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New insights on upper airway diseases

Guest Editors: Giorgio Ciprandi, Desiderio Passali

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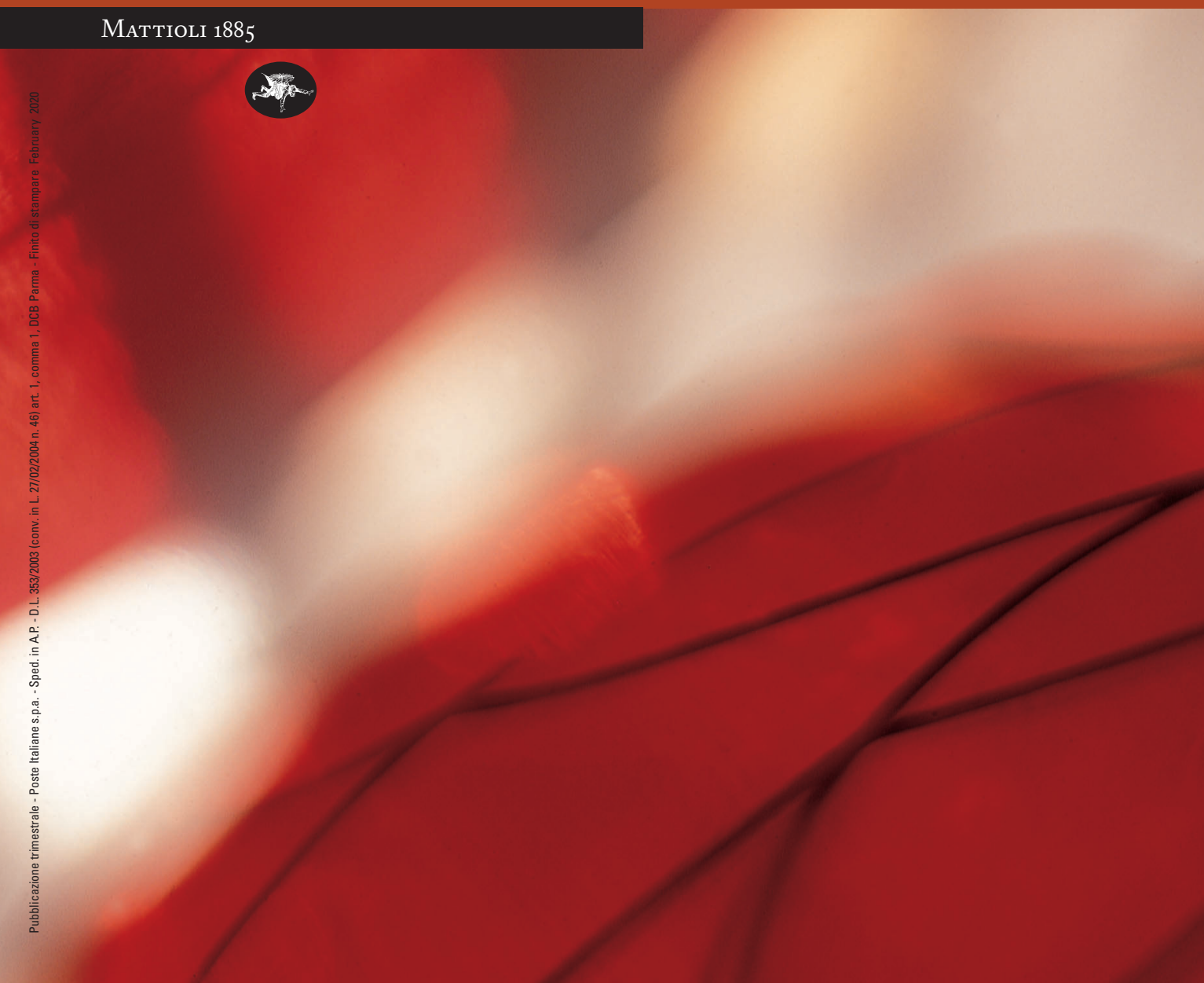

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Original articles

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Original article

An International Survey on the pragmatic management of epistaxis

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Abstract. Epistaxis is one of the most common ear, nose and throat emergencies. The management of epistaxis has evolved significantly in recent years, including the use of nasal cautery and packs. However, a correct treatment requires the knowledge of nasal anatomy, potential risks, and complications of treatment. Epistaxis is often a simple and readily treatable condition, even though a significant bleed may have potentially severe consequences. At present, there are very few guidelines concerning this topic. The current Survey explored the pragmatic approach in managing epistaxis. A questionnaire, including 7 practical questions has been used. The current International Survey on epistaxis management reported a relevant prevalence (21.7%), mainly during childhood and senescence, an important hospitalization rate (11.8%), the common use of anterior packing and electrocoagulation, and the popular prescription of a vitamin supplement and intranasal creams.(www.actabiomedica.it)

Key words: epistaxis, otorhinolaryngology, emergency, medical treatment, surgery

Introduction

Epistaxis is one of the most common otorhinolaryngology (ORL) emergencies. The management of epistaxis has evolved significantly in recent years, including the use of nasal cautery and packs. However, a correct treatment requires the knowledge of nasal anatomy, potential risks, and complications of treatment. Epistaxis is often a simple and readily treatable condition, even though a significant bleed may have potentially severe consequences.

From an epidemiological point of view, the lifetime incidence of epistaxis has been reported to be as high as 60% (1-3). However, a real number is difficult to be estimated as only a very small proportion requires specialist management and therefore many cases escape to evaluation. Only 10% of patients with epistaxis will present to a physician, but only a very few are ever seen by an otorhinolaryngologist. Noteworthy, although epistaxis can occur at any age, there is a bimodal distribution of children up to age 10 and adults greater than age 50. Individuals older than age 50 represent 40% of those requiring medical attention and tend to have more serious bleeds. Children younger than 10 years of age with a nosebleed tend to have an uncomplicated course because their nosebleeds are usually from the anterior nasal

blood supply and require limited intervention. Children under the age of 2 with nosebleeds are rare and warrant consideration of trauma (accidental and nonaccidental), nasal foreign body, and/or a systemic medical condition (coagulation disorder).

It has to be underlined that epistaxis accounts for the 33% of all emergent admissions for ear, nose, and throat problems and the median age for hospital admission is 70 years (4). Interestingly, anterior epistaxis is more common in the winter months in all age groups secondary to air from heating systems drying out the nasal mucosa thus making it more prone to irritation and bleeding (5, 6).

From a clinical point of view, epistaxis is most commonly classified into anterior or posterior bleeds. This division lies at the piriform aperture anatomically. More than 90% of episodes of epistaxis occur along the anterior nasal septum, which is supplied by Keisselbach's plexus in a site known as the Little's area (6). The Keisselbach's plexus is an anastomotic network of vessels located on the anterior cartilaginous septum. It receives blood supply from both internal and external carotid arteries. Approximately 10% of episodes of epistaxis are posterior bleeds. Posterior bleeds are most commonly arterial in origin. It presents with a greater risk of airway compromise, aspiration and difficulty in controlling the haemorrhage.

Epistaxis can also be divided into primary or secondary. Primary causes account for 85% of episodes and are idiopathic, spontaneous bleeds without any notable precipitant. Bleeds are considered secondary if there is a clear and definite cause (eg trauma, anticoagulant use, post-surgical).

About the aetiology, the cause of epistaxis can be divided into local, systemic, environmental, medications or, in the majority of cases, idiopathic. Local causes of epistaxis include trauma, neoplasia, septal abnormality, inflammatory diseases and iatrogenic causes. Local trauma is common among children who present with post-digital trauma or irritation. Causes such as neoplasia are uncommon. Examples of the systemic causes of epistaxis include age, hypertension, bleeding diathesis and alcohol. The association between hypertension and epistaxis is often misunderstood. Hypertension is rarely the direct cause of epistaxis and is perhaps related to underlying vasculopathy in this group of patients (7). It has been suggested that hypertension may be related to anxiety, but studies have failed to find conclusive evidence. About the environmental cause, the number of presentations of epistaxis has been found to increase during the dry winter months, often associated with changes in temperature and humidity. The incidence of epistaxis is also related to circadian rhythm, with peaks in the morning and late afternoon. About medications involved in epistaxis, the use of many over-the-counter and prescribed medications can alter coagulation. Nonsteroidal anti-inflammatory drugs (NSAIDs), warfarin, clopidogrel and the increasingly popular oral factor X inhibitors are commonly used medications that can affect clotting. It is imperative, therefore to take a thorough medication history. The use of complementary and alternative medicine must also be considered. Their use is increasing and can interfere with regular medications and clotting. Another practical classification of the causes of epistaxis has been proposed by Diamond (8) and reported in Table 1.

About the management, an algorithm could be useful in common practice. In 65% to 70% of cases of

Table 1. Causes of epistaxis in clinical practice

● Traumatic
– Digital manipulation
– Nasal fracture/contusion
– Foreign body in the nose
– Iatrogenic (e.g., nasogastric tube, surgical interventions)
● Neoplastic
– Juvenile nasopharyngeal angiofibroma– Tumours of the nasal cavity and paranasal sinuses
● Haematological
– Thrombocytopenia
– Hemophilia A and B
– Von Willebrand disease – Liver failure
● Structural
– Mucosal dryness
– Septal perforation
– Osler–Weber–Rendu disease (hereditary hemorrhagic telangiectasia)
● Drug-related
– Anticoagulants and antiplatelet drugs – Glucocorticoid nasal sprays
– Nasal consumption of drugs
● Inflammatory
– Allergic rhinitis
– Acute infectious diseases

epistaxis, simple first aid measures provided by the primary care physician or emergency physician are effective, including the use of tranexamic acid (9,10). If the direct application of pressure for approximately fifteen to twenty minutes fails, there are other methods available to achieve hemostasis. Vasoconstrictive agents and silver nitrate cautery may be useful. If epistaxis remains unresolved at that stage, anterior nasal packing may be necessary (11).

If bleeding persists, patients should be urgently referred to the ENT Department. So long as the source of the bleeding is visible, most cases of epistaxis can be successfully treated using electrical or chemical cautery. For posterior epistaxis, surgical intervention is markedly superior to packing.

Surprisingly, there are only three recent national guidelines (British, French, and German) on the management of epistaxis (12-14). Therefore, the aim of the present Survey was conducted to evaluate the most common approach to manage epistaxis in clinical practice.

Materials and Methods

The current Survey was performed using a questionnaire administered and completed in 43 Countries, including Albania, Angola, Armenia, Azerbaijan, Brazil, Chile, China, Cyprus, Colombia, Croatia, Czech, Egypt, El Salvador, Philippines, France, Germany, Japan, Guatemala, Hong Kong, Hungary, Italy, Guatemala, Kazakhstan, South Korea, Lebanon, Lithuania, Macedonia, Malaysia, Mexico, Moldova, New Zealand, Oman, Peru, Poland, Romania, Russia, Serbia, Slovakia, Spain, South Africa, Sweden, Ukraine, Venezuela.

Table 2. Questions included in the worldwide questionnaire

1) What is the current prevalence of nose bleeding in your Country?
2) What is the age distribution (in percentage) of nose bleeding in your Country? (0-6 years, 6-12, 12-18, 18-40, 40-60, >60)
3) What is the sex distribution (in percentage) of nose bleeding in your Country?
4) What is the hospitalization rate for nose bleeding in your Country?
5) What is the most commonly used treatment for nose bleeding in children in your Country?
6) What is the most commonly used treatment for nose bleeding in adults in your Country?
7) What is the most commonly used treatment to prevent nose bleeding in your Country?

The questionnaire included 7 queries, reported in detail in Table 2. The International Survey was performed in August 2019.

The analysis of the data was descriptive. Data were expressed as absolute numbers or frequency.

Results

The current mean prevalence of epistaxis was 21.7% worldwide. It ranged between 3% in New Zealand and Moldavia and 60% in Russia.

The mean age distribution of nose bleeding was 18.2% in the age range 0-5 years, 21.9% in 6-12, 14.6% in 13-17, 13.1% in18-40, 16.8% in 41-60, and 21% >60, as reported in Figure 1.

About the sex distribution of nose bleeding, there was a higher frequency in males: 53.2%.

The mean rate of hospitalization for epistaxis was 11.8% worldwide, with wide differences ranging from 1% in Colombia, Moldavia, and Slovakia, to 35% in Macedonia.

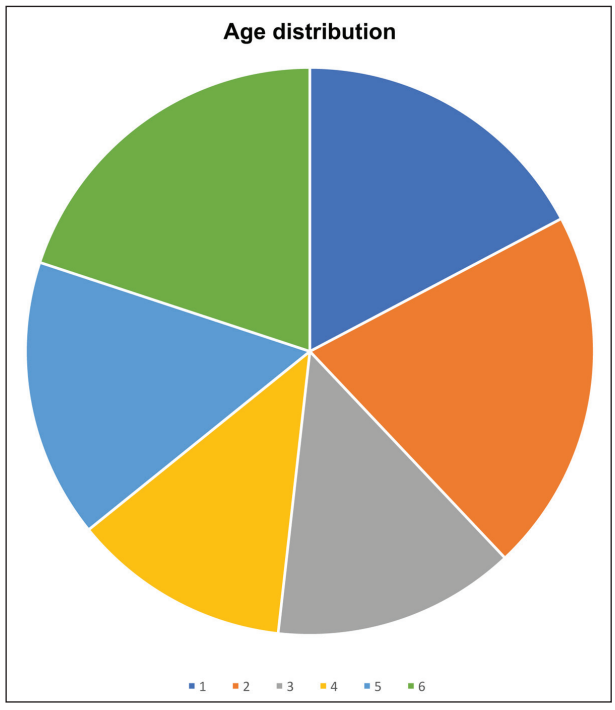

Figure 1. Age distribution: 1= 0-5 years; 2= 6-12 y; 3=13-17 y; 4=18-40 y; 5= 41-60 y; 6= >60 y

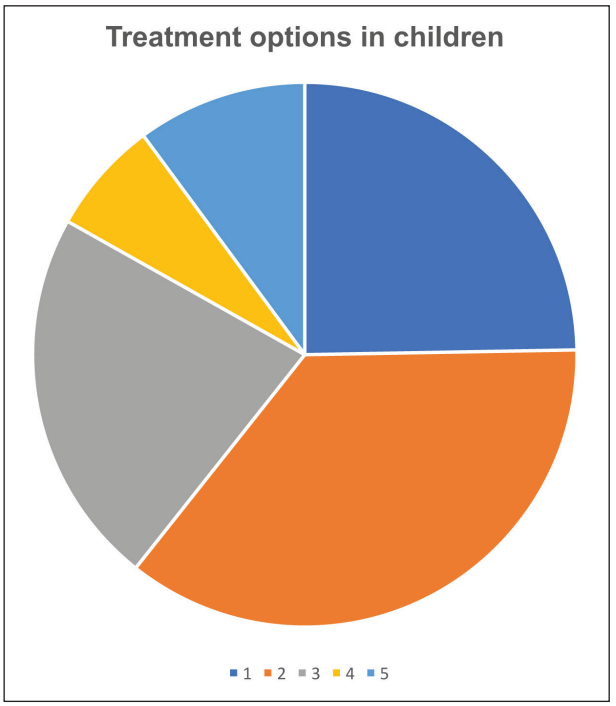

Figure 2. Treatment options in children: 1= electrocoagulation; 2= anterior packing; 3= nasal creams; 4= topical vasoconstrictors; 5= silver nitrate

