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AR prevalence and epidemiology

- **Adults**
  - prevalence based on NHANES II (based on skin testing)
    - 15-18% of white population
  - higher rates in African-Americans and Latino populations

- **Children**
  - prevalence appears to be increasing
  - prevalence of AR 3x greater than that of asthma

- The vast majority of patients with asthma have rhinitis.

## Allergic rhinitis: pathophysiology

<table>
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<th>Sensitization</th>
<th>genetic susceptibility</th>
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<td>mucosal allergen exposure</td>
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<tr>
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<td>involves dendritic cells, CD4 T cells</td>
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| Immediate allergic response (IAR)                  | primarily involves mast cell |
| (15 minutes)                                       | degranulation, release of: |
|                                                   | histamine, PGD2, LTs, tryptase, |
|                                                   | preformed cytokines (IL-4, -5, -6) |

| Late allergic response (LAR)                        | primarily involves basophil |
| (4-8 hours later)                                   | degranulation (little release of PDG2) |
|                                                   | and |
|                                                   | influx of CD4 T cells, eos, eos/basophil |
|                                                   | progenitor cells (CD34^+/IL-5Rα^+) |
Allergic Rhinitis: the basics

Immediate phase response - within 15 minutes
- sneezing
- nasal itch
- runny nose/nose blowing
- nasal congestion

Late phase response - 6 - 24 hours later
- runny nose/nose blowing/postnasal drainage
- nasal congestion

Symptoms can be reproduced by:
- nasal allergen challenge
- environmental chamber unit
- high-intensity natural exposure (“park study”)
- natural exposure (“open trial”)
Allergic Rhinitis: Mediators

Mast Cell Degranulation:

- **Histamine**: Itching, Sneezing, Cholinergic glandular secretion
- **PGD$_2$**: Increased Vasodilation & Vascular Permeability
- **LTC$_4$, LTD$_4$, LTE$_4$**: Increased Vasodilation & Vascular Permeability (causing rhinorrhea, nasal congestion but not sneezing)

### Preformed mediators
- Histamine
- Proteases

### Newly formed mediators
- Cys LTs, PGs, PAF
- Bradykinin
- TNF-$\alpha$, GM-CSF
Late phase cellular constituents

**Cellular Infiltration/Inflammation**

- **Eosinophil**
  - CysLTs, GM-CSF, TNF-α, IL-1, IL-3, PAF, ECP, MBP

- **Basophil**
  - Histamine, CysLTs, TNF-α, IL-4, IL-5, IL-6

- **Monocyte**
  - CysLTs, TNF-α, PAF, IL-1

- **Lymphocyte**
  - IL-4, IL-13, IL-5, IL-3, GM-CSF

Signs and Symptoms of LPR

- Rhinorrhea
- Congestion
- Sneezing

**Allergen**

- **Histamine**
  - IL-4, IL-6

- **PGs**
- **CysLTs**

**Mast Cell**

**Chemotactic Factors** (CysLTs, PAF, IL-5)
Eos/basophil hematopoietic progenitor cells

The progenitor for both eosinophils and basophils.

Express a CD34+/IL-5Rα+ phenotype in peripheral blood and sites of allergic inflammation, including airway in asthma, allergic rhinitis and in NP.

Differentiate in the presence of IL-5 into mature eosinophils.

Accumulate at sites of allergic inflammation after allergen exposure (c/w late-phase of allergic inflammation).

The mechanism of homing of these cells to allergic inflammation has not been elucidated.

Objective measures in allergen-induced nasal inflammation

Nasal lavage

- increased histamine during IAR and LAR
- increased tryptase and PGD2 during IAR only
- increase in basophil # during LAR only
- difficult to show increase in lavage histamine during natural allergen exposure

AR is a risk factor for asthma: adult studies

- Settipane study of college students at Brown University followed prospectively for 23 years:
  - At entry to college, the presence of AR was associated with 10.5% incidence of asthma whereas the incidence was 3.6% in those students without AR.

