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CRITIQUE OF TRIALS IN ABPA AND FUNGAL ALLERGY

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ABPA was recognized in 1952 in asthma and in 1965 in cystic fibrosis. Treatment protocols emerged from uncontrolled series of patients responding to regimes of oral glucocorticosteroids lasting several months. Oral steroids remain the mainstay of treatment, but dose regime and duration have never been standardized. Wang et al suggested an oral steroid regime based on experience with 25 patients with asthma-ABPA, and similar results were reported in 33 patients by Capewell et al.[1,2] Unfortunately, oral steroids in ABPA are problematic due to frequency of relapse after taper or discontinuation; lack of steroid effect on airway fungal burden; and toxicities, several of which are exaggerated in patients with CF due to their underlying disease, as well as a possible increased risk of non-tuberculous mycobacterial infection.

Other therapies were tested in several small case series or uncontrolled trials in ABPA patients with underlying asthma or cystic fibrosis, and in prospective randomized double-blind placebo-controlled trials of inhaled corticosteroids (n=1) or oral itraconazole (n=2) in patients with asthma-ABPA. While inhaled steroids have been used with apparent success in several case reports and small series, the only controlled study was unsuccessful.[3] However this study employed beclomethasone in modest dose without spacers, and more recent positive reports employed higher doses, spacers and newer agents such as budesonide. Use of inhaled budesonide with itraconazole can lead to adrenal suppression due to itraconazole inhibition of hepatic cytochrome P4503A4.

Case reports and uncontrolled series with improved treatment success upon addition of itraconazole to steroids were validated by a randomized controlled trial in 55 asthma-ABPA patients, in which more responders were found in the itraconazole group.[4] A study in stable asthma-ABPA patients showed clinical benefit and an anti-inflammatory effect of itraconazole in that sputum eosinophils and eosinophil cationic protein as well as serum total IgE and *Aspergillus* IgG antibodies declined.[5] In ABPA patients with CF, itraconazole has also been reported to be clinically beneficial in several uncontrolled studies.

Despite combined use of oral steroids and itraconazole, ABPA relapses, and steroid dependence or toxicity, have led to examination of alternative agents in several small uncontrolled studies. Reports of nebulized amphotericin B in several patients with ABPA and CF suggest a potential benefit. Voriconazole has also been used with some success but also some toxicity. Both itraconazole and voriconazole have been used in some CF-ABPA patients as monotherapy with mixed results. A recent report described treatment of refractory CF-ABPA with monthly high-dose intravenous methylprednisolone, also with mixed results. No controlled trials of voriconazole, inhaled amphotericin, or intravenous pulse steroids have been published.

Conclusions:
1. Systemic corticosteroids remain the mainstay of treatment, but have never been evaluated by randomized controlled trials, and toxicity is high.
2. Itraconazole is an effective steroid-sparing agent with anti-inflammatory aspects.
3. A possible role for inhaled corticosteroids, voriconazole, nebulized amphotericin, and pulse iv corticosteroids is suggested in case reports but there have been no controlled trials.
4. Future studies should focus on controlled trials of antifungal and immunomodulatory agents since conventional steroid therapy remains problematic.

References
1. Wang JL et al. Am Rev Respir Dis. 1979;120:87.
2. Capewell S et al. Thorax 1989;44:925.
3. Br Thor Assoc, Br J Dis Chest 1979;73:349.
4. Stevens DA, et al. N Engl J Med 2000;342:756.
5. Wark PA, et al. J Allergy Clin Immunol 2003;111:952.

Critique of Trials in ABPA and Fungal Allergy

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2nd Advances Against Aspergillosis
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Diagnostic Criteria for ABPA

At least 5:

- Asthma
- Central bronchiectasis on CT
- Immediate skin test reactivity to *A. fumigatus*
- Total serum IgE > 1000 ng/mL (417 IU/mL)
- Elevated IgG and/or IgE antibodies to *A. fumigatus*
- Pulmonary infiltrates on CXR
- Serum precipitins to *A. fumigatus*
- Eosinophilia

Pharmacotherapy for ABPA-Corticosteroids

Indications: All except those with steroid toxicity

Initial: 0.5 - 2.0 mg/kg/d *po* prednisone equivalent (maximum 60 mg) for 1-2 weeks