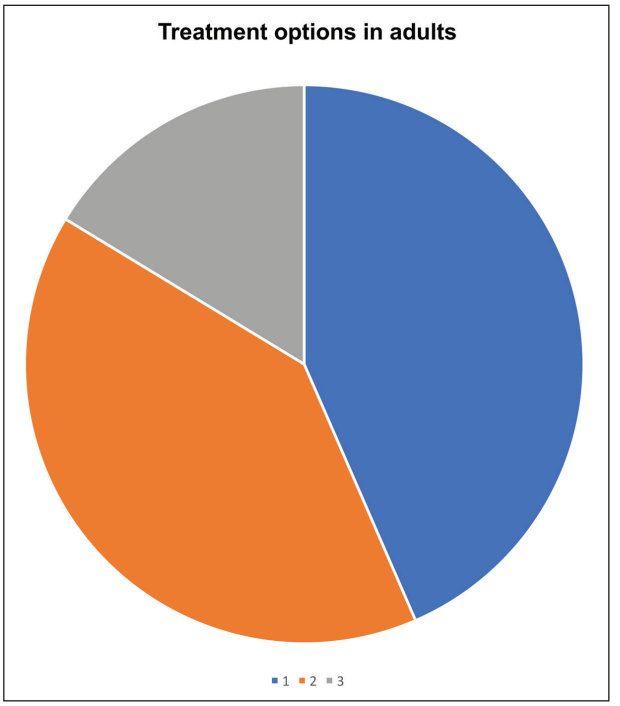

Figure 3. Treatment options in adults: 1= electrocoagulation; 2= anterior packing; 3= oral medications

The most commonly used treatment for nose bleeding in children were: anterior packing used in 32 countries, electrocoagulation in 22, nasal creams in 20, silver nitrate in 9, and vasoconstrictors in 6, as reported in Figure 2.

The most commonly used treatment for nose bleeding in adults were: electrocoagulation in 40 countries, anterior packing in 37, and oral drugs, including tranexamic acid, Vitamin C, E, and K, as shown in Figure 3.

The most common used treatment and/or measure to prevent nose bleeding were: treatment of arterial hypertension in 19 countries, nasal creams in 16, coagulation monitoring in 14, oral drugs, including tranexamic acid, Vitamin C, E, and K, in 11, otorhinolaryngological clinical follow-up in 10, and nasal lavage in 3, as reported in Figure 4.

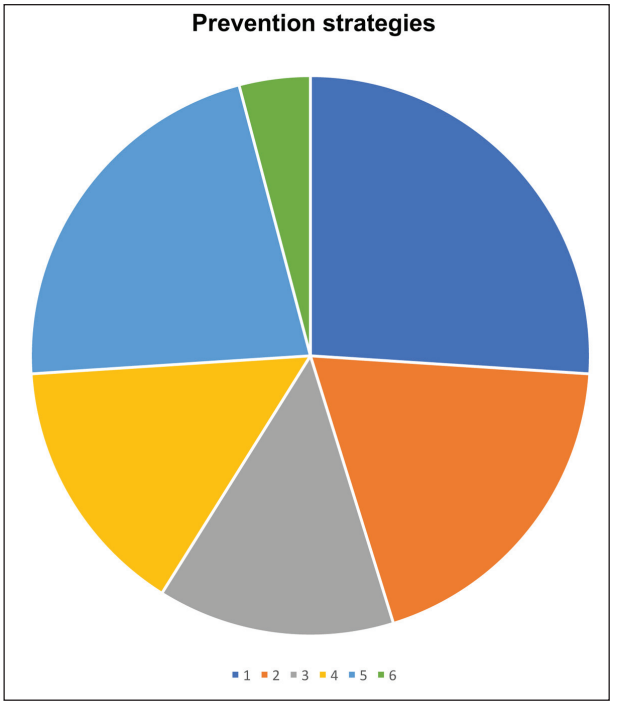

Figure 4. Prevention strategies: 1=management of arterial hypertension; 2= control of coagulation dysfunction; 3= ORL follow-up; 4= oral medications; 5= nasal creams; 6= nasal lavage

Discussion

Currently, the most common first-line ORL-specialty-based treatment of idiopathic epistaxis is nasal

packing, although there is a clear trend away from the use of nasal packs. Although it is a quick and easy to learn technique, emerging evidence show that cauterization provides economic advantages and is easy to teach, especially for anterior epistaxis, to non-otolaryngologists. In this regard, the current survey explored the worldwide pragmatic approach in managing epistaxis in the ORL setting. The current prevalence of epistaxis was 21.7%, but with wide inter-countries variations ranging from 3 to 60. This large variability could depend on different factors, including climatic difference and socio-economic-cultural factors. Turning to medical aid may vary significantly between countries, so many cases of epistaxis might be in-house self-treated. Childhood and ageing are mostly affected by epistaxis: the current finding is consistent with the literature data. The current Survey shows that there is a slight preponderance for males. The hospitalization rate is about 12%, but the variability is rather large as it ranges from 1 to 35%. This finding could also depend on peculiar aspects typical for every country, mainly concerning socio-economic factors. About the treatment of epistaxis, anterior packing and electrocoagulation are very popular worldwide both for children and adults. However, topical treatments are more frequently prescribed in children, whereas oral medications are preferred in adults. About the management, different approaches are used: particular attention is given to potential comorbidity, mainly concerning arterial hypertension and coagulation dysfunction, including iatrogenic causes. Vitamin supplement and tranexamic acid are commonly prescribed to prevent epistaxis recurrence as well as topical creams.

The nasal packing still represents the first-line approach to epistaxis, although, at present, it appears that there is clear evidence in the literature suggesting that it is less effective and associated with more admissions and longer hospital stays than endoscopic electrocoagulation-based management of epistaxis. In 65% to 70% of cases of epistaxis, simple first aid measures provided by the primary care physician or emergency physician are effective. If bleeding persists, patients should be urgently referred to the ORL Department. So long as the source of the bleeding is visible, most cases of epistaxis can be successfully treated using electrical or chemical cautery. For posterior epistaxis, surgical intervention is markedly superior to packing. The method of choice is endoscopic clipping or coagulation of the sphenopalatine artery, which controls bleeding in 98% of cases.

A recent review analyzed the most common treatments of idiopathic epistaxis, including nasal packing, electrocoagulation, Floseal, tranexamic acid, silver nitrate, endoscopic surgical procedure, endovascular embolization, and laser (6). However, only three national guidelines have published still now.

The British Consensus on Epistaxis recommended a five-management-domain-flow: initial assessment, cautery, intranasal agents, haematological factors, and surgery and radiological intervention (12). The British consensus recommendations combined a wide-ranging review of the relevant literature with established and rigorous methods of guideline generation. Given the lack of high-level evidence supporting the recommendations, an element of caution should be used when implementing these findings.

The French guidelines stated that arterial embolization should be performed by an experienced interventional neuroradiologist with adequate technical facilities, to reduce the risk of complications (13). Cerebral and supra-aortic vessel CT angiography should be performed in case of post-traumatic epistaxis with a suspected internal carotid injury. In case of persistent bleeding despite endoscopic hemostasis of the sphenopalatine artery, anterior ethmoidal artery hemostasis should be performed via a medial canthal incision, with endoscopic assistance as needed. In case of persistent epistaxis despite the usual surgical and neuroradiological procedures, surgical exploration of the sinonasal cavities should be performed, with elective coagulation in case of bleeding from secondary branches, and/or ethmoidectomy in case of diffuse bleeding. A decision-tree was drawn up for the management of second-line treatment of epistaxis.

The German guidelines stated that 65–75% of the patients who require treatment can be adequately cared for by their primary care physician or by an emergency physician with baseline measures (14). If there is persistent anterior epistaxis, an otorhinolaryngologist can control the bleeding satisfactorily in 78–88% of cases with chemical or electrical cauterization. Nasal packing is used if this treatment fails, or for posterior epistaxis.

In a retrospective study, surgical treatment was found to be more effective than nasal packing in the treatment of posterior epistaxis (97% versus 62% treatment success). Percutaneous embolization is an alternative treatment for patients whose general anaesthesia would put at high risk. The German guidelines concluded that the treatment of severe or recurrent epistaxis requires the interdisciplinary collaboration of the primary care physician, the emergency physician, the practice-based otolaryngologist, and the hospital otolaryngology service. Therefore, uniform guidelines and epidemiological studies on this topic would be desirable.

On the other hand, epistaxis management is frequently in-house self-made or in a primary care setting. In this regard, the use of intranasal creams is popular. Many compounds are available, including hemostatic ointment. In particular, a mix of saturated fatty acids, yeast protein extract (vegetal collagen), phosphatidylcholine, tocopheryl acetate, beeswax, soya oil, stearyl alcohol, calcium, potassium, magnesium chlorides, glyceryl monostearate (Emofix, DMG, Italy) has been evaluated in a study conducted in 100 patients affected by epistaxis (15). The haemostatic ointment significantly reduced the percentage of patients affected by epistaxis and the number and severity of bleeding episodes. Therefore, the therapeutic and preventive use of ointment medical device is favourably accepted in clinical practice.

In conclusion, the current International Survey on epistaxis management reported a relevant prevalence, mainly during childhood and senescence, an important hospitalization rate, the common use of anterior packing and electrocoagulation, and the popular prescription of a vitamin supplement and intranasal creams.

Conflict of interest: all the authors, but DV employee of DMG, have no conflict of interest about this matter.

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ORIGINAL ARTICLE

Chronic rhinosinusitis with nasal polyposis: the role of personalized and integrated medicine

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Abstract. Chronic rhinosinusitis with nasal polyposis (CRSwNP) is a frequent disorder. From a clinical and an immunopathological point of view, different phenotypes and endotypes have been identified. The frequent comorbidity with asthma allowed to pave the way to the use of biological agents for the treatment of CRSwNP. Biological agents are targeted to antagonize IgE, interleukin (IL) 4, IL-5, and IL-13 at present. However, a correct and appropriate workup is mandatory, mainly concerning the exact definition of the specific pheno-endotype. The preliminary outcomes are promising, even though there is a need for well-established indications, criteria of responsiveness, duration, and safety. On the other hand, this personalized medicine could be fruitfully integrated with gold-standard medications, such as intranasal corticosteroids. As CRSwNP is a chronic disorder, treatment should be long-lasting, so complementary anti-inflammatory treatments could be opportunely integrated and/or alternated to steroids. (www.actabiomedica.it)

Key words: chronic rhinosinusitis, nasal polyposis, biological agents, corticosteroids, enoxolone, mannitol

Clinical and immunopathological background

Chronic rhinosinusitis (CRS) is a frequent disorder as it affects about 10-12% of the European population (1). CRS may be classified into 2 phenotypes based on endoscopy and computed tomography (CT) findings: CRS with nasal polyposis (CRSwNP) and CRS without nasal polyposis (CRSsNP) (2). CRSwNP is defined by the presence of nasal polyps and by signs and symptoms lasting longer than 8–12 weeks (3,4). Nasal polyps are benign edematous masses in the nasal cavities, paranasal cavities, or both. Their occurrence depends on an exaggerated inflammatory reaction. As nasal polyps occupy space into nasal cavities they can cause nasal obstruction, rhinorrhea, postnasal drip, and hypo- or anosmia (5). The CRSwNP overall prevalence is approximately estimated to be 2% to 4% of the general population. Treatment options consist of local or systemic corticosteroids as the first-line choice, if ineffective there is the need for functional endoscopic sinus surgery. Especially patients with CRSwNP and comorbid asthma have a poor therapeutic response and a high recurrence rate, so the disease is more difficult to treat. Both CRSwNP and asthma share a serious impairment of quality of life (QoL) and cause a large financial burden for society (3). On the other hand, recent technological advances, mainly in the fields of genetics and engineering, increased the information concerning the phenotypes and the endotypes of chronic respiratory disorders, mainly concerning the type of inflammation and the type of immune response (6-9). This information could enable more targeted, effective, and efficient Precision Medicine (PM). PM refers to the "ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease, in

the biology or prognosis of those diseases they may develop, or in their response to a specific treatment" (10). Consequently, PM allows to stratify patients into subgroups and to tailor treatment based on their peculiar pheno-endotypes (11). This approach has been defined as Personalized Medicine (12).

From an epidemiological point of view, CRSwNP may be frequently associated with asthma: among patients with CRSwNP, approximately 30% have asthma and 15% have aspirin intolerance (13). Asthma is a chronic inflammatory disease of the lower airways characterized by bronchial inflammation, airway hyperresponsiveness, and usually reversible airflow obstruction, leading to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing (14). The disease has a high prevalence, ranging between 5-10% of the general population (15). Asthma frequently is associated with many comorbidities, including upper airways diseases, including rhinitis and rhinosinusitis (16, 17). In particular, the CRSwNP-asthma phenotype, characterized by the association of CRSwNP with asthma, is particularly severe (18).

Although some effective therapies exist for mild-moderate asthma, severe asthma remains difficult to treat, and the costs of the disease are relevant (19). A breakthrough in the treatment of severe asthma has been the discovery of biological agents. Indeed, it has been more than 15 years since the US Food and Drug Administration approved omalizumab for the therapy of moderate-to-severe perennial allergic asthma (20). At that time, the concept of removing one of the main triggers of asthma, such as IgE, excited the scientific and medical community. Indeed, 80% of children and 50% of adults have allergic asthma, such as an IgE-dependent bronchial inflammation, this approach could, therefore, lead to longstanding asthma remission for many patients. This lesson has been successively applied in the field of CRSwNP treatment (21,22). Many trials have been conducted using biologics for treating CRSwNP in these last years (23-26). However, there was a need for reflecting on the precise positioning of these biological therapies also for upper airway diseases (27, 28). In this regard, the European Forum for Research and Education in Allergy and Airway Diseases EUFOREA has nowadays provided a consensus on this issue (29).