- Tucson Epidemiologic Study of Obstructive Lung Disease
  - Odds ratio (OR) for development of asthma in people with AR was 2.59 (CI: 1.54 - 4.34).
  - Odds ratio (OR) in people with AR and sinusitis was 6.28 (CI: 4.01 - 9.82)

- Copenhagen Allergy Study - a study of 734 individuals surveyed 8 years apart (1990 and 1998):
  - 28 incident cases of asthma. AR was present in all 28 cases.

Nasal hyperresponsiveness

- Reflex neural activity is upregulated in the presence of allergic inflammation.

- The results of studies of nasal hyperresponsiveness are dependent on the stimulus and what outcome is measured.

- Histamine provocation induces higher sneezing scores in subjects with PAR than in nonallergic healthy control subjects.

- Histamine, but not methacholine, induces contralateral nasal responses, indicating involvement of neural pathways.

Sarin S et al. (J Allergy Clin Immunol 2006;118:999-1014.)
Nasal hyperresponsiveness - cont.

- Patients with AR have almost 100-fold stronger secretory response to capsaicin than healthy controls, both ipsilateral and contralateral.

- Patients with AR also have secretory hyperresponsiveness to hypertonic saline.

- The secretory hyperresponsiveness to capsaicin and hypertonic saline is mediated by capsaicin-sensitive nociceptive sensory nerves that carry the transient receptor potential vanilloid subtype 1 (TRPV1) receptor.

Sarin S et al. (J Allergy Clin Immunol 2006;118:999-1014.)
Nasal hyperresponsiveness in nonallergic rhinitis (NAR = idiopathic rhinitis = vasomotor rhinitis)

- Nasal hyperresponsiveness to cold dry air is a feature
- This stimulus activates capsaicin-sensitive sensory nerves:
  - Inhalation of cold air in one nostril produces bilateral secretory response,
  - The contralateral response is blocked with pretreatment of the challenged nostril with lidocaine
  - The secretory response to cold air is blocked by atropine
  - Repetitive capsaicin application reduces responsiveness of the nasal mucosa to cold air
- Other studies suggest a dysfunction of sympathetic (vasoconstriction) or parasympathetic (glandular secretion) nerve pathways

Nitric oxide (NO) and nasal/sinus function

A product of constitutive or induced enzymatic activity (nitric oxide synthases:
Constitutive: ENOS, NNOS
Inducible: iNOS

Specific inhibitors are needed to differentiate their activities.

In sinus epithelium, there is a high level of constitutive NO production possible due to a unique form of NOS.
Nasal nitric oxide (NO)

- The levels of NO in nasal air are at least 100-fold higher than in orally exhaled air.

- Nasally NO plays a protective role in the lower airway, with antiviral properties, bacteriostatic activity and bronchodilating properties.

- Nasal NO is reduced in sinusitis due to obstruction of sinus ostia.

- NO levels are increased by allergic inflammation, associated with increased iNOS production, in both the upper and lower airway.

Symptoms of allergic rhinitis

- Symptoms of AR
  - sneezing, clear rhinorrhea, itching, nasal congestion
  - redness and itchy eyes
  - itchy throat and ears

- Symptoms in children (> adults)
  - mouth breather, snoring at night
  - sniffling, nocturnal snoring, repetitive throat clearing
  - allergic salute
Objective findings in allergic rhinitis

Objective findings: face (children > adults)
- alterations in facial development with dental malocclusion, and the allergic facies (open mouth and gaping habitus)
- allergic salute
- allergic nasal crease over the lower third of the nose.
- edema and darkening of the tissues beneath the eyes (“allergic shiners”)

Objective findings: nose
- clear nasal secretions
- nasal mucous membranes appear edematous without erythema
- nasal mucosa appears boggy and blue-gray.
Objective measures in allergen-induced nasal inflammation

- Nasal lavage
  - Eosinophils and ECP levels show rise during allergy season
  - ECP levels also elevated in PAR
  - Increase in eosinophils in IAR and LAR
  - Rise in LTB4 and LTC4 in IAR and LTC4 only in LAR (could be due to eosinophils or basophils)

Nonallergic rhinitis

No seasonality of symptoms. Can be triggered by:
- change in temperature or relative humidity
- odors of perfumes, chemical cleansers
- passive tobacco smoke, alcohol
- sexual arousal, emotional factors

No signs of systemic allergy:
- negative allergy tests and RAST tests to aeroallergens

Subtypes:
- noneosinophilic:
  - occupational, hormonal, drug-induced, gustatory, and vasomotor rhinitis.