Begin taper: 0.5 - 2 mg/kg *qod* for 1-2 weeks

Taper off: Attempt to taper off within 2-3 months

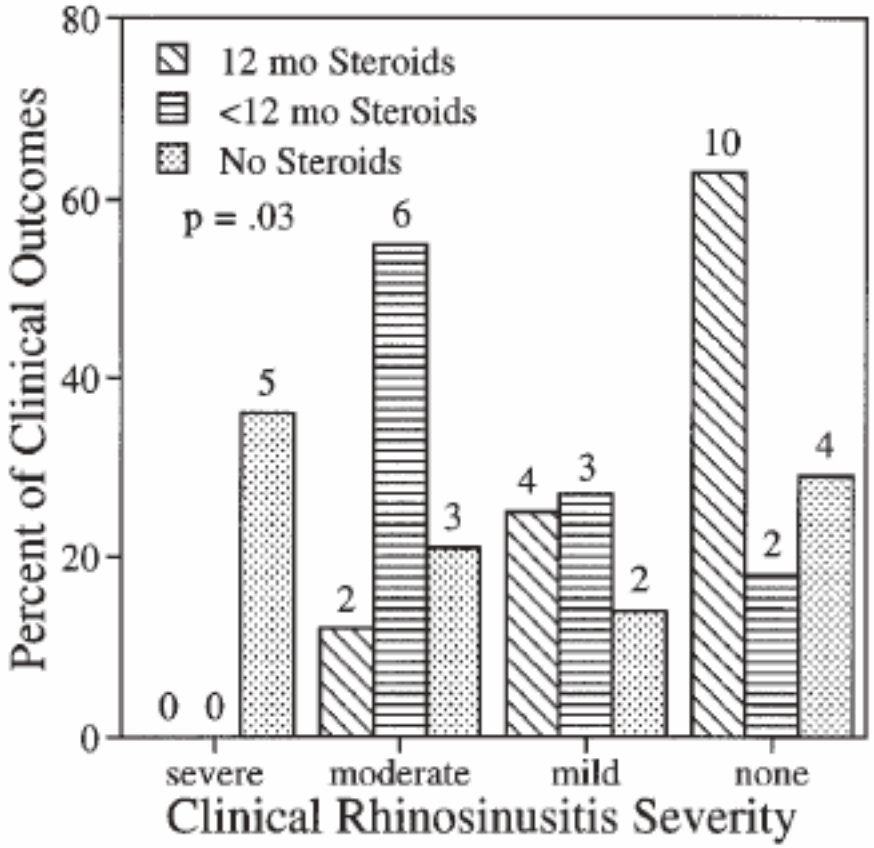
Relapse: Increase dose, add itraconazole, taper steroids when clinically improved