The rationale for the use of biologics in CRSwNP is based on the existence of clinical-morphological characteristics and unbalanced immune response, that define specific polyps phenotypes and endotypes (30). CRSwNP may be classified based on the polarization of the immune response type. Type 1 immune response is sustained by a Th1 polarization associated with neutrophilic infiltration and IFN-γ overproduction; this endotype is most common in Asia (31). Type 2 inflammatory response is defined by interleukin 4 (IL-4), IL-5, and IL-13 and a nasal infiltrate of eosinophils, mast cells, basophils, and T-helper 2 (Th2) cells; also, comorbidity with asthma and allergic diseases is frequent (32). Type 3 immune response is characterized by increased release of the IL-17 cytokine family and is associated with frequent exacerbations (33). It has to be noted that CRSwNP is a pleiomorphic disorder, for example, the type 1 NP may include other phenotypes, such as cilia motility defects, cystic fibrosis, and infectious sinus diseases (34). Consistently, type 2 NP may account for several CRSwNP phenotypes, including allergic fungal rhinosinusitis (AFRS) and NSAID-exacerbated (typically by aspirin) respiratory disease (N-ERD). In particular, AFRS and N-ERD phenotypes can display increased IL-4, whereas other eosinophilic polyp phenotypes can be associated with high IL-5 and IL-13 levels (34). AFRS is also characterized by overexpressed periostin. N-ERD patients show high levels of cysteinyl leukotriene and leukotriene C4 (LTC4), so novel treatments may be designed (35). Moreover, a mixed type 1 and type 2 endotype has been also reported as well as imbrications with type 3 endotype (36). A possible explanation for these pleiomorphic endotypes might depend on the plasticity of type 2 innate lymphoid cells (ILC2), which might define also most severe forms (37). ILC2 cells may induce and amplify type 2 inflammation apart allergic pathogenic mechanisms (38). In other words, an eosinophilic infiltrate may occur without allergic reaction: a typical example is a non-allergic rhinitis with eosinophils (NARES), characterized by nasal eosinophilia without sensitization (39). Based on this immunopathological background, the clustering analysis is very fruitful for identifying specific endotypes. Initial clustering analysis considered only symptoms and quality of life aspects (40,41). Successively, a se-

ries of immunological parameters were investigated in patients suffering from CRSwNP, including IL- 5, eosinophilic cationic protein (ECP), *S. aureus* enterotoxin (SE-IgE), and albumin to define endotypes (42).

Pragmatic approach

At present, physicians stratify the patients with CRSwNP to define the optimal therapeutic strategy and formulate an appropriate prognosis resorting, in current clinical practice, to nasal endoscopy and CT findings and clinical outcomes, including the severity of symptoms, their response to treatments and recurrence, and asthma comorbidity. This clinical approach has been used to create simple management algorithms based upon clinical parameters, such as the visual analogue scale (VAS) and the sino-nasal outcome test (SNOT-22) score (40, 41). Further, a series of biomarkers were investigated to improve diagnosis, response to treatment, and prognosis (28). Initially, tissue eosinophilia and IgE (classical type 2 biomarkers) were envisaged as predictors for corticosteroid sensitivity. Further, another type 2 biomarkers were evaluated in the context of the Precision Medicine approach. In this regard, sialic acid-binding Ig-like lectin 8 (Siglec-8), a surface receptor of type 2 immune cells, thymic stromal lipoprotein (TSLP), an epithelial cell-derived innate cytokine, and IL-25, a proinflammatory cytokine promoting type 2 inflammation, were considered the potential target of antagonism in clinical trials (42). The 24-h urinary LTC_4 has been proposed as a biomarker for N-ERD phenotype and consequently for identifying patients who could be potentially responder to leukotriene antagonists (43). Therefore, the biomarkers may be useful for applying the concepts of Precision Medicine and Personalized Medicine in the management of patients with CRSwNP (44). However, it has to be considered that there are still important limitations in daily practice. Indeed, a satisfactory biomarker has not been still identified for earlier and more aggressive surgical treatment, i.e. the reboot approach, for patients with severe type 2 CRSwNP (28, 45-47). Similarly, there is no reliable biomarker able to classify type 1 endotype, as well as anti-type 3 targeted biologics, that were ineffective in the asthma model (48).

Trials with biological agents

Some trials provided evidence about the effectiveness of biologics in the treatment of CRSwNP. The first experience was conducted in patients with severe asthma and an (unexpected) improvement of NP was contemporarily observed. Consequently, different molecules were tested in this topic.

Omalizumab, an anti-IgE monoclonal, was the first experienced biologic in the treatment of patients with CRSwNP. A series of convincing proofs have been documented both by randomized controlled trials (21, 49, 50) and real-life studies (51). Interestingly, omalizumab was effective in treating NP also in non-allergic patients (21, 52). This outcome could open the possibility to explore new indications for this biological agent.

Mepolizumab is an anti-IL-5 monoclonal antibody that reduces peripheral and bronchial eosinophils in asthmatic patients (53). Mepolizumab has been investigated successfully also in patients with CRSwNP (54, 55). In particular, it has been recently reported that mepolizumab could reduce the need for sinus surgery (56).

Reslizumab is an anti-IL-5 monoclonal antibody that binds to IL-5, preventing it from binding the subunit of the IL-5 receptor. It has been evaluated the effects of Reslizumab on patients with asthma and self-reported nasal polyposis (57).

Benralizumab is an anti-IL-5 monoclonal antibody that binds to the α-chain of the IL-5 receptor initiating a direct, rapid depletion of eosinophils through enhancing the antibody-dependent cell-mediated cytotoxic pathway via the NK cells (58). A case report of severe asthma with eosinophilic CRS has been successfully treated with benralizumab (59).

Dupilumab is an anti-IL-4 monoclonal antibody which functions by targeting the alpha chain of IL-4Ra, a common receptor for both IL-4 and IL-13. These 2 cytokines play a prominent role in the Th2 pathway and pathogenesis of nasal polyp formation (60). In a randomized, double-blind, placebo-controlled phase 2 study of dupilumab in patients with CRSwNP with and without asthma, the dupilumab group experienced significant improvement in endoscopic, radiographic, and QoL endpoints relative to

placebo (61). These clinical changes were accompanied by a statistically significant reduction in circulating concentrations of the type 2 biomarkers, such as total serum IgE and eotaxin-3. More recently, it has been reported that dupilumab was able to reduce biomarkers of type 2 inflammation, including eotaxin, eotaxin 3, eosinophilic cationic protein, in polyps of patients with CRSwNP (62).

Biomarkers in clinical practice

These reported outcomes were encouraging and could pave the avenue to a new promising approach in patients with CRSwNP even though a need a precise classification of the patients is still mandatory (63). However, it has to be noted that CRSwNP is a multifaceted disease frequently characterized by multiple phenotypes and endotypes, that can imbricate between them. Patients with CRSwNP may belong to type 1, type 2, or type 3 endotype, but could display mixed phenotypes as well as multiple endotypes. In this regard, the identification of reliable biomarkers could be useful in precise phenotyping and allow the targeting of specific biologic mechanisms underlying the disease process. On the other hand, most of the investigated biomarkers are experimental and cannot be applied to routine practice. In this regard, it has been recently proposed a list of four biomarkers able to differentiate type 2 from non-type 2 inflammation: serum specific IgE, peripheral eosinophils, nasal cytology, and fractional exhaled nitric oxide (FeNO), that are easily available in daily clinical activity (64). Allergy is diagnosed by the demonstration of allergen-specific IgE production, in fact, IgE production, such as sensitization, is the *condicio sine qua non* to identify type 2 response (65). A real-world study showed that peripheral blood eosinophils correlated well with the presence of nasal eosinophils in patients with nasal symptoms, as assessed by nasal scraping and microscopic observation; consequently, peripheral eosinophils could be reasonably considered a biomarker for suspecting type 2 inflammation also at nasal level (66). Nasal cytology is a standardized procedure that can define the inflammatory phenotype of rhinitis, so allowing the precise diagnosis of rhinitis, mainly concerning the documentation of eosinophilic infiltrate (67). FeNO is a reliable biomarker able to identify type 2 bronchial inflammation as associated with eosinophil activation (68). Interestingly, NO can be measured also at nasal level (69). Also, type 2 immune response could be in turn stratified in two subgroups: the allergic endotype and the non-allergic endotype. To document sensitization, such as the production of allergen-specific IgE, could easily differentiate the two subgroups.

Personalized and integrated treatments

As previously discussed, the current challenge for the doctor managing patients with CRSwNP is the choice of the more appropriate therapy for the single patient, hopefully, according to the approach proposed by the Precision Medicine and the Personalized Medicine. In this regard, a multidisciplinary board of the EUFOREA suggested the positioning of biologics in this topic (29). First, a careful selection of patients was recommended: five prescriptive criteria were identified: i) evidence of type 2 inflammation, ii) need of systemic corticosteroids in the past two years, iii) significant QoL impairment, iv) significant hyposmia, and v) asthma comorbidity. Contraindications could be CRSsNP diagnosis, non-type 2 inflammation, cystic fibrosis, unilateral polyps, mucoceles, immunodeficiency, and factors associated with scarce compliance. Another relevant point was the recognition of criteria for defining response to biological therapy after one year: reduced nasal polyp size, reduced need for systemic corticosteroids, improved QoL, improved olfaction, and reduce the impact of comorbidities (29).

At present, biologic agents for CRSwNP could be therefore prescribed exclusively in patients with severe asthma. Moreover, as carefully pointed out by the Consensus, a multidisciplinary integrated care pathway should be performed in clinical practice. A thorough evaluation of both upper and lower airways should be done at every visit, monitoring symptoms, available biomarkers, airway function, and control medications use.

On the other hand, it has to be underlined that the enthusiastic interest obtained by biological agents

should not obfuscate the relevant importance of the so-called small molecule drugs (SMD), as recently highlighted by an EAACI Taskforce on Immunopharmacology (70). SMD is an umbrella definition that includes several medications belonging to different classes, such as topical and systemic corticosteroids, antagonists of leukotrienes, β2-agonists, antimuscarinic agents, mast cell stabilizers, and other active compounds (70). In this regard, intranasal corticosteroids represent the first-line choice in the management of CRSwNP (3, 4). Intranasal corticosteroids could be opportunely integrated with biologics.

There are different topical corticosteroid molecules, all of them are effective in reducing nasal inflammation. However, mometasone furoate nasal spray (MFNS) has a specifical indication for the treatment of nasal polyps in adult patients (71, 72). Its anti-inflammatory and anti-allergic has been documented also in the model of experimental allergic rhinitis (73). Also, its efficacy and safety have been proved by more than 20 years of presence on the market. There is also recent evidence that MFNS is effective in the postoperative management of CRSwNP (74). The long-lasting use of MFSN is safe as it does not affect the DNA of nasal mucosal cells (75). Also, MFSN is well-tolerated in the pediatric population and pregnant women (76, 77).

On the other hand, it has to keep in mind that CRSwNP is a chronic disease, thus prolonged corticosteroid treatment should be required to control the patients and to prevent a recurrence. In this regard, complementary treatments could be favourably integrated to spare the corticosteroid use. The intranasal route is the preferable and different medical devices are currently available. In this regard, Narivent® is a medical device containing enoxolone and mannitol. Enoxolone is the 18-β-glycyrrhetinic acid, it exerts potent anti-inflammatory and immunomodulatory activity as documented in *in vitro* studies (78, 79). Also, it has been demonstrated that enoxolone reduced nasal eosinophilia in children with allergic rhinitis acting on the cytokine HMGB1 (80). Enoxolone was also able to improve the nasal mucociliary transport time (81). Mannitol is a well-known osmotic anti-oedema agent. Clinical studies have demonstrated that this medical device was able to significantly improve the severity of nasal congestion (82, 83).

Conclusive remarks

Biological agents are a promising therapy for CRSwNP that could be adequately addressed to selected patients after a careful workup. However, conventional anti-inflammatory therapy should continue to be prescribed as effective, safe, and cheap. Of course, biologics and intranasal corticosteroids could be integrated between them. Moreover, as CRSwNP is a chronic disorder, non-steroidal active compounds could be effectively and safely integrated and/or alternated to intranasal corticosteroids and other anti-inflammatory ancillary treatment. Therefore, personalized and integrated therapies could be favourably prescribed in patients with CRSwNP.

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Original article

The impact of allergic rhinitis in clinical practice: an Italian Survey

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Abstract. Allergic rhinitis (AR) is a very common disorder. The current Survey was conducted on a sample of about 5,000 adult subjects in 5 Italian cities. A questionnaire, containing 15 questions, was administered on the road. AR affects about 20% of the general population. The most common diagnostic test was the skin prick test, but only 12% of patients performed an allergy test to confirm the diagnosis. About 50% of patients did not take any medicine. Even about 40% of treatments were suggested by friends or pharmacists. In conclusion, the current Survey demonstrated that AR is a common disorder in Italy, the diagnostic work-up is still incorrect, and the therapeutic approach does not adhere to the guidelines. Therefore, there is a need to implement adequate information on this topic in Italy. (www.actabiomedica.it)

Key words: allergic rhinitis, Italy, Survey, general population, questionnaire, on the road

Introduction

Allergic rhinitis (AR) is an inflammation of the nasal membrane which is characterized by symptoms, including sneezing, rhinorrhoea, nasal congestion, and nasal itching. It is often associated with eye symptoms, such as tearing, redness, and itching. AR is caused by sensitization, such as the production of specific IgE, to one or more aeroallergens. It is a very common disorder worldwide, as it may affect up to 40% of the general population. In Italy, its prevalence has steadily increased over the last decades in almost all the age classes and currently is estimated at 25% (1,2). The diagnosis of AR is based on the demonstration of the production of allergen-specific IgE and the concordance between allergy testing and history, such as the symptom occurs after the inhalation of the sensitizing allergen.

Allergic rhinitis was conventionally classified into seasonal AR and perennial AR based on the duration of exposure and symptoms (3). The common allergens for perennial AR include indoor allergens such as house dust mites, moulds, and animal dander, while those for seasonal AR are usually outdoor allergens such as tree pollen, grass pollen, weed pollen and moulds (4). Some patients sensitized to seasonal allergens have symptoms throughout the year and some patients sensitized to perennial allergens have symptoms during specific seasons. Moreover, many patients are sensitized to both perennial allergens and seasonal allergens simultaneously. The conventional classification has some limitations from a therapeutic standpoint due to its poor association with clinical symptoms. In 2001, the World Health Organization (WHO) proposed a new Allergic Rhinitis and its Impact on Asthma (ARIA) classification, which classifies allergic rhinitis according to the severity and symptom duration (5).

