

Diagnostic Value of Nasal Allergen Challenge Combined With Radiography and Ultrasonography in Chronic Maxillary Sinus Disease

Zdenek Pelikan, MD, PhD

Objective: To investigate the possible role of nasal allergy in chronic disease of the maxillary sinuses (CDMS) by means of nasal provocation test (NPT) with allergen combined with radiography and ultrasonography.

Design: Prospective clinical controlled study.

Setting: Academic referral center.

Patients: Seventy-one patients with CDMS and 16 control subjects with allergic rhinitis but no history of sinus disease.

Interventions: In the 71 patients, a total of 135 NPTs and 71 control challenges with phosphate-buffered saline were performed by rhinomanometry combined with radiography and ultrasonography. In the control patients, 16 positive NPTs were repeated and combined with radiography and ultrasonography.

Main Outcome Measures: Number, type, and timing of nasal responses with accompanying changes on radiographs and ultrasonograms.

Results: Of the 71 patients, 67 developed 104 positive nasal responses of various types ($P < .001$), 89 of which were accompanied by significant changes on radiographs ($P = .008$), whereas 83 were also associated with significant changes on ultrasonograms ($P = .007$). No significant changes on the radiographs or the ultrasonograms were recorded during the 71 phosphate-buffered saline control tests in the patients with CDMS ($P = .14$ and $.06$, respectively) or during the 16 NPTs in control subjects ($P = .15$ and $.12$, respectively). The radiographic and ultrasonographic findings were significantly correlated ($r = 0.81$; $P < .01$).

Conclusions: Nasal allergy may be involved in some patients with CDMS, resulting in appearance of a maxillary sinus response. Monitoring this response by means of serial ultrasonography and, if necessary, also by conventional radiography or computed tomography simultaneously with the nasal challenge with allergen seems to be a very useful diagnostic supplement allowing additional therapeutic measures focused on the nasal allergy.

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CHRONIC DISEASE OF THE maxillary sinuses (CDMS) is a common disorder, affecting a wide adult as well as pediatric population.¹⁻⁴ Although the involvement of hypersensitivity mechanisms, and especially of nasal allergy, in CDMS has been recognized, the diagnostic procedures for this disorder and this relationship vary.^{1,3-27} There is a dearth of information regarding the direct causal involvement of hypersensitivity mechanisms of the nasal mucosa and potential consequences within the maxillary sinuses.^{1-3,7,8,28-30} Moreover, few data are available to illustrate the possible existence of various types of maxillary sinus response caused by immunologic events in the nasal mucosa.^{1,8,29} Another issue dis-

cussed is the recording of particular changes in the paranasal sinuses and their mucosal membrane.^{1,2,11-27} Diagnostic value of the various imaging techniques differs and depends on a variety of factors, such as purposes, basic indications, practice facilities, and costs.^{1,9-16,19-23,31} The imaging techniques are usually used in a single application for evaluation of the temporary state of the particular sinuses.^{1,20,22} However, most of these techniques are not suitable for serial application for several reasons, such as relatively higher costs and unnecessary exposure to radiation or magnetic resonance.^{1,32-35} On the other hand, hypersensitivity mechanisms, such as allergic reaction in the nasal mucosa, represent a dynamic process necessitating a dynamic approach, which means recording of the rel-

Author Affiliation: Allergy Research Foundation, Breda, the Netherlands.

evant variables before and repeatedly after the allergen exposure.³²⁻³⁷ Therefore, although they may gather excellent data, not all imaging techniques are suitable for this aim.³²⁻³⁵ In our previous studies, we demonstrated involvement of nasal allergy in chronic maxillary sinus disease as monitored by conventional radiography.³²⁻³⁵ The purpose of this study was (1) to investigate the existence of particular types of maxillary sinus response induced by nasal allergy as recorded by radiography and ultrasonography and (2) to evaluate the suitability of ultrasonography in combination with nasal challenge for diagnostic screening of the role of nasal allergy in patients with CDMS.

METHODS

PATIENTS

Eighty-four patients with CDMS of longer than 3 years' duration, without an air-fluid level on radiographs, were referred to the Department of Allergology and Immunology, Institute of Medical Sciences "De Klokkenberg," Breda, the Netherlands, from 1999 through 2000 by otolaryngologists with the request to perform further diagnostic procedures focused on possible involvement of allergy in their CDMS. All of these patients had previously been examined by otolaryngologists using standard procedures, including computed tomographic scans of the paranasal sinuses. They had been previously treated with various antibiotics, decongestants, and H₁-receptor antagonists. They had undergone sinus puncture and some had also had tonsillectomy and adenoidectomy, but without satisfactory improvement of their complaints. None of them was treated with immunotherapy, oral corticosteroids, nasal cromolyn sodium (disodium cromoglycate), or leukotriene modifiers. Of these 84 consecutively referred patients, 71 were willing to participate voluntarily in this study (**Table 1**). These patients, 16 to 48 years of age, underwent a routine diagnostic procedure consisting of a detailed disease history, physical and basic laboratory examination, bacteriologic examination of the nasal secretions and sputum, blood differential cell count, nasal secretion cytogram, serum skin tests with basic inhalant allergens, paper radioimmunosorbent test, radioallergosorbent test, rhinoscopy, and screening plain radiography of paranasal sinuses. Nasal histamine thresholds were determined, and 135 nasal provocation tests (NPTs) with various inhalant allergens were performed by means of rhinomanometry combined with simultaneous conventional radiography and ultrasonography of the maxillary sinuses.

In each patient, a control nasal challenge with phosphate-buffered saline (PBS) was also performed according to the same schedule as that used for the NPTs with allergens and supplemented with radiographs and ultrasonograms of the maxillary sinuses. A 4-day interval was always inserted between the consecutive tests. Patients were examined when they were without manifest sinus and nasal complaints and without nasal infection. Topical glucocorticosteroids and long-acting H₁-receptor antagonists were withdrawn 6 weeks before the study, whereas short-acting H₁-receptor antagonists and nasal decongestants were stopped 48 hours before the study. The local ethics committee approved this study, and informed consent was obtained from all participants.

CONTROL GROUP

Sixteen patients with allergic rhinitis, confirmed by positive history, skin tests, and nasal challenges with various inhalant allergens but without any history of sinusitis and with normal radio-

Table 1. Characteristics of Patients and Control Subjects

Characteristic	Patients (n=71)	Control Subjects (n=16)
Age, mean (SD), y	29.3 (8.4)	26.7 (10.1)
Sex, M/F	32/39	7/9
Disease history, mean (SD), y	6.7 (2.3)	8.1 (3.4)
Positive skin tests	71	16
Blood eosinophil count, mean (SD), cells/ μ L ^a	537 (83)	494 (69)
Eosinophil count in nasal secretions, mean (SD) ^b	29 (6)	25 (4)
Nasal histamine threshold ^c		
$\leq$ 8.0 mg/mL	52	11
$>$ 8.0 mg/mL	19	5
Changes on MS radiographs ^d	69	0
Changes on CT scan ^e	71	ND
Changes on MS ultrasonograms ^f	67	0

Abbreviations: CT, computed tomographic; MS, maxillary sinus; ND, not done.

^aSI conversion factor: To convert blood eosinophil count to cells $\times 10^9$ per liter, multiply by 0.001.

^bNormal value, less than 300/ μ L.

^cNormal value, less than 7 per moderate-power field ($\times 250$ magnification).³⁸

^dNormal value, more than 8.0 mg/mL.^{35,37}

^eSlight thickening of MS mucosal membrane.

^fSlight thickening of mucosal membrane in both MSs.

