

ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

How could we diagnose it earlier?

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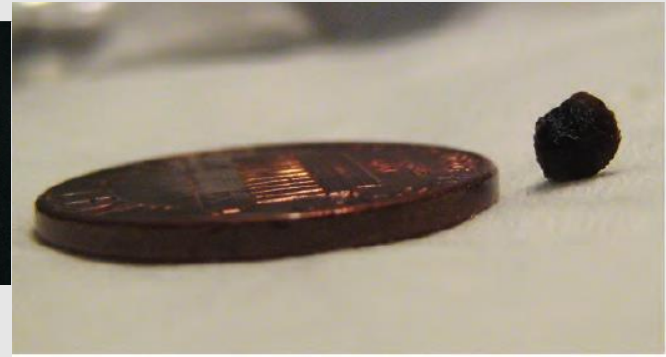
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Take home message

Rare

When do you need to think about it?



1)





- 2) Pulmonary infiltrate or clinical deterioration do not respond to one week of antibiotherapy
- 3) Major increase of the total serum IgE upon annual screening (even if not specific)

ABPA: introduction



- **Definition**

-  Complex hypersensitivity reaction, often in patients with asthma or cystic fibrosis (CF),
-  Occurs when the bronchi become colonized by *Aspergillus fumigatus* (AF)



- **Incidence**

-  Comprise 2-10% of the subjects with CF (rare)
-  Not all CF patients colonized with AF will develop ABPA

- **Symptoms: non-specific**

-  Repeated episodes of bronchial obstruction, inflammation, and mucoid impaction
-  Lead to bronchiectasis, fibrosis, and respiratory compromise

- **Gaps in clinical management**

-  **Tests are not optimal:** skin test, specific IgE, sputum culture
-  Therapies not optimal: steroids, antifungal, anti-IgE

Aspergillus fumigatus

- Is widespread in nature: soil and decaying organic matter

- Spores are ubiquitous in the atmosphere

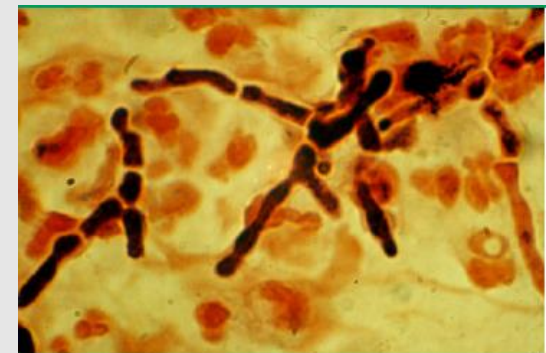
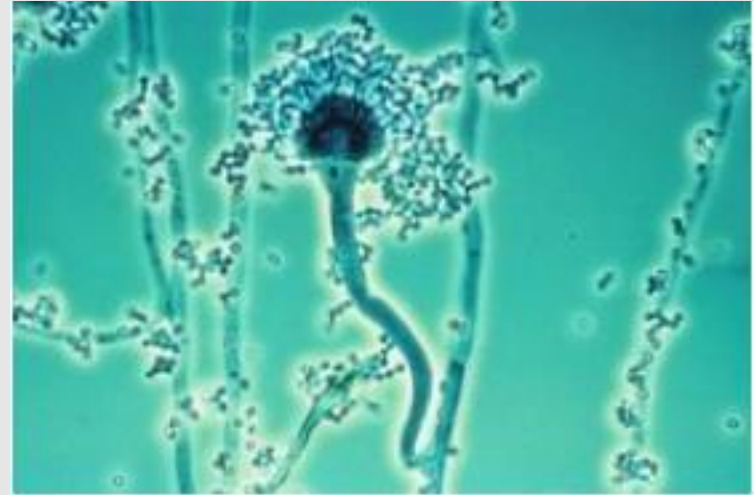
- Everybody inhales several hundred spores each day quickly eliminated in HC

