REVIEW ARTICLE

Pathophysiology, favoring factors, and associated disorders in otorhinosinusology

Matteo Gelardi[1], Paola Marchisio[2], Davide Caimmi[3], Cristoforo Incorvaia[4], Giada Albertario[2], Sonia Bianchini[2], Silvia Caimmi[3], Camilla Celani[5], Susanna Esposito[2], Miriam Fattizzo[2], Maria Luisa Fiorella[1], Franco Frati[6], Elena Labò[3], Gualtiero Leo[7], Amelia Licari[3], Alessia Marseglia[3], Elena Piacentini[7], Lorenzo Pignataro[8], Nicola Quaranta[1], Rossana Tenconi[2], Sara Torretta[8], Gian Luigi Marseglia[3] & Nicola Principi[2]

[1]Department of Ophtalmology and Otolaryngology, Otolaryngology Clinic, University of Bari, Bari, Italy; [2]Department of Maternal and Pediatric Sciences, Milan, Italy; [3]Pediatric Clinic, Foundation IRCCS Policlinico San Matteo, University of Pavia, Pavia, Italy; [4]Allergy/Pulmonary Rehabilitation, Istituti Clinici di Perfezionamento, Milan, Italy; [5]Department of Pediatrics, Sapienza University, Rome, Italy; [6]Spin-Off ATRP Srl, Allergic Tests Research and Production, Perugia, Italy; [7]Pediatric Allergy and Respiratory Pathophysiology Unit, Buzzi Children's Hospital, Istituti Clinici di Perfezionamento, Milan, Italy; [8]Department of Specialist Surgical Sciences, University of Milan and Foundation IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy

To cite this article: Gelardi M, Marchisio P, Caimmi D, Incorvaia C, Albertario G, Bianchini S, Caimmi S, Celani C, Esposito S, Fattizzo M, Fiorella ML, Frati F, Labò E, Leo G, Licari A, Marseglia A, Piacentini E, Pignataro L, Quaranta N, Tenconi R, Torretta S, Marseglia GL, Principi N. Pathophysiology, favoring factors, and associated disorders in otorhinosinusology. *Pediatr Allergy Immunol* 2012: **23** (Suppl. 22): 5–16.

Keywords:
pathophysiology; rhinosinusitis; children; nasal cytology; otitis media; adenoids; atopy

Correspondence
Cristoforo Incorvaia, Istituti Clinici di Perfezionamento, via Bignami 1, 20126 Milan, Italy
Tel.: +39 0257993289
Fax: +39 0257993579
E-mail: cristoforo.incorvaia@gmail.com

Accepted for publication 16 April 2012

DOI:10.1111/j.1399-3038.2012.01323.x

Abstract

The pathogenesis of rhinosinusitis (RS) is related to inflammation, caused by infections in the acute form of the disease but also by other agents in the chronic forms. Cytology allows to evaluate the defensive components, such as hair cells and muciparous cells, while the presence in the nasal mucosa of eosinophils, mast cells, bacteria and/or fungal hyphae, or spores indicates the nasal pathology. The anatomic and physiologic characteristics of the otorhinosinusal system account for the frequent concomitant involvement of the different components. The pivotal pathophysiologic sites are the ostiomeatal complex, the spheno-ethmoidal recess, and the Eustachian tube. The latter is the link with acute otitis media (AOM), which is the most common disease in infants and children and has major medical, social, and economic effects. Moreover, because of the strict relationship between upper and lower airways, nasal sinus disease may contribute to asthma and sinusitis may be considered as an independent factor associated with frequent severe asthma exacerbations. Concerning the role of allergy, the available data do not permit to attribute a central role to atopy in sinusitis and thus allergy testing should not be a routine procedure, while an allergologic evaluation may be indicated in children with OM, especially when they have concomitant rhinitis.

The pathophysiology of rhinosinusitis (RS) is related to the anatomic and physiologic characteristics of the otorhinosinusal (ORS) system, which account for the frequent concomitant involvement of the different components. The pivotal pathophysiologic sites are the ostiomeatal complex, the spheno-ethmoidal recess, and the Eustachian tube. Indeed, such system belongs to the upper airway, and this makes understandable also the frequent association with the low airway disease, particularly bronchial asthma. In this article, the immunologic and cytologic aspects will pave the way to the analysis of the relationship between RS and other disorders of upper and lower airways, as well as of risk factors linked to anatomic issues such as adenoid hypertrophy and to predisposing conditions such as atopy.

Immunologic and cytologic aspects of the oto-rhino-sinusal district

The ORS district, although is constituted by organs with different neurosensory functions, presents many immunocellular common aspects (1, 2). Upper airways mucosa is the most sensible interface between the human being and the environment.

The mucosa has an important immunologic role related to the presence of mucosal-associated lymphoid tissue (MALT) that in the nasal mucosa is called nasal-associated lymphoid tissue (NALT). This is constituted by lymphocytes aggregated in follicles as a part of the Waldeyer ring, free lymphocytes, and macrophages (3, 4). A large number of immunologic processes occur in this district, and the biochemical and clinical phenomena related to them are well known (5).

Immunologic aspects

The respiratory epithelium, once considered as a mechanical barrier, is actively involved in the NALT; in fact, its cells express major histocompatibility complex class II antigens and Langerhans-type dendritic cells, present in the submucosal layer, are able to present antigens to and activate T-lymphocytes through interleukin 1 (IL-1) (6).