- eosinophilic:
  - nonallergic rhinitis with eosinophilia syndrome (NARES)
  - frequent evolution to nasal polyposis or ASA triad

Other forms of nonallergic rhinitis

Drug-induced rhinitis
- oral contraceptives, ACE-inhibitors, beta-blockers,
- certain antihypertensives, chlorpromazine, aspirin, NSAIDs

Gustatory rhinitis
- cholinergically-mediated watery rhinorrhea

Skier’s nose (cold-induced rhinitis)
- cholinergically-mediated watery rhinorrhea

Atrophic rhinitis
- nasal congestion, constant bad smell in the nose (ozena)
Asthma and Allergic Rhinitis: “One Linked Airway Disease”

AR and asthma: “one airway hypothesis”

- Thickness of the reticular BM is increased in the nose and lungs in patients with both PAR and asthma.

- Patients with AR and no asthma show abnormalities of the lower airway, such as thickening of the reticular BM and mucosal eosinophilia.

- Allergen provocation studies have shown a similar pattern of allergic cellular inflammation in both conditions.
  - inflammatory cells,
  - cellular activation,
  - cytokine and chemokine expression or production in the nasal and bronchial tissue or their respective secretions

- Airway remodeling is not quite as clearly similar in the nose and lungs.

"One Airway, One Disease" effects of remote allergen challenge: "Cross-talk"

Patients with allergic rhinitis or allergic asthma manifest allergic inflammation at airway mucosal sites remote from allergen exposure. E.g.

Nose ---&gt; Lung
Lung ---&gt; Nose
Nose ---&gt; Sinus

Mucosal biopsies from the remote sites contain eosinophils, basophils and upregulation of VCAM-1 all resembling late-phase type allergic inflammation.

This is not due to direct allergen exposure.

This is an important component of the "nose-lung" connection and the "sinus-lung" connection.
Mechanisms Linking Allergic Rhinitis and Rhinosinusitis

In allergic rhinitis:
- Edema of nasal mucosa
- Mucous hypersecretion
- Blockage of sinuses ostia

Normal Transportation Pathways of Mucus in the Maxillary Sinus

The ostiomeatal unit or complex (OMU) is the 3-D area of confluence of drainage from the maxillary and anterior ethmoid sinuses.

Uncinate process
Maxillary infundibulum
Ethmoid sinus
Maxillary sinus
Middle turbinate
Anatomic Drainage Pathways in the Sinuses

Sinus area

Frontal
Anterior ethmoid/ Maxillary
Posterior ethmoid/ Sphenoid

Drainage pathway
Nasofrontal duct
Ostiomeatal unit
Sphenoethmoidal recess
Factors important to maintaining healthy sinuses against acute bacterial rhinosinusitis

* Ostial patency
* Gas exchange
* Mucociliary action
* Enzymatic defense
* Immunoglobulins
Chronic rhinosinusitis (CRS): an inflammatory disorder of the nose and paranasal sinuses

CRS is **unlike** ABRS and should be viewed and treated differently.

... look for things that can cause inflammation, i.e.

- Chronic allergic inflammation
- Chronic eosinophilic inflammation
- Chronic bacterial infection
- Bacterial colonization
- Fungal colonization
Clinical classification of CRS

Anatomic abnormalities, humoral immune deficiency, abnormal mucociliary function

Bacterial Infection

Chronic rhinosinusitis (CRS)

With eosinophilic Inflammatory features

Without fungal hyphae

ASA tolerant

ASA sensitive

CRS without NP

With other Inflammatory features

Vaso-motor rhinitis

Non-allergic rhinitis

GERD

Sarcoidosis

Non-allergic rhinitis

CRS with NP

With eosinophilic Inflammatory features

With other inflammatory features

Eosinophilic mucin with fungal hyphae (and positive fungal skin tests) “classic AFRS”

ASA tolerant

ASA sensitive

Allergic rhinitis

Symptom profiles in CRSsNP and CRScNP

Nasal obstruction and hyposmia/anosmia more common in CRScNP.