- NO** relation between the intensity of exposure and the rate of sensitization to the fungus as measured by

kin

test

Not much can be done to reduce exposure



A. fumigatus and human disease: 3 distinct entities

Chronic pulmonary Aspergillosis

In patients with preexisting lung-cavities or damage

Hemoptysis, cough
Low grade fever

Invasive infection

In mildly immunodeficient patients

Most commonly kidney, liver, spleen,
and central nervous system

Pulmonary, nasal involvement

ABPA

In CF or asthma

Lung damage,
fibrosis, bronchiectasis

ABPA: therapeutic management (2003 consensus)

- **Anti-inflammatory: Glucocorticoids**

0.5-2 mg/kg/day for 1-2 weeks

0.5-2 mg/kg/evryother day for 1-2 weeks

Taper off within 2-3 months

- **Antifungal: Itraconazole-Sporanox**

Slow or poor response to corticosteroids, relapse, corticodependent or toxicity

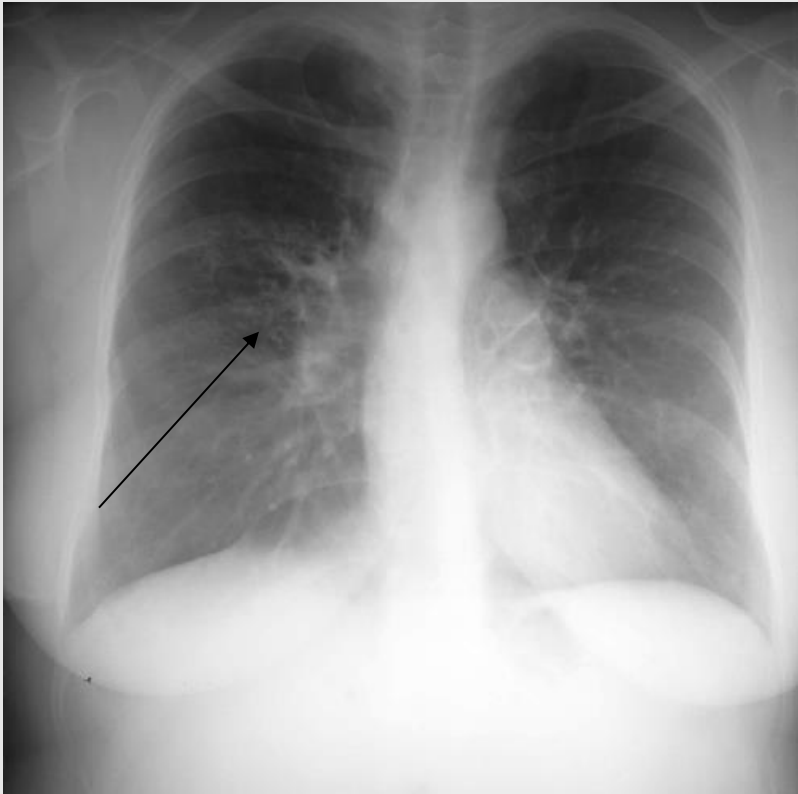
5 mg/kg/day, max 400 mg/day for 3-6 months

- **+/- Anti-IgE-Omalizumab**

If poor response to corticosteroids, relapse, corticodependent or toxicity

ABPA: radiographic criteria

- ☰ New or recent changes in chest radiograph/CT (infiltrate, mucous plugging)