In normal mucosa, both T-suppressor and T-helper cells are present, but they are functionally quiescent as demonstrated by the absence of the IL-2 receptor (7). B-lymphocytes mainly produce IgA, grow within the Waldeyer ring, and then reach the NALT tissue, localizing within the lamina propria (8). Dimerized sIgA through the secretory fragment are secreted in the mucosal film, where they inhibit the absorbtion of inhaled pathogens (9). IgG are generated in NALT, through plasmatic filtration reach the subepithelial layer in a concentration analogous to IgA, but increase in the case of inflammation. They can fix the complement and enhance phagocytosis and antibody-mediated cytotoxicity (10). Cells producing IgD are present as well as cells producing IgM, while plasma cells producing IgE are absent in the normal mucosa and present in case of allergy (11).

The different pathogenetic aspects of allergic inflammation such as hyperproduction of IgE, enhanced release of mediators, and aspecific tissue hyper-reactivity are now more unitarily considered (12). In fact, symptoms of allergy are only the final moment of an immunologic pathway that forms a condition of atopy, comes to clinical sensitization and finally becomes a disease. The passage from a condition to the other is mandatory even if time can vary from patient to patient. Atopy is genetically transmitted through a complex pattern with variable penetrance (13). Sensitization starts when T-helper type 2 (Th2) cells activate and release cytokines (IL-4, IL-5, IL-12, IL-13, etc) that induce both the transformation of B-cells into plasma cells and the production of IgE and IL-5. IL-5 is involved in the differentiation and maturation of eosinophils that will play a major role in the allergic inflammation. Th2 produce also IL-9 that potentiate IgE response and increase allergic inflammation in the airways (14).

An allergic disease is the expression of a IgE-mediated immunologic response (type I) that takes place when the Fc portion of IgE binds high-affinity receptors present on the mast cell surface (FcϵRI e FcϵRII) and, in presence of the antigen, induces cell degranulation. Among the released mediators, histamine is responsible for the immediate response, while the synthesis of other mediators such as leukotrienes (LTC4, LTD4, etc), prostaglandins (PGD2, PGE2, PGF2), eosinophil chemotactic factor, and platelet-activating factor is responsible, after 6–12 h, of a late response (15). The late response is characterized by the recruitment of inflammatory cells (neutrophils, eosinophils, T-lymphocytes), the hyperexpression of intercellular adhesion molecule 1 (ICAM-1) that keeps all these cells in situ (16) and by the ability of IL-5 to attract and activate eosinophils (17).

All this mediators determine in the target organ vasodilatation, increase vascular permeability and secretion of muciparous glands, and stimulate nerve endings that lead to the clinical symptoms (nasal obstruction, aqueous discharge, itching, and sneezing) (18). The clinicopathologic profile reflects the allergen nature; allergic rhinitis (AR) secondary to pollens is mainly seasonal, while AR attributed to animal epithelium or to house dust mite is mainly perennial.

Cytologic aspects

Respiratory mucosa is a pseudostratified epithelium with hair cells, muciparous cells, strial cells, and basal cells. Hair cell, shown in Fig. 1, is the most differentiated cell of the nasal mucosa (19). Hair cells and muciparous cells are the first defensive line of the upper airways (mucociliary system) and are present in the mucosa in a 5 : 1 ratio. Apart from these cells, in a normal mucosa, only rare neutrophils can be found. The presence in the nasal mucosa of eosinophils, mast cells, bacteria and/or fungal hyphae or spores is a sign of nasal pathology (20). Nasal diseases affect hair cells and determine a remodeling of the mucosa with an increase in muciparous cells (muciparous metaplasia). This leads to an increased production of mucous, while the reduction in hair cells impairs the mucociliary transport (TMC). There is therefore an accumulation of secretions and an higher risk of bacterial superinfection (21). As the normal turnover time for hair cells is 3 wk, recurrent inflammation does not allow the normalization within the nasal mucosa of the cells ratio and determines a self-maintaining vicious circle (22).

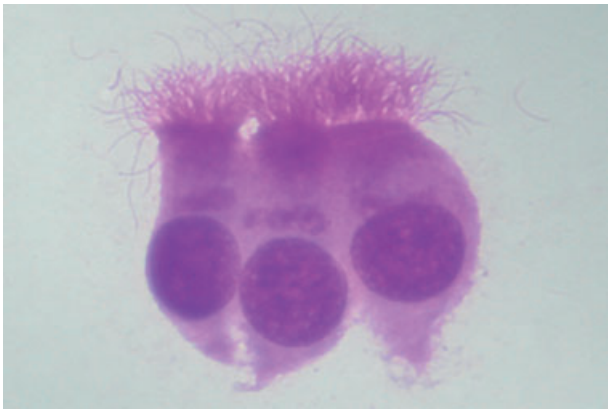

Figure 1 Nasal mucosa: Hair cells with an evident and well-conformated ciliary system. Staining MGG, 1000× magnification.

Cytologic aspects of allergic and non-allergic rhinitis

Patients affected by AR, seasonal or perennial, when stimulated by allergens develop an early and a late nasal response (23, 24). From a microscopic point of view, they are both characterized by the presence in the nasal mucosa of inflammatory cells such as eosinophils, mast cells, neutrophils, and lymphocytes (Fig. 2), which releasing chemical mediators, are responsible for the clinical manifestation of the disease such as itching, nasal congestion, discharge, and sneezing. When the allergenic concentration is low but persistent over time, as in perennial AR, a 'minimal persistent inflammation'characterized by neutrophils and scarce eosinophils is apparent. Rarely, mast cells are present as degranulating cells, this cytologic pattern leading to a chronic clinical condition characterized mainly by nasal obstruction and mucous discharge.