[†]Slight thickening of MS mucosal membrane.

graphic findings, volunteered to participate in this study. In these patients, 16 positive NPTs with *Dermatophagoides pteronyssinus* or grass pollen were repeated out of season and supplemented with radiographs and ultrasonograms of the maxillary sinuses.

ALLERGENS

Dialyzed and lyophilized allergen extracts (Allergopharma, Reinbek, Germany) were diluted in PBS and used in concentrations of 500 biological units/mL for skin tests and 1000 to 3000 biological units/mL for NPTs (**Table 2**). If indicated, the higher dilutions of the allergen extracts were used for the skin tests as well as for the NPTs.

SKIN TESTS

The intradermal tests were performed and evaluated 20 minutes after the injection, according to a standard schedule. A skin wheal reaction (>7.0 mm in diameter) appearing 20 minutes after the injection was considered to be a positive immediate skin response.³²⁻³⁷

NASAL PROVOCATION TESTS

The NPTs with allergens were performed by the rhinomanometry technique, described previously.³⁴⁻³⁷ The nasopharynx-nostril pressure gradients (NPGs) (ΔP , expressed in centimeters of water) recorded by this technique were considered to be the basic measures of the nasal mucosa response (nasal obstruction). The NPTs were performed according to the following schedule: (1) initial (baseline) values were recorded at 0, 5, and 10 minutes; (2) PBS control values were recorded at 0, 5, and 10 minutes after a 3-minute application of PBS to the nasal mucosa of the nonintubated nasal cavity by means of a saturated wad of cotton wool on a nasal probe, inserted under the concha media and placed away from the natural ostia of the maxillary sinus; and (3) test values were recorded simi-

Table 2. Allergens Used for Nasal Provocation Tests

Allergen	Concentration, BU/mL	Total (n=135)	Nasal Responses (n=135)			
			Positive (n=104)		Negative (n=31)	
			MSR+ (n=89)	MSR- (n=15)	MSR+ (n=5)	MSR- (n=26)
<i>Dermatophagoides pteronyssinus</i>	1000	35	25	3	1	6
<i>Dermatophagoides farinae</i>	1000	6	4	1	0	1
Animal danders						
Dog	3000	9	5	2	0	2
Cat	2000	15	9	3	1	2
Hamster	2000	3	2	0	0	1
Rabbit	2000	4	3	1	0	0
Feathers						
Canary	3000	5	3	0	0	2
Parakeet	3000	1	1	0	0	0
Parrot	3000	3	2	1	0	0
<i>Aspergillus fumigatus</i>	1000	3	2	0	0	1
Pollen						
Grass mix 1 ^a	1000	27	19	2	1	5
Grass mix 2 ^b	1000	8	5	1	0	2
Birch	500	5	3	0	1	1
Tree mix ^c	2000	7	4	1	0	2
Weed mix ^d	1000	4	2	0	1	1

Abbreviations: BU, biological units; MSR, maxillary sinus response; -, negative; +, positive.

^a *Dactylis glomerata*, *Lolium perenne*, *Phleum pratensis*, and *Poa pratensis*.

^b *Festuca pratensis*, *Holcus lanatus*, *Agrostis alba*, and *Anthoxanthum odoratum*.

^c *Betula pendula*, *Corylus avellana*, *Juniperus communis*, and *Salix alba*.

^d *Artemisia vulgaris*, *Plantago lanceolata*, *Rumex acetosa*, and *Taraxacum officinale*.

larly after a 3-minute application of allergen at 0, 5, 10, 20, 30, 45, 60, 90, and 120 minutes, then every hour up to the 12th hour, and then every second hour between the 24th and 38th hours and between the 48th and 56th hours. Nasal response (NR) was considered to be positive when the mean NPG values after the allergen challenge increased by at least 2.0 cm H₂O (mean [SE], 1.2 [0.3] cm H₂O) with respect to the mean PBS values, recorded during at least 3 consecutive time intervals. The NPG changes occurring within 60 minutes after the allergen challenge were considered to be a positive immediate NR; those appearing within 4 to 12 hours, a positive late NR; and those occurring later than 24 hours, a positive delayed NR. Allergens for the NPTs were chosen with respect to the patient's history, positive skin test, or positive radioallergosorbent test results (Table 2).

RADIOGRAPHS

Conventional radiographs of maxillary sinuses in Waters projection, while other parts have been shielded, were performed before and then 0.5, 1, 2, 6, 8, 12, 24, 36, and 48 hours after the nasal allergen challenge and evaluated by a radiologist in a blinded manner, without knowledge of the patient as well as the sequence. The following parameters and their changes on the radiographs were evaluated: (1) osseous skeleton; (2) air-fluid level; (3) profile of the increased mucosal membrane in the maxillary sinuses (an increase in the mucosal thickening >3 mm, due to edema and/or infiltration, was considered to be abnormal); (4) decrease in aeration; and (5) appearance of opacification.³³⁻³⁵ The changes were evaluated by means of a grading score system (Pelikan scoring system) and calculated

Table 3. Pelikan Scoring System in Maxillary Sinuses^a

Measure and Score	Criteria
Radiographs ^b	
Mucosal membrane	
0	<3 mm
1	3 mm
2	4 mm
3	>4 mm
Opacification	
0	None
1	Slight
2	Moderate
3	Distinct
4	Total
Air-fluid	
0	None
1	Present
Ultrasonograms ^c	
Distance (x-axis)	
0	<1 cm
1	1 to <2 cm
2	2 to <3 cm
3	3 to <4 cm
4	4 to <5 cm
5	≥5 cm
Intensity (density, y-axis)	
0	<1 mm
1	1 to <2 mm
2	2 to <3 mm
3	≥3 mm

^a Each of the maxillary sinuses has been evaluated separately, and then the total mean score was calculated.

^b Maximal radiographic score, 8 points; statistically significant difference, 3 points or more ($P < .05$).

^c Maximal ultrasonographic score, 7 points; statistically significant difference, 2 points or more ($P < .05$).

from both the maxillary sinuses as a total mean score (Table 3).

ULTRASONOGRAPHY

Ultrasonography was performed by means of a 1-dimensional A-scan (Enterscan model 270; Pie Medical Imaging BV, Maas-tricht, the Netherlands) with a single crystal 3.5- to 5.0-MHz probe and a printer (model P50E; Mitsubishi Digital Electronics America, Irvine, California). The ultrasonograms were recorded before and repeatedly after the nasal allergen challenge at the same time intervals as the NPG recording. The ultrasonograms were evaluated in a blinded manner. The ultrasonographic findings were evaluated according to the following criteria: (1) x-axis (scale in centimeters), visualizing the depth of the maxillary sinus: (a) 0 to 0.3 cm = "initial echo" (standard calibration) and (b) the echo distances of less than 1.0 cm = normal appearance, representing echo penetration through the skin and frontal wall of maxillary sinus (no pathology) (grade 0); 1.0 to less than 2.0 cm = slight thickening of the sinus mucosal membrane (grade 1); 2.0 to less than 3.0 cm = moderate thickening of the sinus mucosal membrane plus mucus layer (grade 2); 3.0 to less than 4.0 cm = distinct thickening of the sinus mucosal membrane plus mucus layer (grade 3); 4.0 to less than 5.0 cm = distinct thickening of the sinus mucosal membrane plus fluid in the sinus cavity (grade 4); greater than or equal to 5.0 cm = back wall echo (grade 5); (2) y-axis (scale in millimeters), representing the volume (intensity) of the echo signal (correlating with the density of the particular tissue or

Table 4. MSRs Accompanying Positive and Negative NRs^a

Patients (n=71)	MSR			
	Positive		Negative	
	Radiography	Ultrasonography	Radiography	Ultrasonography
67 Patients				
104 Positive NRs	89	83	15	21
19 Negative NRs	2	2	17	17
4 Patients				
12 Negative NRs	3	3	9	9
71 Control tests (PBS)	0	0	71	71

Abbreviations: MSR, maxillary sinus response; NR, nasal response; PBS, phosphate-buffered saline.

