELISA methodology is more sensitive and quantitative, but also relies on unstandardized reagents and is not validated with regard to cutoffs (some laboratories use a pool of non-ABPA *Aspergillus*–sensitive sera and report the results as a multiple or index of the control pooled value).

Therefore, preliminary results using an adaptation of the ImmunoCAP method to test for *Aspergillus*-specific IgG antibodies represent a potential breakthrough in serologic diagnosis. In 2 published studies, however, the cutoff for ABPA diagnosis differed somewhat, varying from 35 to 90 µg/mL, with the latter value showing optimal receiver operator characteristics (sensitivity, 91%; specificity, 88%).¹² Use of various disease control groups may influence the suggested cutoff and need to be taken into account.

Alternative serologic markers have also been investigated. In the 1990s, considerable enthusiasm was generated by the discovery and production of purified recombinant *Aspergillus* allergens as diagnostic reagents in specific IgE antibody tests (both as skin test reagents and in ELISA) in several European studies. However, subsequent studies in North and South America have called their utility into question, at least as single allergen diagnostic tests.³⁴ Recently, understanding the role of dendritic cells (specialized antigen-presenting cells in the respiratory epithelium) in orchestrating adaptive immune responses has led to the identification of TARC/CCL17 as a key molecule in generating the T helper 2 cell–dominant response characteristic of ABPA. In studies from Germany and Switzerland, blood TARC/CCL17 levels have been shown to distinguish ABPA from disease controls and to correlate with ABPA disease activity.⁵⁶ Validation of these results in larger multicenter studies is needed before general adoption of TARC as a serologic biomarker of ABPA. In preliminary longitudinal analysis, TARC levels have been found to be elevated months to years prior to the onset of clinical ABPA.

References

Triazole antifungals have assumed a central role in the management of ABPA since, unlike glucocorticosteroids, they reduce the fungal burden and thereby act as steroid-sparing agents. Double-blind, placebo-controlled, randomized clinical trials have established the safety and efficacy of itraconazole for ABPA in patients with asthma and led to their widespread use in persons with CF, where open trials have also demonstrated good results. The 2001 CFF ABPA Consensus Conference recommended the use of itraconazole as a second-line treatment for ABPA in patients with (1) slow or poor response to corticosteroids; (2) relapse after initial episode; (3) steroid dependence; and/or (4) steroid toxicity. It is difficult to achieve optimal efficacy with itraconazole in patients with CF, however, because of the poor bioavailability of the agent and the need for acidic gastric pH for absorption (hindered by the widespread use of acid-suppressing drugs in CF). As itraconazole is highly lipophilic, a suspension in cyclodextrin is 20% to 50% more bioavailable than is the capsule formulation. In order to ameliorate these challenges, monitoring of blood levels is recommended whenever therapeutic response is disappointing or concern exists regarding toxicity.

Hope and colleagues recently reviewed the role of therapeutic monitoring of triazoles currently licensed in the United States (fluconazole, itraconazole, voriconazole, and posaconazole). Itraconazole is metabolized via hydroxylation to equally bioactive hydroxyitraconazole and ultimately disposed of via cytochrome P450 (CYP)3A4–dependent hepatic metabolism. Measurement of itraconazole by high-performance liquid chromatography (HPLC) assesses only the parent molecule, whereas use of a bioassay includes the active hydroxylated metabolite, resulting in reported itraconazole levels that are 2- to 10-fold higher with a bioassay than with HPLC (most reference laboratories use the latter method). This is important, because itraconazole displays nonlinear pharmacokinetics and concentration-dependent antifungal activity and toxicity. The recommended minimal steady-state (trough) level, based on Aspergillus minimum inhibitory concentration (MIC) and clinical studies in a variety of disease states, is \(0.5 \mu\text{g/mL}\) by HPLC assay. Prediction of toxicity (fluid retention, gastrointestinal intolerance, elevated liver function tests, rash, headache, peripheral neuropathy, tremor, and sleep disturbance, all reported in \(\geq 4\%) \text{ of patients}) as a function of steady-state level has been described, but only using a bioassay. The Consensus Conference recommendation for itraconazole dosing is 5 mg/kg/day, with twice-daily dosing if >200 mg/day. However, recent pharmacokinetic modeling via a two-compartment model with first-order metabolism to the hydroxyl metabolite using pharmacokinetic data from 30 adults with CF, and defining a target therapeutic range of 0.5 to 2.0 \(\mu\text{g/mL}\) by HPLC or 1.5 to 6.0 \(\mu\text{g/mL}\) by bioassay, yielded a higher optimal dosing regimen of 500 mg twice daily for the treatment of adult patients with CF. No clinical studies have reported results with this higher dosing regimen.
Voriconazole has at least equal activity to itraconazole against *Aspergillus* but has better oral bioavailability (96% in healthy persons), and encouraging results have been reported in 2 small, open trials in a combined total of 23 CF patients with ABPA.\(^3\),\(^4\) However, voriconazole has multiple CYP-dependent hepatic interactions (CYP2C19, CYP3A4, and CYP2C9), resulting in notoriously unpredictable steady-state levels and drug-drug interactions. Voriconazole thus has much greater interpatient variability than itraconazole (~100-fold vs ~15-fold, respectively). A validated assay methodology using liquid chromatography-tandem mass spectrometry in various clinical settings has led to a recommended steady-state (trough) target range of 1 to 6 µg/mL. Although the recommended dose in adults is 200 mg twice daily, which generally produces steady-state levels of 2 to 3 µg/mL, higher doses of 4 to 13 mg/kg may be required in children because of enhanced clearance.\(^5\) Levels of >6 µg/mL are predictive of increased toxicity, including hepatic, ophthalmologic, and photosensitive dermatologic adverse reactions, as well as rare but more serious cardiac (torsades de pointes) and neurologic events. It should also be emphasized that the cost of voriconazole is 10 to 30 times higher than that of itraconazole. Finally, it is worrisome that resistance to both itraconazole and voriconazole has now been reported in patients with ABPA; thus far, some of these individuals remain sensitive to the newest available triazole agent—posaconazole.\(^6\) Posaconazole also exhibits few drug interactions and is intrinsically more active against *Aspergillus* than either itraconazole or voriconazole.

