Allergic Fungal Sinusitis

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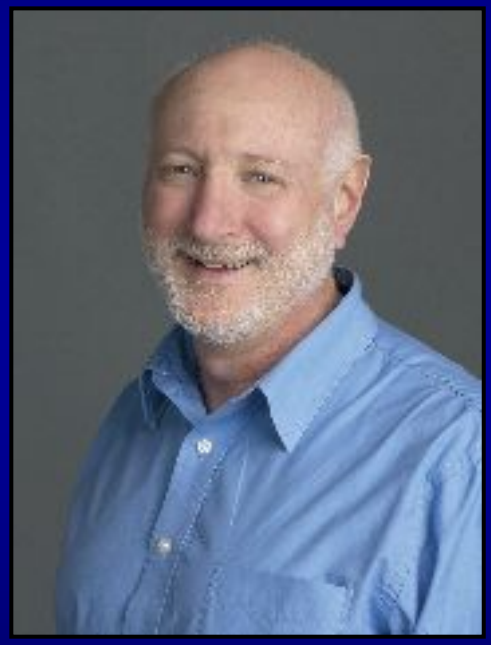
Disclosures/Conflicts of Interest

- None- over the years I have extricated myself from all “Speaker Bureaus,” Consultative Agreements, etc.

I want to thank Dr. Rick Moss of Stanford University



Invasive Fungal Rhinosinusitis

- Acute necrotizing fungal rhinosinusitis
- Chronic invasive fungal rhinosinusitis
- Granulomatous invasive fungal rhinosinusitis

Noninvasive Fungal Rhinosinusitis

- Fungal ball (sinus mycetoma)
- Allergic fungal rhinosinusitis (AFS)

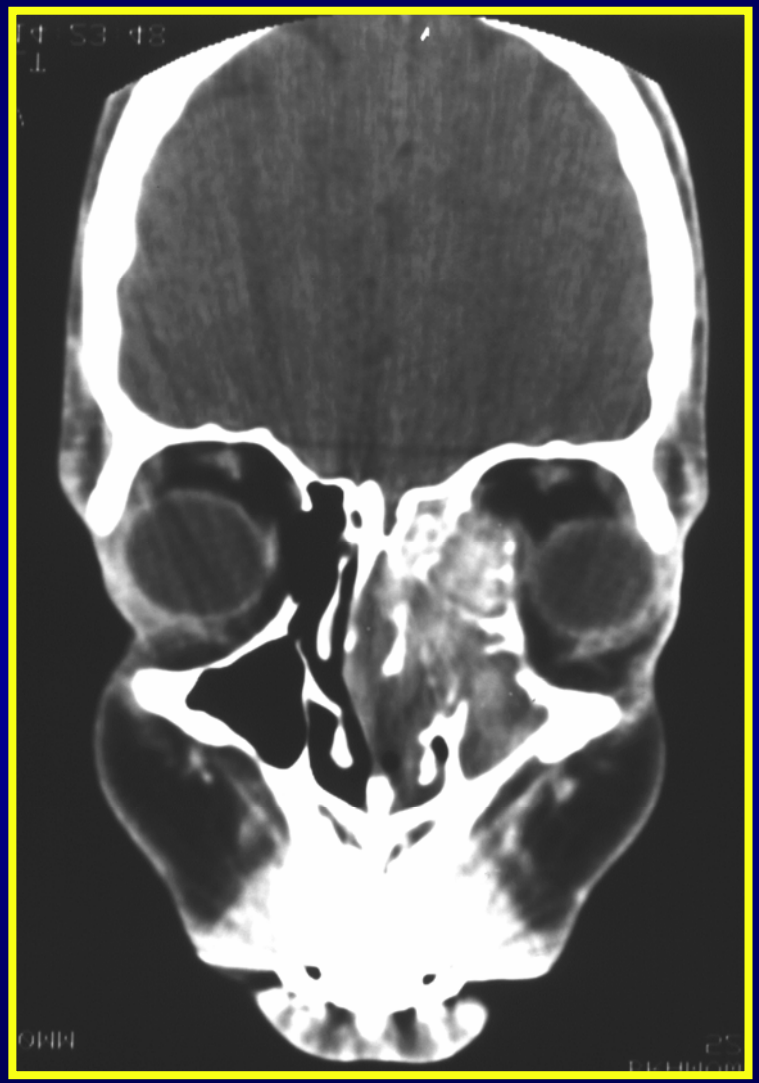
From: deShazo RD, Chapin K, Swain RE. N Engl J Med 1997;337:254-9.

“The Fungal Conundrum”

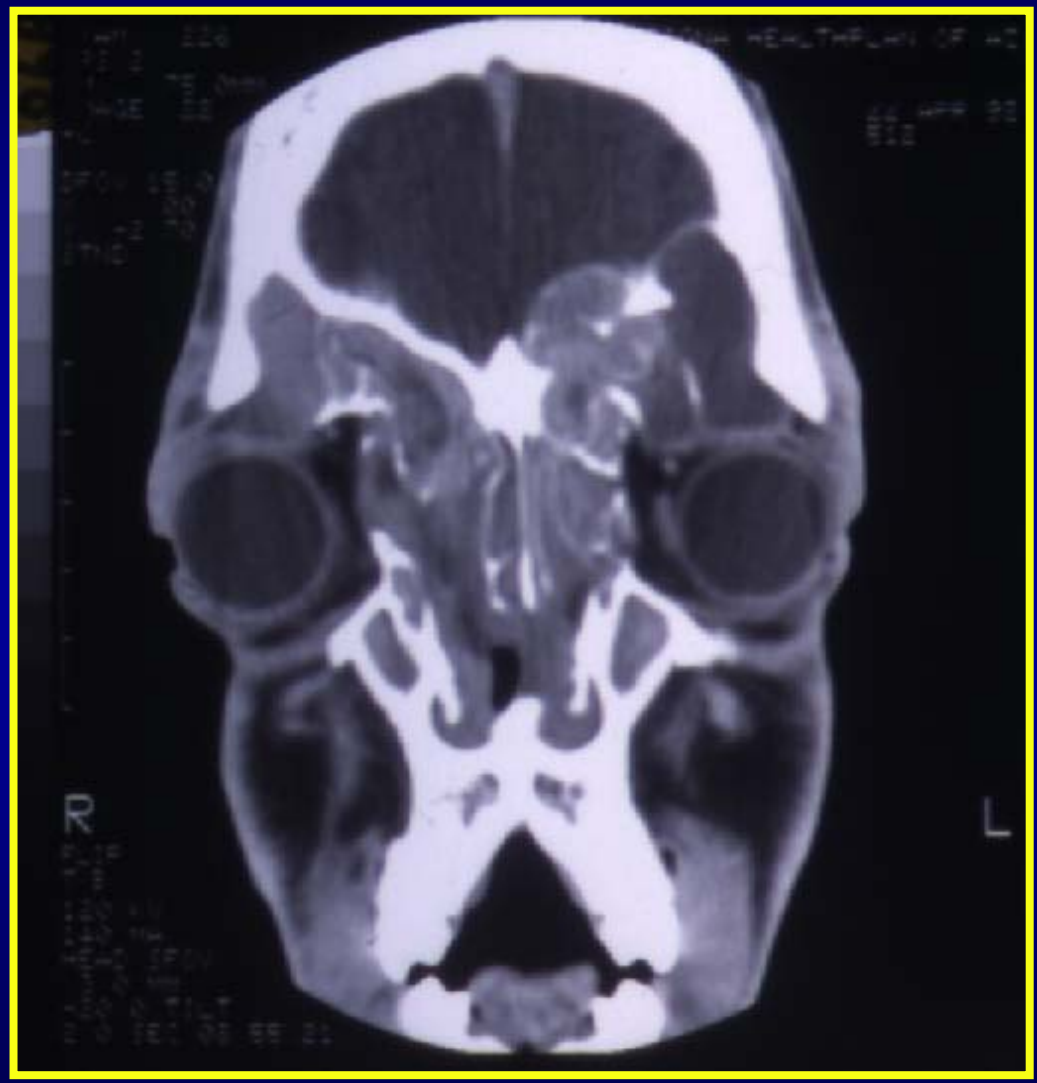
DeShazo R. *Ann Allergy Asthma Immunol* 2006:96:256-7.