^aThe agreement between positive NR and positive MSR was statistically significant for both radiography ($P < .001$) and ultrasonography ($P < .01$).

medium): less than 1.0 mm = weak signal or low volume (normal appearance) (grade 0); 1.0 to less than 2.0 mm = moderate volume (abnormal) (grade 1); 2.0 to less than 3.0 mm = distinct volume (grade 2); greater than or equal to 3.0 mm = large volume (distinct pathology) (grade 3).^{11,16,18,19,24,26,27} The changes were evaluated by means of our grading scale and calculated from both of the maxillary sinuses as a total mean score (Table 3).

STATISTICAL ANALYSIS

The NRs and the PBS control tests recorded in individual patients were statistically evaluated by Wilcoxon matched-pair signed rank test, comparing the NPG values recorded after the allergen or PBS challenge at each time point with the mean prechallenge values. The positive and negative NRs of the same type were compared and statistically evaluated by the Mann-Whitney test.

The correlation between the positive as well as negative radiographic and ultrasonographic changes was analyzed by the Spearman rank correlation coefficient. The agreement between the radiographic and ultrasonographic changes during the particular types of NR was analyzed by means of the Mann-Whitney test. $P < .05$ was considered to be statistically significant for all statistical methods used.

RESULTS

NASAL RESPONSES

In the 71 patients, 135 NPTs were performed. Sixty-seven patients developed 104 positive NRs ($P < .001$) compared with the PBS control tests (**Table 4**): 31 isolated immediate NRs ($P < .001$), 48 isolated late NRs ($P < .001$), 10 dual late NRs (immediate + late; $P < .01$ and $P < .001$, respectively), 13 isolated delayed NRs ($P < .01$), 2 dual delayed NRs (immediate + delayed; $P < .01$ and $P < .05$, respectively), and 19 negative NRs ($P > .05$) (**Tables 4, 5, and 6; Figures 1B, 2B, and 3B**). The remaining 4 patients showed 12 negative NRs ($P > .05$). The 71 PBS control tests did not display any significant changes in the NPG values with respect to the baseline values ($P > .1$). The difference between the positive and the negative NRs was statistically significant ($P < .01$). No significant differences were found in the appearance of particular NR types with respect to the individual allergens ($P > .05$). The agreement between the positive skin test results and positive NRs was 77% ($P \leq .05$).

Table 5. MSRs Accompanying Particular Types of NR

NR Type	MSR				
	Total (n=135)	R+ U+	R- U-	R+ U-	R- U+
Positive	104	83	15	6	0
Isolated immediate	31	25	3	3	0
Isolated late	48	41	5	2	0
Dual late	10	5	4	1	0
Isolated delayed	13	11	2	0	0
Dual delayed	2	1	1	0	0
Negative	31	5	26	0	0
Controls (PBS)	71	0	71	0	0

Abbreviations: MSR, maxillary sinus response; NR, nasal response; PBS, phosphate-buffered saline; R, radiography; U, ultrasonography; -, negative; +, positive.

RADIOGRAPHS OF THE MAXILLARY SINUSES

In 69 of the 71 patients (97%), a slight thickening of the maxillary sinus mucosa (1-2 mm) had already been recorded on the radiographs before the NPTs. Eighty-nine of the 104 positive NRs (28 isolated immediate, 43 isolated late, 6 dual late, 11 isolated delayed, and 1 dual delayed) and 5 of the 31 negative NRs were accompanied by significant changes of the radiographs of maxillary sinuses ($P = .008$) (Table 4 and Table 5). The changes included a distinct increase in the thickening of the mucosal membrane (> 3.0 mm) and sometimes also a decrease in aeration and the appearance of opacification (Table 6; **Figures 4, 5, and 6**). The mean (SD) total point score of radiographic changes after allergen challenge, evaluated by the Pelikan point grading score (Table 3), was 476 (48). The mean total point scores of the radiographic changes recorded at individual time intervals are presented in **Table 7**, and those recorded during each type of NR are displayed in Figures 1A, 2A, and 3A. The agreement between the positive NRs and the appearance of radiographic changes was statistically highly significant ($P < .001$). No significant radiographic changes were recorded during the 71 PBS control tests ($P = .14$).

Table 6. Changes on Radiographs and Ultrasonograms Recorded During Particular Types of NR

Changes in MSs	Type of NR											
	Isolated Immediate (n=31)		Isolated Late (n=48)		Dual Late (n=10)		Isolated Delayed (n=13)		Dual Delayed (n=2)		Negative (n=31)	
	R	U	R	U	R	U	R	U	R	U	R	U
Increase in mucosal edema (thickening)	24	25	42	41	6	5	10	11	1	1	5	5
Air-fluid level	0	0	3	2	0	1	1	1	0	0	0	0
Decrease in aeration	17	NM	30	NM	4	NM	8	NM	1	NM	4	NM
Opacification	14	NM	27	NM	5	NM	9	NM	1	NM	5	NM

Abbreviations: MS, maxillary sinus; NM, not measurable; NR, nasal response; R, radiograph; U, ultrasonography.

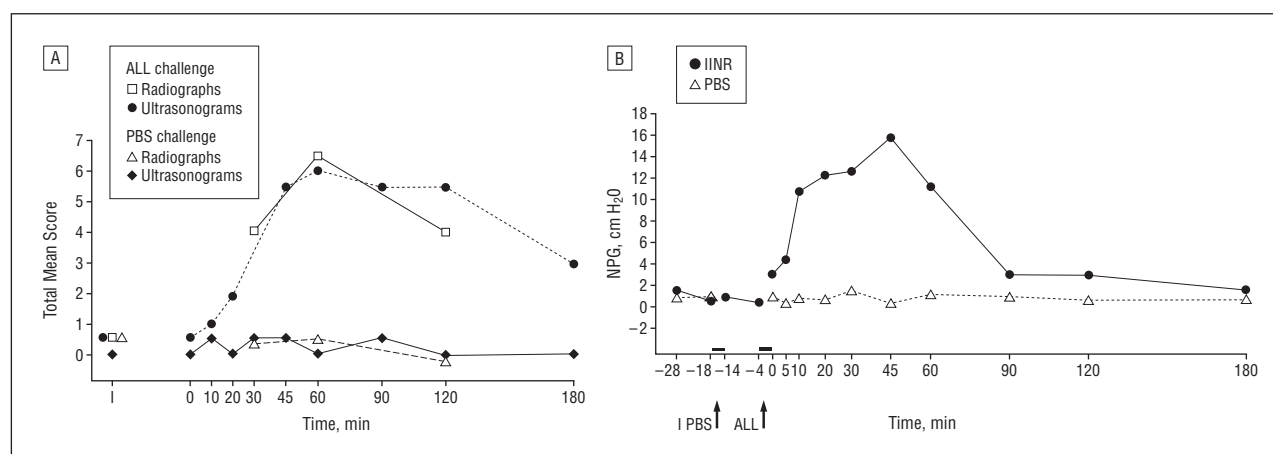


Figure 1. Maxillary sinus responses accompanying isolated immediate nasal responses (IINR; n=31). A, Mean point score of changes recorded on ultrasonograms and radiographs after allergen challenge (ALL) and on ultrasonograms and radiographs after phosphate-buffered saline (PBS) challenge. B, Mean rhinomanometric values (nasopharynx-nostril pressure gradient [NPG]) recorded during IINR and PBS. I indicates initial (baseline) values.