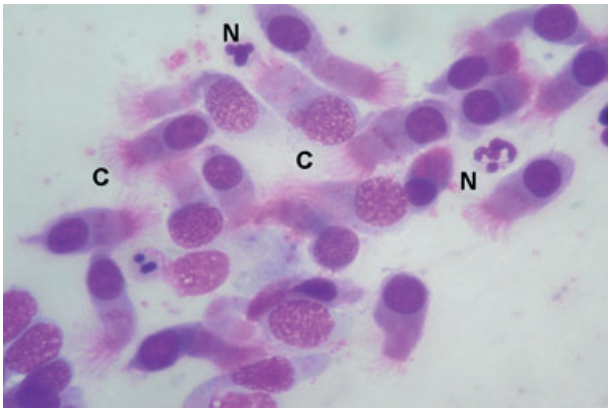

Figure 2 Nasal cytology in seasonal allergic rhinitis: Several eosinophils (E), neutrophils (N), lymphocytes (L), and rare mast cells (M). Staining MGG, 1000× magnification.

In seasonal AR, the rhino-cytograms may change according to the season. When allergens are present, nasal cytology will reveal the presence of neutrophils, lymphocytes, eosinophils, and mast cells mainly degranulated, while in the absence of allergens, nasal cytology will be negative as clinical symptoms, especially after 30 days from the end of pollination. Of note, in a recent study, the kind of inflammation as detected by nasal cytology was correlated with the clinical stage of AR as defined by the ARIA classification (25).

Patients affected by perennial AR to dust mites show higher number of muciparous cells (muciparous metaplasia), a condition typical of chronic inflammation. Eosinophils are present in patients with AR of any age, and the presence of intra or extracellular bacteria is a sign of infection (allergic rhinosinusitis).

In addition, chronic non-allergic rhinopathies such as non-allergic rhinitis with eosinophils (NARES), with mast cells (NARMA), with neutrophils (NARNE), and with both eosinophils and mast cells (NARESMA) (Fig. 3a,b,c,d) can occur at any age (26, 27). These 'cellular' rhinopathies have a chronic progressive pattern, intense symptoms, and lead to locoregional (rhinosinusitis, recurrent otitis, adenoiditis) and distant complications (bronchitis, pneumonitis, asthma, rhino-bronchial syndrome). When not adequately treated, they may be complicated over time by nasal polyposis. In particular, NARESMA has the highest tendency to complicate with nasal polyposis and asthma, is burdened by the poorest quality of life, and is also associated with sleep disorders (28).

Another important aspect in chronic rhinopathies is the need to recognize clinical entities characterized by the 'superimposition' of different pathologies. It has been shown as in 12% of patients affected by AR, allergy is associated with other pathologic conditions such as NARES, NARESMA, or others (29). The recognition of these conditions allows the correct therapeutic intervention. These patients show usually

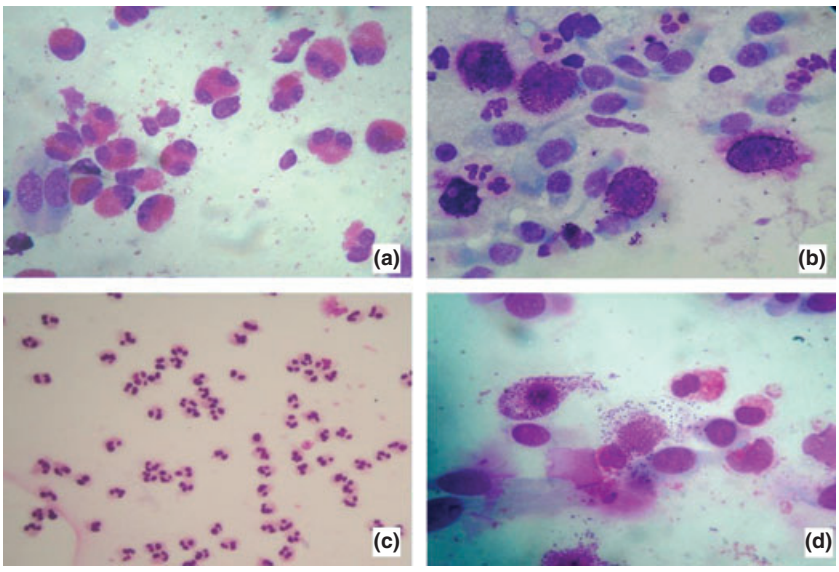

Figure 3 Nasal cytology in NARES, NARMA, NARNE, and NARESMA. Typical inflammatory infiltrate is evident: eosinophils (a), mast cells (b), neutrophils (c), and mast cells associated with eosinophils (d). Staining MGG, 1000× magnification.

positive skin prick tests (SPT) for seasonal pollens, chronic symptoms, and rhino-cytogram with eosinophils and/or mast cells even outside the pollen season.

Infectious aspects

Rhinologists, when studying infectious rhinitis, have focused their attention only on the presence or absence of bacteria in the planktonic state. Ultramicroscopic studies have, however, shown that 10% of the bacteria are present in the planktonic and 90% are organized in biofilms. Over the years, several ultramicroscopic methods such as scanning electron microscopy, transmission electron microscopy, and confocal laser scanning microscopy (30, 31) have shown that biofilms are constituted by bacterial colony for the 15% and by an esopolysaccaridic (EPS) organic matrix in the remaining 85%. The quantity of EPS varies according to the type of bacteria and increases with the biofilm age. Apart from EPS, proteins and extracellular DNA have been described in the organic matrix.

The structure of the biofilm and the characteristics of the organisms in the matrix are responsible for the resistance to antimicrobial agents such as antibiotics, disinfectants, and detergents. Antimicrobial resistance is secondary to the ability of the single bacteria within the biofilm to differentiate in a phenotypic state tolerating antibiotics (32) that is secondary to a delayed penetration of the antimicrobials through the matrix of the biofilm or the abnormal growth of organisms within the biofilm (33). The electron microscope techniques are expensive, poorly accessible, and require special processing of samples, which can also result in artifacts. A method was recently described, which allows the visualization of biofilms with a simple optic microscope staining in scrapings of the nasal mucosa stained with May-Grunwald Giemsa (34). In this cytologic study, in a large proportion of patients with infectious rhinitis, particular chromatic spots, which were variable in size, had irregular and blurred margins, and an intense cyan coloration were repeatedly observed. These spots were found to be of biofilm-related nature. Of note, the infectious spots may have variable shades that are likely to be attributable to the age of biofilm, which when more mature is more rich in polysaccharides, and consequently has a more intense coloration. This suggests that nasal cytology should be part of each rhinologist armamentarium, to complete the diagnostic work-up and to allow a precise diagnosis and adequate therapeutic approach.