Also see abstract #59 from this conference- Harrison, Descalmes, Smith, Gore, Denning, Bowyer.

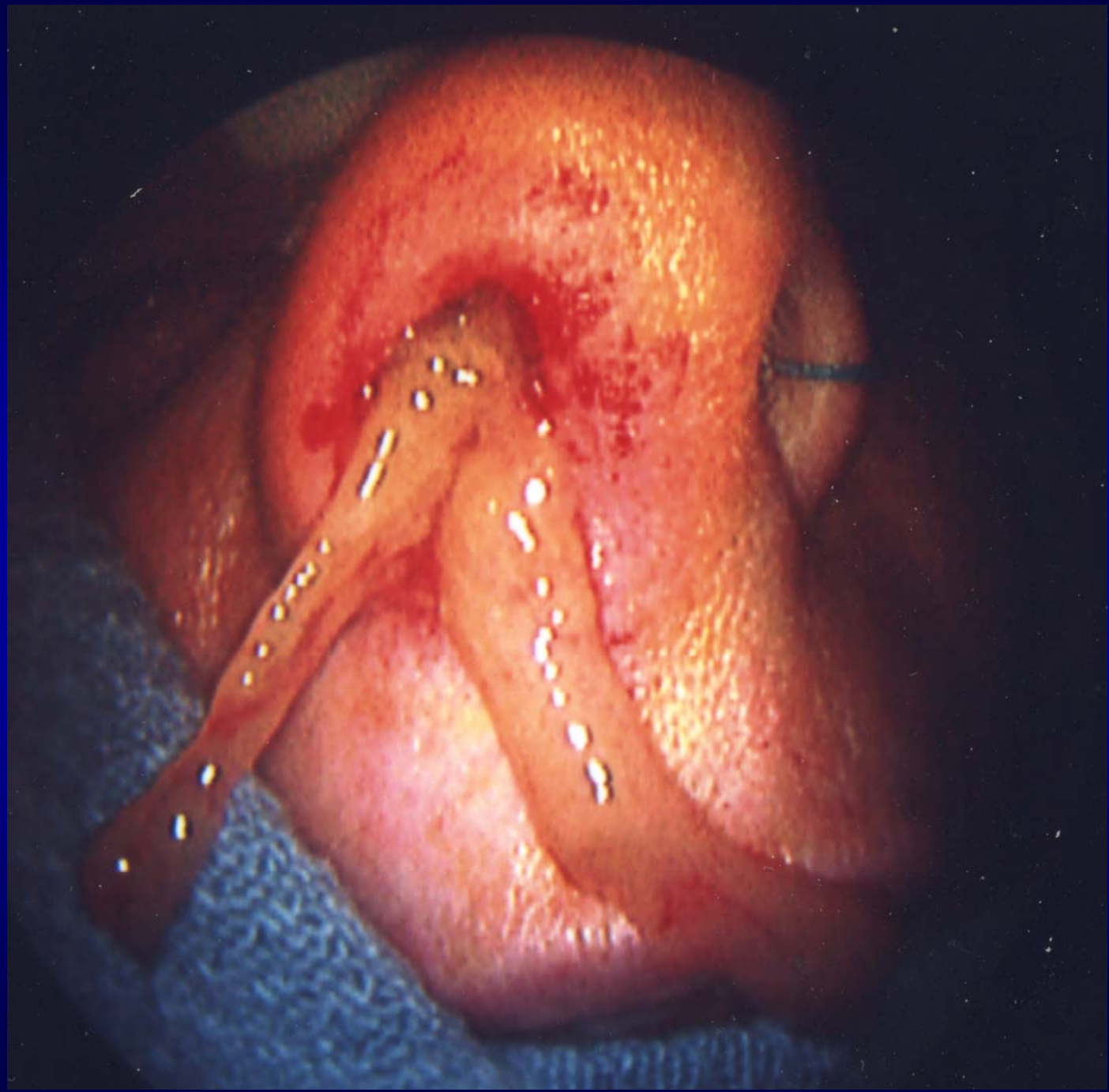
Allergic Fungal Sinusitis



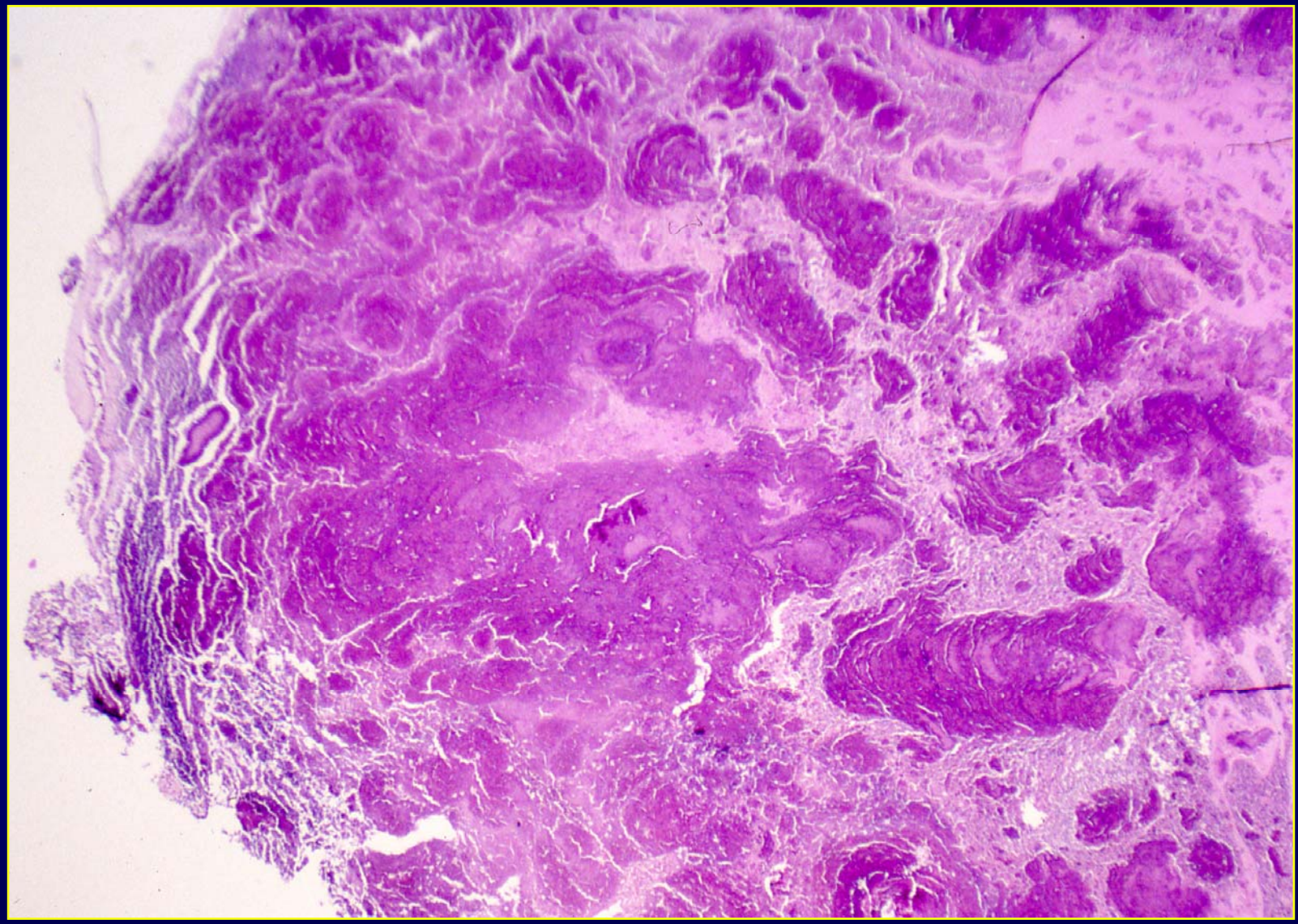
Patient 1



Patient 2

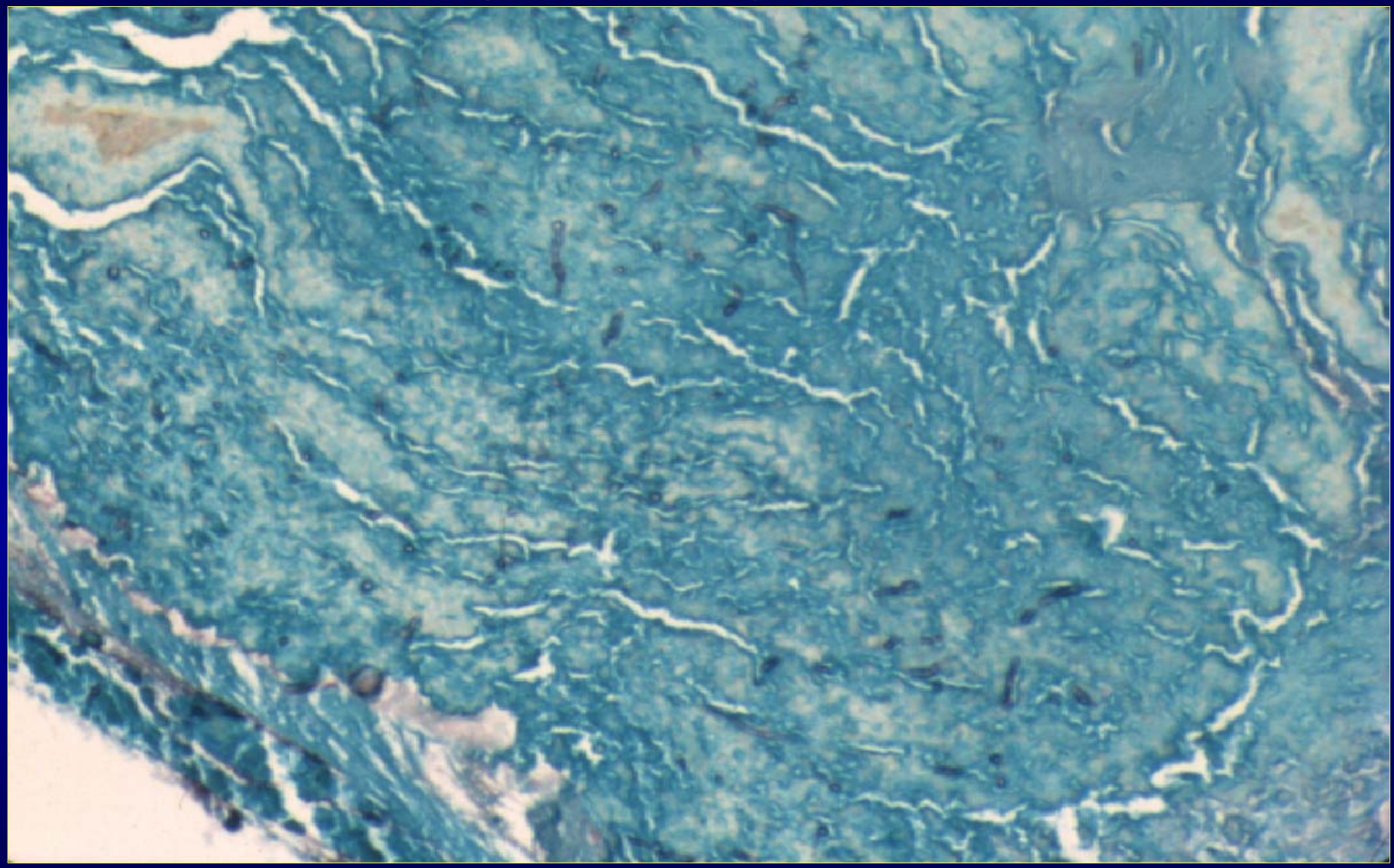


Allergic Mucin



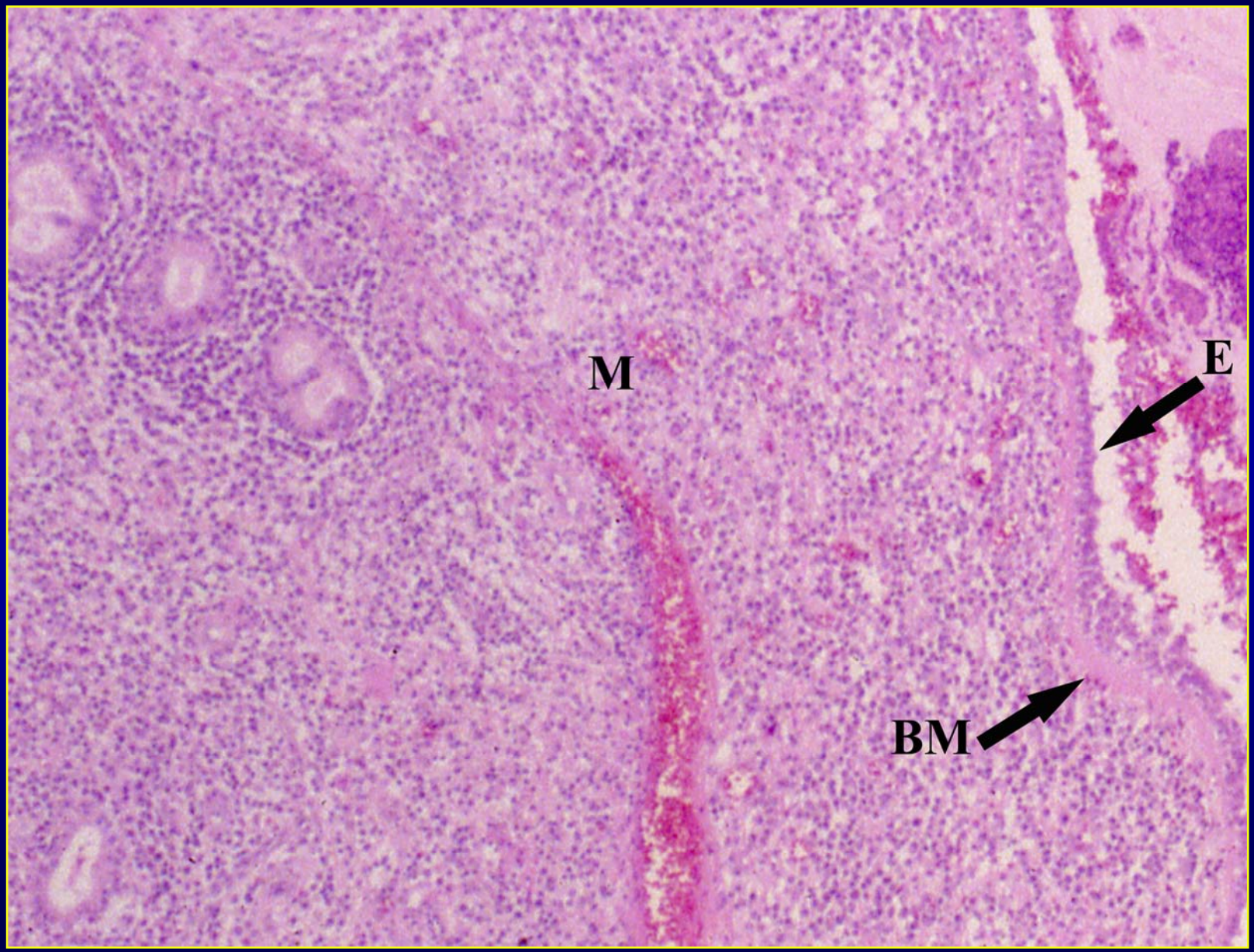
H&E stain, x40

Allergic Fungal Sinusitis



Sinus, allergic mucin- GMS stain, x100

Allergic Fungal Sinusitis Mucosa



H&E stain, x40

Allergic Fungal Sinusitis (1)

Clinical/Surgical Presentation

- Chronic rhinosinusitis with nasal polyps (also called “hypertrophic/hyperplastic sinus disease or HSD”, or “chronic rhinosinusitis or CRS”).
- Sinus CT hyperattenuation.
- Can be bi- or unilateral.
- Can erode through sinus bone margins into orbit or intracranium.

Allergic Fungal Sinusitis (2)

Clinical/Surgical Presentation (cont.)

- Characteristic “allergic mucin” (a sinus luminal peanut-buttery inspissate of massive numbers of pyknotic eosinophils) is seen grossly at surgery and further defined histopathologically.
- Allergic mucin is fungal stain positive for sparse scattered hyphae; non-tissue-invasive.
- Surgical sinus fungal culture positive.

Allergic Fungal Sinusitis (1)

Definitions/Findings

- Allergic/hypersensitivity response to the presence of fungi within the sinus cavity(s).
- All pts. are atopic- will be allergy skin test positive to multiple aeroallergens.
- All pts. will have specific IgE to the AFS etiologic fungus when properly identified by surgical culture.

From: Schubert MS, Goetz DW. *J Allergy Clin Immunol* 1998;102:387-394.

Allergic Fungal Sinusitis (2)

Definitions/Findings (cont.)

- Incidence- 6-9% of all surgical sinusitis.
- Southern and Southwestern U.S. are endemic, but has been reported throughout the country and world.
- Surgically recurrent.