ULTRASONOGRAMS OF THE MAXILLARY SINUSES

Significant changes on the ultrasonograms of the maxillary sinuses ($P=.007$) were found in association with 83 of the 104 positive NRs (25 isolated immediate, 41 isolated late, 5 dual late, 11 isolated delayed, and 1 dual delayed) and 2 of the negative NRs recorded in 67 patients, as well as with 3 of the 12 negative NRs recorded in the remaining 4 patients (Table 4 and Table 5). The ultrasonographic changes included increased thickening of the mucosal membrane in the maxillary sinuses, sometimes associated with a transient accumulation of the secretions at the bottom of the sinuses (Table 6; Figures 4, 5, and 6). The mean (SD) total point score of ultrasonographic changes after allergen challenge, evaluated by the Pelikan point grading score (Table 3), was 399 (41). The mean total point scores of the ultrasonographic changes recorded at individual time intervals are summarized in Table 7, and the mean point scores recorded during each type of NR are presented in Figures 1A, 2A, and 3A. The agreement between the positive NRs and the appearance of the ultrasonographic changes was statistically significant ($P<.01$). No ultrasonographic changes were observed during the 71 PBS control tests ($P=.06$).

RELATIONSHIP BETWEEN RADIOGRAPHIC AND ULTRASONOGRAPHIC CHANGES

The agreement between the appearance of radiographic and ultrasonographic changes recorded during the positive and negative NRs, during the particular types of positive NRs and at individual time intervals after the allergen challenge, was statistically significant ($P<.01$) (Tables 4, 5, 6, and 7). However, this agreement demonstrated some smaller nonsignificant variations with respect to the individual types of NRs. The total correlation between the radiographic and ultrasonographic changes evaluated by means of Spearman rank correlation coefficient was highly significant both for the positive and for the negative cases ($r=0.89$, $P<.001$; $r=-0.73$, $P<.01$, respectively). The correlation coefficients between the radiographic and ultrasonographic changes recorded at individual time intervals after the allergen challenge are presented in Table 7.

CONTROL SUBJECTS

In 16 control subjects who developed 16 positive NRs to the repeated allergen challenge (5 isolated immediate NRs [$P<.01$] and 11 isolated late NRs [$P<.01$]), no significant radiographic or ultrasonographic changes of

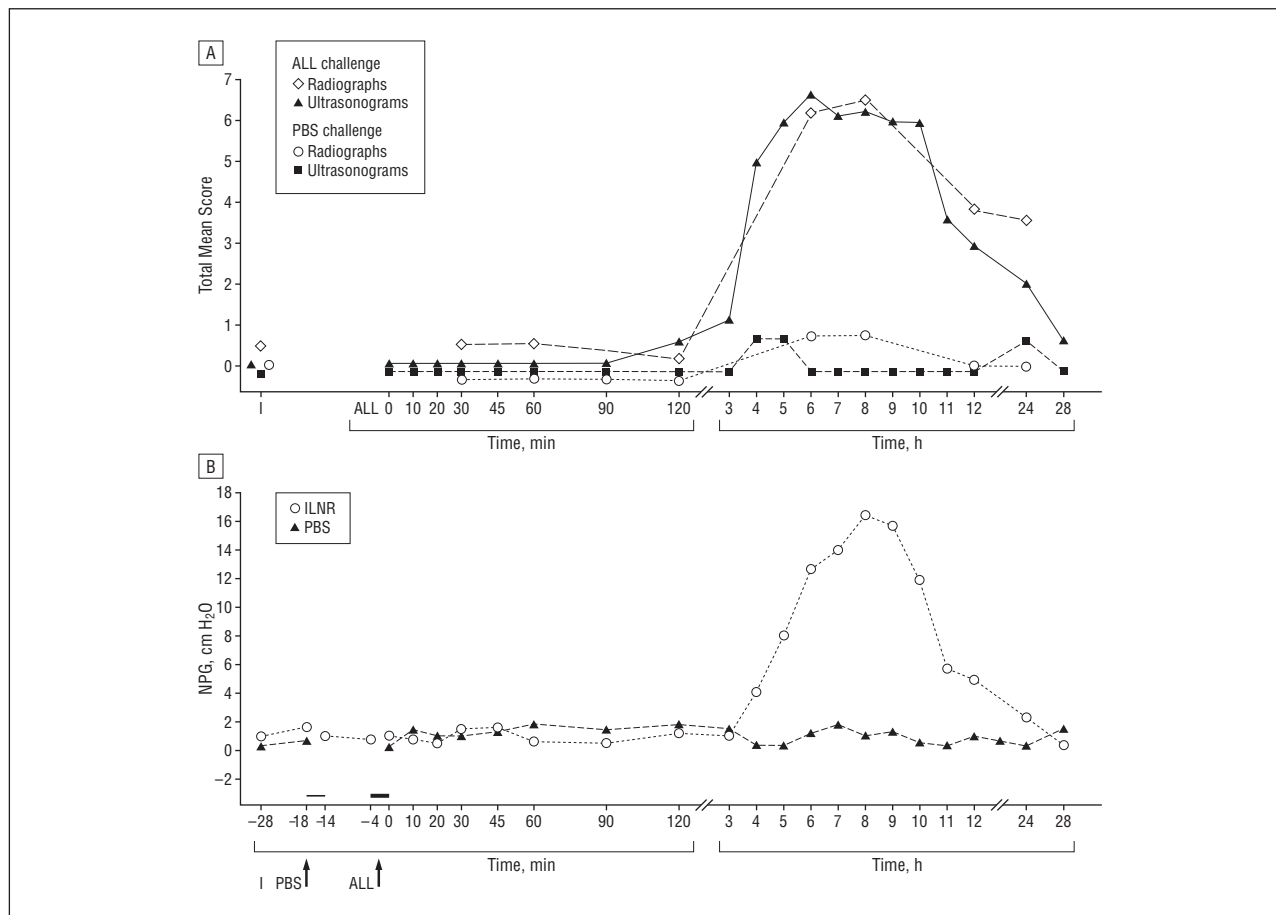


Figure 2. Maxillary sinus responses accompanying isolated late nasal responses (ILNR; n=48). A, Mean point score of changes recorded on ultrasonograms and radiographs after allergen challenge (ALL) and on ultrasonograms and radiographs after phosphate-buffered saline (PBS) challenge. B, Mean rhinomanometric values (nasopharynx-nostril pressure gradient [NPG]) recorded during ILNR and PBS. I indicates initial (baseline) values.

the maxillary sinuses were observed ($P=.15$ and $.12$, respectively).