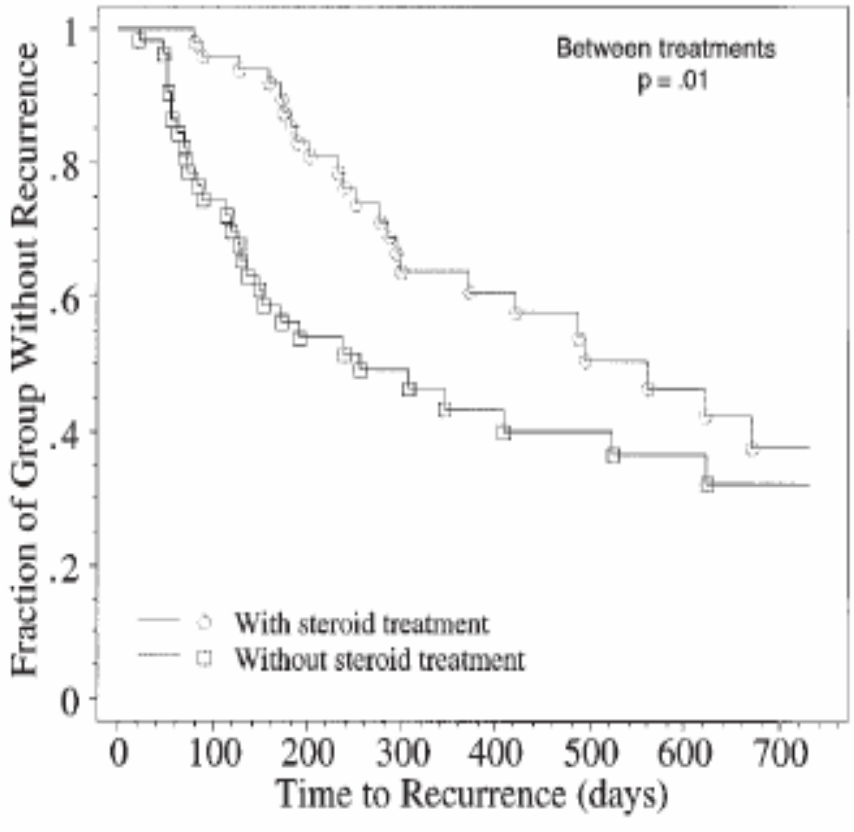
Oral Steroids in ABPA

- 247 episodes in 65 patients with pulmonary eosinophilia (33 with APBA)
- 186 (75%) treated with prednisolone
- Complete CXR clearing and reduction in eosinophils more common in steroid treated patients
- Long-term steroids in 28/33 ABPA patients (mean 7.4 mg/d x 11 yr) with no decline in lung function

Capewell S et al. *Thorax* 1989;44:925

Effect of Oral Steroids on Severity and Recurrence of Allergic Fungal Sinusitis





Schubert MS, Goetz DW. *JACI* 1998;102:395

Is Oral Steroid Treatment of ABPA a Risk Factor for Nontuberculous Mycobacteria?

- 139 CF patients 2-52 yr
- 12 (8.6%) sputum + for NTM, 6 (4.3%) met criteria for NTM lung disease
- 5 of these had ABPA (vs 1/133 w/o NTM)
- 5 had received systemic steroids

Mussafi H et al, *Eur Respir J* 2005;25:324

Pharmacotherapy for ABPA-Itraconazole

- Indications: Slow/poor response to steroids, relapse, steroid-dependent, steroid toxicity
- Dosing: 5 mg/kg/day (maximum 400 mg) *po* unless itraconazole levels obtained. *BID* dosing when daily dose >200 mg
- Duration: 3-6 months
- Monitor: LFTs in all. Itraconazole levels if concerns with absorption, lack of response, or drug-drug interactions.