CXR: bronchial wall thickening and impressive central bronchiectasis

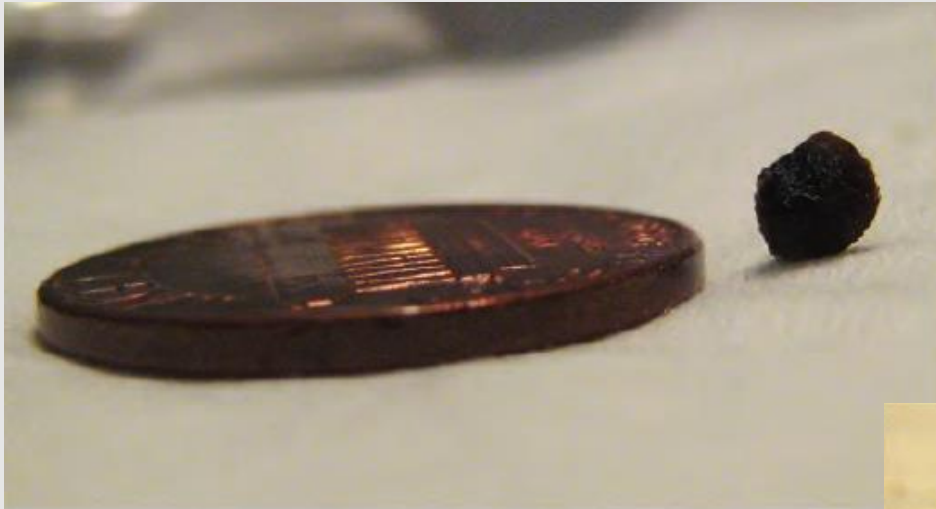


CT: varicoid and cystic central bronchiectasis in all 5 lobes and mucous plugging

ABPA: diagnostic criteria

- **Criteria for CF-ABPA were updated in 2003 (CFF)**

☞ Acute or sub acute clinical deterioration (cough, expectoration of **brownish mucous plugs**, hemoptysis)



ABPA: diagnostic criteria

- **Criteria for CF-ABPA were updated in 2003 (CFF)**

- Acute or sub acute clinical deterioration (cough, expectoration of brownish mucous plugs, hemoptysis)

- Serum total IgE > 1,000 UI/ml

- Immediate positive skin test to *A. fumigatus* >3 mm or positive specific IgE to *A. fumigatus*

- *A. fumigatus* positive precipitins or presence of anti-*A. fumigatus* antibodies

- New or recent changes in chest radiograph/CT (infiltrate, mucous plugging)

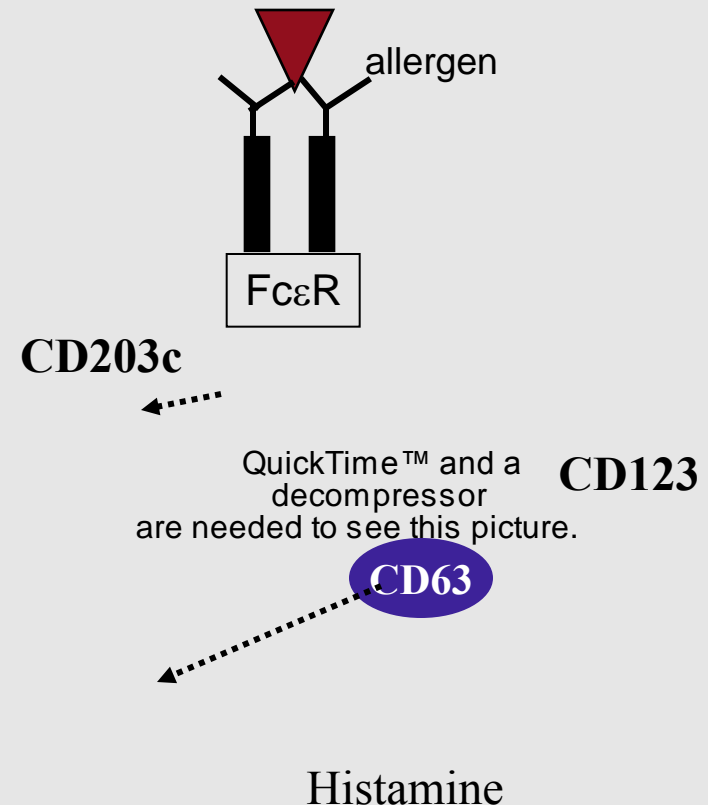
- Should be suspected if patient with pulmonary infiltrate or clinical deterioration that do not subside after one week of antibiotherapy