Facial pain/pressure/headache are more common in CRSsNP.

Distribution of adult CRS cases in the outpatient setting

At MGH (N=100 patients with CRS):

• 64% had prior surgery

• Approx. 32% had polyps or polypoid mucosa

• Approx. 50% have perennial allergies

• Approx. 12% had either confirmed or suspected AFRS (suspected AFRS have “allergic mucin” with negative fungal stains and culture)

Patterns of illness in CRSsNP versus CRScNP

- CRSsNP is more commonly associated with:
  - Facial pain/pressure/headache
  - Hypogammaglobulinemia

- CRScNP is more commonly associated with:
  - Anosmia/hyposmia
  - Asthma
  - Aspirin sensitivity
  - Dust mite allergy
  - AFRS and EMRS

Key distinction: CRS without NP versus CRS with NP

Chronic rhinosinusitis (CRS)

**CRS without NP**
- Histologic similarity to COPD:
  - glandular mucus cell hyperplasia
  - inflammatory cells predominantly PMNs (low #s eosinophils)
  - more prominent fibrosis

**CRS with NP**
- Histologic similarity to asthma:
  - mucosal edema
  - greater extent of tissue eosinophils mostly edematous tissue
  - (sometimes fibrotic)
  - reduced #s of vessels and glands
The role of allergy in CRsNP and CRScNP

> 60% of patients with CRS have positive allergy skin tests.

Perennial allergens are more prevalent than seasonal.

Biopsies from the maxillary or ethmoid sinus or NP typically contain eosinophils, mast cells and lymphocytes. This is independent of allergic status.

The cytokine profile in sinus or NP tissue reflects the **systemic** allergic phenotype:

- **allergic**: Th2 profile:
  - IL-4, IL-5, IL-13
- **nonallergic**: mixed Th1/Th2 profile:
  - IL-5, IL-13, IFN-γ
Diagnosis of CRS

A. Symptoms present for $\geq 12$ weeks
B. Requires $\geq 2$ of the following symptoms:
   - Ant or post mucopurulent drainage
   - Nasal congestion
   - Facial pain/pressure
   - Decreased sense of smell
C. Objective documentation
   - Rhinoscopic exam
   - X-ray (sinus CT preferred)

CRScNP: requires bilateral nasal polyps in middle meatus.
Pathogenesis of CRS and CRSwithNP: role of bacteria

- **CRS (without NP):**
  - The role of bacterial infection is still controversial.
    - Occult infection, with aerobic or anaerobic bacteria
    - Bacterial colonization with commensal organisms, s/a coagulase-negative *Staphylococci*
    - Osteitis
    - Biofilms or intraepithelial bacteria

- **CRSwithNP:**
Bacterial biofilm properties

- Unique extracellular bacterial microenvironment.
- Commonly associated with growth of bacteria on an inert surface.
- Involves formation of clusters of microbial organisms held together by an extracellular glycocalyx with interspersed water channels.

Courtesy of Dr. David Davies, Binghamton University, Binghamton, NY. http://www.erc.montana.edu/biofilmbook/MODULE_01/Mod01_IntroPage.htm.
Bacterial biofilm in CRS

Results:

- 24 of 30 CRS patients had evidence of biofilm.
- 0 of 4 healthy controls had evidence of biofilm.

Transmission EM confirmed that structures seen at the mucosal surface in the biofilm on SEM corresponded to bacteria on TEM cross sections.

Bacterial cultures were positive on all patients.