Itraconazole in Asthma with APBA

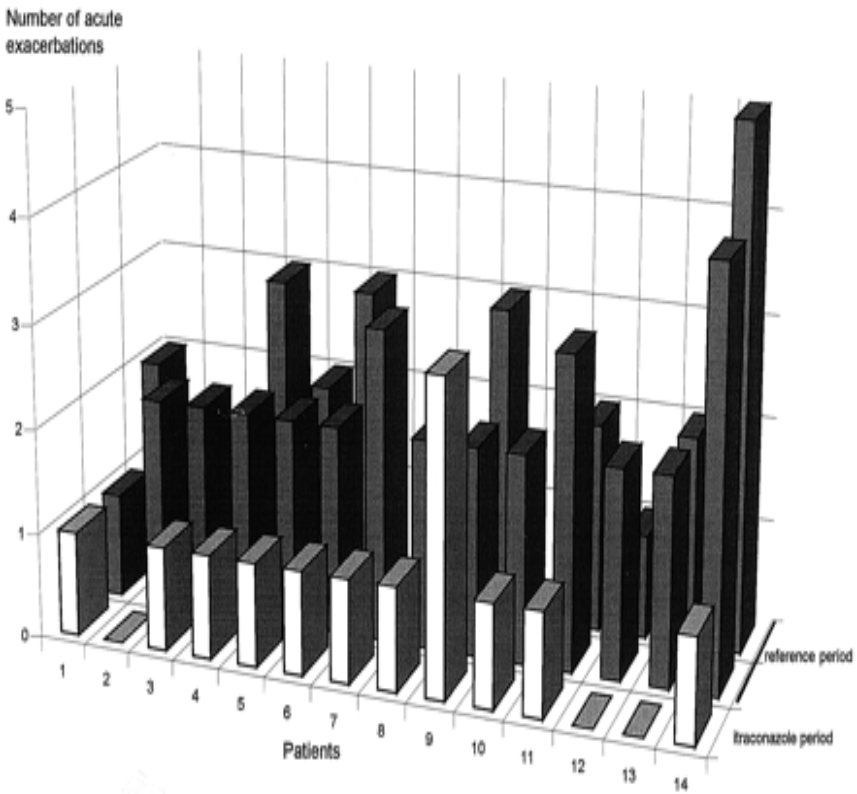
- Effective (n=1), Af-sIgG ⇓

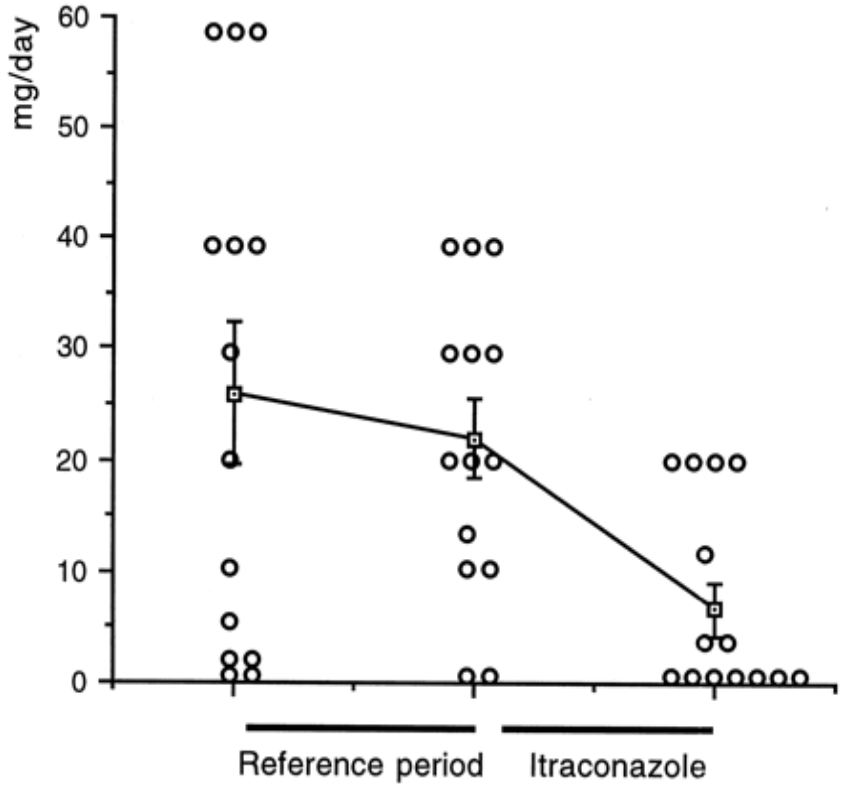
Pacheco et al, *Chest* 1993;103:980

- Effective in 11/12
- Prevented exacerbation in 6 off steroids

Germaud & Tuchais, *Chest* 1995;107:883

Effect of Itraconazole on Asthma with ABPA





Salez F et al. *Chest* 1999; 116:1665-8

Itraconazole in Asthma with ABPA

- Randomized DBPC multi-center trial; no CF
- n = 55 (28 Itra, 27 Placebo) x 16 weeks
- Response improvements
  - >50% in steroid, >25% in IgE, >25% PFT/exercise tolerance/resolved infiltrates
- Responses: 46% I *v* 19% P (p=0.04)
- 33% of non-responders in DBPC trial responded in 16 wk open-label extension
- No relapses