Skin prick test (SPT) and serum allergen-specific IgE (sIgE) measurements are the most common meth-

ods used to diagnose an allergy. Both techniques are widely accepted diagnostic tools. Several authors have investigated the concordance between the level of sIgE and SPT (6-11). SPTs have been used for decades to prove or exclude sensitization to allergens. Also, sIgE assessment is very popular and, particularly in polysensitized patients, allows to define the relevance of sensitizing allergens more appropriately than SPT in choosing the allergen extract for allergen immunotherapy (12).

The International guidelines proposed pharmacological treatments, mainly concerning antihistamines and intranasal corticosteroids, and allergen-specific immunotherapy (5, 13).

On the other hand, precise data about prevalence, clinical features, and pragmatic management are lacking. Therefore, an Italian Survey has been performed aiming to describe these characteristics in clinical practice.

Methods

The current Survey was performed using a questionnaire administered to subjects in 5 Italian cities: Ferrara, Viterbo, Reggio Calabria, Trapani, and Cagliari. The choice of these cities was made to guarantee a homogeneous distribution among the North, Centre, South Italy and the two major islands.

The interviewees were adults of both genders, randomly enrolled (the interview was performed on the road).

The questionnaire included 15 questions, reported in detail in Table 1.

The analysis of the data was descriptive.

Table 1. Questionnaire

Questions	Possible answers
1 Do you think of suffering from allergic rhinitis?	a) Yes b) No c) I do not know
2 At what age did your illness begin?	a) <10 years b) 10-20 years c) 21-30 years d) 31-40 years e) 41-50 years f) >50 years
3 Are there other members of your family with allergic rhinitis?	a) Yes, my father b) Yes, my mother c) Yes, my brother/sister d) Nobody
4 Have you another allergic disease?	a) Urticaria b) Conjunctivitis c) No d) I do not know
5 Who did the diagnosis perform?	a) General practitioner b) Otorhinolaryngologist c) Allergist d) Homoeopathy doctor e) Pharmacist f) Yourself
6 Have you ever performed tests to confirm the diagnosis?	a) Yes b) No c) I do not know

(continued on next page)

Table 1 ***(continued)*****.** Questionnaire

Questions	Possible answers
7 If yes, what?	a) Skin prick test b) Serum specific IgE c) Serum total IgE d) Other
8 In which season are the symptoms more severe?	a) Spring b) Summer c) Autumn d) Winter e) Always
9 What are your symptoms?	a) Nasal obstruction b) Rhinorrhea c) Sneezing d) Nasal itching e) Headache f) Dysosmia g) Lacrimation h) Padded ear i) Sinusitis
10 Do you do any therapy for your problem?	a) Yes, conventional medicine b) Yes, homoeopathy c) Yes, both d) No treatment
11 When do you use medicine?	a) During the acute phase b) Before the acute phase c) Before and during the acute phase d) During the whole year e) On-demand
12 Who did the conventional therapy prescribe?	a) General practitioner b) Otorhinolaryngologist c) Allergist d) Homoeopathy doctor e) Pharmacist
13 If you take homoeopathy, who did homoeopathy suggest?	a) General practitioner b) Otorhinolaryngologist c) Allergist d) Homoeopathy doctor e) Pharmacist f) Other (friends)
14 What kind of treatment do you use?	a) Environmental prevention (allergen avoidance) b) Systemic Antihistamines c) Intranasal Antihistamines d) Chromones e) Systemic corticosteroids f) Intranasal corticosteroids g) Nasal decongestants h) Allergen immunotherapy i) Nasal irrigation j) More medications
15 Do you remember the name of the homoeopathy product?	

Results

Globally, 4942 subjects (2798 males and 2144 females; mean age 37 years) participated in the Survey, equally distributed along Italy.

The results are reported in Table 2 and Figures.

The 22% of the sample think to have allergic rhinitis (Figure 1A), however, 17% do not know what respond. Most patients had the onset of RS between 10 and 30 years (74%). Family atopy was frequent as 62% of patients had a family member with allergic disease (Figure 1B). Allergic comorbidity was quite rare: 11% reported allergic conjunctivitis and 6% urticaria.

The diagnosis of AR was mostly self-made (28%), AR diagnosis was performed by ORL specialists in 22% of patients, in 17% by GPs, in 16% by allergists, and in 15% by pharmacists (Figure 1C). Allergy tests were performed in 12% of patients (Figure 1D): skin prick test was the most popular (82%), serum specific IgE assay in 41%, and serum total IgE in 42% (Figure 2A).

Spring (64%) was the most frequent period with symptoms (Figure 2B).

The most common symptoms were: rhinorrhea (90%), nasal obstruction (80%), sneezing and nasal itching (70% for both), and headache (20%), as reported in Figure 2C.

Table 2. Answers

Questions	Possible answers	Answers
1 Do you think of suffering from allergic rhinitis?	Yes	22%
	No	61%
	I do not know	17%
2 At what age did your illness begin?	<10 years	12%
	10-20 years	41%
	21-30 years	33%
	31-40 years	8%
	41-50 years	5%
	>50 years	1%
3 Are there other members of your family with allergic rhinitis?	Yes, my father	19%
	Yes, my mother	21%
	Yes, my brother/sister	22%
	Nobody	38%
4 Have you another allergic disease?	Urticaria	6%
	Conjunctivitis	11%
	No	39%
	I do not know	44%
5 Who did the diagnosis perform?	General practitioner	17%
	Otorhinolaryngologist	22%
	Allergist	16%
	Homoeopathy doctor	2%
	Pharmacist	15%
	Yourself	28%
6 Have you ever performed tests to confirm the diagnosis?	Yes	12%
	No	88%
7 If yes, what?	Skin prick test	82%
	Serum specific IgE	41%
	Serum total IgE	42%
	Other	0

(continued on next page)

Table 2 ***(continued)*****.** Answers

Questions	Possible answers	Answers
8 In which season are the symptoms more severe?	Spring	64%
	Summer	7%
	Autumn	7%
	Winter	0
	Always	22%
9 What are your symptoms?	Nasal obstruction	80%
	Rhinorrhea	90%
	Sneezing	70%
	Nasal itching	70%
	Headache	20%
	Dysosmia	15%
	Lacrimation	15%
	Padded ear	25%
	Sinusitis	25%
10 Do you do any therapy for your problem?	Yes, conventional medicine	51%
	Yes, homoeopathy	3%
	Yes, both	1%
	No treatment	45%
11 When do you use medicine?	During the acute phase	42%
	Before the acute phase	9%
	Before and during the acute phase	11%
	During the whole year	14%
	On-demand	24%
12 Who did the conventional therapy prescribe?	General practitioner	20%
	Otorhinolaryngologist	16%
	Allergist	16%
	Homoeopathy doctor	3%
	Pharmacist	17%
	Friends	28%
13 If you take homoeopathy, who did homoeopathy suggest?	General practitioner	0
	Otorhinolaryngologist	0
	Allergist	0
	Homoeopathy doctor	21%
	Pharmacist	0
	Other (friends)	79%
14 What kind of treatment do you use?	Environmental prevention (allergen avoidance)	0
	Systemic Antihistamines	20%
	Intranasal Antihistamines	5%
	Chromones	0
	Systemic corticosteroids	15%
	Intranasal corticosteroids	50%
	Nasal decongestants	20%
	Allergen immunotherapy	7%
	Nasal irrigation	30%
	More medications	14%
15 Do you remember the name of the homoeopathy product?		No

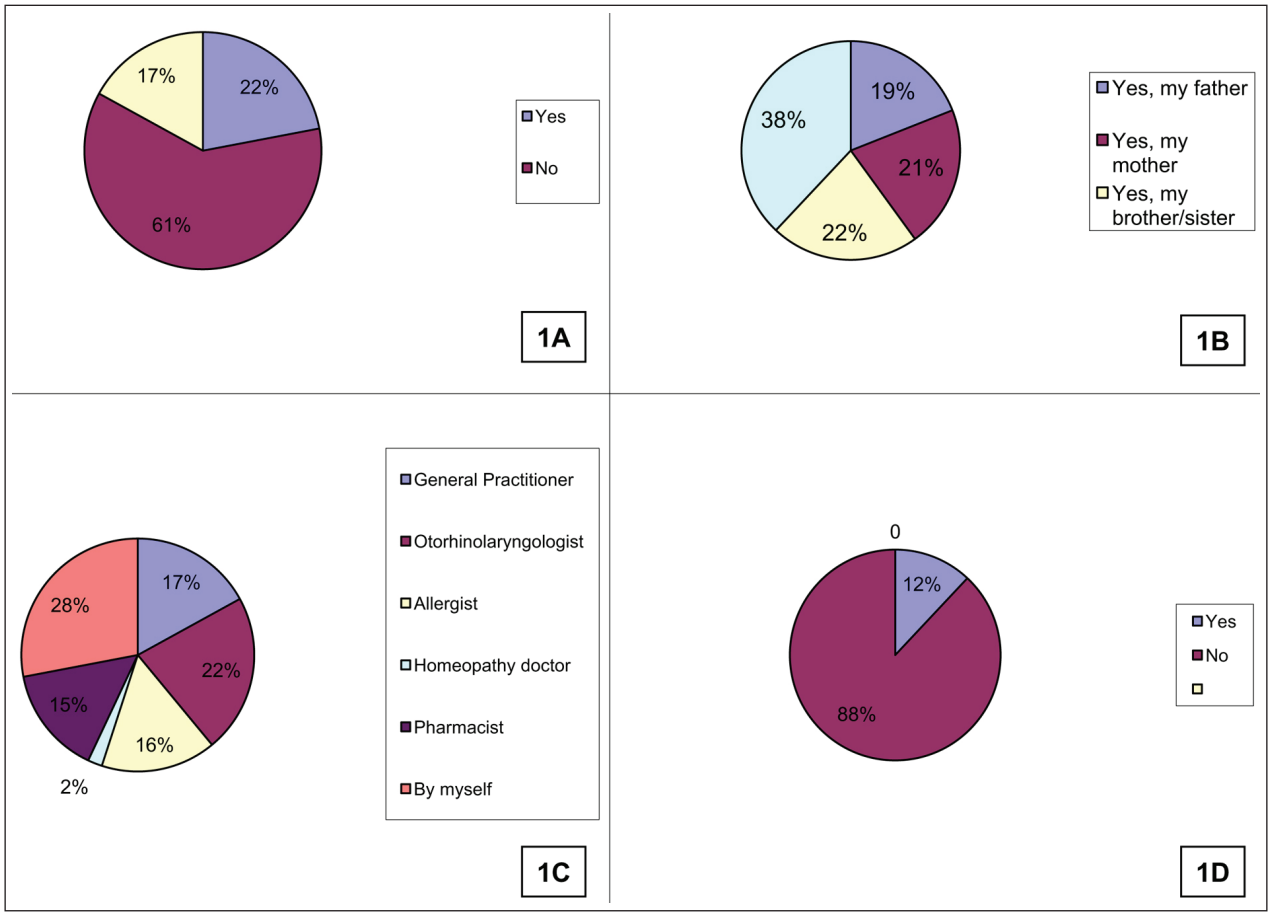

Figure 1. A = Prevalence of allergic rhinitis; B = Familiar atopy; C = Who perform the diagnosis of allergic rhinitis; D = Use of diagnostic tests

Conventional therapy was used by 51% of patients, 3% took homoeopathy, and 1% both; 45% did not take any medicine (Figure 2D). Most patients used medicines during the acute phase (42%) or on-demand (24%), as reported in Figure 3A. Treatments were mostly suggested by friends (28%) or by the pharmacist (17%), GPs prescribed therapy to 20% of patients, allergists as well as ORL specialists prescribed medicines in 16% (for both). Homoeopathy was prescribed only by homoeopathy doctors.

The kind of medicine is reported in Figure 3B: intranasal corticosteroids was the most common treatment (50%), followed by nasal irrigation (30%), nasal decongestants and systemic antihistamines (20% for both), and systemic corticosteroids (15%).

Discussion

Allergic rhinitis is a very common disease and may be classified both considering the seasonality or the duration/severity of nasal symptoms. Its prevalence is very high. However, there a very few studies that investigated the pragmatic approach concerning the work-up and the therapy in clinical practice in Italy. For these reasons, the current Survey was conducted in a wide sample of the Italian general population in 5 cities. Moreover, the questionnaire was administered on the road, so, the findings represented the real-world situation that may mirror what usually happens in the daily clinical setting.

Firstly, the rough prevalence is 22%, substantially this outcome is consistent with the International

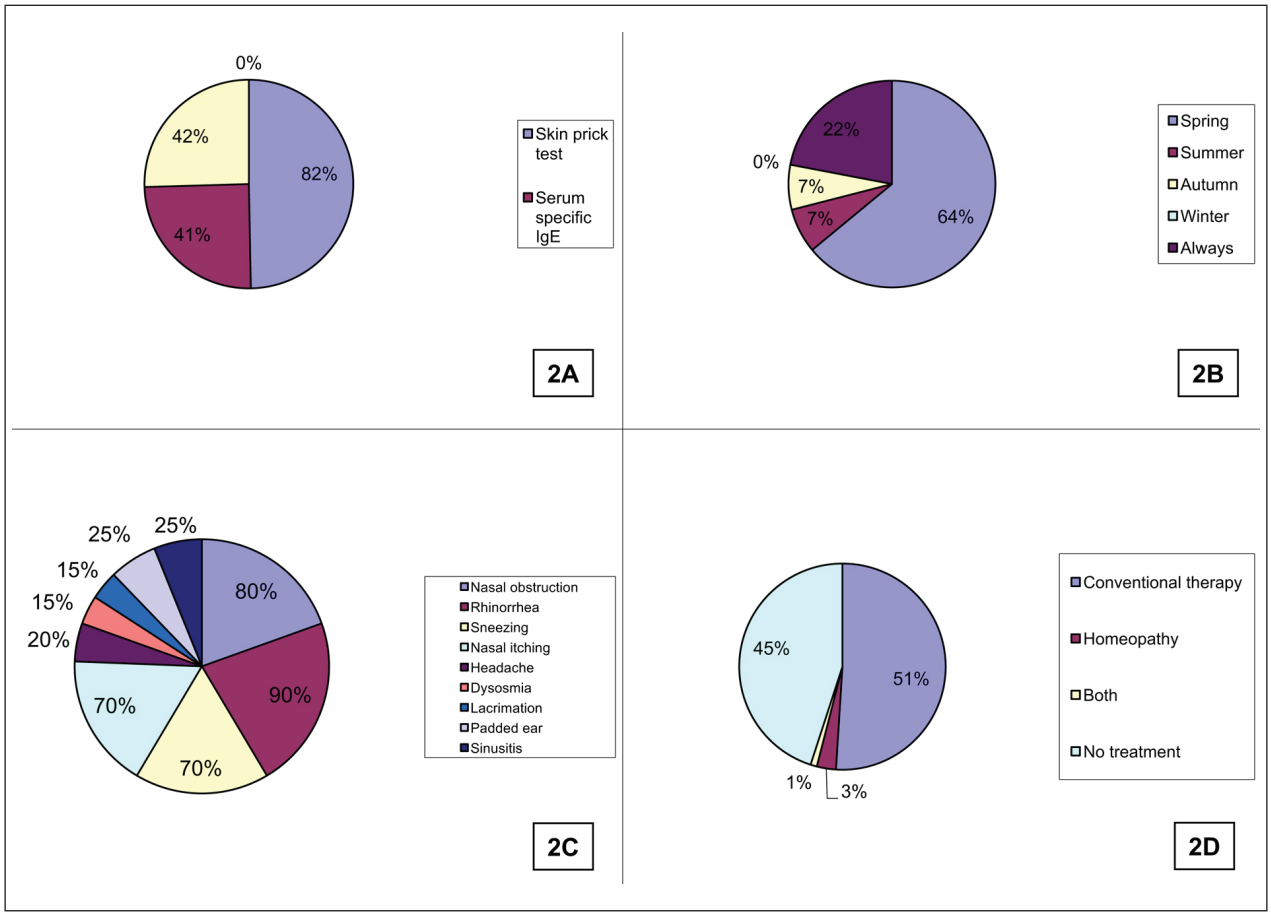

Figure 2. A = The most common test used to confirm the AR diagnosis; B = Season of symptom presence; C = The most common symptoms of AR; C = Kind of used treatment

reports. Most subjects showed that the age at onset ranges between adolescence and young adulthood, such as between 10 and 30 years. It means that AR is a disease characterized by an early beginning. Also, family atopy is very common: 62% of patients have at least a family member with allergy. This finding underlines the genetic component of allergy. Surprisingly, allergic comorbidity is rather rare it has to be noted that this was the perception of the interviewed subjects.