Otitis media: a daily challenge for pediatricians

Acute otitis media (AOM) is the most common disease in infants and children: almost all children experience at least one episode in their first 3 yr of life, and about one-third experience two or more. The disease has major medical, social, and economic effects (35). It always has considerable financial implications because it involves at least one examination by a doctor and the prescription of antipyretics (and sometimes antibiotics, depending on the country); furthermore, it can cause major complications such as mastoiditis. Indirect costs are just as high and often higher, mainly because of the working days lost by one of the parents. Finally, its acute symptoms and frequent recurrences mean that AOM has a considerable impact on the quality of life of children and their families (36).

AOM used to be considered a quite trivial pediatric disease, but recent epidemiologic, microbiologic, and clinical data have now shown that it encompasses severe and non-severe, and complicated and uncomplicated episodes, as well as recurrences (37, 38).

Controversies have also accumulated concerning diagnostic methods and treatment options. At a time of increasing bacterial resistance, there is general agreement that it is essential to identify children with certain AOM and distinguish them from those with otitis media with effusion (OME) (36, 39). But diagnosis is often challenging in everyday practice, especially for pediatricians who have to cope with difficulties in performing otoscopy and interpreting otoscopic findings, as demonstrated by the reports of incorrect diagnoses throughout the world (40). Over the last few years, a number of European and American Scientific societies have issued guidelines concerning the diagnosis and treatment for AOM, but adherence to them has been suboptimal among pediatricians in the USA and Italy (41, 42).

Diagnosis

There is agreement that AOM can only be diagnosed when the following can be simultaneously demonstrated in a single patient: (i) acute symptom onset; (ii) the presence of signs of inflammation in the tympanic membrane; and (iii) the presence of exudates in the tympanic cavity (43). A correct diagnosis is essential to avoid useless, unjustified, costly, and potentially harmful therapeutic procedures.

An acute onset means the appearance of symptoms in the 72 h preceding the first clinical examination. Earache is the most reliable symptom but, like fever, it may be absent in a high proportion of cases, especially in younger children. Laine et al. (44) have recently reported that up to 50% of a group of children aged <3 yr whose parents suspected the presence of AOM had no fever, 13% had no irritability, and no individual symptom was capable of predicting AOM (Table 1).

The demonstration of tympanic membrane inflammation and middle ear effusion is essential (AOM cannot be diagnosed without looking at the eardrum) and should be based on: (i) otoscopic findings of marked erythema of the tympanic membrane, with bulging because of the presence of middle ear effusion; or (ii) otoscopic findings of a yellowish membrane by observing in transparency the presence of purulent material in the middle ear; or (iii) the presence of spontaneous perforation with otorrhea. Hyperemia of the tympanic membrane or the evidence of reflected light is not sufficient by itself for a diagnosis of certain AOM. Bulging is the most important clinical sign because, alone, it has the closest correlation with bacterial AOM confirmed by tympanocentesis (positive likelihood ratio, LR, 51; 95% CI 36–73) (45, 46).

Table 1 Occurrence and mean duration of symptoms in children younger than 3 yr of age with parental suspicion of acute otitis media (AOM) (modified, from reference 10)

	Occurrence n (%)		
Symptoms[a]	AOM (N = 237)	Non-AOM (N = 232)	p
Parentally reported ear pain	219 (92)	213 (92)	0.811
Child's verbal expression of ear pain	44 (19)	31 (13)	0.124
Ear rubbing	165 (70)	180 (78)	0.050
Fever	102 (43)	81 (35)	0.071
Cough	187 (79)	172 (74)	0.223
Irritability	206 (87)	216 (93)	0.026
Nasal congestion	177 (75)	171 (74)	0.809
Restless sleep	205 (87)	199 (86)	0.821
Rhinitis	222 (94)	220 (95)	0.591
Conjunctivitis	44 (19)	33 (14)	0.204
Diarrhea	31 (13)	22 (10)	0.219

Optimal diagnostic instruments

The simplest and most efficient means of supporting a diagnosis of AOM and confirming the presence of middle ear effusion is to use a pneumatic otoscope. An otoscopic examination should lead to the identification and description of all of the features on both sides of the tympanic membrane. The acronym COMPLETES summarizes the features that should be described for each tympanic membrane: entire surface, color, position, transparency, lighting, and mobility (47). Moreover, the laterality of the episode should be recorded in the child's chart as there is evidence that bilateral cases benefit more from the use of antibiotics (48).

The otoscope must have an appropriate light source (with batteries that are periodically replaced) and be equipped with uncolored specula of different sizes to avoid light dispersion and allow selection on the basis of the size of the auditory canal (which varies with age). A pneumatic otoscope can determine the mobility of the tympanic membrane, but is not necessary in the case of bulging of the full eardrum or spontaneous otorrhea (49). There is no published evidence of any pain or discomfort being associated with otoscopy (even pneumatic otoscopy) performed by a trained pediatrician. Obviously, infants and children are more difficult to examine than adults and should be kept still while undergoing otoscopy (as in the case of all procedures that may be affected by abrupt movements, such as examining the nose, pharynx, abdomen, and chest).