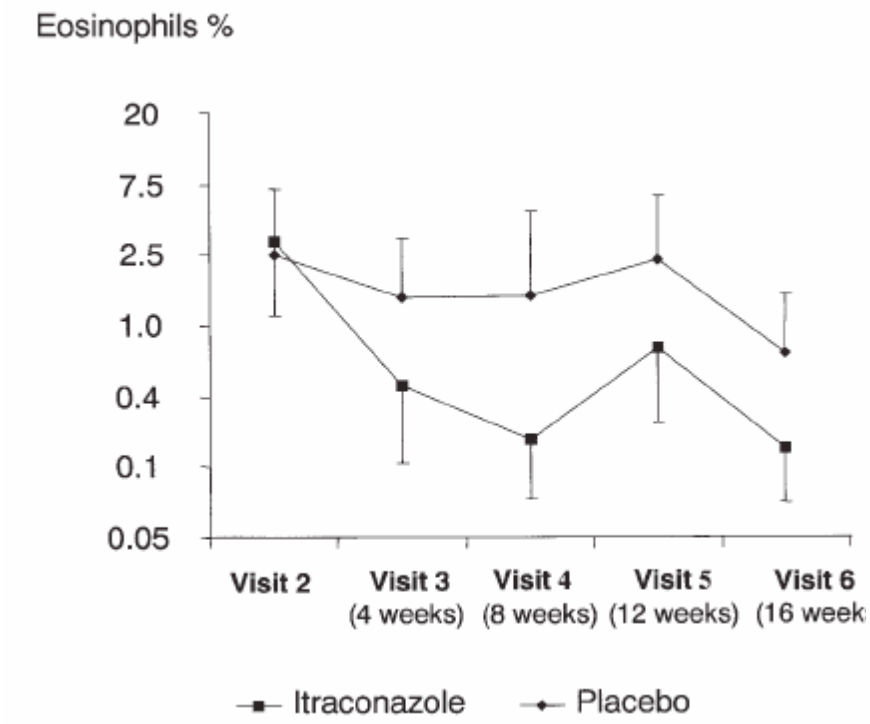
Stevens D et al. *NEJM* 2000; 342:756

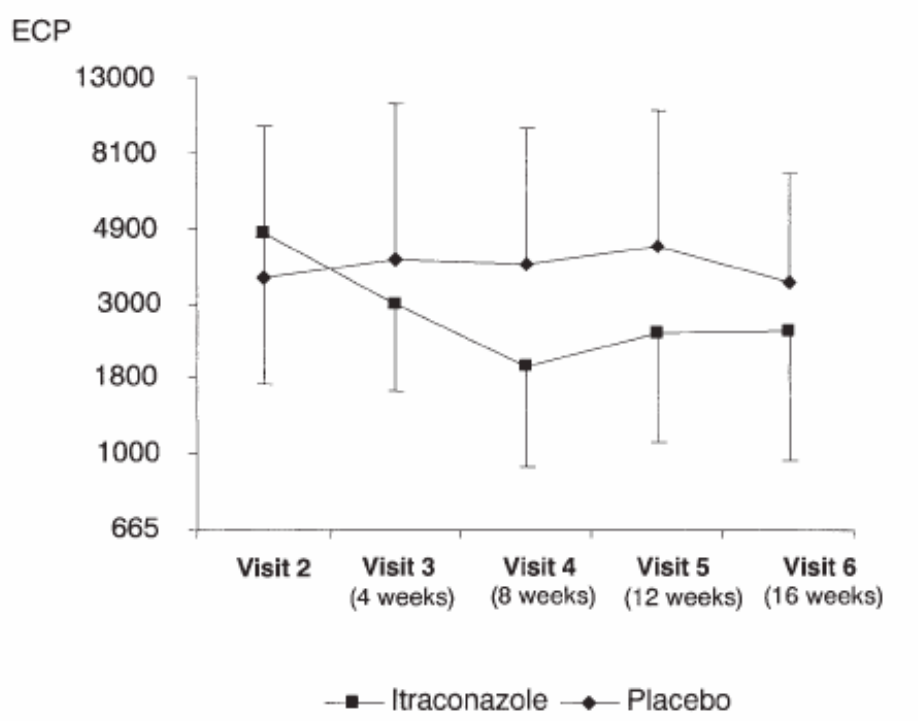
Itraconazole in Stable Asthma with ABPA

- Randomized DBPC single center trial; no CF
- n = 29 (15 Itra, 14 Placebo) x 16 weeks, 400 mg/d Itra
- All on inhaled steroid (~2 mg/d), 1/3 on oral steroid, 1/2 on leukotriene receptor antagonist
- Response favored Itraconazole
  - Normalization of sputum eosinophilia ($p<0.01$), ECP level ($p<0.001$)
  - Decrease in IgE ($p<0.01$), Af-sIgG ($p=0.03$)
  - Fewer ABPA exacerbations (median 0 vs 1.5, $p=0.03$)

Wark PA et al. *JACI* 2003;111:952

Effect of Itraconazole on Sputum Eosinophilic Inflammation In Stable Asthma with ABPA