Unfortunately, only 12% of patients referred that performed allergy tests to confirm AR diagnosis. In this context, the skin prick test was the most popular. However, total IgE is still assayed, even though they have no real diagnostic value. These results reinforce the concept that AR is underestimated and consequently underdiagnosed and undertreated. It depends on the scarce information on AR in the medical class and also in the general population.

Spring was the most frequent season with the symptom. AR is frequently experienced as a seasonal, mainly concerning spring, disease.

Another negative finding was the modest use of treatments for AR, in fact, only 51% of patients took medications and consequently, 45% of patients did not take any drug for AR. Interestingly, AR treatment is limited to only the acute phase (66%): during this period, it could be continuous or on-demand. Moreover, therapy was suggested by pharmacists in 17% of patients and even by friends in 28% of patients. ORL and allergy specialists had a prescriptive role only in 32% of patients.

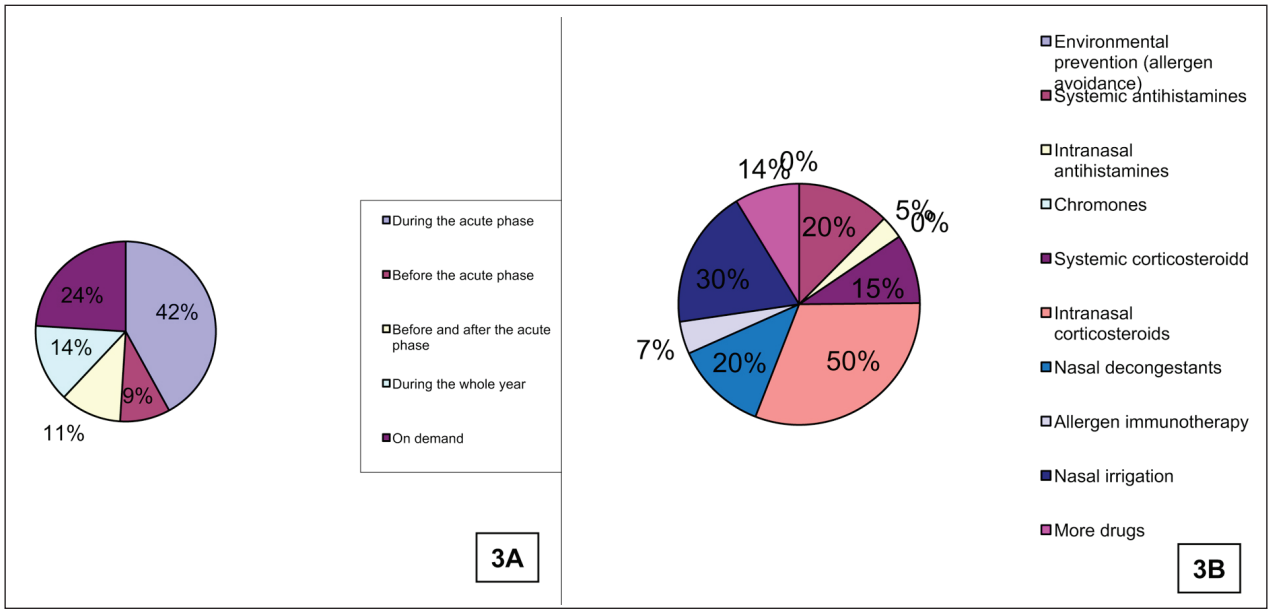

Figure 3. A = When the treatment was performed; C = The most common medicines used to treat AR.

These outcomes are very impressive and underline the lack of updated knowledge about diagnostic and therapeutic criteria by Italian doctors and the scarce confidence of patients.

From a therapeutic point of view, intranasal corticosteroids seem to be the most common medication used by patients (50%) as well as nasal irrigation was a popular remedy. Antihistamines were used by 20% of the interviewed subjects.

Globally, the scenario that appears from this Survey is rather unsatisfying and highlights the need for adequate information for the medical class and also for the general population.

The current Survey has some limitations, including the cross-sectional design, the lack of a methodologically correct definition of the questions, and the answers based only on patients' impressions. On the other hand, the strength of this study is based on the high number of participants and the conduction on the general population.

In conclusion, the current Survey demonstrated that AR is a common disorder in Italy, the diagnostic work-up is still incorrect and frequently underused, and the therapeutic approach does not adhere to the guidelines. Therefore, there is a need to implement adequate information on this topic in Italy.

Conflict of interest: all the authors, but DV employee of DMG, have no conflict of interest about this matter.

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Original article

The impact of rhinosinusitis in clinical practice: an Italian Survey

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Abstract. Rhinosinusitis is a common disease that is classified in acute (ARS) and chronic (CRS). The current Survey was conducted on a sample of about 5,000 adult subjects in 5 Italian cities. A questionnaire, containing 15 questions, was administered on the road. RS affects about 20% of the general population. The most common diagnostic test was the skull x-ray. Antibiotics were the most frequently prescribed therapy. In conclusion, the current Survey demonstrated that RS is a common disorder in Italy, the diagnostic work-up is still incorrect, and the therapeutic approach does not adhere to the guidelines. Therefore, there is a need to implement adequate information on this topic in Italy. (www.actabiomedica.it)

Key words: Italy, Survey, rhinosinusitis, general population, questionnaire, on the road

Introduction

Sinusitis usually refers to inflammation localized in the nasal sinuses and, as it is usually associated with the inflammation of nasal mucosae, such as the rhinitis, the term rhinosinusitis (RS) is considered more correct (1). It has to be noted that RS may affect any age.

In clinical practice, RS should be suspected in the presence of nasal symptoms, including nasal congestion and rhinorrhea, persisting for more than 7-10 days without any improvement. Noteworthy, a chronological cut-off is useful to differentiate RS from the common cold that is usually self-limiting and usually resolves by 7-10 days (3-5). The symptoms of acute RS (ARS) tend to resolve within 3-4 weeks; however, if sinus inflammation persists (regardless of the medical management), it is evolving to chronic RS (CRS), defined by a duration longer than 8-12 weeks (1,2). Therefore, the diagnosis of RS often relies on the clinical ground, including the duration of nasal symptoms, the characteristics of nasal discharge (purulent), and other symptoms, such as facial pain and fever. Computerized tomography (CT) may be required whenever the suspicion of extra-sinus complications should arise (6-9). Moreover, CT is useful to detect nasal polyps in CRS patients.

According to the endoscopic and/or radiological findings, there are two main phenotypes: CRS with nasal polyposis (CRSwNP) and CRS without nasal polyposis (CRSsNP).

From an epidemiological point of view, there is evidence that CRS is frequently associated with asthma, and is a frequent comorbidity in patients with immunodeficiency, cystic fibrosis, and aspirin intolerance (9-11). In particular, RS frequently triggers and/or worsens asthma (12,13).

Matsuno and colleagues reported a 36.7% prevalence of RS in asthmatic patients. Notably, sinus CT abnormalities were detected in 66.3% of patients, more frequently in moderate to severe asthma. Another study confirmed that RS was more frequent in severe

and steroid-dependent asthma (14-18). Consistently, RS is more frequent in patients with poorly controlled asthma (19). Also, RS is frequent in patients with hospital admission for asthma exacerbation (20). Further, it has been reported that about 50% of children diagnosed with persistent asthma presented concomitant RS diagnosed by nasal endoscopy (21). Therefore, according to the concept of the so-called United Airways Disease, RS should be ever suspected in asthmatic patients (22).

On the other hand, precise data about prevalence, clinical features, and pragmatic management are lacking. Therefore, an Italian Survey has been performed aiming to describe these characteristics in clinical practice.

Methods

The current Survey was performed using a questionnaire administered to subjects in 5 Italian cities: Ferrara, Viterbo, Reggio Calabria, Trapani, and Cagliari. The choice of these cities was made to guarantee a homogeneous distribution among the North, Centre, South Italy and the two major islands.

The interviewees were adults of both genders, randomly enrolled (the interview was performed on the road).

The questionnaire included 15 queries, reported in detail in Table 1.

The analysis of the data was descriptive.

Table 1. Questionnaire

Questions	Possible answers
1 Do you think of suffering from rhinosinusitis?	a) Yes b) No c) I do not know
2 How do you define your rhinosinusitis?	a) Acute b) Recurrent c) Chronic d) I do not know
3 In which season are the symptoms more severe?	a) Spring b) Summer c) Autumn d) Winter e) Always
4 At what age did your illness begin?	a) <10 years b) 10-20 years c) 21-30 years d) 31-40 years e) 41-50 years f) >50 years
5 What are your symptoms?	a) Nasal obstruction b) Rhinorrhea c) Facial pain d) Sneezing e) Nasal itching f) Headache g) Dysosmia h) Heavy head i) Fever

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Table 1 ***(continued)*****.** Questionnaire

Questions	Possible answers
6 Who did the diagnosis perform?	a) General practitioner b) Otorhinolaryngologist c) Allergist d) Homoeopathy doctor e) Pharmacist
7 Have you ever performed tests to confirm the diagnosis?	a) Yes b) No c) I do not know
8 If yes, what?	a) Nasal endoscopy b) RX skull c) CT head d) Nasal function testing e) Allergy tests f) Nasal swab culture g) Nasal cytology
9 Do you do any therapy for your problem?	a) Yes, conventional medicine b) Yes, homoeopathy c) Yes, both d) No treatment
10 When do you use medicine?	a) During the acute phase b) Before the acute phase c) Before and during the acute phase d) During the whole year
11 Who did the therapy prescribe?	a) General practitioner b) Otorhinolaryngologist c) Allergist d) Homoeopathy doctor e) Pharmacist
12 What kind of drugs do you use?	a) Antibiotics b) Antihistamines c) Systemic corticosteroids d) Intranasal corticosteroids e) Nasal decongestants f) Nasal irrigation
13 Do you remember the name of the antibiotic?	
14 Who did homoeopathy suggest?	a) General practitioner b) Otorhinolaryngologist c) Allergist d) Homoeopathy doctor e) Pharmacist f) Other (friends)

Results

Globally, 4999 subjects (2923 males and 2076 females; mean age 35 years) participated in the Survey, equally distributed along Italy.

The results are reported in Table 2 and Figures.

The 20% of the sample think to have rhinosinusitis (Figure 1A); 7% suffered from acute RS, 28% from recurrent, and 48% from CRS. Winter and the whole year are the most frequent periods (Figure 1B).

Table 2. Answers

Questions	Possible answers	
1 Do you think of suffering from rhinosinusitis?	Yes	20%
	No	53%
	I do not know	27%
2 How do you define your rhinosinusitis?	Acute	7%
	Recurrent	28%
	Chronic	48%
	I do not know	17%
3 In which season are the symptoms more severe?	Spring	16%
	Summer	4%
	Autumn	11%
	Winter	39%
	Always	30%
4 At what age did your illness begin?	<10 years	3%
	10-20 years	12%
	21-30 years	38%
	31-40 years	30%
	41-50 years	12%
	>50 years	5%
5 What are your symptoms?	Nasal obstruction	72%
	Rhinorrhea	38%
	Facial pain	83%
	Sneezing	5%
	Nasal itching	5%
	Headache	77%
	Dysosmia	18%
	Heavy head	91%
	Fever	81%
6 Who did the diagnosis perform?	General practitioner	33%
	Otorhinolaryngologist	42%
	Allergist	14%
	Homoeopathy doctor	0
	Pharmacist	11%
7 Have you ever performed tests to confirm the diagnosis?	Yes	21
	No	71%
	I do not know	8%
8 If yes, what?	Nasal endoscopy	35%
	RX skull	62%
	CT head	13%
	Nasal function testing	3%
	Allergy tests	2%
	Nasal swab culture	2%
	Nasal cytology	0
9 Do you do any therapy for your problem?	Yes, conventional medicine	74%
	Yes, homoeopathy	4%
	Yes, both	4%
	No treatment	18%

(continued on next page)

Table 2 ***(continued)*****.** Answers

Questions	Possible answers	
10 When do you use medicine?	During the acute phase	83%
	Before the acute phase	6%
	Before and during the acute phase	7%
	During the whole year	4%
11 Who did the therapy prescribe?	General practitioner	22%
	Otorhinolaryngologist	59%
	Allergist	12%
	Homoeopathy doctor	2%
	Pharmacist	5%
12 What kind of drugs do you use?	Antibiotics	63%
	Antihistamines	8%
	Systemic corticosteroids	19%
	Intranasal corticosteroids	20%
	Nasal decongestants	15%
	Nasal irrigation	0
13 Do you remember the name of the antibiotic?		No 100%
14 Who did homoeopathy suggest?	General practitioner	0
	Otorhinolaryngologist	0
	Allergist	0
	Homoeopathy doctor	77%
	Pharmacist	0
	Other (friends)	23%
15 Do you remember the name of the homoeopathic product?		No 100%

Most patients had the onset of RS between 21 and 40 years (68%), as reported in Figure 1C.