From: Schubert MS, Goetz DW. *J Allergy Clin Immunol* 1998;102:387-394.

Allergic Fungal Sinusitis (3)

Definitions/Findings (cont.)

- Adults and children (mean age 33 y.o., range 8 y.o.- 67 y.o.).
- Nasal casts- 75%.
- Asthma- 64%.

From: Schubert MS, Goetz DW. *J Allergy Clin Immunol* 1998;102:387-394.

Allergic Fungal Sinusitis (4)

Definitions/Findings (cont.)

- Immunocompetent.
- HLA-DQB1*0301 and *0302 (other CRS HLA-DQB1*0301-0305).
- Analogous (but not identical) to allergic bronchopulmonary aspergillosis (ABPA).
- Dematiaceous fungi most common cause (e.g., *Bipolaris spicifera*), followed by *Aspergillus spp.*

From: Schubert MS, Goetz DW. *J Allergy Clin Immunol* 1998;102:387-394 and Schubert MS, et al. *J Allergy Clin Immunol* 2004;114:1376-83.

Minimum Required AFS Diagnostic Criteria (developed over 8 years and 67 consecutive AFS patients)

1) Characteristic "allergic mucin" must be seen: on surgical sinus histopathology or grossly at surgery.
2) Evidence for fungi- GMS (or similar) fungal stain must be positive for hyphae within the allergic mucin or surgical sinus fungal culture positive.
3) Characteristic sinus mucosal inflammatory infiltrate- small lymphocytes, plasma cells, eosinophils; no necrosis, granulomas, or fungal invasion.
4) Other fungal diseases are excluded.

From: Schubert MS, Goetz DW. *J Allergy Clin Immunol* 1998;102:387-394.

An Additional AFS Conditional Diagnostic Criterion (1)

From: Meltzer EO, Hamilos DL, Hadley JA, et al. *J Allergy Clin Immunol* 2004; 114(6 Suppl.):155–212.

- Evidence of fungal-specific IgE to the etiologic fungus.

Why Is This A Conditional Dx Criterion?

1) Requires a positive surgical sinus fungal culture that accurately identifies the etiologic fungus (problem #1: 15% fungal culture negative rate despite histopathological confirmation of AFS; problem #2: What if no culture sent? Can still diagnose AFS by the minimum required histopathological criteria).