ABPA: questions

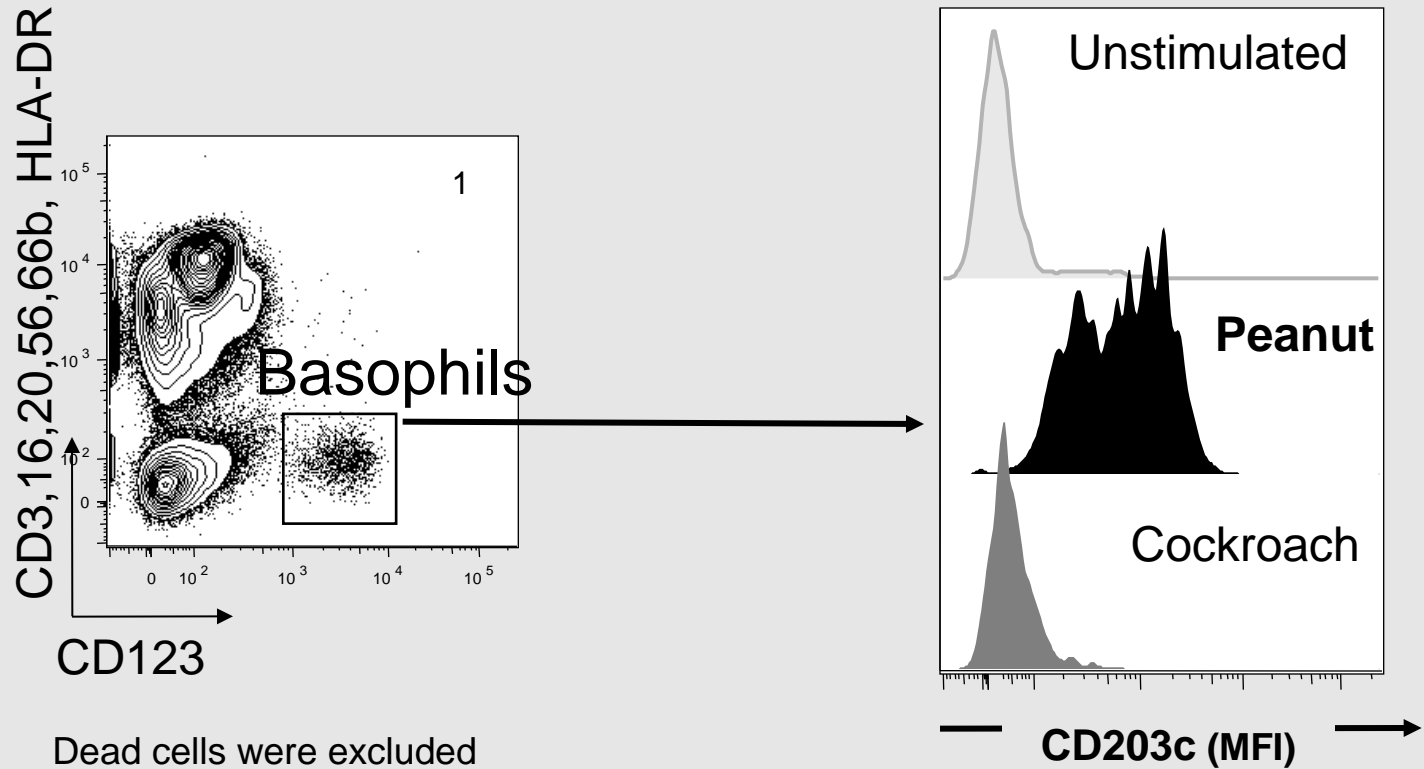
- **Unmet need for better diagnostic test, ideally:**
 - ☐ Blood-based (minimally invasive)
 - ☐ Will discriminate CF subjects with ABPA from CF subjects with stable Aspergillus colonization
 - ☐ Will provide objective, quantitative assessment of treatment response in patients under therapy

□ A basophil assay for CF-ABPA?