COMMENT

The possible involvement of allergy, and especially of nasal allergy, in some forms of sinus disease has already been reported in the literature.^{1,3-10,29,30,32-35} There are a number of anatomic and physiologic similarities between the nasal mucosa and mucosa of the maxillary sinuses.^{1-4,7,8,27,30,33-35} The maxillary sinuses open into the middle meatus of the nasal cavity through the ostium, which plays a pivotal role in their functions. The ostium acts as an anatomic and functional valve, facilitating secretion drainage and gas exchange from the sinus into the nasal cavity. The factors disturbing the drainage functions of ostia, and thus leading to the retention of secretions and gases and negative pressure in the maxillary sinuses, include (1) edema of the nasal mucosa causing limitation of ostium patency, (2) reduced transport capacity of mucus on the surface of sinus mucosal membrane due to abnormalities of the cilia and their function, and (3) increased production of secretions and gases in the sinuses, exceeding the drainage capacity of ostia.^{1-4,6,7,35,38,39} The cross-sectional area of the ostium is also the primary determinant of the gas exchange in the

human maxillary sinuses.^{33,38-41} In addition, the nasal air-flow influences gas exchange in the sinuses, which is twice as fast by nasal breathing than during oral breathing.³⁹⁻⁴² The increased nasal mucosal edema may lead not only to mechanical occlusion of the maxillary ostia from outside by surrounding nasal mucosal tissue but sometimes also to extension of the edematous nasal mucosa beyond the ostium margin.^{1,5,33,34,38-41}

All of these changes lead to partial or total closing of the ostia, resulting in accumulation of secretions, gases, and soft-tissue mass in the sinus. This process leads to subsequent edema and/or infiltration of the sinus mucosa, expressed as mucosal thickening, decreased aeration, appearance of opacification, and sometimes formation of fluid level and soft-tissue mass, which is referred to as a sinus response.³²⁻³⁵

Two possible pathways—one of them upon involvement of the nasal mucosa, and the other upon passing the nasal mucosa without affecting it—could probably explain some of our results.³³⁻³⁵ Of the 104 positive NRs, 89 positive NRs were accompanied by radiographic and 83 by ultrasonographic changes of the maxillary sinuses (Table 4). In these cases, which can be viewed as a “secondary” form of sinus response, the immunologic event located primarily in the nasal mucosa may induce an additional sinus response.³³⁻³⁵ This mechanism is identical

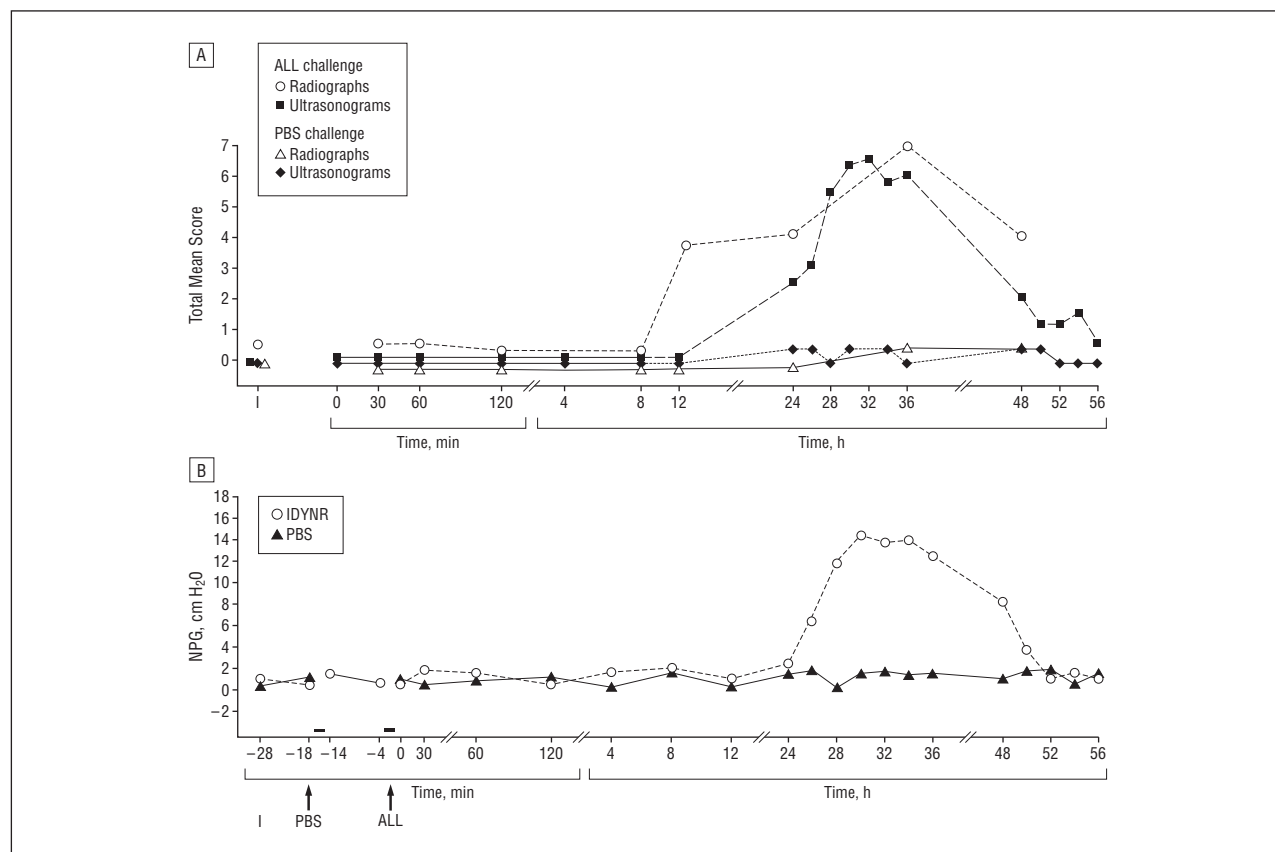


Figure 3. Maxillary sinus responses accompanying isolated delayed nasal responses (IDYNR; n=13). A, Mean point score of changes recorded on ultrasonograms and radiographs after allergen challenge (ALL) and on ultrasonograms and radiographs after phosphate-buffered saline (PBS) challenge. B, Mean rhinomanometric values (nasopharynx-nostril pressure gradient [NPG]) recorded during IDYNR and PBS. I indicates initial (baseline) values.