Wark PA et al, *JACI* 2003;111:952

Diagnostic Criteria for ABPA in Cystic Fibrosis

- Clinical deterioration (cough, wheeze, exercise intolerance/bronchospasm, ⇓ PFT, ⇑ sputum)
- Serum IgE >1000 IU/mL
- Immediate skin test reactivity or elevated *A. fumigatus* serum IgE antibodies
- Elevated serum *A. fumigatus* IgG antibodies or precipitins
- Abnormal chest radiograph (infiltrates, mucus plugging, or change from baseline)

Stevens DA et al, *Clin Infect Dis* 2003;37:S225

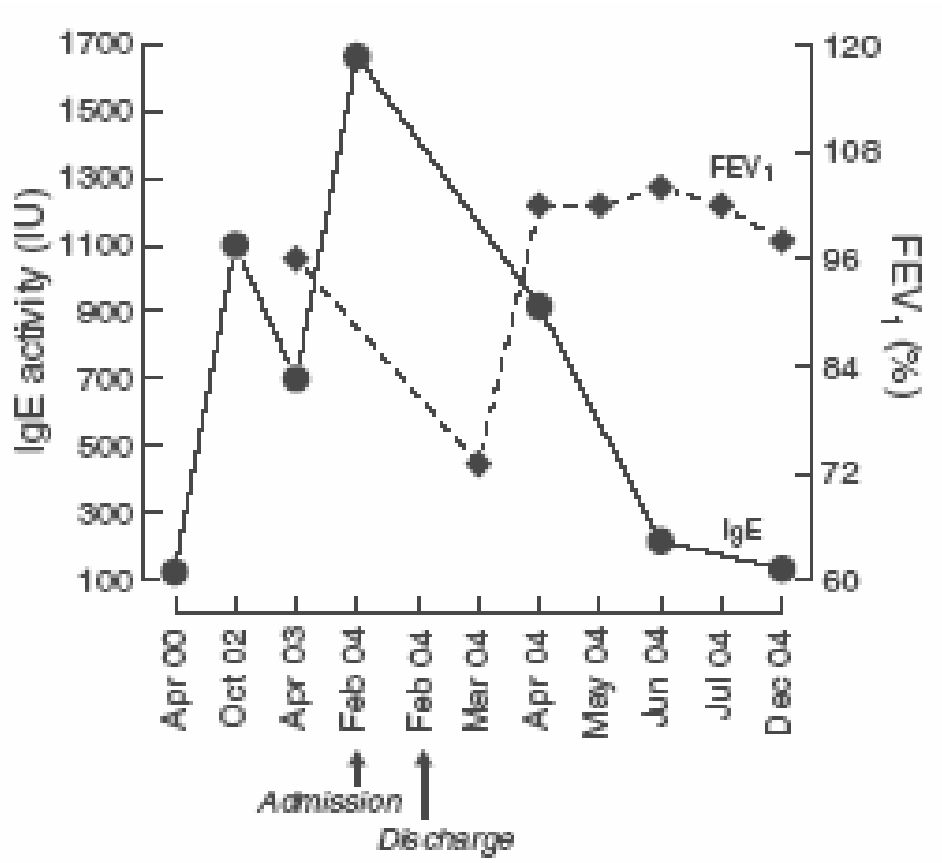
APBA in CF Exacerbations

Stanford CF Center Admissions (1995)

- 162 admissions, 92 patients
- IgE >500 IU/mL: 14% admits, 13% patients
- Acute ABPA: 6% admits, 10% patients

Nepomuceno I et al, *Chest* 1999; 115:364

Relation between IgE Levels and Lung Function (FEV_1) in an 8 Year Old Child with CF and Acute Severe APBA



Skowronski E, Fitzgerald DA, *Med J Aust* 2005;182:482

Itraconazole in CF with ABPA

- 3 CF (& 3 asthma): allowed ⇓ steroids, IgE ⇓, PFT ⇑
- Serum level ≥ 5 μg/mL best, sputum levels variable (0-17 μg/mL)

Denning et al, *Chest* 1991;100:813

- CF-ABPA in twins: allowed ⇓ steroids, IgE ⇓, *Af*-sIgG ⇓

Mannes et al, *Lancet* 1993;341:49

- 21 CF-ABPA (8.4% of clinic) treated with steroid/Itra (9) or Itra alone (12): ⇓ *Af*+ cultures, *Af* precipitins, *Af*-sIgE, IgE; improved PFT only in combination-treated patients (but these had lower baseline values)