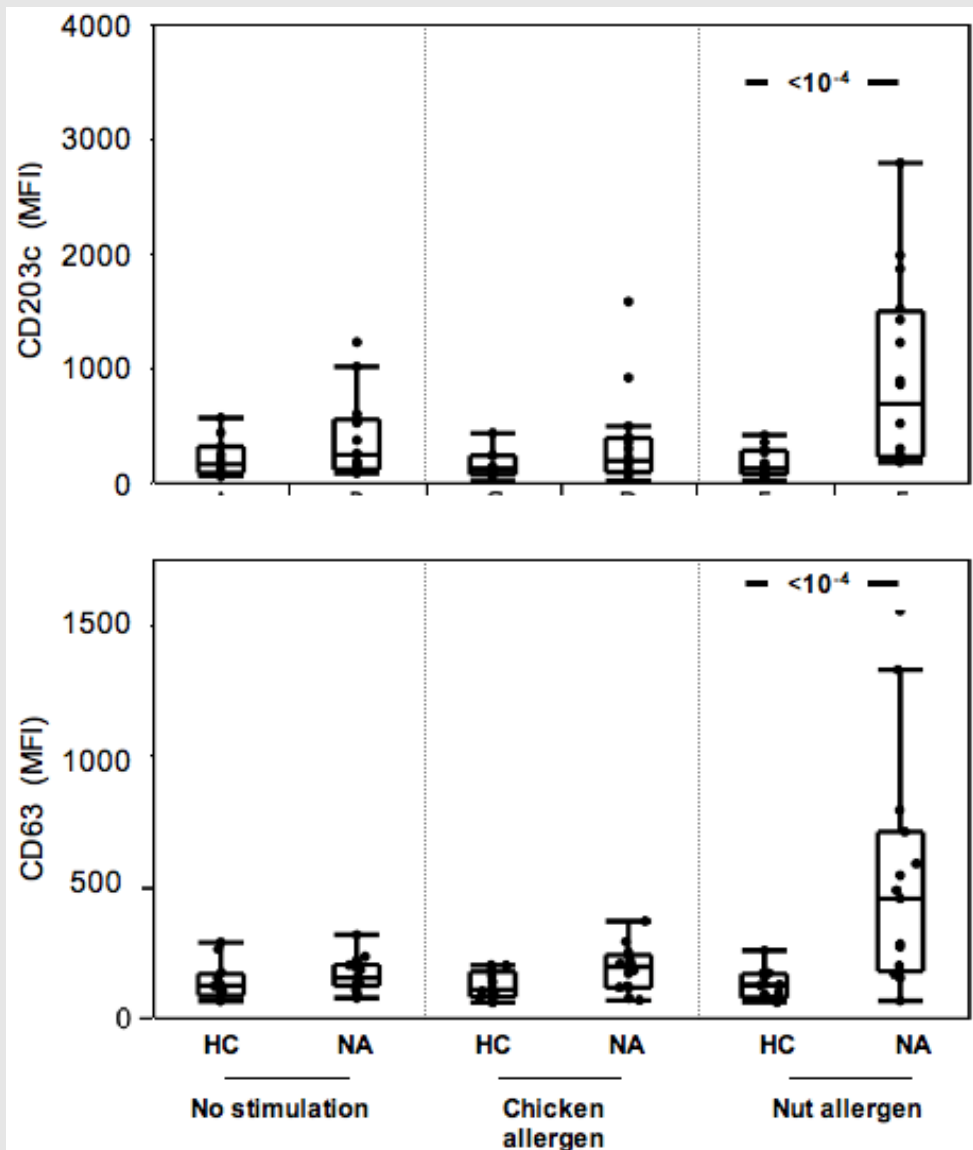
- Mediates the hypersensitivity type I: ALLERGY which is a key element in ABPA
- Represent less than 1% of total leukocytes (white cells in blood).
- Originate and develop in bone marrow from hematopoietic CD34+ stem cells
- Are released into circulation as mature cells (# from mast cells).
- Survival: 2-3 days (<< mast cells).