In uncertain cases, and in the absence of a pneumatic otoscope, pediatricians can use a static otoscope combined with a tympanometer or reflectometer, or recommend an otolaryngologic examination using otomicroscopy and/or otoendoscopy in addition to the above-mentioned instruments (36).

Ear wax removal

To use an otoscope correctly, the external canal has to be completely free and the tympanic membrane fully visible. The most common situation is one in which the membrane is partially or totally covered by ear wax that should always be removed. This may be necessary in up to 60% of infants with otitis media to visualize most of the eardrum (49). No method of ear wax removal (irrigation, eardrops, or manual removal) has yet been shown to be superior to others (50) but, if AOM is suspected, the use of eardrops would obviously not be suitable as it usually takes several days to work (50). Cerumen should be removed by a pediatrician or otolaryngologist, depending on the methodologic difficulties and peculiarities of local settings (36). Removal by means of a blunt ear curette under direct visualization (by displacing the lens of the otoscope) or a lighted ear curette with magnification (50) is relatively simple and painless if the amount is not excessive and the child is held still. Any other obstructions of the external auditory canal should only be removed by an otolaryngologist.

Pediatricians vs. otolaryngologists

Pediatricians and otolaryngologists may view otitis media differently. The former typically see mainly uncomplicated cases of AOM or recurrent AOM in large numbers of children aged < 3 yr, and diagnosis is definitely a major issue, whereas otolaryngologists typically see mainly complicated cases of more chronic OME and severe recurrent AOM in small numbers of children aged more than 3 yr. There have been reports of incorrect diagnoses by pediatricians throughout the world and reports of conflicting diagnoses between pediatricians and otolaryngologists.

It has been suggested that one of the main means of improving the management of AOM is education during medical school and residency, but training is often limited (51, 52). In Italy, most pediatricians and otolaryngologists do not receive adequate medical education concerning AOM when qualifying and tend to neglect AOM evidence-based guidelines in their everyday clinical practice. This extremely limited medical school training is in contrast with recommendations to begin such education early (43) (Table 2).

Only a minority of Italian physicians report using an appropriate method of diagnosing AOM, with otolaryngologists seeming better than pediatricians. The scarce use of pneumatic otoscopy by Italian physicians is noteworthy and, as far as pediatricians are concerned, these findings are in agreement with those of Vernacchio et al. (53), who found that fewer than 40% in the USA had used a pneumatic otoscope in the preceding 3 months (Table 3).

Hence, there are considerable differences between otolaryngologists and pediatricians, and as AOM is encountered by

Table 2 Proportions of pediatricians receiving formal medical education on acute otitis media at different time periods: Italy vs. USA

	Italy (%)	USA (%)
Medical school	9.2	0
Residency	27.4	59
Post-residency	63.4	0

Data derived from references 43 and 46.

Table 3 Proportions of pediatricians using diagnostic tools for the diagnosis of acute otitis media: Italy vs. USA

	Italy (%)	USA (%)
Pneumatic otoscopy	9.7	16.2
Tympanometry	1.7	6.3
Static otoscopy	88.6	77.5

Data derived from references 43 and 46.

both types of specialist, the use of different diagnostic procedures may cause confusion and prevent the adoption of a common clinical language, thus hampering an optimal multidisciplinary approach.

The future

In the future, AOM requires better diagnostics, continuing education, and broader agreement among specialists. Performing otoscopy is challenging but, although true, this does not justify its limited use – being challenging is not the same as being useless. Like many other pediatric procedures (e.g. listening to heart sounds with a stethoscope), otoscopy needs teaching, training and continuing education, practice, time, and especially, a willingness to learn. The new technologies allow personal continuing education on the Internet, and interactive computer programs are already available (51). New instruments such as digital otoscopes not only offer the possibility of extending the otoscopic view, but also the opportunity of archiving and sharing images with colleagues and parents. As they are not particularly expensive, they can be efficiently used by primary care pediatricians.

Finally, specific educational programmes concerning pediatric AOM should be implemented before physicians become fully trained specialists, focusing (in the case of limited economic resources) on the period of residency. Post-residency medical education should be further encouraged, monitored, and supported by academic sources to reduce the role of industrial sponsorship and self-reported experiences.

The relationship between rhinosinusitis and asthma in children

Many centuries ago, Galen first noted the coexistence of RS and asthma (54). Since then, several Authors described such association, postulating that these two diseases are actually two different expressions of a common pathologic process (55–57). Most of the published studies include adults, but some of them focus on children. Nevertheless, none of the published works can definitely point out the exact link between the two conditions. Besides that, it has to be said that recent progress in understanding the biology of airway disease has identified inflammation as the key to understand these diseases. Besides inflammation, several other mechanisms that link the upper (nose, sinuses, larynx, pharynx, and trachea) and lower (bronchi and lungs) airway segments may be involved as well (54).

The European Position Paper on the Primary Care Diagnosis and Management of Rhinosinusitis and Nasal Polyps defines RS as a complex inflammatory condition with great variability in presentation, diagnosis, and management (58). RS is a common disease in children and can be classified as infectious or allergic, acute or chronic, and associated or not with nasal polyps (59, 60). Typical signs and symptoms include nasal congestion, nasal discharge, nasal purulence, post-nasal drip, facial pressure, hyposmia, cough, fever, halitosis, dental pain, ear fullness, and headache. The diagnosis and management of sinusitis are often challenging, but generally unsatisfactory (58).

Asthma is defined as a chronic inflammatory condition resulting in reversible airway obstruction; diagnosis of asthma is currently considered as mainly clinical; diagnostic tools include measures of lung function and bronchial hyperreactivity. Clinical manifestations include dry cough, expiratory wheezing, chest tightness, and dyspnoea; such symptoms are intermittently triggered by allergens, infections, and airways irritants (61).