Skov M et al, *Allergy* 2002;57:723

ABPA at the Stanford CF Center 1992-1996

- N = 15 (9% prevalence), 14 atopic to common aeroallergens
- Atopy as a major risk factor: 22% of atopic vs 2.4% nonatopic CF patients (p = 0.001)
- Treatment regimens
  - Prednisone - Itraconazole 11
  - Prednisone alone 2
  - Inhaled steroid - Itraconazole 1
  - Inhaled steroid alone 1

Nepomuceno et al, *Chest* 1999; 115:364

Itraconazole in CF with ABPA

	Without Itraconazole	**With Itraconazole**	***p***
– Days:	4,851	8,495	
	mean±SE, 323 ± 123	386 ± 134	n.s.
– Dose-days:	102,319	107,924	
	6,821 ± 2,246	4,906 ± 2,028	n.s.
– Avg daily oral steroid dose (mg):			
	26.7 ± 6.5	14.19 ± 3.6	0.05
– ABPA flares:	22	10	
	1.1 ± 0.2	0.46 ± 0.29	0.0009

Nepomuceno I et al, *Chest* 1999; 115:364

Inhaled Steroids in Asthma with ABPA

Efficacy? ⇓ oral steroids/ ⇓ sxs/ ⇑ PFT

- no ($p = 0.07$), n = 32, BPD 400 µg/d, RCT trial, 6 months cross-over

  Br Thor Assoc, *Br J Dis Chest* 1979;73:349

- yes, in 8/15, BDP 400 µg/d, 8-24 months

  Hilton, *Postgrad Med J* 1975;51 Suppl 4:98

- yes, n =2, BUD 1600 µg/d, 18 months

  Heinig et al, *Allergy* 1988;43:24

Inhaled Steroids in Asthma with ABPA

- yes, n =1, BDP 1 mg/d, 22 mos

  Balter & Rebuck, *Respir Med* 1992;86:441

- yes, n = 2, BDP 1.5 mg/d, 11 mos

  Imbeault & Cormier, *Chest* 1993;103:1614

- yes, n =5, BDP/BUD, 15 yrs

  Seaton et al, *Q J Med* 1994;87:529

Amphotericin B for CF with ABPA

- 16-40 mg/day neb used successfully in a CF patient after lung transplant and new-onset ABPA

  Casey P et al, *J Heart Lung Transpl* 2002;21:1237

- 5 CF patients with steroid-dependent ABPA (4 Cushingoid, 1 progressive NTM) received liposomal Amphotericin
- 50 mg/8 mL delivered weekly via Halolite breath-actuated nebulizer (~2 μM particles)
- First dose under observation, then at home
  - Up to 2.5 hr to nebulize a dose, but preferred by patients
- Steroid-sparing effect; no change in serology

Tiddens HA et al, *Pediatr Pulmonol* 2003; Suppl 25:301

Voriconazole for CF with ABPA

- 21 children with CF (5-16 yrs)
- 13 with ABPA; 8 with sputum *Af*+ but no ABPA
- Voriconazole for 1-50 weeks, monorx in 2
- Improvements in ABPA but not *Af*+ patients
- Side effects in 7 (33%)

Hilliard T et al, *J Cystic Fibrosis* 2005;4:215

Pulse IV Methylprednisolone for CF with ABPA

- 4 children with CF and ABPA (3.5-12 yrs)
- Relapses despite daily oral steroids and itraconazole, toxicity
- IV methylprednisolone 15-20 mg/kg/d x 3, then q 4-9 wks
- Improvements in ABPA in 2 with less toxicity
- Side effects in 2 (hypertension, lethargy/ malaise) led to d/c; no improvement in 1

Thomson JM et al, *Pediatr Pulmonol* 2005;Nov 29 ePub

Conclusions

- Systemic steroids remain mainstay of ABPA treatment but have never been evaluated by RCT, and toxicity is high
- Itraconazole is an effective steroid-sparing and anti-inflammatory agent
- Role for inhaled steroids, other azoles, ampho neb, pulse iv steroids suggested by case reports but no large or controlled trials