FACS analysis of basophils

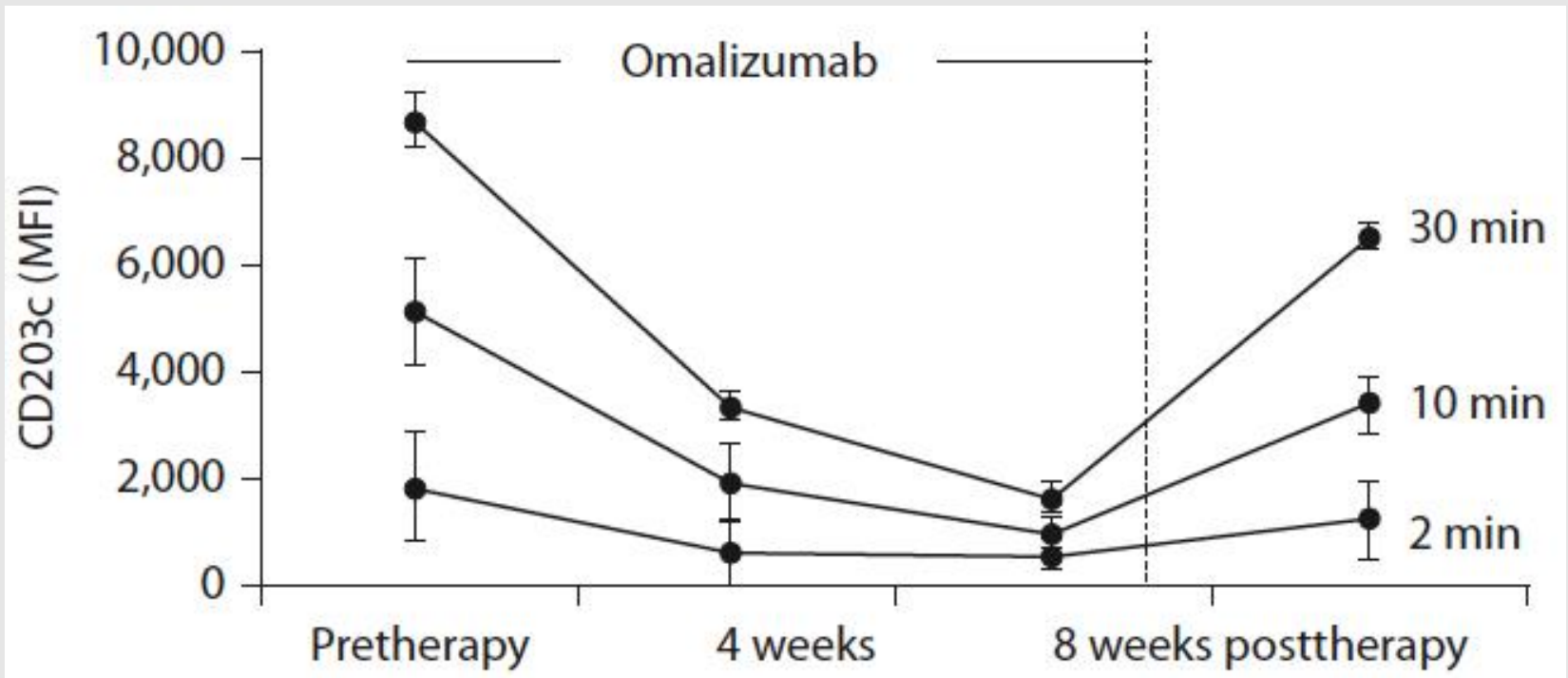


Basophil CD203c and CD63 in blood from patients with nut allergy could discriminate the allergic patient from the HC and could identify the offending food allergen



NA: patients with nut allergy
HC: Healthy controls

Anti-IgE therapy decreases basophil CD203c



Development of a FACS-based blood basophil assay for CF-ABPA

ONE DROP
OF WHOLE
BLOOD



Baseline

In vitro stimulation
within 10/30 minutes

Surface staining for
basophil CD203c and CD63

Fixation

FACS

- 4 groups of patients:

- 1) CF and ABPA
- 2) CF with *A. Fumigatus* in their sputum
- 3) CF patients (without ABPA/*A. fumigatus* colonization)
- 4) Healthy controls