Healthy control with no biofilm

Bacterial biofilm in CRS patient

Pathogenesis of CRS: the “fungal hypothesis”

- Emerging evidence demonstrates an important role for fungal Th2 hypersensitivity in CRS pathogenesis.
  - Fungal hyphae in mucus in >90% of cases
  - Eosinophils in mucus attack hyphae and degranulate

Pathogenesis of chronic hyperplastic sinusitis with nasal polyposis

Pathologically:

1. Chronic inflammatory infiltrate significantly increased numbers of eosinophils.
2. Increase in IL-5 producing T lymphocytes in both allergic and nonallergic patients.
# Classic allergic fungal rhinosinusitis

- **Accounts for** 7% of CRS cases overall.

- **Wide geographic differences in prevalence.**

- **Usually caused by** dematiaceous fungi, s/a
  - Bipolaris
  - Alternaria
  - Aspergillus

## I. Diagnosis of “Classic” AFRS

### A. Pattern of symptoms
- Symptoms present for $>12$ weeks

### B. Symptoms for diagnosis
- Requires $>1$ of the following symptoms:
  - Anterior and/or posterior mucopurulent drainage
  - Nasal congestion
  - Decreased sense of smell
  - Facial pain/pressure

### C. Objective documentation by all:
  - Endoscopy to required to document presence of inflammation such as discolored mucus or edema of middle meatus or ethmoid area, or nasal polyps.
  - Imaging by CT or MRI
  - Presence of allergic mucin (containing fungal hyphae with degranulating eosinophils)
  - Evidence of fungal-specific IgE
Allergic fungal rhinosinusitis (AFRS)
zIn order for CRS to be AFRS, allergic mucin must be present, and 2 additional criterion must be met:
▲positive fungal stain or culture of allergic mucin
▲evidence of IgE-mediated fungal allergy

Allergic fungal rhinosinusitis (AFRS): and it’s look alikes

- In order for CRS to be AFRS, allergic mucin must be present, and 2 additional criterion must be met:
  - positive fungal stain or culture of allergic mucin
  - evidence of IgE-mediated fungal allergy

- If only 1 additional criterion is met:
  - + fungal stain, - fungal allergy
  - - fungal stain, +fungal allergy

- If neither additional criterion is present:
  - Eosinophilic mucin rhinosinusitis

“AFRS”

“AFRS candidate”

“EMRS”
**CRS: antimicrobial treatment**

Antibiotics to remove chronic bacterial infection or colonization. controlled trials are lacking

Antifungals to remove fungal colonization.
- amphotericin B sinus irrigation:
  - 12 wks treatment caused 9% reduction in inflammatory mucosal thickening vs. 2% in control
    (Ponikau J et al. JACI 2005;115:125-31.)

- amphotericin B nasal spray:
  - 8 wks treatment failed to improve sinus CT score
    (Weschta M, et al. JACI 2004;113:1122-8.)

- systemic terbinafine:
  - oral 625 mg daily for 8 wks failed to improve sinus CT
    (Kennedy DW et al Laryngoscope. 2005; 115:1793-9.)
**CRS with NP: intranasal steroids**


N = 354 patients with mild to moderate NP
Treatment with Mometasone 200 ug daily, 200 ug bid or matching placebo for 4 months

Endpoints:
- change from baseline in polyp grade (0 – 3)
- change from baseline in nasal congestion/obstruction score avg. over first month of Rx.

Results:

1. decrease in polyp grade in MFNS by 27% and 22% for qd and bid dosing (P = 0.001 and 0.01, respectively) versus placebo of 12%.
2. symptomatic improvement, including improvement in hyposmia.
CRS with NP: topical steroid drops


N = 54 Rx with fluticasone propionate nasal drops (FPND) or placebo, 200 ug per nostril once daily for 12 weeks (approx. 200 ul/nostril).

Procedure: Patients lie on their back with their head hanging down in a vertical position over the edge of the bed while administering the FPND to each nostril. They remained in this position for 2 minutes.