The natural history of asthma is still poorly characterized; however, we know that a small proportion of patients with asthma have a most severe form that requires, despite new and improved inhalation therapies, a continuous and long-term treatment with oral steroids to control symptoms (62). Because difficult asthma is rare in childhood, when asthma is difficult to treat and poorly controlled, a special evaluation should include the review of diagnosis with accurate lung function and the evaluation of possible comorbidities. In fact, occult sinusitis may be a significant pathogenic factor in patients with asthma, mainly in children. For this reason, it may be beneficial to determine the presence of RS in a patient presenting with poorly controlled asthma (56). On a clinical basis, it is well known that sinusitis may induce a worsening of asthma and that rigorous treatment for comorbid factors, such as RS, could result in less exacerbations, and better asthma control (55, 61). Therefore, the link between sinusitis and asthma is not only a speculative issue, because understanding the link between the two conditions could lead to optimal management of these diseases and, maybe, to a possible modification of the natural history of asthma.

Epidemiology

Most of the data concerning the epidemiology and the incidence of RS, of asthma and of the two conditions at the same time come from studies conducted in Western Countries. RS coexists with asthma in 34–50% of patients (63). Nevertheless, in patients presenting with asthma, the incidence of concomitant RS rise up to 84%, especially during asthma exacerbations (63). Burgess et al. found that childhood AR is associated with a significant 2- to 7-fold increased risk of developing asthma during adolescence or adulthood (64). The observation that asthma and RS coexist in patients at a higher frequency than would be expected from the prevalence of each in the general population provides a strong connection between the upper and lower airways (59).

Another epidemiologic interesting issue concerns the fact that, besides classical allergens, some other environmental factors may cooperate with AR to increase the risk for asthma. In fact, for example, it was showed that tobacco smoke increases the risk of developing asthma by 3-fold in a cohort of patients presenting with AR (65).

Contribution of various microorganisms in the pathogenesis of RS and asthma

Several authors have recently demonstrated the role of fungi and bacteria in the pathogenesis of chronic inflammatory airways diseases. Allergic fungal RS is a phenotype of chronic RS (CRS) with nasal polyposis, characterized by type 1 hypersensitivity to fungi, eosinophilic mucin with fungal hyphae in sinus secretions, and propensity for mucocele formation and bone erosion (66). The role of mold (i.e., *Alternaria*) in the pathogenesis of CRS has been stressed in other works, but results are not always consistent (67). As far as asthma is concerned, there is evidence that patients sensitized to molds (mostly *Aspergillus spp*.) present more severe forms of asthma (68). These patients with asthma, after a treatment with oral itraconazole associated with standard asthma therapy, achieve an increase in morning peak flow, and better results of rhinitis and asthma scores (69).

Bacteria are known to play a role in the pathogenesis of both sinusitis and asthma as well. *Staphylococcus aureus* can be frequently found in the nasal vestibulum, and it may have various effects on mucosal tissues. Specifically, surface protein A induces mast cell degranulation, whereas enterotoxins induce the release of cytokines, with a Th2-skewed pattern in nasal polyps, supporting the stimulatory role of superantigens in the development of inflammatory diseases of the nose (70). Moreover, *S. aureus* may lead to increased tissue remodeling and eosinophilic inflammation of the nose, which can be associated with comorbid asthma (71, 72).

The link between RS and asthma

RS and asthma are inflammatory processes in which eosinophils and the airway epithelium play a central role. The damaged epithelium react by releasing cytokines and chemokines that further attract eosinophils, thus starting a vicious circle of actions and reactions that activates and sustains inflammation (62). Thus, it seems clear that RS and asthma represent a range of overlapping diseases with a similar pathophysiologic mechanism, where chronic airway mucosal inflammation and remodeling are playing a critical and integrating role in these diseases (63). Precipitants of asthma are generally also precipitants of RS, and therefore, the association of RS with asthma exacerbations may be an epiphenomenon and the two conditions may be the progressive manifestations of a common disease process. In fact, RS manifested in asthmatics has clinical and biologic differences from that detected in the general population; inflammation of upper and lower airways is similar in patients presenting with both diseases; the severity of the two conditions is somehow related.

Possible explanations for the observed association of RS and asthma include the nasobronchial reflex, pharyngobronchial reflex, post-nasal drainage of inflammatory mediators from the upper to lower airway, inhalation of dry, cold air and environmental pollutants, and the 'shared pathogenesis' of RS and asthma (73).

Moreover, the airways epithelium seems to play a role in this association. Actually, it was shown that, even in non-asthmatic patients, during chronic rhinosinusitis (CRS) a thinning of pharyngeal epithelium with increased submucosal nerve density and increased nasal lavage fluid eosinophils occurs, which are associated with an increased bronchial hyperresponsiveness. Also, it was demonstrated that this bronchial hyper-responsiveness improves after RS therapy (74).

The data from nasal endoscopy

The few studies conducted in children have tried to discover new approaches to the evaluation and treatment for RS in relation to asthma (57). Even though computed tomography (CT) scanning is more accurate and able to identify abnormalities than traditional radiography, the introduction of rhinosinusal endoscopy with rigid and flexible instruments, for diagnostic and surgical aims, offers the possibility of a direct in situ examination of the sinusal area (56). After an appropriate local topical anesthesia, endoscopy may indeed be considered as a first level diagnostic tool in children with asthma, even in very young ones. In fact, it provides reliable visualization of all the accessible areas of the sinus drainages and adenoids, and should be performed before the evaluation by CT scanning (75). Nasal endoscopy allows guidance of micro swab sampling of purulent drainage from specific sinus drainage regions, minimizing contamination by the general nasal flora, to identify the involved pathogens. This new approach allows a better diagnosis in pediatric asthma, to identify some worsening factors, such as RS and adenoiditis, and to treat them adequately.