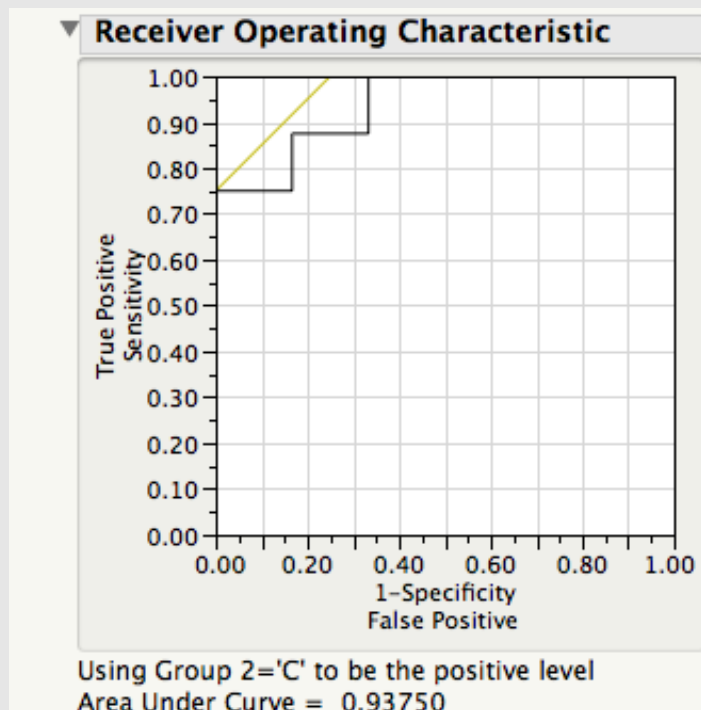


Basophil CD203c and CD63 in blood from CF subjects with ABPA, following a stimulation with the fungus

QuickTime™ and a
decompressor
are needed to see this picture.

Blood basophil CD203c levels were significantly increased in CF patients with ABPA following 10-minute of *ex vivo* activation with *A. Fumigatus* compared to the 2 other groups

Level of basophil CD203c, following stimulation with the fungus could distinguish CF subjects with ABPA from CF subjects with *Aspergillus* in their sputum



ROC Curve : Basophil CD203c could distinguish patients with CF and ABPA from CF patients with *A. Fumigatus* in their sputum (P=0.0039)

Question

In the group of CF patients with ABPA, was the increase of basophil CD203c specific to *A. fumigatus*?

Basophil CD203c and CD63 response in blood from 8 CF subjects with ABPA

QuickTime™ and a decompressor are needed to see this picture.

Blood basophil CD203c and CD63 levels were specifically increased in the sample from CF patients with ABPA following 10-minute of *ex vivo* activation with *A. fumigatus*

Ag1: offending allergen
Ag2: non offending allergen

ABPA project: Summary and future directions

High unmet needs for blood assays to both diagnose and monitor response to therapy and for new targeted therapies in patients with CF-ABPA

Our blood basophil CD203c assay could improve:

- the diagnosis of ABPA in Cf patients (CD203c following *ex vivo* stimulation)
- the monitoring of responses to therapy

Most important : **FAST, SAFE, EASY, REPRODUCIBLE**, appropriate for all ages,

ABPA project: Summary

Future goals

Study the interaction Fungus-host immune response
(sputum)

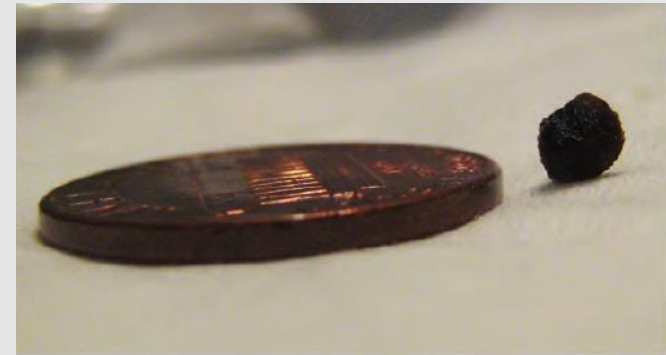
Collect additional samples to establish the value of this assay
as a new diagnostic blood assay, which, hopefully will be
beneficial
to CF patients

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**THANK YOU SO MUCH
to Kriss Benson**

For her review

**THANK YOU SO MUCH
to all the patients :)**

It could not be done without you

ABPA: Management (2003 consensus)

Table 9. Treatment recommendations for allergic bronchopulmonary aspergillosis (ABPA) in cystic fibrosis (CF).