References

is 20 mg nebulized twice daily. However, published studies specifically dealing with ABPA in patients with CF are limited to reported results on 10 patients; far larger numbers are available on the treatment of *Aspergillus* infection in neutropenic patients and in lung transplant recipients.1

Another alternative, adopted to reduce chronic prednisone toxicity, is the use of monthly “pulse” high-dose IV methylprednisolone infusions. In several small series describing a total of 21 CF patients with ABPA, doses of 10 to 20 mg/kg infused on 3 consecutive days every 4 to 8 weeks for up to 4 years have been used, with improvement in steroid toxicity and control of ABPA reported. Despite small numbers, adverse events have occurred in some patients (flushing, myalgia, malaise, restlessness, transient hyperglycemia, hypertension) that can lead to discontinuation of pulse therapy.2-4

The availability and efficacy of omalizumab, a humanized monoclonal antibody to IgE approved for use in patients >12 years of age with moderate to severe allergic asthma, has aroused much interest because of its possible efficacy in ABPA. Several case reports and small series have suggested the potential use of the agent in CF patients with ABPA.5-9 A double-blind, placebo-controlled, randomized clinical trial of omalizumab in patients with CF complicated by ABPA has been initiated (ClinicalTrials.gov identifier NCT00787917).

References


**EFFECTS OF CHRONIC A. FUMIGATUS INFECTION ON HOSPITALIZATION AND LUNG FUNCTION IN PATIENTS WITH CF**


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Colonization of sputum by *Aspergillus* is common in persons with CF. The reported prevalence of *A. fumigatus* colonization of CF airways ranges from 16% to 57%, depending on methodology, frequency and duration of monitoring, and patient population.1 The possibility that *Aspergillus* might aggravate lung disease in patients with
CF even in the absence of ABPA was raised in a paper from Jerusalem, Israel, and Leeds, United Kingdom, describing 6 patients with respiratory deterioration who had *Aspergillus* in sputum cultures but not ABPA, and who did not respond to conventional antibiotic treatment but did improve with itraconazole.\(^2\)

A recent epidemiologic study from the Hospital for Sick Children in Toronto, Canada, lends some credence to this hypothesis. Amin and colleagues used their Center's CF database to examine the effect of *A. fumigatus* infection on lung function and hospitalization for pulmonary exacerbation. The study sample comprised 230 patients followed from 1999 to 2006. Inclusion requirements were patient age <19 years, with the ability to perform spirometry and produce sputum. Data were censored for the first isolation of *Burkholderia cepacia*. Adapting the Leeds criteria for chronic *P. aeruginosa* infection,\(^3\) persistent *Aspergillus* infection was defined as ≥2 positive cultures per year, whereas transient infection was defined as 1 positive culture per year. In this study, 37 of the 230 patients (16%) were thus defined as having persistent *Aspergillus* infection. The persistent *Aspergillus* infection group had lower baseline lung function (mean FEV\(_1\), 79.2% vs 86.1% predicted; \(P=0.04\)), higher *P. aeruginosa* infection rate (54.1% vs 44.1%; \(P=0.01\)), and higher ABPA rate (10.8% vs 1%; \(P<0.001\)) compared with the other subjects. Patients with persistent *Aspergillus* infection or with *P. aeruginosa* infection had lower lung function over the study period than did those without chronic infection. There was a significant interaction, such that co-infection was associated with the lowest lung function (see Figure 2). Intermediate levels of lung function were observed in patients with transient *Aspergillus* infection, *Aspergillus* infection without *Pseudomonas*, and vice versa. Persistent *Aspergillus* infection was associated with increased risk for hospitalization for pulmonary exacerbation (relative risk [RR], 1.94; \(P=0.0002\)), which trended toward significance after adjusting for baseline FEV\(_1\) (RR, 1.4; \(P=0.06\)). Transient *Aspergillus* infection was also associated with risk for hospitalization (RR, 1.43; \(P=0.047\)).

These data suggest that persistent recovery of *Aspergillus* from sputum cultures by itself worsens CF lung disease, as well as interacts negatively with *P. aeruginosa* infection. However, as acknowledged by the authors, the retrospective cohort design is a weak signal, as potential confounding factors not accounted for in multivariate analysis render cohort studies notoriously prone to bias. In addition, reliance on expectorated sputum

**Figure.** Decline in FEV\(_1\)% predicted over time for the Aspergillus and Pseudomonas interaction (baseline FEV\(_1\) 85% predicted and starting at age 7).

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cultures excludes a sizable portion of pediatric patients (and itself biases the group toward greater baseline lung disease). It is also impossible to determine if the lower baseline FEV1 in the persistent *Aspergillus* group identifies it as a causal risk factor or if it represents an epiphenomenological result of other factors. Fortunately, this has led to initiation of a double-blind, placebo-controlled, randomized trial of antifungal therapy with itraconazole in Canadian patients with CF who are persistently infected with *Aspergillus* (ClinicalTrials.gov identifier NCT00528190).

**References**


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