The most common symptoms are the heavy head (91%), facial pain (83%), fever (81%), headache (77%), nasal obstruction (72%), and rhinorrhea (68%), as reported in Figure 1D. The diagnosis was made most frequently by the ORL specialist (42%), the GP (33%), the allergist (14%), and the pharmacist (11%). Twenty-one % performed a test to confirm the diagnosis. The most common tests were: RX skull (62%), nasal endoscopy (62%), and CT head (13%), as reported in Figure 2A.

Seventy-four % took conventional therapy, 4% homoeopathy, and 4% both; 18% did not take any medicine. Most patients used medicines during the acute phase (83%). The kind of medicine is reported in Figure 2B: antibiotics were used in 63% of subjects and corticosteroids in about 20%.

Homoeopathy was prescribed exclusively by the homoeopathy doctor or suggested by friends.

Discussion

Rhinosinusitis is a common disease that is classified in acute (ARS) and chronic (CRS). ARS follows usually acute upper respiratory infections, the mainly common cold. However, epidemiological data are very few about Italy.

CRS is a chronic inflammation of the sinus. From an epidemiological point of view, it is estimated that CRS affects 5%-12% of the general population worldwide (23-26). The European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) proposed a statement about CRS diagnosis that is clinically based on symptoms supported by signs of mucosal inflammation found on imaging or with nasal endoscopy (27). It has been recently reported that the prevalence of clinically based CRS ranged between 3% and 6.4% (28,29). CRS is classically divided into a phenotype with and without nasal polyps. Using patient questionnaires to measure the prevalence of CRSwNP yielded estimates

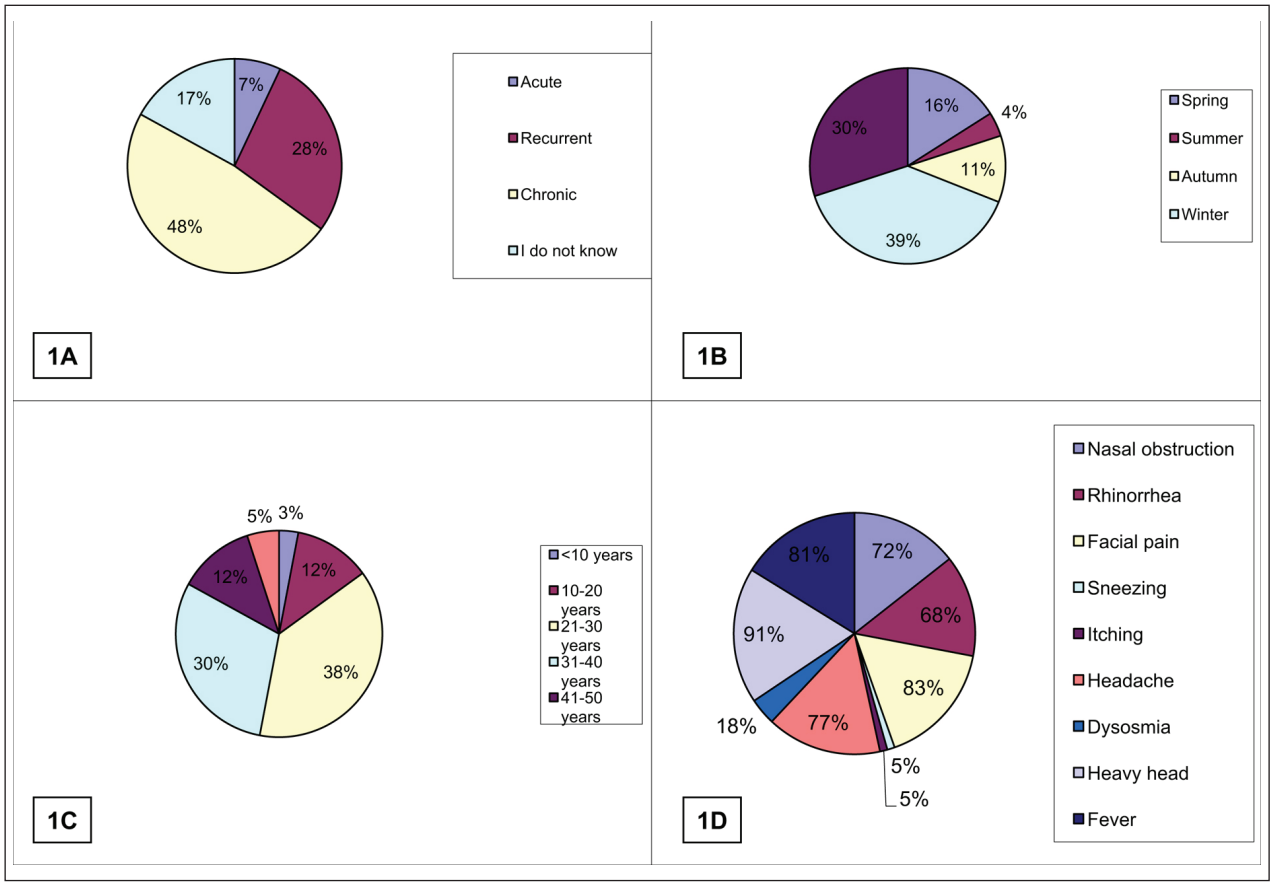

Figure 1. A = Distribution of the classification of Rhinosinusitis; B = Distribution of the seasons when RS occurred; C = Distribution of the age at the onset of RS; D = Distribution of the most common symptoms of RS

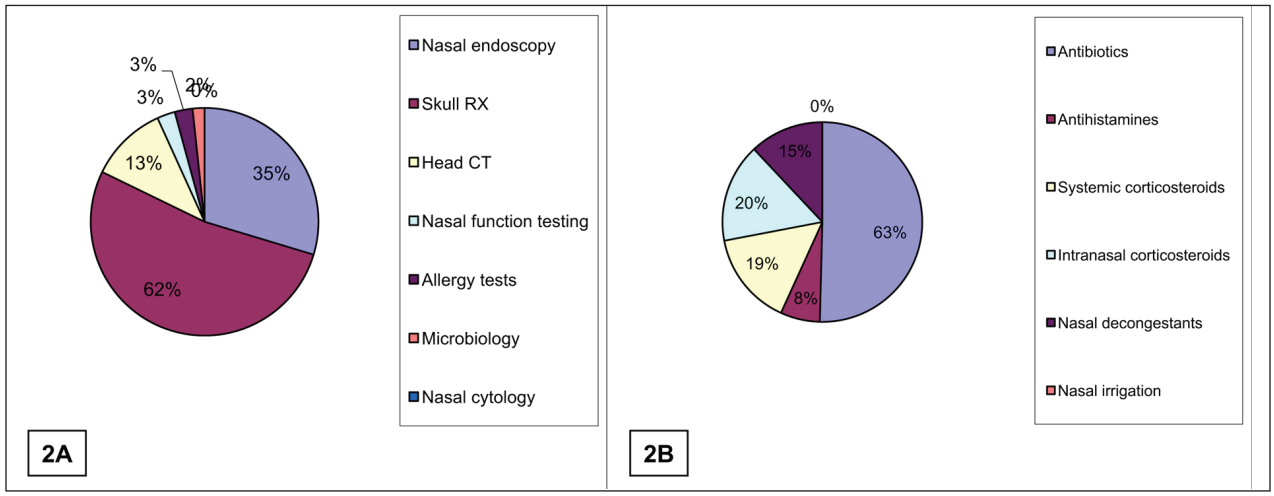

Figure 2. A = The most common test used to confirm the RS diagnosis; B = The most common medicines used to treat RS

of 2.1% (France) to 4.3% (Finland) in Europe and 1.1% in China (30). CRSwNP comprises a heterogeneous group of patients who differ for coexisting asthma, allergy, NSAID-exacerbated respiratory disease (N-ERD), smoking, age of onset, and disease severity (31-34). Asthma affects 30%-70% of the CRSwNP patients (35,36). Conversely, the presence of nasal polyps is associated with the severity of asthma, regardless of smoking status ranging from 10%-30% in mild asthma to 70%-90% in severe asthma (37,38).

Based on this background, the current Survey was conducted in 5 Italian cities enrolling about 5,000 adult subjects. The results are interesting as it was conducted on the general population, so the outcomes can mirror the situation that may occur in clinical practice.

Firstly, the rough prevalence is about 20%, including both ARS and CRS. The winter is the most common season for RS occurrence.

The distribution of the frequency of symptoms and signs is consistent with the clinical diagnostic criteria proposed by the EPOS. However, the most interesting data concerned the pragmatic approach performed by physicians. From a diagnostic point of view, the diagnosis is made primarily by ORL specialists. However, a skull x-ray is the most requested diagnostic test. This result is impressive and underlines the lack of updated knowledge about diagnostic criteria by Italian doctors.

From a therapeutic point of view, antibiotics are the main pharmacological class prescribed for RS, probably for ARS. Corticosteroids, both topical and systemic, are relatively underused: also, in this case, it could depend on the ignorance of the guidelines.

Globally, the scenario that appears from this Survey is rather unsatisfying and highlights the need for adequate information for the medical class.

The current Survey has some limitations, including the cross-sectional design, the lack of a methodologically correct definition of the questions, and the answers based only on patients' impressions. On the other hand, the strength of this study is based on the high number of participants and the conduction on the general population.

In conclusion, the current Survey demonstrated that RS is a common disorder in Italy, the diagnostic work-up is still incorrect, and the therapeutic approach does not adhere to the guidelines. Therefore, there is a need to implement adequate information on this topic in Italy.

Conflict of interest: all the authors, but DV employee of DMG, have no conflict of interest about this matter.

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Original article

A new therapeutic approach for the Dry Eye Syndrome in patients with laryngopharyngeal reflux: first data

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Abstract. Laryngopharyngeal reflux (LPR) is a common disorder. Pepsin has been detected also at eye level, this was a starting point for newest theories about LPR impact on Dry Eye Syndrome. The current preliminary study compared two treatments in patients with Dry Eye Syndrome and LPR. Patients were treated with Gastroftal eye drops and Gastroftal tablets or hyaluronic acid eye drops for 3 months. The following parameters were evaluated: Ocular Surface Disease Index (OSDI), OSDI categories, Reflux Symptom Index (RSI), Reflux Finding Score (RFS), Fluorescein Tear Breakup Time (B-TUT), and Schirmer test before and after treatment. On the whole, 21 patients were enrolled: 10 were treated with hyaluronic acid Atlantis (Group A) and 11 with Gastroftal eye drops and tablets (Group B). After treatment, in Group A only OSDI significantly diminished (p=0.029); in Group B there were significant reductions concerning OSDI (p=0.0277), OSDI categories (p=0.0211), RSI (p=0.0172), Schirmer test (p=0.0172), T-BUT (p=0.0265), and RFS (p=0.0205). The current preliminary demonstrated that the combined ocular and systemic therapy with hyaluronic acid, Magnesium alginate, Simethicone, and *Camelia sinensis* may be considered a promising treatment in patients with Dry Eye Syndrome due to LPR. (www.actabiomedica.it)

Key words: laryngopharyngeal reflux, eye reflux, dry eye syndrome, magnesium alginate, hyaluronic acid, simethicone, *Camelia sinensis*

Introduction

Gastroesophageal reflux disease (GERD) is a very common disorder, namely the prevalence is up to 40% in the USA adult population (1,2). The symptoms mainly involve the upper digestive tract, but extra-oesophageal symptoms have been also identified. In this regard, the Montreal Classification includes chronic cough, asthma, and laryngopharyngeal reflux (LPR) as extra-oesophageal manifestations of GERD (3). LPR is the consequence of aggressive refluxate exposure on upper airways, specifically larynx and pharynx (4). LPR symptoms typically consist of hoarseness, sore throat, *globus* sensation, and throat clearing. LPR may be associated with GERD, but it may also occur as alone disorder without typical oesophageal symptoms (5,6). It has to be underlined that LPR is common in clinical practice and represents a relevant burden concerning both social and personal costs, and significantly affects the quality of life (7).

The pathogenic pathway consists of mucosal damage, as low pH of refluxate and pepsin play a major role in inducing chronic mucosal inflammation (8,9,10). Pepsin is a proteolytic enzyme deriving from pepsinogen and activated by low pH (at least <4) that is produced only in the stomach. Therefore, pepsin detection outside the gastric area may be considered incontrovertibly a biomarker for gastric reflux (11). In agree-

ment with this evidence, the presence of pepsin was detected in different organs, including larynx, pharynx, paranasal sinus, mouth, and internal ear (12,13). Further, it has been demonstrated the presence of pepsin also in the tears of subjects with LPR (14,15). A recent study confirmed the pathogenic role of LPR in a group of patients with dry eye (16). That study concluded that LPR may be common (34%) in patients with the ocular surface disease, such as Dry Eye Syndrome a very challenging syndrome in order of aetiology and medical treatment either for General Practitioner and moreover for Ophthalmologists.

LPR treatment is a demanding problem in clinical practice; alginates represent a common treatment as recently reported (17). The present study evaluated a group of subjects with dry eye and LPR comparing two treatments: the first (Group A) was hyaluronic acid 0.2% eye drops (Atlantis), the second (Group B) included a combined topical (Gastroftal eye drops, containing hyaluronic acid, Magnesium alginate, and *Camelia sinensis* extract) and oral therapy (Gastroftal tablet, containing Magnesium alginate and Simethicone).

Materials and Methods

In the current study, the patients were enrolled if fulfilled the inclusion and exclusion criteria. The inclusion criteria were: i) adult age between 18 and 80 years; ii) an Ocular Surface Disease Index (OSDI) score >12; and iii) a Reflux Symptom Index (RSI) score >13. The exclusion criteria were: i) glaucoma diagnosis; ii) bacteria, viral, or fungal eye infection; iii) allergic conjunctivitis; iv) cancer; v) ocular or nasal surgery in the 3 months before the trial; vi) concomitant medications able to interfere with the findings; vii) current pregnancy or breastfeeding.

At baseline, a series of pathogenic factors were investigated: lacrimal dysfunction syndrome (LDS; such as exposure to computer light and/or contact lens), alcoholic overconsumption, tobacco smoking, GERD, and *H pylori* infection.

The diagnosis of LPR was based on symptoms, and specific questionnaires, such as the RSI and RFS. The Dry Eye Syndrome was evaluated by the OSDI, the fluorescein tear breakup time (TBUT), and the Schirmer test.

The RSI asked about symptoms such as hoarseness, throat clearing, cough, a7nd heartburn to create a composite score whereby an RSI > 13 suggests LPR (18). The RFS was calculated after fibreoptic endoscopy and an RFS > 7 suggests LPR (19).