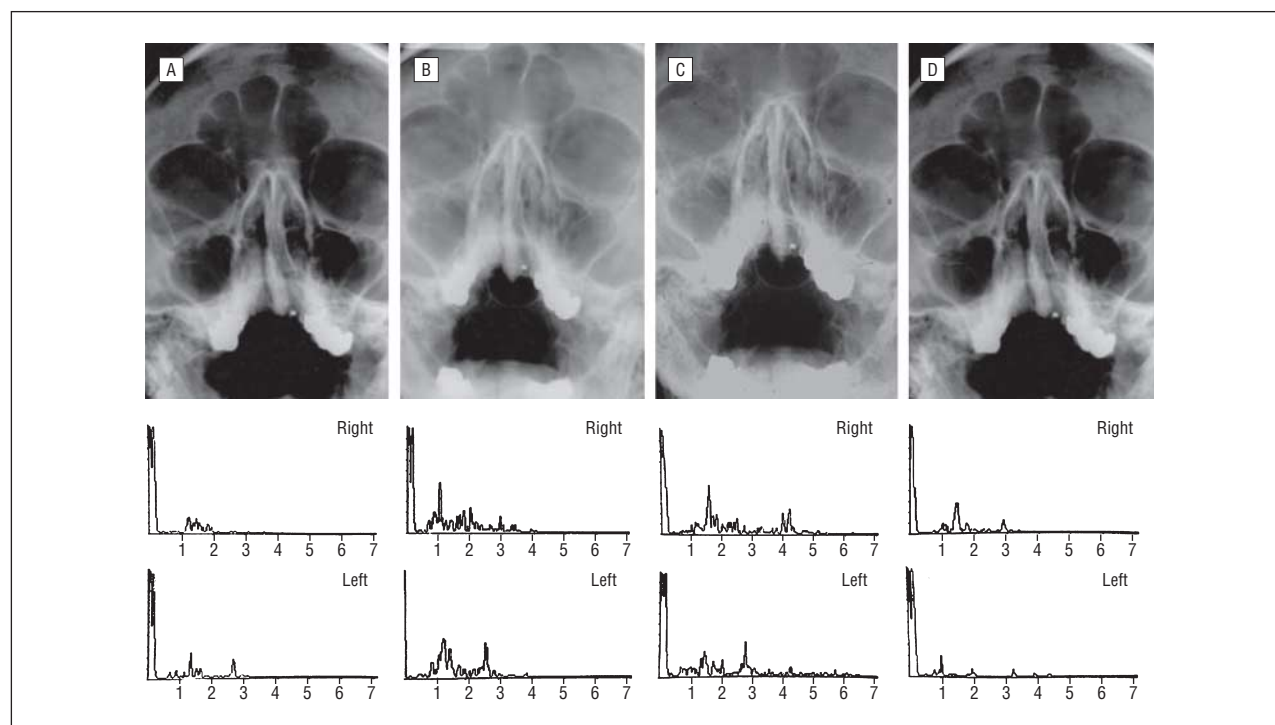


Figure 4. Radiographs (top) and ultrasonograms (bottom) of maxillary sinuses in a patient who developed an associated form of maxillary sinus response induced by primary isolated immediate nasal response to challenge with dog danders (500 biological units/mL). A, Before allergen challenge; B through D, 1 hour, 2 hours, and 12 hours after challenge, respectively.

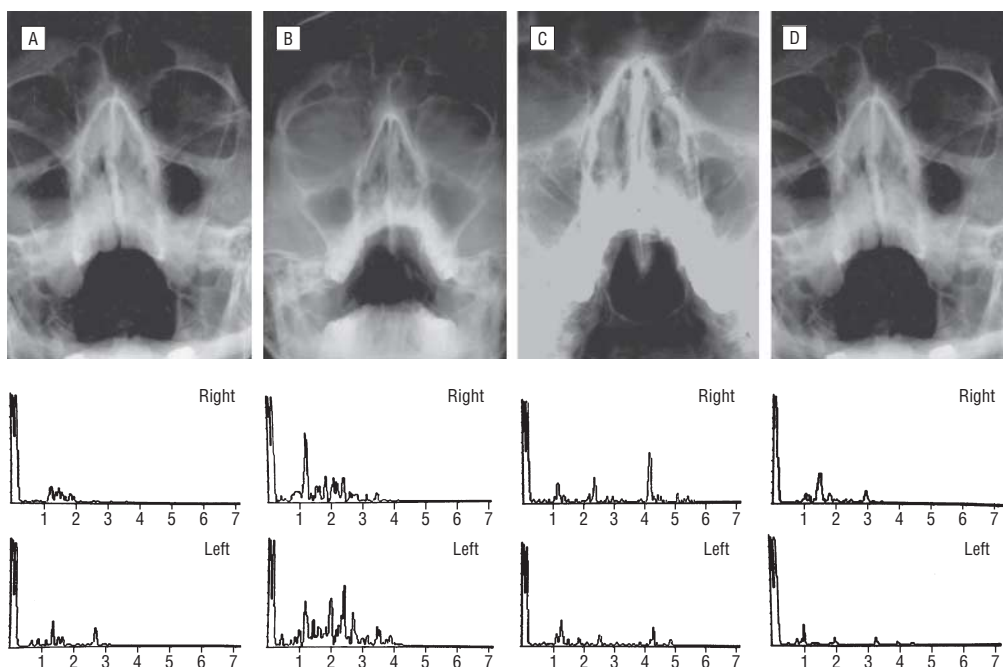


Figure 5. Radiographs (top) and ultrasonograms (bottom) of maxillary sinuses in a patient who developed an associated form of maxillary sinus response induced by primary isolated late nasal response to challenge with grass pollen mix (1000 biological units/mL). A, Before allergen challenge; B through D, 6 hours, 12 hours, and 24 hours after challenge, respectively.

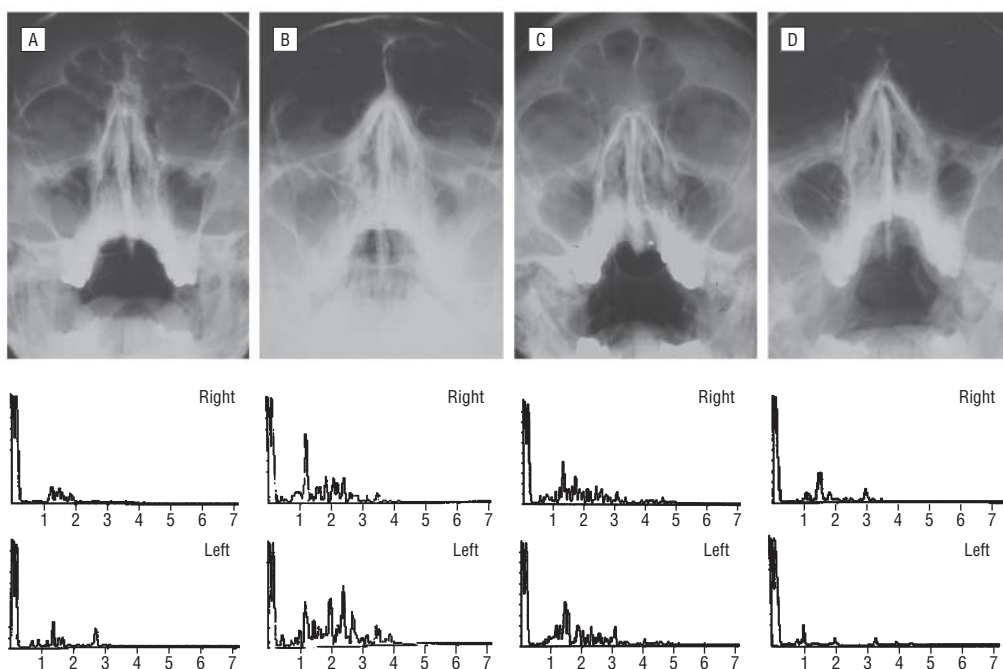


Figure 6. Radiographs (top) and ultrasonograms (bottom) of maxillary sinuses in a patient who developed an associated form of maxillary sinus response induced by primary isolated delayed nasal response to challenge with *Dermatophagoides pteronyssinus* (1000 biological units/mL). A, Before allergen challenge; B through D, 24 hours, 36 hours, and 56 hours after challenge, respectively.

to that leading to the obstruction of the ostia through the edema of the nasal mucosa as reported by other investigators.^{6-8,28-30,38-42} In contrast, during 5 of 31 negative NRs to allergen challenge, significant radiographic and ultra-

sonographic changes were also recorded (Tables 4, 5, and 6). In such cases, which represent a "primary" form of sinus response, the allergen may pass the nasal cavity barrier and penetrate through the ostium into the sinus

Table 7. Comparison of Total Point Score Recorded on Radiograms and Ultrasonograms for 135 NPTs by Time Intervals

Time, h	Total Point Score, Mean (SD)		<i>r</i> ^c	<i>P</i> Value ^c
	Radiography ^a	Ultrasonography ^b		
Before allergen	225 (31)	143 (18)	0.73	<.02
After allergen				
Immediate NR				
0.5	396 (51) ^d	338 (43) ^e	0.78	<.01
1	587 (58) ^e	421 (27) ^e	0.87	<.001
2	503 (42) ^e	415 (36) ^e	0.82	<.01
Late NR				
6	409 (48) ^d	373 (50) ^d	0.71	<.01
8	634 (75) ^e	541 (55) ^e	0.84	<.001
12	611 (63) ^e	404 (51) ^d	0.85	<.01
Delayed NR				
24	328 (45) ^f	423 (43) ^d	0.80	<.01
36	435 (34) ^e	402 (28) ^d	0.83	<.01
48	381 (22) ^d	279 (37) ^f	0.74	<.001

Abbreviations: NPT, nasal provocation test; NR, nasal response.