Uncontrolled asthma and occult RS

Often, children who present both RS and asthma generally have a poorly controlled asthma. In general, it is sometimes difficult to obtain a good clinical remission of RS in children presenting with concomitant asthma (76). The main reasons for this include a poor compliance to the prescribed treatment, an increasingly frequent steroidophobia, a lack of understanding of the pathology by the caregivers, a plurisensitization of the patient (in case of allergy) or an unappropriate therapy. All these factors lead not only to an incomplete treatment for RS, but also to a lower control of asthma. On the other hand, asthma treatment in children is slightly different than in adults. In pediatrics, clinicians begin prescribing a monotherapy, then increase doses and drugs until adequate symptom control, and finally try to step down. Children presenting with a concomitant RS need more medications to control their respiratory condition, and therefore they need to take many drugs, with an increased risk of lack of compliance. Indeed, in these children, it is even more diffi-

cult to obtain a good asthma control. At last, some asthmatic children, even when not showing clinical signs or symptoms of RS, do not achieve a clinical control of asthma. We believe that in these children, it is needed to perform nasal endoscopy, because behind a non-controlled asthma, despite the apparent lack of comorbidities, occult sinusitis may be often detected. We define occult sinusitis as a condition in which there is no clinical evidence of sinusal disease, but in which nasal endoscopy is capable of detecting signs of inflammation of the nasal mucosa, with mucopurulent drainage from the sphenoethmoidal recess or from the ostiomeatal complex. The disease should be systematically investigated in children who present with non-controlled asthma in spite of proper treatment and with an apparent lack of comorbidities.

We can conclude that sinusitis and asthma are not simply localized disease processes but are part of a systemic inflammatory disease affecting the respiratory system. Nasal sinus disease may contribute to asthma, and sinusitis may be considered as an independent factor associated with frequent severe asthma exacerbations. It is very important to understand that in children with sinus disease, both upper and lower airways need to be evaluated and treated and that in patients with uncontrolled asthma, the sinusal area should always be investigated, mainly through nasal endoscopy, even when nasal symptoms are not present.

Although, during these last years, the scientific community has produced a lot of evidence about the association of RS and asthma, bringing new data that support the hypothesis that RS and asthma may be progressive manifestations of a common, chronic, inflammatory disease, will favor the complete understanding of the link between the two diseases.

The role of atopy in nose, ear, and sinus disorders

The role of allergic sensitisation in rhinitis is well established; in fact, AR is the most common IgE-mediated immunologic disorder induced by the allergen exposure (77). Nevertheless, rhinitis may be induced also by non-allergic causes, which comprise viral, hormonal, drug-induced, structural, and occupational (irritant) causes, as well as non-allergic rhinitis with eosinophilia syndrome, known as NARES (78). Recently, nasal cytology studies allowed other non-allergic rhinitis types with the involvement of neutrophils to be identified, that is, the neutrophilic non-allergic rhinitis, NARNA; mast cells, that is, the non-allergic rhinitis mast cell, NARMA; both eosinophils and mast cells, that is, the eosinophil-mast cell non-allergic rhinitis, NARESMA (79). On the other hand, the importance of allergy in other disorders of the upper airway still needs to be definitely clarified. In particular, AR is commonly considered a predisposing factor for the development of sinusitis, but the clinical picture on the prevalence of allergen sensitisation found in pediatric patients is far from conclusive, and even the features of sinusitis in children with suspected respiratory allergy are uncertain (80–84). Concerning the ear, the relationship between OME and atopy seems more solid, especially based on recent investigations (85, 86). Here, we review the current knowledge on the possible connections between allergic sensitisation and pathology of nasal sinuses and the middle ear.

Allergy and sinusitis

Studies are available investigating the relationship between both acute and chronic RS. The first study in 1989 reported that in patients with acute maxillary sinusitis, SPT to environmental allergens were positive in 25% of patients with a history suggestive for allergy and in an additional 6.5% without such history (80). In 1992, a review on studies available at that time, most being abstracts, estimated a concordance between allergy and sinusitis ranging from 25% to 70% (82). However, the concurrent study by Orobello et al. did not find any correlation between the two conditions (81), and two other surveys confirmed this observation in the ensuing years (83, 84). In fact, the 1998 Practice Parameters on Diagnosis and Management of Rhinitis justifiably described the relationship between allergy and sinusitis as 'in need of elucidation' (87). However, considering new studies based on computed tomographic findings, which reported sinus abnormalities in many more subjects with AR than in normal subjects (88–90), although in other studies using the same computed tomography assessment such an association was not found (84, 91), the Practice Parameter on sinusitis in 2005 stated that 'Patients with sinusitis, especially of a chronic or recurrent nature, should have an allergy evaluation' (92). A cross-sectional study evaluated the prevalence of sensitization to common inhalant allergens in children with CRS (93). Among 2200 children referring for the evaluation of chronic respiratory symptoms, subjects satisfying at least two of the major criteria for the definition of CRS were recruited and underwent an allergen sensitization diagnostic workup by SPT with common inhalant allergens and total IgE measurement. Participants were stratified according to age inferior to 3 yr (Group 1), age between 3 and 6 yr (Group 2), and above 6 yr of age (Group 3) for the purpose of evaluation. The results showed that 351 children (217 boys; 134 girls; mean age, 5.23 yr; range, 4–15 yr) were available for evaluation and were stratified (27 in Group 1, 261 in Group 2, and 63 in Group 3). Prevalence of both sensitization to at least one inhalant allergen by SPT and of high total IgE was 29.9%. Prevalence of SPT sensitization was significantly different across age groups, with a value of 7.4% in Group 1, 31.4% in Group 2, and 33.3% in Group 3 ($p = 0.028$), but after adjusting for age, the presence of sinusitis and aeroallergen sensitization did not correlate significantly. The difference across groups for high total IgE did not reach statistical significance, with 22.7%, 30.1%, and 32.1% for each group, respectively. These findings showed that the prevalence of sensitization to aeroallergens in children with CRS in Italy is comparable to that of the general pediatric population, as assessed in the Italian arm of the ISAAC study (94), and this does not account for routine investigation for allergy in children diagnosed with such disease. This observation was substantially confirmed in a recent review that examined the current evidence for IgE- and non-IgE-mediated hypersensitivity mechanisms in acute and