The conjunctiva and cornea were examined using a slit-lamp. OSDI is a 12-item questionnaire to investigate ocular symptoms (20). The OSDI scoring was performed and quoted according to the reference guidelines: OSDI was defined as pathological if >12 (21). In addition, OSDI result was calculated by the formula: OSDI value x 25/number of responses, and was categorized as normal (scored 0) if OSDI score was between 0 and 12, borderline (scored 1) if between 13 and 22, pathological (scored 2) if between 23 and 32, and severe (scored 3) if between 33 and 100.

TBUT was evaluated by introducing a fluorescein strip moistened with 1 drop of non-preserved normal saline into the inferior conjunctival fornix with minimal stimulation (22). The quantity of saline was also controlled by carefully shaking the fluorescein strip to remove excess fluid. The patient was asked to blink several times and then hold the eye open. The cornea was scanned with a slit-lamp using cobalt blue illumination. Time from the last complete blink to the first appearance of a random dry spot on the cornea was recorded in seconds. The test was repeated 3 times in each eye, and the meantime for 3 consecutive measurements was obtained. The test was considered positive if the average T-BUT was less than 10s.

The Schirmer I test without anaesthesia was then performed (23). A standard 5×35-mm2 strip of dry filter paper was placed in each lower fornix at the junction of the lateral and middle thirds, taking care to avoid touching the cornea and left in place for 5min. After 5min, the strips were removed, and the amount of wetting in millimetres was recorded. The test results were considered positive if the length of wetting obtained was less than 10 mm in 5min.

Selected patients were screened and if met inclusion and exclusion criteria were recruited and randomly (1:1) treated with hyaluronic acid 0.2% (Atlantis) eye drops (Group A) or with a combined therapy, topical (Gastroftal eye drops, containing hyaluronic acid,

Magnesium alginate, and *Camelia sinensis* extract) and oral therapy (Gastroftal tablets, containing Magnesium alginate and Simethicone). The patients were treated for 3 months; patients in Group A took Atlantis eye drops 1 drop 3 times/day; patients in Group B took Gastroftal eye drops 1 drop 3 times/day plus Gastroftal tablets 2 tablets after lunch and after dinner.

The primary outcome was the evaluation of OSDI change between Groups. The secondary outcomes were the evaluation of change for RSI, RFS, Schirmer test, and T-BUT assessed by both intragroup and intergroup analysis, of the tolerability and compliance of both treatments.

The patients were evaluated and scored at baseline and after the treatments. Also, a visual analogue scale (VAS) was measured for the perception of efficacy, tolerability, and compliance. Adverse events were recorded if occurred.

Demographic and clinical characteristics are described using medians with lower and upper quartiles (LQ-UQ). Any statistically significant difference in the mean values or the median values of each continuous variable was evaluated with the Wilcoxon signed-rank test or with Mann U Whitney test, respectively. Statistical significance was set at $p < 0.05$, and the analyses were performed using GraphPad Prism software, GraphPad Software Inc, CA, USA.

Results

At baseline data

Globally, 21 patients were included in the study: 10 in Group A and 11 in Group B. The demographic data and the outcomes in the two groups of patients, at baseline, are reported in Table 1. Median age was 54 years in Group A and 56 in Group B; there were 5 males in Group A and 6 in Group B. About risk factors, 9 patients of Group A and 8 patients in Group B had LDS; two patients had alcohol overconsumption in both Groups; 1 patient in Group A and 2 in Group B were smokers; 5 and 7 patients had respectively GERD; and 2 patients in Group A had H pylori infection. The two groups were homogeneous for all these parameters at baseline as reported in Table 1.

Table 1. Demographic and clinical characteristics in the two groups at baseline

	Group		p-value
	A 10 (47.62%)	**B** 11 (52.38%)	
Age (years)	54 (41 : 75)	56 (39 : 76)	0.7509
Males	5	6	0.8210
Risk factors			
LDS	9	8	0.1810
Alcohol overconsumption	2 (20%)	2 (18.18%)	0.9999
Tabacco smoking	1 (10%)	2 (18.18%)	0.9999
GERD	5 (50%)	7 (63.64%)	0.6699
***H.pylori* infection**	2 (20%)	0 (0%)	0.2143

After treatment data

During the study, two subjects dropped out: 1 in Group A and 1 in Group B. Table 2 shows the clinical outcomes in both groups before and after treatment.

Group A

Median OSDI (Figure 1) significantly diminished ($p=0.029$), whereas median OSDI categorized (Figure 2), RSI (Figure 3), Schirmer test (Figure 4), T-BUT (Figure 5), and RFS (Figure 6) did not significantly changed after treatment.

Group B

Median OSDI (Figure 1) significantly diminished ($p=0.0277$), median OSDI categorized (Figure 2) significantly diminished ($p=0.0211$), RSI (Figure 3) significantly diminished ($p=0.0172$), Schirmer test (Figure 4) significantly diminished ($p=0.0172$), T-BUT (Figure 5) significantly diminished ($p=0.0265$), and RFS (Figure 6) significantly diminished ($p=0.0205$).

Safety and tolerability

Both treatments were well tolerated and no adverse event was reported during the study.

Table 2. Intra-Group analysis of the clinical outcomes in the groups (see the text for abbreviations and further details

	Group A			Group B		
	Time T0	**Time T1**	**p-value**	**Time T0**	**Time T1**	**p-value**
OSDI	17 (10 : 26)	9.5 (4 : 23)	**0.0290**	17 (11 : 35)	6 (5 : 32)	**0.0277**
OSDI categorized	2 (1 : 3)	1 (0 : 3)	0.0890	3 (1 : 3)	1 (0 : 3)	**0.0211**
RSI	15 (8 : 26)	9 (6 : 26)	0.0592	21 (14 : 27)	11 (6 : 24)	**0.0172**
Schirmer test	8.5 (2 : 15)	5 (1 : 15)	0.3096	6 (1 : 16)	6 (2 : 20)	**0.0172**
T-BUT	4 (2 : 7)	5 (2 : 8)	0.6202	3 (2 : 7)	6 (3 : 10)	**0.0265**
RFS	11 (0 : 16)	4.5 (0 : 18)	0.1148	13 (10 : 15)	7 (0 : 17)	**0.0205**

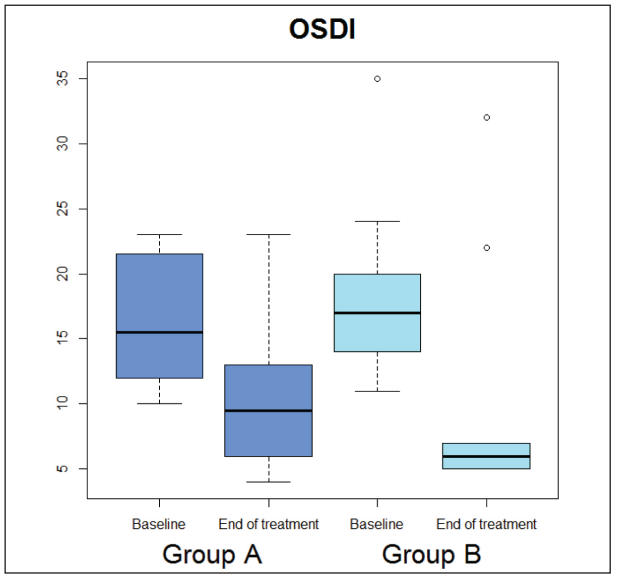

Figure 1. Box-plot concerning medians and interquartile ranges of OSDI values at baseline and after the treatment in Group A and B

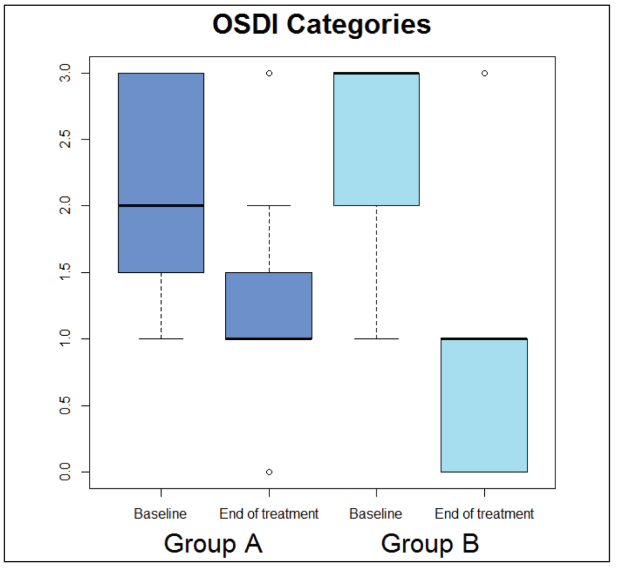

Figure 2. Box-plot concerning medians and interquartile ranges of OSDI categories values at baseline and after the treatment in Group A and B

Discussion

Laryngopharyngeal reflux is a common disorder, even though the diagnosis is debated and there is no pathognomonic sign. Anyway, there is convincing evidence the LPR plays a role in airways inflammation involving some organs, such as larynx, pharynx, paranasal sinus, and middle ear (24). These outcomes paved the way to investigate a possible LPR impact also on the eye. Pepsin's presence has been recently documented in the tears (15). The possible explanation of this way could depend on a peculiar mechanism. Pepsin can move to lacrimal film passing through the nasal cavity, the inferior meatus, and the nasolacrimal duct. More recently, it has been reported that LPR is frequent in patients suffering from an ocular surface disease (16).

On the other hand, LPR treatment should be based on protective agents and lifestyle changes. Alginates are commonly used to treat LPR and they have been demonstrated effective (17).

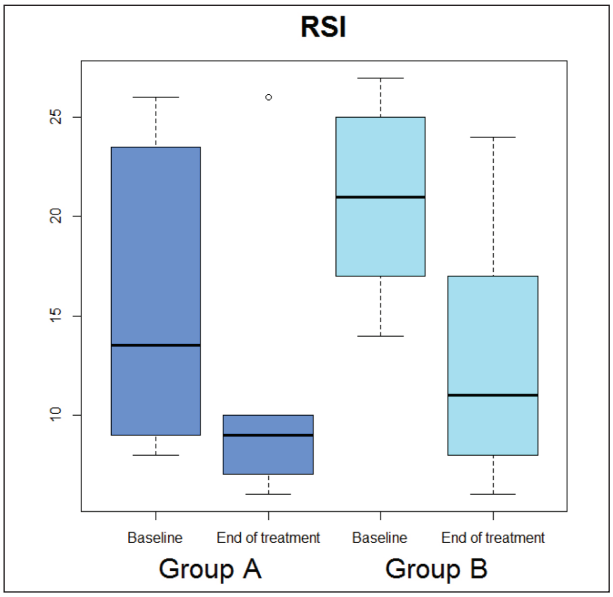

Figure 3. Box-plot concerning medians and interquartile ranges of RSI values at baseline and after the treatment in Group A and B

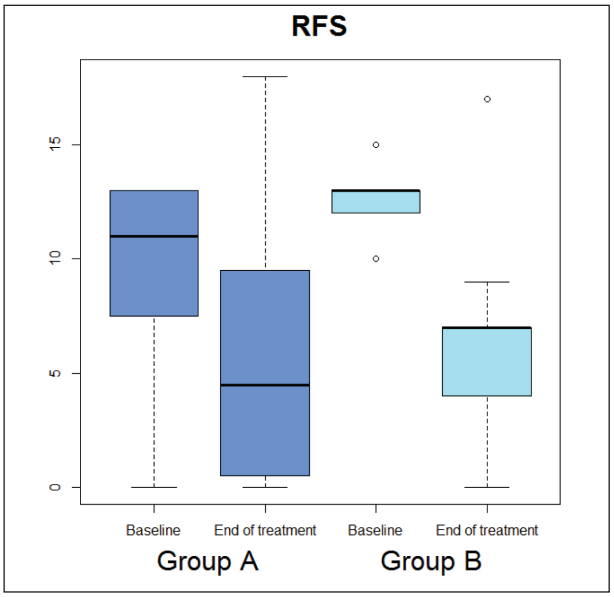

Figure 4. Box-plot concerning medians and interquartile ranges of RFS values at baseline and after the treatment in Group A and B

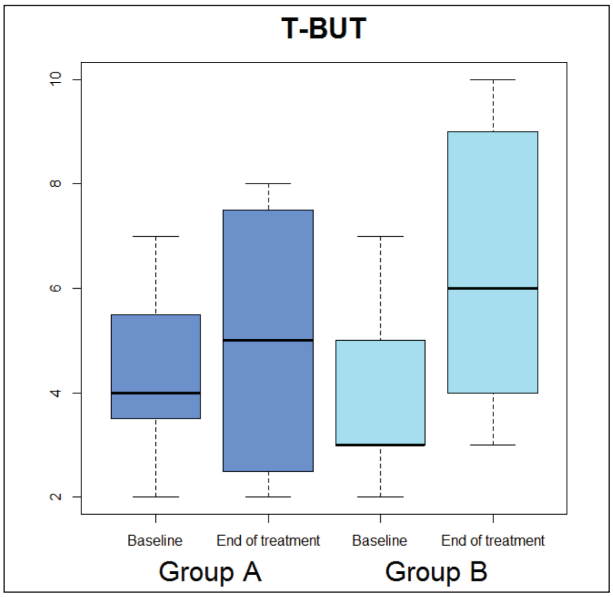

Figure 5. Box-plot concerning medians and interquartile ranges of T-BUT values at baseline and after the treatment in Group A and B

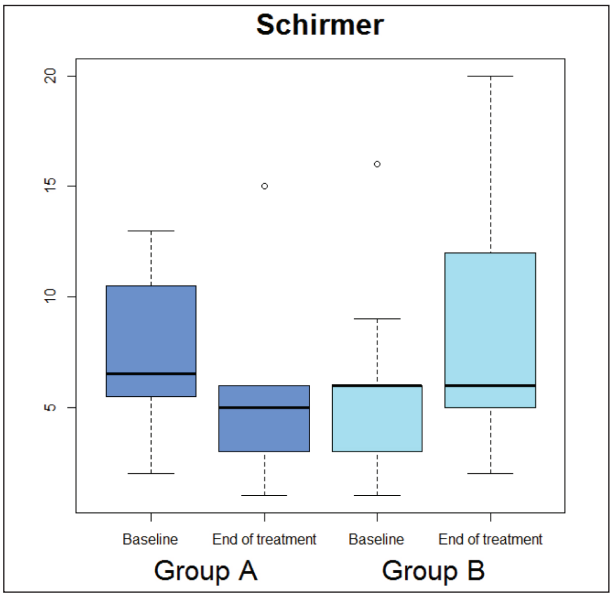

Figure 6. Box-plot concerning medians and interquartile ranges of Schirmer test values at baseline and after the treatment in Group A and B

The current study tested two treatments: hyaluronic acid eye drops and a combined topical and oral therapy, including hyaluronic acid, Magnesium alginate, *Camelia sinensis,* and Simethicone.