^aMaximal score per radiogram, 8 points; statistically significant difference, 3 points or more ($P < .05$).

^bMaximal score per ultrasonogram, 7 points; statistically significant difference, 2 points or more ($P < .05$).

^cCorrelation between radiograms and ultrasonograms; point scores evaluated by Spearman rank correlation coefficient. Statistical evaluation of postchallenge vs prechallenge point score by Mann-Whitney test.

^d $P < .01$.

^e $P < .001$.

^f $P < .05$.

without causing any nasal response.^{28,33-35,42} This mechanism seems to be similar to that described by Slavin⁴ as "trapping of foreign particles" (allergens) into the mucus of the sinuses. The secondary form of sinus disease occurs more frequently than the primary form; preliminary data indicate an approximate ratio of 1:150.³⁴

The diagnostic noninvasive imaging techniques for paranasal sinuses include a number of radiation techniques, such as conventional radiography (plain film), plain tomography, computed tomography (CT scan), and single-photon emission computed tomography (SPECT); techniques on electromagnetic principle, such as magnetic resonance imaging (MRI); or, finally, ultrasonography (echography) techniques.* The advantages and disadvantages of these techniques can be evaluated by various criteria, such as indication (eg, preoperative assessment, screening examination, and evaluation of therapy), accuracy of the imaging, radiation dose, capability for serial use, and costs.^{1,11-27,31,33,34,42-46}

In our study, radiography and ultrasonography were compared and tested on their capability for serial documentation of the changes in the maxillary sinuses due to hypersensitivity mechanisms. Conventional radiography is an easy, inexpensive technique, producing limited radiation, that can be repeated up to certain limits, and the results are reproducible.

This technique is suitable for evaluation of the changes appearing in the whole sinuses, including osseous skeleton, air-fluid level, aeration and opacification, and partial changes of the mucosal membrane. Nevertheless, the

radiation, even limited, remains a disadvantage of this technique.† Undoubtedly, computed tomography, used currently as a standard technique for imaging of paranasal sinuses, is more accurate and generates more information than conventional plain radiographs.^{20,22,31} However, for purposes of this study, plain radiographs were sufficient to provide simple comparative data to ultrasonography. Ultrasonography is an inexpensive, easy, time- and labor-saving technique generating directly accessible results and without ionizing radiation.‡ The important advantage of this method is its unlimited use in time and in number, the possibility of its use also in extramural offices, and low costs.³³⁻³⁵ This technique is suitable for reliable evaluation of mucosal thickening adjacent to the anterior and posterior sinus wall and presence of fluid level. However, this technique cannot visualize aeration and opacification of the sinus, and its results depend on the investigator's skill. There are 2 basic types of ultrasonography: A- and B-mode.^{11,13,26,27} The A-scan is a 1-dimensional method, modulating amplitude, whereas the B-scan modulates the brightness in a 2-dimensional manner. We have used the A-scan because of its reliable evaluation of the mucosal thickening and presence of fluid and its simple operation.³³⁻³⁵

The changes on the ultrasonograms and radiographs were evaluated by means of the previously developed Pelikan grading and score system.^{34,35,47} This semiquantitative system allows comparison of results not only within the same technique, eg, ultrasonography, but also between the different techniques, such as radiography and ultrasonography. In the past my group has also studied reproducibility of ultrasonography, the results of which have been published in part.^{34,47} The repeated ultrasonograms did not demonstrate any significant differences from the initial ultrasonograms ($P > .01$).

The results of this study demonstrated significant correlation between the radiographic and ultrasonographic changes of the maxillary sinus mucosal membrane accompanying both positive NRs ($P < .001$) and negative NRs ($P < .01$). The differences between the positive and negative responses of maxillary sinuses were statistically highly significant both for the radiographic ($P < .001$) and for the ultrasonographic ($P < .001$) changes. Our results showing a correlation of 95% between the radiographic and ultrasonographic findings in the maxillary sinuses are in agreement with results of some investigators,^{11,12,14-16,19,24,25,43} whereas they disagree with data reported by other authors.¹⁷ This disagreement may be related to differences in diagnostic procedures, clinical indications, and variables measured.

In conclusion, nasal allergy may be involved in CDMS in some patients. Nasal challenge with allergen combined with ultrasonography and, if necessary, also with one of the radiographic imaging methods may be a useful supplement for the diagnosis of this disorder in the clinical practice, especially in children. The confirmation of involvement of nasal allergy in patients with CDMS would indicate an additional treatment of the nasal allergy.

*References 1, 12, 13, 15-17, 20, 22, 27, 31, 33, 34, 43-46.

†References 1, 11-16, 18-20, 24-27, 32-35.

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Correspondence: Zdenek Pelikan, MD, PhD, Allergy Research Foundation, Effenseweg 42, 4838 BB Breda, the Netherlands (zpelikan@casema.nl).