2) No skin test or RAST commercially available for some of the known published AFS etiologic fungi, like *Exserohilum rostratum*. AFS still diagnosed by minimum required criteria.

RE: The Additional AFS Conditional Diagnostic Criterion (cont.) (2)

(Demonstration of fungal-specific IgE to the etiologic fungus)

Where Is This Conditional Dx Criterion Most Valuable?

- If allergic mucin seen on histopath., and fungal stain negative, but fungal culture positive due to nasal contamination or colonization: fungal-specific IgE will be negative to cultured fungus. Cannot diagnose AFS. Dx is "eosinophilic mucin rhinosinusitis" (EMRS). If pt. is non-atopic, cannot be AFS. If pt. is atopic, Dx is EMRS and "AFS candidate."

From: Schubert MS. *Clin Rev Allergy Immunol* 2006;30:205-216.

ABPA And AFS Compared

	ABPA	AFS
• allergic mucin with noninvasive fungal hyphae	yes	yes
• respiratory atopy	yes	yes
• allergy skin test positive to fungal organism	yes	yes
• total serum IgE elevated	yes	yes
• fungal-specific IgG elevated	yes	yes
• fungal-specific IgE elevated beyond common atopy	yes	no
• serum precipitins to fungal organism	yes	no
• peripheral eosinophilia	yes	no/yes
• change in total serum IgE prognostic	yes	yes

From: Schubert MS, Goetz DW. *J Allergy Clin Immunol* 1998;102:387-394, and 395-402.

ABPA And AFS Compared (cont.) (2)

	ABPA	AFS
• MHC class II association	yes[a]	yes[b]
• Favorable clinical response to systemic corticosteroids	yes	yes

[a] HLA-DR2 and DR5; DQ2 was found to be protective.
From: Chauhan B, Santiago L, Hutcheson PS, et al. *J Allergy Clin Immunol* 2000;106:723-9.

[b] HLA-DQB1*0301 and *0302.
From: Schubert MS, Goetz DW. *J Allergy Clin Immunol* 1998;102:387-394, and 395-402.
C From: Schubert MS, Goetz DW. *J Allergy Clin Immunol* 1998;102:395-402.