chronic RS (95). The authors stated that 'there is conflicting evidence whether the prevalence of IgE-mediated allergy is greater in CRS than in individuals without CRS' and that 'despite the presence of classical IgE-mediated allergy, based on elevated allergen-specific serum IgE levels and positive SPT, currently there is no direct evidence for allergy as a major cause of sinonasal inflammation in CRS'. Instead, non-IgE-mediated fungal hypersensitivity and non-allergic IgE-associated inflammation may contribute to the pathogenesis in some forms of CRS, and specific IgE to bacterial superantigens may also modulate allergic inflammation (96). This requires further studies in well-defined patient groups and controls to better understand the role of IgE- and non-IgE-mediated hypersensitivity mechanisms in RS. A recent prospective study evaluated the incidence of acute sinusitis in children with seasonal rhinitis during the period of exposure to the specific pollen; 133 children (95 boys; 38 girls; mean age, 8.9 yr; range, 3–18 yr) with allergic sensitization to grass pollen, demonstrated by positive SPT, and rhinitis symptoms in the months of April, May, and June were included in the study (97). The symptoms suggesting acute sinusitis were, according to consensus documents (98), nasal blockage or stuffiness, nasal discharge or post-nasal drip (often mucopurulent), facial pain or pressure, headache, reduction/loss of smell, and cough. The diagnosis of certainty was obtained by nasal fibroendoscopy, which allows a complete inspection, including the vision of the ostiomeatal complex, and is positive when mucopurulent drainage is shown and/or edema. In 10 children (7.5%), clinical symptoms of acute sinusitis occurred during the period of grass pollen, and in eight of them (6%), the diagnosis was confirmed by nasal fibroendoscopy: two subjects had only edema and six had both edema and mucopurulent drainage. The mean age of children developing acute sinusitis was 6.7 yr. This suggests that in children with seasonal AR induced by grass pollen, the incidence of acute sinusitis during exposure to the causative pollen, as assessed by nasal fibroendoscopy, is low, and therefore seasonal rhinitis does not seem to be an important risk factor for sinusitis.

Allergy and OME

The strict anatomic and functional relationship accounts for the frequent disorders of the middle ear in subjects with nose and sinuses pathologies (99). In particular, it was reported that about 80% of children with OME have sinuses abnormalities (100). The favoring role of allergy for developing OME was evaluated in a number of studies. In 1993, a literature review found that the incidence of allergy in OME ranged from 5% to 80% (101). A more recent study evaluated the prevalence of middle ear dysfunction, as assessed by tympanometry, in children with CRS (102). From a population of 1,810 children with respiratory symptoms referred to a Pediatric Allergy center, subjects with CRS diagnosed by clinical criteria were selected. Children underwent testing of the middle ear function by tympanometry and of allergy by SPT with environmental allergens. Patients were divided into three groups according to age; 288 children (15.9%) had clinical diagnosis of CRS according to the established criteria, 24 patients were in group 1 (<3 yr), 220 in group 2 (3–6 yr), and 44 in group 3 (more than 6 yr). Altered middle ear pressure was found in 76.4% of patients, with a significantly higher rate of altered tympanograms in younger children ($p < 0.001$). A positive SPT was found in 29.9% of children, with a significantly higher rate of positivity in older children ($p = 0.01$). The decrease with age in the rate of tympanometric alterations was likely to be associated with the anatomic development of the upper airways, while the presence of atopy did not seem to play a role in their occurrence.

However, Alles et al. (85) studied 209 children with OME, assessing the atopic status by medical history, physical examination, nasal smears and SPT in all children, and by blood eosinophil counts, and total IgE levels in a randomly selected subset. The main outcome measures were the number of children with rhinitis, asthma, eczema, positive SPT, raised IgE level (>100 IU/l), and nasal and blood eosinophilia. Allergic rhinitis was found in 89%, asthma in 36%, and eczema in 24%. SPTs were positive to one or more of eight common inhalant aeroallergens in 57% of children. Blood tests in the selected subset revealed eosinophilia in 40% and a raised serum IgE in 28%. The authors argued that this prevalence was much higher than generally estimated in children, and that whole-population studies were required to confirm these findings, which could have important therapeutic implications for OME. Such a study was recently performed in Norway, based on a cross-sectional questionnaire survey of 40,000 randomly selected subjects aged 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, and 80 yr stratified by age and gender (86). Main outcome measures were recurrent childhood OME, childhood myringotomy, ventilation tubes or adenoidectomy, and lifetime allergy. The prevalence of recurrent OME was 24.3% and OME surgery was 12.4%. An increase in the proportion of OME surgery by age cohort was found, with the highest surgery rate of 0.52 for the 1955 age cohort, followed by a gradual decrease until the 1980 age cohort when surgery stabilized at 0.42. OME and OME surgery were more common in respondents with allergy. In conclusion, the currently available data indicate that attributing a central role to allergy in sinusitis could mean overdiagnosis, over-testing, or over-referral and could have implications for public as well as children's health. On the other hand, an allergologic evaluation may be indicated in children with OME, especially when rhinitis symptoms are concomitant.

Conflict of interest

The authors declare no conflict of interest.

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