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REFERENCES

- Slavin RG, Spector SL, Bernstein IL, et al; American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. The diagnosis and management of sinusitis: a practice parameter update. *J Allergy Clin Immunol*. 2005;116(6)(suppl):S13-S47.
- Christodoulou P, Cameron L, Durham S, Hamid Q. Molecular pathology of allergic disease, II: upper airway disease. *J Allergy Clin Immunol*. 2000;105(2, pt 1):211-223.
- Meltzer EO, Hamilos DL, Hadley JA, et al; American Academy of Allergy, Asthma and Immunology (AAAAI); American Academy of Otolaryngic Allergy (AAOA); American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS); American College of Allergy, Asthma and Immunology (ACAAI); American Rhinologic Society (ARS). Rhinosinusitis: establishing definitions for clinical research and patient care. *J Allergy Clin Immunol*. 2004;114(6)(suppl):155-212.
- Slavin RG. Sinusitis in adults. *J Allergy Clin Immunol*. 1988;81(5, pt 2):1028-1032.
- Berrettini S, Carabelli A, Sellari-Franceschini S, et al. Perennial allergic rhinitis and chronic sinusitis: correlation with rhinologic risk factors. *Allergy*. 1999;54(3):242-248.
- Ramadan HH, Fornelli R, Ortiz AO, Rodman S. Correlation of allergy and severity of sinus disease. *Am J Rhinol*. 1999;13(5):345-347.
- Kirtsreesakul V, Naclerio RM. Role of allergy in rhinosinusitis. *Curr Opin Allergy Clin Immunol*. 2004;4(1):17-23.
- Smart BA. The impact of allergic and nonallergic rhinitis on pediatric sinusitis. *Curr Allergy Asthma Rep*. 2006;6(3):221-227.
- Hao J, Pang Y, Wang D. Role of allergy and inflammation in nasal polyps and sinusitis [abstract 589]. *J Allergy Clin Immunol*. 2003;111(1)(suppl 2):S216.
- Gutman M, Torres S, Keen KJ, Houser SM. Prevalence of allergy in patients with chronic rhinosinusitis. *Otolaryngol Head Neck Surg*. 2004;130(5):545-552.
- Puhakka T, Heikkinen T, Mäkelä MJ, et al. Validity of ultrasonography in diagnosis of acute maxillary sinusitis. *Arch Otolaryngol Head Neck Surg*. 2000;126(12):1482-1486.
- Dobson MJ, Fields J, Woodford T. A comparison of ultrasound and plain radiography in the diagnosis of maxillary sinusitis. *Clin Radiol*. 1996;51(3):170-172.
- Ludwig A, Merten HA, Wiltfang J, Engelke W, Wiese KG. Evaluation of B-scan ultrasound, 3-D ultrasound, roentgen diagnosis and sinus endoscopy in follow-up assessment of the maxillary sinus after sinus floor elevation [in German]. *Mund Kiefer Gesichtschir*. 2002;6(5):341-345.
- Karantanas AH, Sandris V. Maxillary sinus inflammatory disease: ultrasound compared to computed tomography. *Comput Med Imaging Graph*. 1997;21(4):233-241.
- Varonen H, Makela M, Savolainen S, Laara E, Hilden J. Comparison of ultrasound, radiography, and clinical examination in the diagnosis of acute maxillary sinusitis: a systemic review. *J Clin Epidemiol*. 2000;53(9):940-948.
- Revonta M, Kuuliala I. The diagnosis and follow-up of pediatric sinusitis: Water's view radiography versus ultrasonography. *Laryngoscope*. 1989;99(3):321-324.
- Shapiro GG, Furukawa CT, Pierson WE, Gilbertson E, Bierman CW. Blinded comparison of maxillary sinus radiography and ultrasound for diagnosis of sinusitis. *J Allergy Clin Immunol*. 1986;77(1, pt 1):59-64.
- Otten FWA, Engberts GER, Grote JJ. Ultrasonography as a method of examination of the frontal sinus. *Clin Otolaryngol Allied Sci*. 1991;16(3):285-287.
- Lucchin F, Minicuci N, Ravasi MA, et al. Comparison of A-mode ultrasound and computed tomography: detection of secretion in maxillary and frontal sinuses in ventilated patients. *Intensive Care Med*. 1996;22(11):1265-1268.
- Benson ML, Oliverio PJ, Zinreich SJ. Imaging techniques: conventional radiography, computed tomography, magnetic resonance, and ultrasonography of the paranasal sinuses. In: Gershwin ME, Incaudo GA, eds. *Diseases of the Sinuses*. Totowa, NJ: Humana Press Inc; 1996:63-83.
- Esser PD, Alderson PO, Mitnick RJ, Arliss JJ. Angled-collimator SPECT (A-SPECT): an improved approach to cranial single photon emission tomography. *J Nucl Med*. 1984;25(7):805-809.
- Zinreich SJ. Progress in sinonasal imaging. *Ann Otol Rhinol Laryngol*. 2006;115:61-65.
- Catalano PJ, Payne SC, Choi E, Shah R. Correlation between computed tomography and bone single photon emission-computed tomography scintigraphy in patients with chronic rhinosinusitis. *Am J Rhinol*. 2007;21(4):433-438.
- Berger WE. Use of A-mode ultrasound for diagnosis of sinus disease in young children. *Ann Allergy*. 1986;56(1):39-43.
- Landman MD. Ultrasound screening for sinus disease. *Otolaryngol Head Neck Surg*. 1986;94(2):157-164.
- Mann W. A- and B- mode ultrasound diagnosis in diseases of the paranasal sinuses and soft tissues of the face. *Radiologe*. 1986;26(9):427-432.
- Revonta M. Ultrasound in the diagnosis of maxillary and frontal sinusitis. *Acta Otolaryngol Suppl*. 1980;370:1-55.
- Baroody FM, Mucha SM, deTineo M, Naclerio RM. Nasal challenge with allergen leads to maxillary sinus inflammation. *J Allergy Clin Immunol*. 2008;121(5):1126-1132, e7.
- Hamilos DL, Leung DY, Wood R, et al. Evidence for distinct cytokine expression in allergic versus nonallergic chronic sinusitis. *J Allergy Clin Immunol*. 1995;96(4):537-544.
- Hamilos DL. Chronic sinusitis. *J Allergy Clin Immunol*. 2000;106(2):213-227.
- Garcia DP, Corbett ML, Eberly SM, et al. Radiographic imaging studies in pediatric chronic sinusitis. *J Allergy Clin Immunol*. 1994;94(3 pt 1):523-530.
- Pelikan Z. Rhinitis, secretory otitis media and sinus disease caused by food allergy. In: Brostoff J, Challacombe SJ, eds. *Food Allergy and Intolerance*. London, England: Saunders; 2002:497-528.
- Pelikan Z. The role of allergy in sinus disease: children and adults. *Clin Rev Allergy Immunol*. 1998;16(1-2):55-156.
- Pelikan Z, Pelikan-Filipek M, Ossekoppele R. Chronic sinusitis maxillaris (CSM): the role of nasal allergy and the diagnostic value of echography and radiographs [abstract 1500]. *Allergy Clin Immunol News*. 1994(suppl 2):415.
- Pelikan Z. *The Late Nasal Response: Its Clinical and Immunologic Features, Possible Mechanisms and Pharmacologic Modulation* [thesis]. Amsterdam, the Netherlands: Free University of Amsterdam; 1996.
- Pelikan Z. Late and delayed responses of the nasal mucosa to allergen challenge. *Ann Allergy*. 1978;41(1):37-47.
- Meilillo G, Bonini S, Cocco G, et al. EAACI provocation tests with allergens: report prepared by the European Academy of Allergology and Clinical Immunology Subcommittee on provocation tests with allergens. *Allergy*. 1997;52(35)(suppl):1-35.
- Aust R, Stierna P, Drettner B. Basic experimental studies of ostial patency and local metabolic environment of the maxillary sinus. *Acta Otolaryngol Suppl*. 1994;515:7-11.
- Cole P. Physiology of the nose and paranasal sinuses. In: Gershwin ME, Incaudo GA, eds. *Diseases of the Sinuses*. Totowa, NJ: Humana Press Inc; 1996:33-51.
- Paulsson B, Bende M, Larsson I, Ohlin P. Ventilation of the paranasal sinuses studied with dynamic emission computed tomography. *Laryngoscope*. 1992;102(4):451-457.
- Aust R. Measurements of the ostial size and oxygen tension in the maxillary sinuses. *Rhinology*. 1976;14(1):43-44.
- Gwaltney JM Jr, Hendley JO, Phillips CD, Bass CR, Mygind N, Winther B. Nose blowing propels nasal fluids into the paranasal sinuses. *Clin Infect Dis*. 2000;30(2):387-391.
- Roberts DN, Hampal S, East CA, Lloyd GA. The diagnosis of inflammatory sinonasal disease. *J Laryngol Otol*. 1995;109(1):27-30.
- De Sutter A, Spee R, Peersman W, et al. Study on the reproducibility of the Water's views of the maxillary sinuses. *Rhinology*. 2005;43(1):55-60.
- Aaløkken TM, Hagtvedt T, Dalen I, Kolbenstvedt A. Conventional sinus radiography compared with CT in the diagnosis of acute sinusitis. *Dentomaxillofac Radiol*. 2003;32(1):60-62.
- Chen LC, Huang JL, Wang CR, Yeh KW, Lin SJ. Use of standard radiography to diagnose paranasal sinus disease of asthmatic children in Taiwan: comparison with computed tomography. *Asian Pac J Allergy Immunol*. 1999;17(2):69-76.
- Pelikan Z, Pelikan-Filipek M. The role of nasal allergy in chronic sinusitis maxillaris (CSM): X ray and echography during the nasal response to allergen challenge [abstract 933]. *Allergy Clin Immunol News*. 1991;1(suppl):334.