DX	Total IgE	SEA-IgE	SEB-IgE	SEC-IgE	SED-IgE	TSST-IgE	# Positive
EMRS	13	0	0	0	0	0	0
CRS	25	0	0	0	0	0	0
AFS	28	0	0	0	0	0	0
CRS	29	0	0	0	0	0	0
CRS	32	0	0	0	0	0	0
AFS	38	0	0	0	0	0	0
AFS	43	0	0	0	0	0.36	1
AFS	44	0	0	0	0	0	0
EMRS	44	0	0	0	0	0	0
SAM	46	0	0	0	0	1.22	1
AFS	50	0	0	0	0	0	0
EMRS	50	0	0	0	0	0	0
AFS	71	0	0	0	0	0	0
SAM	72	0	0	0	0	0	0
AFS	81	0	0	0	0	0	0
AFS	85	0	0.76	0.66	0	0	2
AFS	96	0	0	0	0	0	0
CRS	96	0	0	0.52	0	0	1
SAM	98	0	0	0	0	0.38	1
EMRS	99	0	0	0	0	0	0
AFS	114	0	0	0	0	0	0
AFS	125	0	0	0	0	0	0
EMRS	151	0	0	0	0	0	0
AFS	162	0	0	0	0	0	0
AFS	166	0	0	0.36	0	0	1
SAM	180	0	0	0	0	1.22	1
CRS	183	0	0	0.41	0	0.75	2
SAM	189	0	0	0	0	0	0
AFS	197	0	0	0	0	0	0
CRS	197	0	0	0	0	0.57	1
AFS	212	0	0	0	0	0	0
AFS	258	0	0	0	0	0	0
CRS	258	0	0	0.46	0	0.38	2
AFS	284	0	0	0	0	0	0
EMRS	288	0	0	0	0	0	0
AFS	294	0	0	0	0	0	0
AFS	336	0	0	0	0	0	0
AFS	366	0.62	0	0	0	0	1
AFS	387	0	0	0	0	0	0
SAM	400	0	0	0	0	0.37	1
AFS	421	0	0.57	0	0.57	0	2
AFS	426	0	0	0	0	0.6	1
EMRS+	453	0	0.88	0.42	0	8.7	3
CRS	512	0	0	0	0	0.76	1
AFS	521	0	0	0	0	0	0
AFS	574	0	0	0	0	0	0
AFS	588	0	0.41	0	0	0	1
AFS	588	0	0	0	0	0	0
AFS	595	0	0	0.36	0	0	1
AFS	624	0.41	1.37	1.19	0.71	0	4
CRS	658	0	0	0	0	0	0
EMRS	667	0	0	0	0	1.24	1
AFS	673	0	0	0.65	0	0	1
CRS	712	0	0	0	0	0.63	1
EMRS	816	0	0	0	0	0	0
AFS	886	0	0	0	0	0	0
AFS	906	0	0.92	0	0	0.86	2
CRS	954	0	0.94	0	0	0	1
AFS	1075	0.36	0.71	0.43	0.35	0	4
AFS	1173	0.63	0.45	0.82	0	1.08	4
AFS	1348	0.36	2.23	5.56	1.73	0.4	5
AFS	1571	0.48	0	1.55	0	1.56	3
AFS	1948	0.49	3.93	1.91	1.63	0.51	5
AFS	3535	0.35	0	0.68	0	0.56	3
AFS	4890	1.51	1.86	3.7	0.7	0.72	5
AFS	6613	2.69	1.37	3.42	0.59	0.56	5
AFS	6740	0.47	0.47	1.49	0.4	0.68	5

Hutcheson PS, Oliver DA, Schubert MS, Slavin RG. The association of total IgE and specific IgE anti-staphylococcal enterotoxin with chronic hyperplastic rhinosinusitis. *J Allergy Clin Immunol* 2006;117:S71.

Allergic Fungal Sinusitis Treatment

- Aggressive sinus surgery.
- Antihistamines.
- Topical corticosteroids.
- Consider antileukotrienes.

From: Schubert MS. *Ann Allergy Asthma Immunol* 2000;85:90-101.

Allergic Fungal Sinusitis Treatment (cont.)

(2)

- Allergen immunotherapy (etiologic mold may be included).
- Oral corticosteroids (OCS)- modified ABPA OCS or similar protocol (pre-op, intra-op, or ASAP post-op).
- Close medical-surgical cooperation and F/U.
- Monitor total serum IgE post-op.

From: Schubert MS. *Ann Allergy Asthma Immunol* 2000;85:90-101.

Allergic Fungal Sinusitis Treatment (cont.)

- Systemic antifungals (oral, parenteral) - not felt to be effective.
- Topical antifungals - not adequately studied yet; does make sense.
- Anti-IgE???

AFS oral corticosteroid (OCS) protocol

- Start post-operatively ASAP:
  - 0.5 mg prednisone/kg q AM for 2 weeks, then 0.5 mg/kg every other AM for 2 weeks with gradual taper to 7.5-5 mg prednisone every other AM by 3 months and continue on this dose.

From: Schubert MS, Goetz DW. *J Allergy Clin Immunol* 1998;102:387-394, and 395-402.

AFS OCS protocol (cont.)

- Short “burst” of prednisone for any intercurrent acute rhinosinusitis episodes (with or without antibiotics as indicated).
- Discontinue prednisone at 1 year, sooner, or later, as indicated.
- If AFS surgically recurrent- restart OCS form time “zero” and repeat.

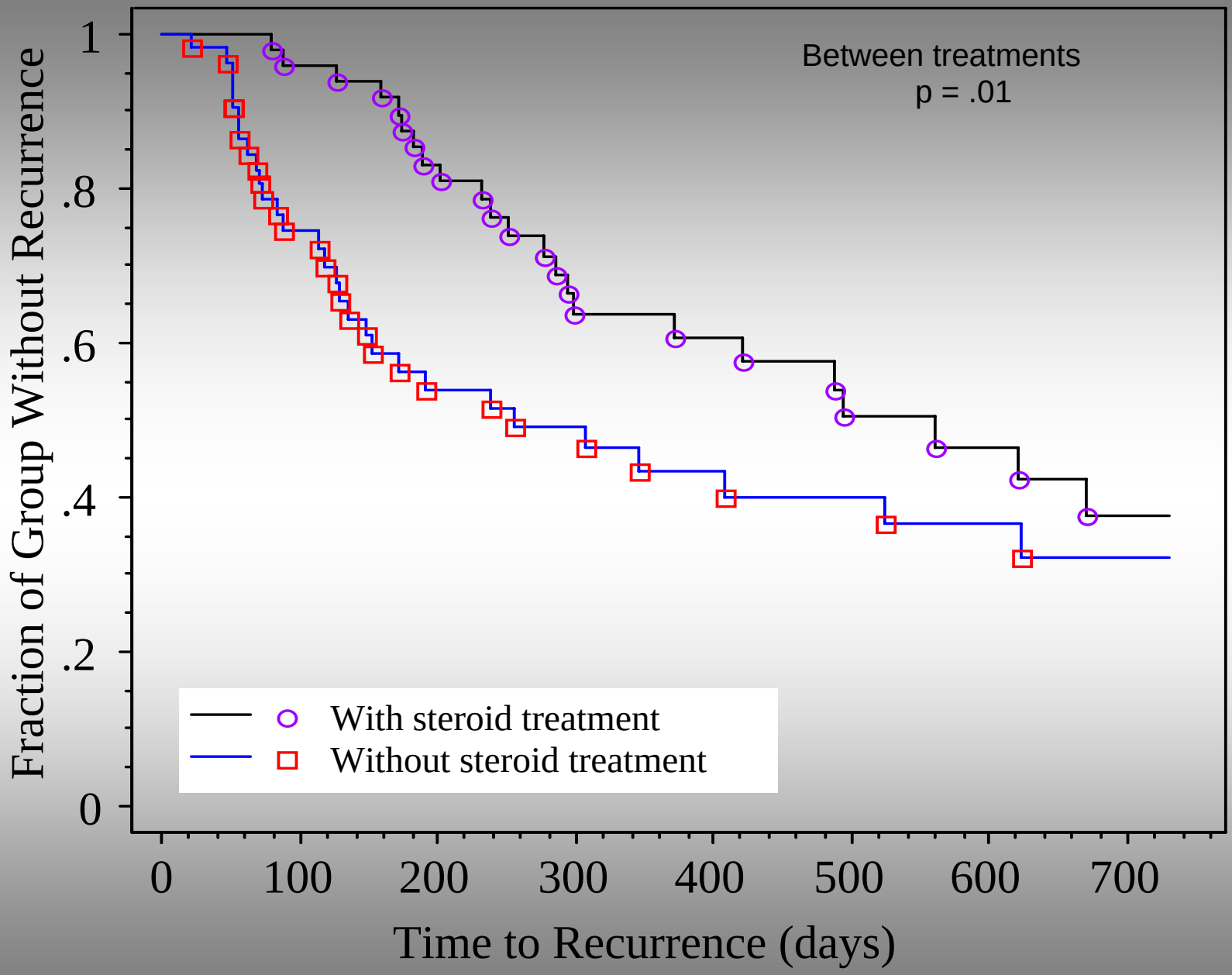
From: Schubert MS, Goetz DW. *J Allergy Clin Immunol* 1998;102:387-394, and 395-402.