Results: FPNDs:
1. increased the number of subjects with “no need for FESS” (13 of 27 versus 6 of 27 on placebo) (P < .05)
2. improved symptoms of nasal obstruction, rhinorrhea PND and loss of smell (P < 0.05)
3. improved NPIF and sinus CT scan score (P < .05)
4. decreased polyp volume by VAS (:P < .05)
Allergic fungal sinusitis: treatment

**Treatment**

- Surgical drainage of allergic mucin
- Prednisone 0.5 mg/kg daily for 2 weeks, then QOD with gradual tapering over several weeks
- Environmental control measures
- Fungal immunotherapy should be considered
- Systemic antifungal therapy is unproven.
- Topical antifungal therapy should be considered (Amphotericin B or itraconazole). Irrigation technique is critical.
- Intranasal corticosteroids are recommended but unproven.
Questions
1. Which of the following is not true regarding differences between CRSsNP and CRSwNP?

a. Facial pain/pressure is more common in CRSsNP, whereas hyposmia/anosmia is more common in CRScNP.

c. CRSsNP is more heterogeneous in underlying cause than CRSwNP.

d. Hypogammaglobulinemia is more common in CRSsNP and uncommon in patients with CRSwNP.

e. Eosinophilic inflammation is not a feature of CRSsNP.
The answer is E.

Although eosinophilic inflammation is the *sine qua non* of nasal polyps, a variable degree of eosinophilic inflammation is commonly seen in CRSsNP.
2. Pathologic processes observed in CRSwithNP but not in CRSwithoutNP include all but which of the following:

A. local production of IgE directed against superantigens from *Staphylococcus aureus*

B. systemic T cell activation (IL-5, IL-13, IFN-γ production by fungal antigens from Alternaria

C. edema formation, dense infiltration with eosinophils and a mild increase in mast cells

D. greater local production of IL-5
The answer is B.

Systemic T cell activation (IL-5, IL-13, IFN-γ) production by fungal antigens from Alternaria has been found in patients with CRSwithoutNP and CRSwithNP by Ponikau et al.
3. The T cell cytokine profile typically seen in CRScNP is:

A. A mixture of Th2 and Th1 cytokines, including IL-5, IL-13 and IFN-γ.

B. Mostly a Th1 profile, including IFN-γ, IL-12 and TNF-α.

C. Unrelated to the allergic status of the patient (i.e. whether the patient has positive or negative allergy skin tests).

D. Highly skewed toward local production of Th2 cytokines, including IL-5 and IL-13. Depending on the allergic status of the patient, IL-4 or IFN-γ may also be present.
The best answer is D.

The T cell cytokine profile typically seen in CRSwithNP is highly skewed toward local production of Th2 cytokines, including IL-5 and IL-13. However, depending on the allergic status of the patient, IL-4 or IFN-γ may also be present.
4. Which of the following does not occur with roughly equal frequency in CRSwNP and CRSsNP?

a. allergic fungal rhinosinusitis (AFRS)

b. a positive immunofluorescent stain of sinus mucus for fungal hyphae.

c. non-IgE mediated T cell sensitization (IL-5 and IL-13 production) \textit{in vitro} to airborne fungi, including \textit{Alternaria tenuis}

d. a positive allergy skin test to pollens
4. The answer is A.

AFRS is almost always seen in association with CRSwNP.

Studies from Taylor et al. (Taylor MJ, et al. OHNS 2002;127:377-83.) showed a very high prevalence of positive immuno-fluorescence staining of mucus for fungal hyphae in both CRSwNP and CRSsNP.

Studies by Shin et al (Shin SH, et al. JACI 2004;114:1369-75.) showed a high prevalence of positive *in vitro* non-IgE mediated T cells sensitization to airborne fungi in both CRSwNP in CRSsNP.

Positive allergy skin tests to pollens occur with equal frequency in CRSwNP and CRSsNP.
5. Which statement is not true regarding the relationship between allergic rhinitis (AR) and allergic asthma?

- A. Thickness of the reticular basement membrane is increased in the nose and lungs in patients with both AR and asthma.

- B. Patients with AR and no asthma consistently show abnormalities of the lower airway, such as thickening of the lamina reticularis and mucosal eosinophilia.

- C. The nasal mucosa is a good surrogate marker for airway remodeling in the lower airway.

- D. Allergen provocation studies have shown a similar pattern of allergic cellular inflammation in both conditions.
5. Which statement is not true regarding the relationship between allergic rhinitis (AR) and allergic asthma?

Answer is C.