Total serum IgE, IU/mL	Pulmonary symptoms and/or worsening PFT results	New infiltrates on CR or CT	Positive serology ^a	Treatment recommendation(s)
>1000 or >2-fold rise from baseline	Yes	Yes	Yes	Treat for ABPA
>1000 or >2-fold rise from baseline	No	No	Yes	No treatment; monitor IgE, CR, PFT
>1000 or >2-fold rise from baseline	No	Yes	Yes	Treat for CF-related infection; consider treatment for ABPA if no response
>1000 or >2-fold rise from baseline	Yes	No	Yes	Consider treatment for ABPA, CF-related infection, and/or asthma
>500 in the past; no change from baseline	Yes	Yes	Yes	Treat for CF-related infection; consider treatment for ABPA or asthma if no response
500–1000	Yes	Yes	Yes	Treat for ABPA

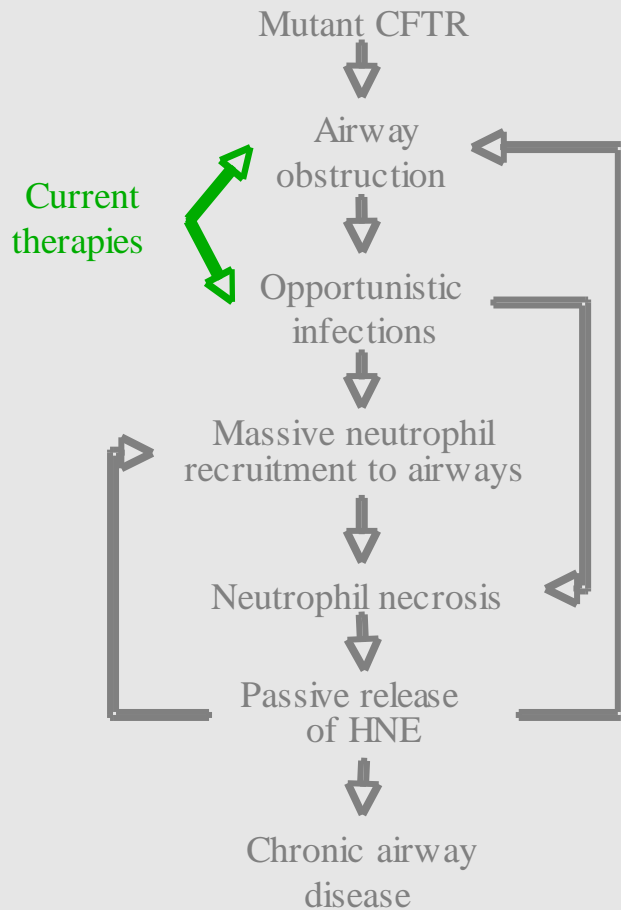
NOTE. CR, chest radiography; PFT, pulmonary function testing.

^a Aspergillus-specific IgG or IgE or presence of precipitins to *Aspergillus fumigatus*. Because these test results may not be available quickly, they are not required for initiation of therapy but should be obtained.

What about the sputum?

- **Measurement of the blood and airway neutrophils might provide
A better understanding of the pathology**

CF airway disease: conventional paradigm



Key assumptions

- Lung inflammation occurs late in the course of the disease
- Inflammation/obstruction is due to neutrophil death in the lung
- CF airway neutrophils are not functional

NEW DISEASE PARADIGM

Large numbers of viable neutrophils are present in CF sputum (airway)