Allergic Fungal Sinusitis

Treatment Conclusions

- OCS significantly reduced rhinosinusitis symptoms and helped to forestall the need for recurrent sinus surgery.
- No significant side effects were seen with this AFS OCS protocol.
- Changes in both total serum IgE and fungal-specific IgG levels correlated with clinical status.

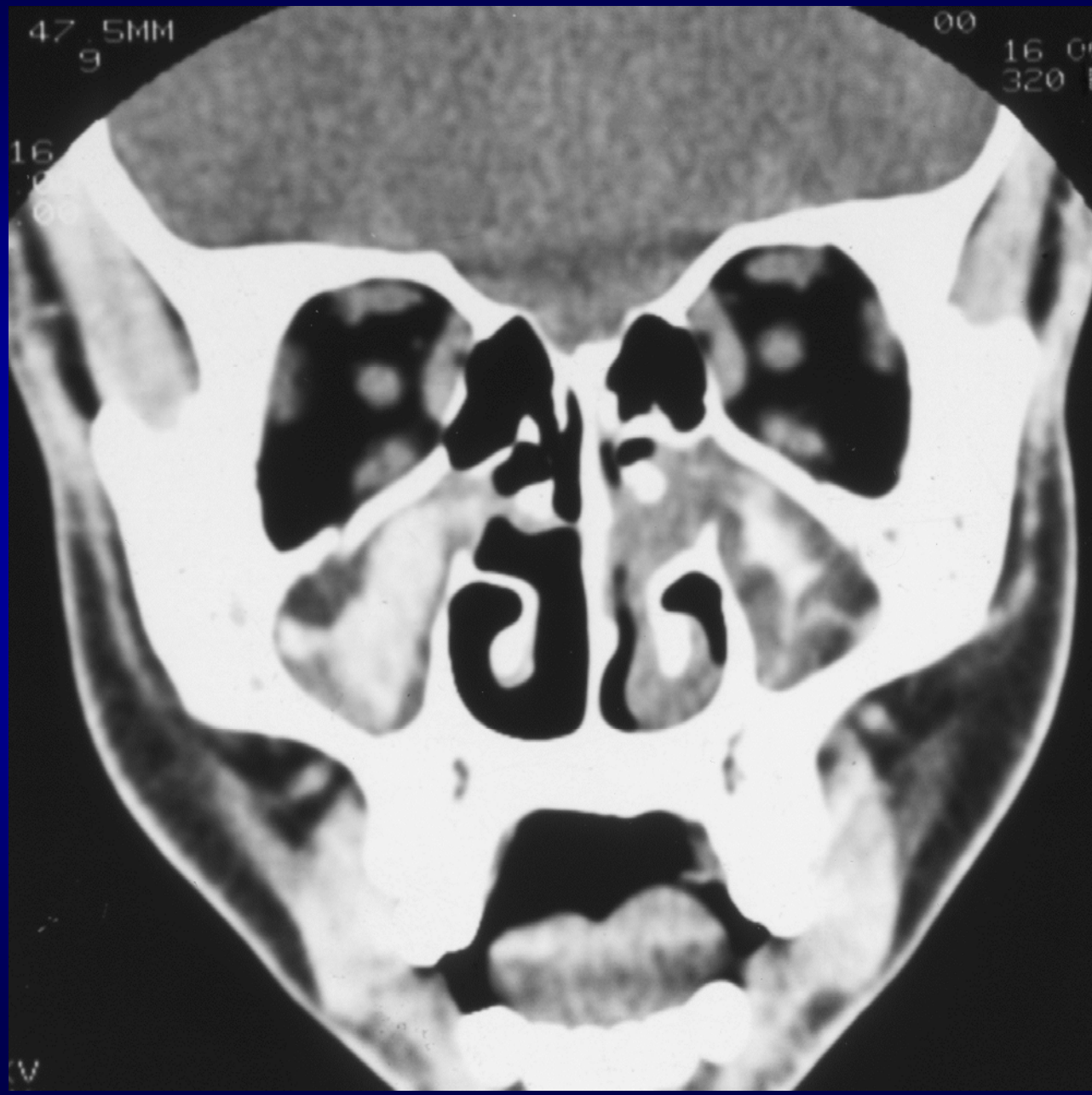
From: Schubert MS, Goetz DW. *J Allergy Clin Immunol* 1998;102:387-394, and 395-402.



From: Schubert MS, Goetz DW. *J Allergy Clin Immunol* 1998;102:395-402.

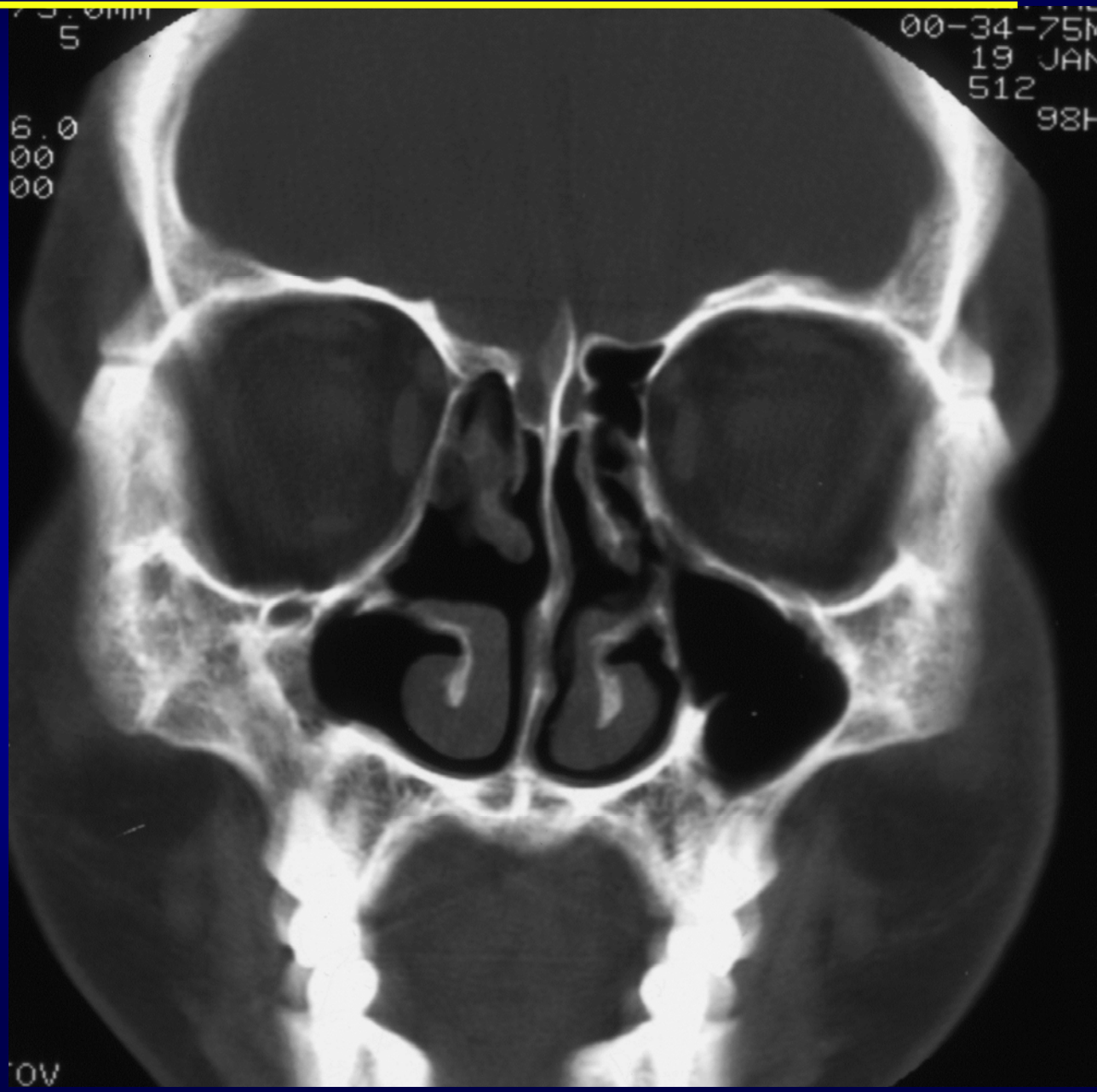
AFS Pre-RX

- 17 y.o. male.
- 3 prior surgeries.
- *Bipolaris spicifera* cultured from previous surgeries.
- Failed 6 mos. oral itraconazole.



AFS Post-RX (3 year F/U)

- Underwent surgery #4.
- Given AFS OCS protocol for 1 yr.
- Topical steroids, antihistamines.
- Allergen IT to all relevant aeroallergens.



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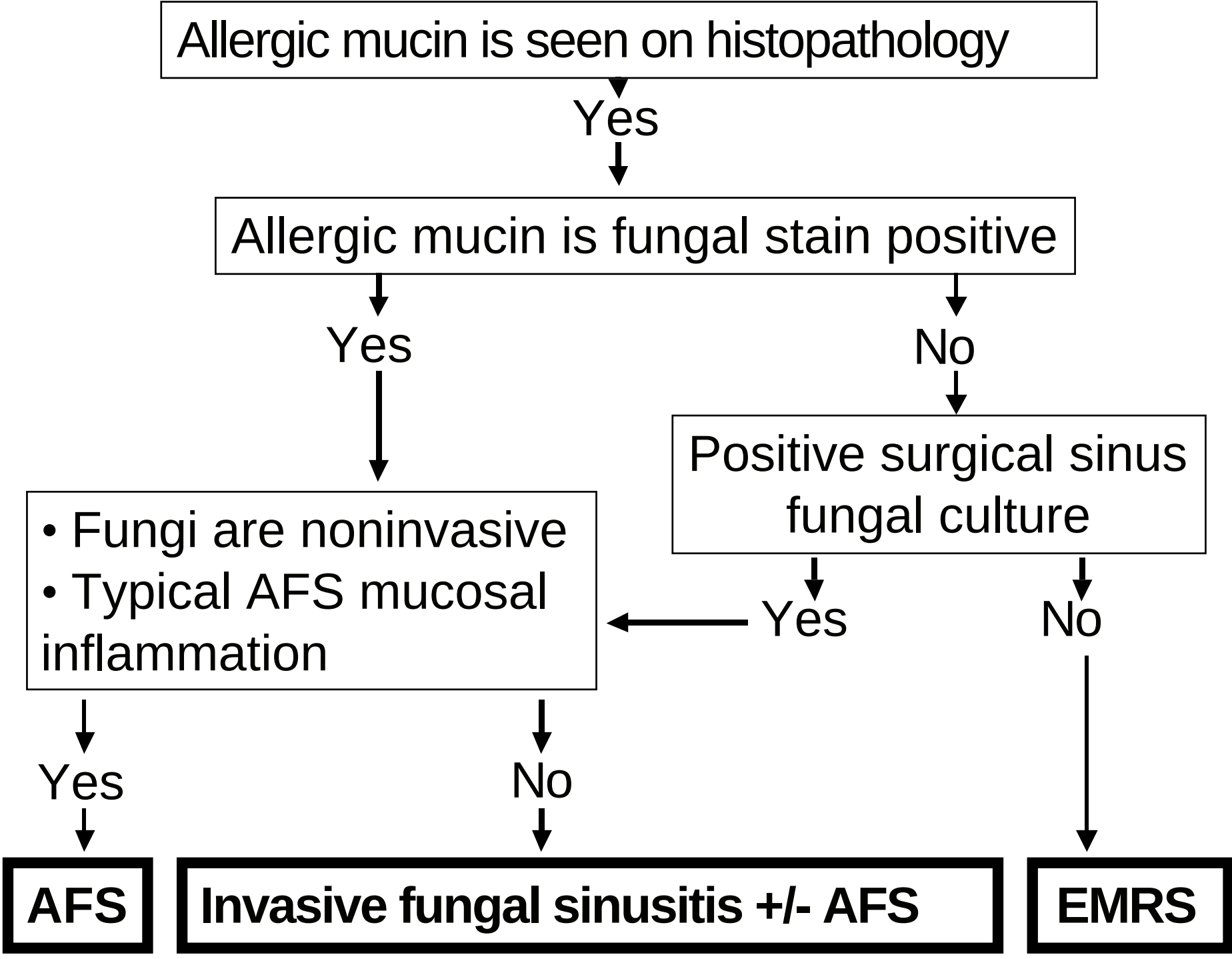
Diagnostic Surgical Sampling Issues Facing The Practicing Physician

- AFS diagnostic option #1: Characteristic allergic mucin is seen on surgical sinus histopathology AND positive fungal stain, or if stain negative due to sampling error, a positive culture.

- AFS diagnostic option #2: Characteristic allergic mucin is NOT seen on surgical sinus histopathology due to sampling error BUT is seen grossly at surgery and culture positive.

From: Schubert MS, Goetz DW. *J Allergy Clin Immunol* 1998;102:387-394.


Allergic mucin is seen on histopathology
Yes
Allergic mucin is fungal stain positive
Yes
No
• Fungi are noninvasive
• Typical AFS mucosal inflammation
Positive surgical sinus fungal culture
Yes
No
Yes
No
AFS
Invasive fungal sinusitis +/- AFS
EMRS

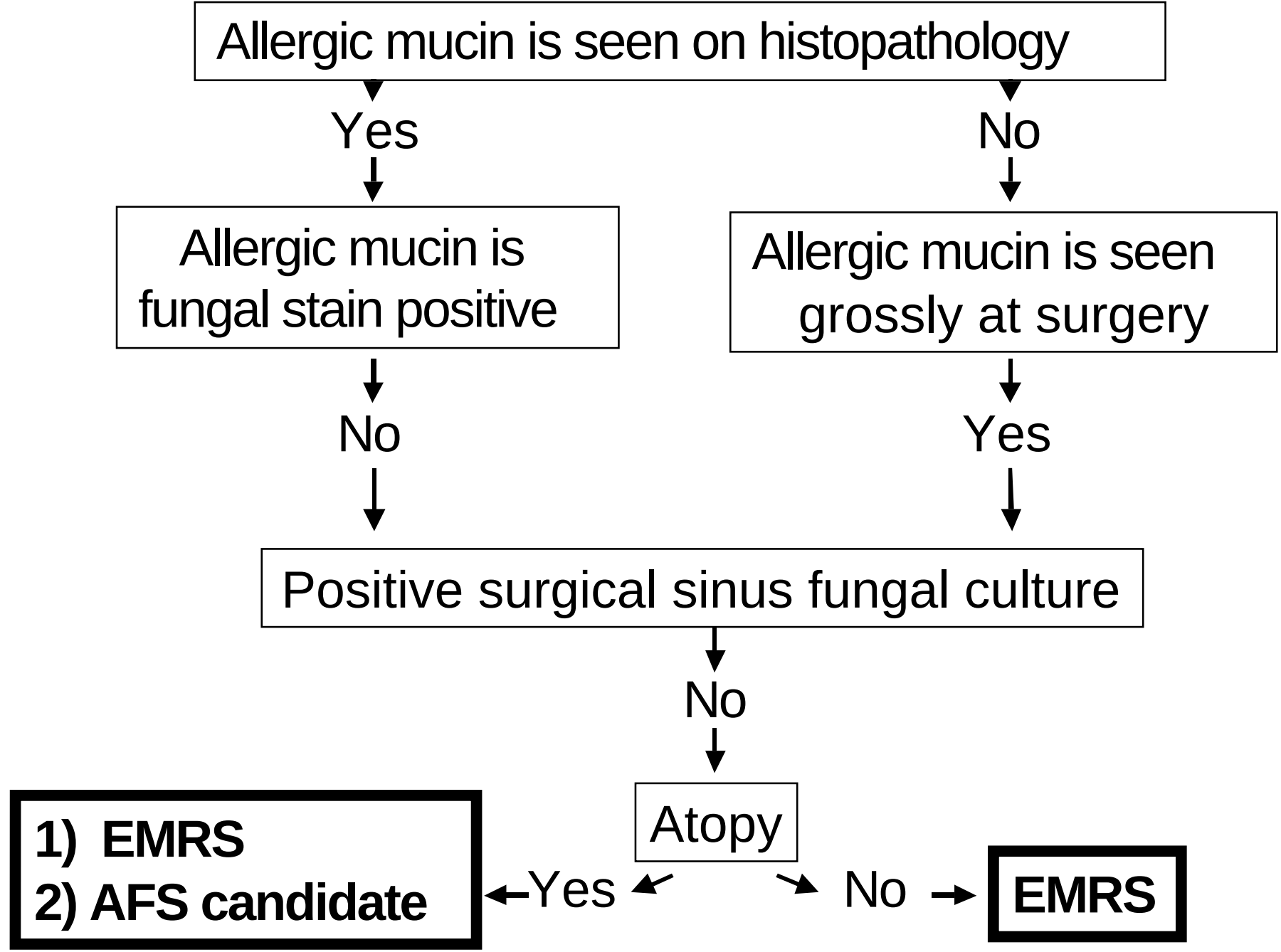

Allergic mucin is seen on histopathology
Yes
No
Allergic mucin is fungal stain positive
Allergic mucin is seen grossly at surgery
No
Yes
Positive surgical sinus fungal culture
No
Atopy
1) EMRS
2) AFS candidate
Yes
No
EMRS

Fig. 3.

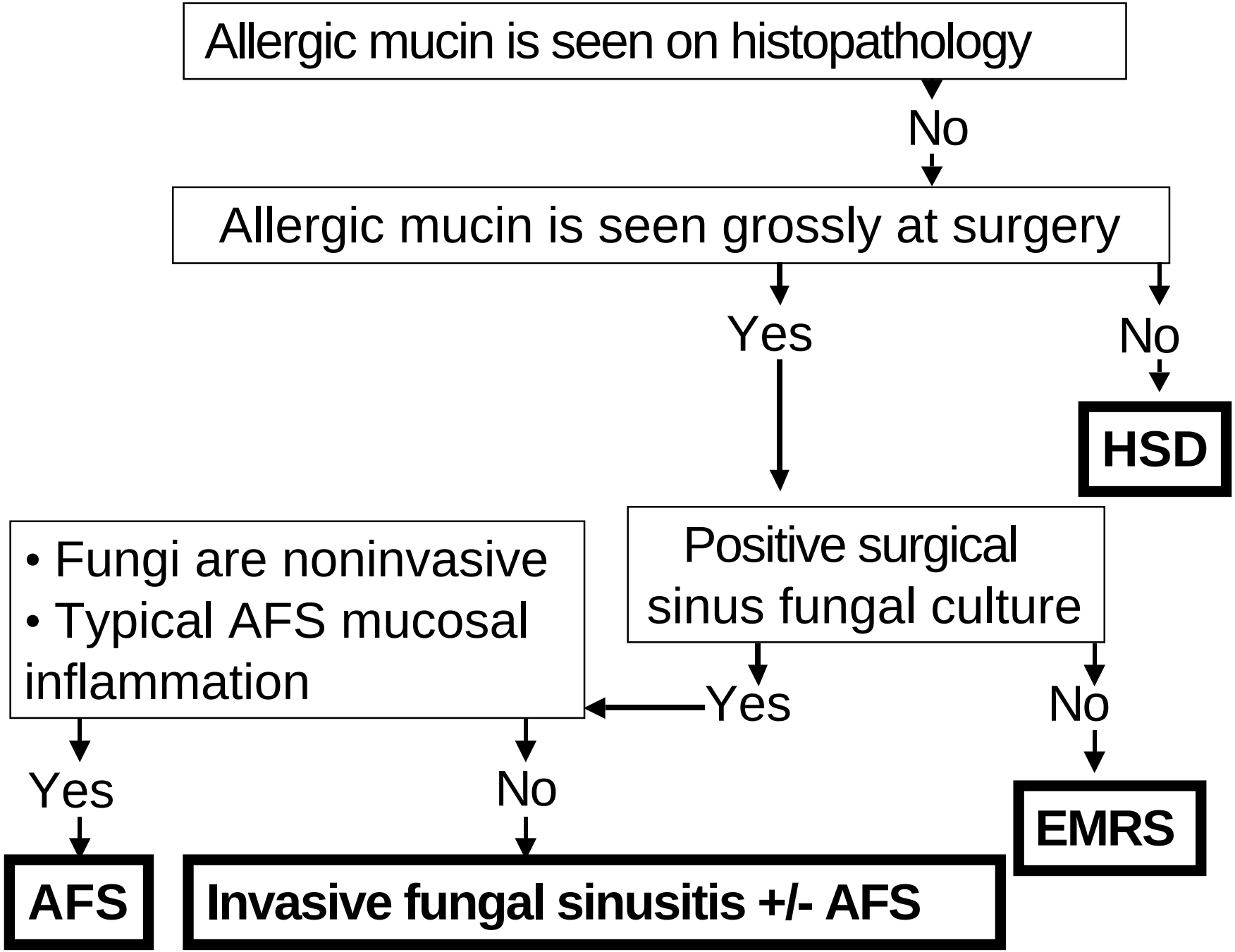

Allergic mucin is seen on histopathology
No
Allergic mucin is seen grossly at surgery
Yes
No
HSD
Positive surgical sinus fungal culture
Yes
No
• Fungi are noninvasive
• Typical AFS mucosal inflammation
Yes
No
EMRS
AFS
Invasive fungal sinusitis +/- AFS

Fig. 4.