The current preliminary study showed that Gastroftal combined treatment was able to significantly improve OSDI, OSDI categories, RSI, RFS, and T-BUT. Also, combined Gastroftal was superior to hyaluronic

acid eye drops concerning OSDI, RSI, and RFS. These results are consistent with a previous survey conducted on a group of otorhinolaryngologists (2).

The effectiveness of combined Gastroftal therapy depended on the simultaneous treatment of eyes discomforts and of laryngopharyngeal reflux disease. Gastroftal eye drops is a Medical Device (class II) containing: hyaluronic acid, Magnesium alginate and *Camelia sinensis* extract. Hyaluronic acid (HA) is a fundamental component of the connective tissue. HA can modulate the inflammatory response, cellular proliferation, and remodeling of the extracellular matrix (25). Magnesium alginate, topically applied, thanks to its molecular egg-box structure, is able to scavenger substances including pepsin, inhibiting its proteolytic activity (26,27). *Camelia sinensis*, such as the green tee, has potent anti-oxidant and anti-inflammatory activity as very recently demonstrated (28). Gastroftal tablets is a Medical device (Class II), containing Magnesium alginate, and Simethicone, per oral usage. Alginate, orally administered, is a fruitful medication in the management of GERD. It precipitates as a gel after the exposure to the gastric acid, thus forming a raft that represents a barrier to the reflux of the gastric content into the oesophagus (29). Interestingly, the current findings were consistent with a recent study conducted in children with uncontrolled asthma and GERD (30). Up to 80% of uncontrolled asthmatic children treated with Magnesium Alginate had a clinically relevant reduction of both asthma control test and asthma control questionnaire. Simethicone is an anti-foam agent able to reduce the severity of symptoms caused by exces- sive gas overload in the stomach. In fact, it has been documented that it was able to significantly improve gastroesophageal reflux in infants (31). However, this study has some relevant limitations, including the cross-sectional design, the limited number of participants, the lack of functional and macroscopic investigation of the upper digestive and respiratory tract, the lack of pepsin assessment in the tears, and the lack of a follow-up.

Anyway, a strength of the current study the contemporary evaluation of digestive and ocular symptoms using validated instruments.

In conclusion, a combined therapy, including topical Gastroftal eye drops and oral Gastroftal tablets may be considered a promising treatment in patients with dry eye due to LPR.

Conflict of interest: all the authors, but DV employee of DMG, have no conflict of interest about this matter.

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Original article

Turbinate hypertrophy in children with allergic rhinitis: clinical relevance

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Abstract. Allergic rhinitis (AR) is the most common immune-mediated disorder in childhood as it may affect up to 40% of children. Turbinate hypertrophy (TH) is an important sign as reliably predicts AR both in children and adults. Consistently, nasal obstruction is a very common symptom in AR patients and is closely linked with turbinate hypertrophy. This study investigated 544 (304 males) children with AR to define factors associated with TH. TH was diagnosed in 438 (80.81%) AR children. The multivariate analysis demonstrated a significant association between age, male gender, and recurrent acute otitis media (RAOM), and TH (p-values: 0.0219, <0.0001, and 0.0003, respectively; OR 0.87, 3.97, and 0.22 respectively). In conclusion, this real-life study showed that TH was very frequent in children with AR and age, male gender, and RAOM were significantly associated with TH. (www.actabiomedica.it)

Key words: clinical visit, nasal endoscopy, allergic rhinitis, children, turbinate hypertrophy

Introduction

Allergic rhinitis (AR) is the most common immune-mediated disorder in childhood as it may affect up to 40% of children (1). AR is frequently associated with relevant comorbidities, including other allergies, rhinosinusitis, recurrent respiratory infections, otitis, adenoid and tonsillar hypertrophy (2). Turbinate hypertrophy (TH) is an important sign as reliably predicts AR both in children and adults (3,4). Consistently, nasal obstruction is a very common symptom in AR patients and is closely linked with turbinate hypertrophy (5). The work-up of AR in children includes history, physical examination, and allergen-specific IgE evaluation, by skin prick test and/or serum assay. Nasal endoscopy is an additional step, mainly if upper airways co-morbidity is suspected (6,7). Nasal endoscopy allows defining the abnormal anatomy of upper airways, including adenoid and tonsil, mucosal characteristics, and turbinate morphology. Very recently, Karabulut and colleagues performed fiberoptic endoscopy in 129 children and concluded that turbinate hypertrophy, the colour of inferior turbinate, and adenoid are predictive of AR (8).

Based on this background, we tested the hypothesis that, in the clinical practice, the medical visit and the nasal endoscopy can define the prevalence of TH and provide information about factors associated with TH in AR. Therefore, this real-life study aimed to evaluate the prevalence of TH and whether some clinical data and endoscopic findings may be predictive factors for TH in children suffering from AR.

Materials and Methods

A series of children were consecutively enrolled in the study. Inclusion criteria were: i) age between 3

and 10 years; ii) AR diagnosis. Exclusion criteria were: i) a craniofacial syndrome, ii) recent facial trauma and infection, and iii) current treatment and diseases able to interfere with the finding interpretation. The study was approved by the local Review Board and informed written consent was obtained by the parents.

The clinical visit included detailed medical history, concerning premature birth, feeding type (breastfeeding or artificial), family atopy, passive smoking, post-infective wheezing, recurrent respiratory infections, and recurrent acute otitis media.

Nasal endoscopy was performed with a pediatric rigid endoscope (diameter 2.7 mm with 30° angle of vision) as previously extensively described (3,9). Tonsil volume was classified according to validated criteria (10) as well as adenoid volume (11). The contact of turbinates was considered a surrogate marker for TH, as previously described and validated (3,4).

Continuous variables were given as means with standard deviations (SD) and categorical variables as the number of subjects and percentage values. TH was considered the primary outcome. The univariate logistic regression models were performed to screen the effect of the clinical and demographic variables on the TH. The odds ratios associated with TH were calculated with their 95% confidence interval for each factor. The Likelihood Ratio test was used as a test of statistical significance and the estimated p-values were adjusted for multiple comparisons by the Bonferroni correction method. Multivariate analysis was performed using again the penalized logistic regression model and the model selection was done by the Akaike an Information Criterion. The multivariate model performance was assayed using K-fold cross-validation. Differences, with a p-value less than 0.05, were selected as significant and data were acquired and analyzed in the R v3.6.1 software environment.

Results

Globally, 544 (304 males) children were evaluated and stratified according to TH presence or absence. The demographic and clinical characteristics are summarised in Table 1. TH was diagnosed in 438 (80.81%) AR children. Children with TH were significantly younger than children without TH, were more frequently males, more frequently had breastfeeding and RAOM. The univariate logistic regression demonstrated a significant association among age, gender, breastfeeding, RAOM, and TH (p-values<0.05). The multivariate analysis confirmed a significant association between age, male gender, and RAOM, and TH (p-values: 0.0219, <0.0001, and 0.0003, respectively; OR 0.87, 3.97, and 0.22 respectively).

The multivariate model performance showed an excellent model average accuracy (accuracy (95%C.I.) = 0.80 (0.79 : 0.81)). All the accuracy scores ranged from 0.59 to 0.96. Moreover, low false positive and negative rates were 0.18 and 0.02, respectively.

Discussion

The present study was based on a real-life setting, such as the children were consecutively visited at a clinical office, undergoing visit and nasal endoscopy.

The main outcome was the very high prevalence of TH in children with AR: about 81%. Therefore, this sign represents a relevant clinical characteristic of AR in childhood. Subsequently, this study identified some clinical parameters associated and potentially predictive for TH: age, male gender, and RAOM history.

In particular, the male gender represented a relevant factor associated with TH. This finding is consistent with our previous study but was more convincing at present, probably as it depended on a larger sample of examined children (3). More interestingly, RAOM history was negatively associated with TH so that it may be considered a protective factor for TH. The possible explanation might depend on the aggressive treatment usually prescribed in RAOM children, including topical corticosteroids that significantly reduce allergic inflammation. TH is a sign closely associated with allergic inflammation and is highly sensitive to corticosteroid treatment (12).

On the other hand, other factors, including family atopy, adenoid and tonsil hypertrophy, passive smoking, and post-infective wheezing, were not significantly associated with TH. This outcome confirms the different pathogenic mechanisms involved in allergic inflammation and infective immunity respectively.

Table 1. Contingency tables and Output of the univariate and multivariate analysis (N=544). OR (95% CI): Odd Ratios with 95% Confidence Interval; p-value: Likelihood Ratio p-value. *Variables entering the multivariate analysis

Univariate analysis	**Descriptive statistic**			
	Turbinate	**Hypertrophy**	**OR (95%C.I.)**	**p-value**
	No *104 (19.19%)*	Yes *438 (80.81%)*		
Age *	6.51 (2.3)	5.92 (1.62)	0.84 (0.75 : 0.94)	0.0326
Gender *				<0.0001
Female	76 (31.93%)	162 (68.07%)	1	
Male	28 (9.27%)	274 (90.73%)	4.53 (2.86 : 7.37)	
Prematurity				0.9999
No	94 (18.47%)	415 (81.53%)	1	
Yes	10 (30.3%)	23 (69.7%)	0.51 (0.24 : 1.13)	
Feeding *				0.0489
Artificial	28 (30.11%)	65 (69.89%)	1	
Breast	76 (16.93%)	373 (83.07%)	2.12 (1.27 : 3.49)	
Passive Smoking				0.9999
No	103 (19.58%)	423 (80.42%)	1	
Yes	1 (6.25%)	15 (93.75%)	2.53 (0.62 : 23.14)	
Family Atopy				0.9999
No	10 (27.78%)	26 (72.22%)	1	
Yes	94 (18.65%)	410 (81.35%)	1.72 (0.78 : 3.55)	
RAOM *				0.0004
Absence	71 (15.81%)	378 (84.19%)	1	
Presence	33 (35.48%)	60 (64.52%)	0.34 (0.21 : 0.56)	
Wheezing				0.9032
No	90 (20.64%)	346 (79.36%)	1	
Yes	14 (13.21%)	92 (86.79%)	1.67 (0.94 : 3.15)	
Recurrent Respiratory Infections				0.0902
No	53 (24.77%)	161 (75.23%)	1	
Yes	51 (15.55%)	277 (84.45%)	1.78 (1.16 : 2.75)	
Tonsillar Hypertrophy				0.9999
no	39 (20.1%)	155 (79.9%)	1	
yes	65 (18.68%)	283 (81.32%)	1.07 (0.78 : 1.46)	
Adenoid Hypertrophy				0.9162
no	52 (16.67%)	260 (83.33%)	1	
yes	52 (22.61%)	178 (77.39%)	0.77 (0.57 : 1.04)	
Multivariate analysis				
(intercept)			6.49 (2.85 : 15.06)	0.0219

(continued on next page)

Table 1 ***(continued)***. Contingency tables and Output of the univariate and multivariate analysis (N=544). OR (95% CI): Odd Ratios with 95% Confidence Interval; p-value: Likelihood Ratio p-value. *Variables entering the multivariate analysis

Univariate analysis	Descriptive statistic			
	Turbinate	Hypertrophy	OR (95%C.I.)	p-value
	No *104 (19.19%)*	Yes *438 (80.81%)*		
Age			0.87 (0.78 : 0.98)	
Gender				<0.0001
Female			1	
Male			3.97 (2.48: 6.51)	
RAOM				0.0003
Absence			1	
Presence			(0.22 : 0.63)	

The main limitations of the present study are: i) the cross-sectional design; ii) the selected population; iii) the absence of immunological investigation, able to clarify the pathogenic mechanisms, and iv) the lack of a detailed past medication accounting. Therefore, further studies should be performed to address these issues.

However, the strength of this study is a large number of children, the careful work-up, and the real-life setting, so the outcomes may mirror what could occur in daily practice. In this regard, turbinate enlargement is the expression of allergic inflammation (13,14). Therefore, anti-inflammatory treatment is indicated in children with TH. Corticosteroid is the most potent anti-inflammatory drug and, in its intranasal formulation, is widely used in common practice. However, safety is a critical issue, mainly concerning in the pediatric age: it is mandatory to prefer corticosteroid molecules with an optimal safety profile, such as mometasone (15). As TH is a chronic condition, intranasal corticosteroid could be opportunely alternated with ancillary anti-inflammatory agents, including glycyrrhetinic acid that can significantly improve mucociliary transport time (16) and allergic symptoms (17).

In conclusion, this real-life study showed that TH was very frequent (about 80%) in children with AR and age, male gender, and RAOM were significantly associated with TH.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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Original article

Complications of adenotonsillectomy in pediatric age

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Abstract. Although in recent years adenotonsillectomy procedures have shown an overall reduction in number, this surgery continues to be the most frequently performed in our speciality, especially in pediatric age. The progressive improvement in both surgical techniques and devices and anaesthesia has made adenotonsillectomy a less risky manoeuvre, but this does not mean that it is free from potential adverse events or even an easy, routine and risk-free procedure, as presented by some para scientific literature and mass media. Here we address issues related to the complications that can arise when performing this surgical procedure, which can be very serious. (www.actabiomedica.it)

Key words: adenotonsillectomy, children, complications

Introduction

Adenotonsillectomy procedures, as can be seen in figures 1A, 1b, and 2, reporting PNE data, have shown a slow but progressive numerical reduction in recent years. Nonetheless, based on data from the SDO (Schede di Dimissione Ospedaliera), in the period 2007 to 2012 the mean incidence of post-surgical hemorrhages had a statistically significant increase, with geographical percentage variations between 0,02% and 1.38%, whereas, in 2013, homogeneous values of 0.69% were reported for the whole national territory.

Tonsillectomy has perioperative morbidity of approximately 2%. The overall incidence of post-surgical complications, as reported in the literature, ranges from 8% to 14% (1), whereas postoperative mortality is close to that of general anaesthesia alone, with one death per 10,000-35,000 cases (2.3). In Italy, in the three years 1999-2001 (Matter), one death per 95,000 was reported. However, it is difficult to obtain accurate data on real mortality based on scientific literature and data from the press.

The main mortality causes can be identified in complications related to anaesthesia and haemorrhage. Postoperative haemorrhage has an overall incidence between 0.5% and 24%. This wide range is because the various studies available in the literature are uneven: many authors only reported haemorrhages requiring surgical treatment, whereas other authors included also bleeding episodes that were managed in an outpatient setting with medical therapy alone. Blakely, in a review of 63 publications, reported a hemorrhagic incidence of 4.5%, with a standard deviation of 9.4%. Lowe, in an audit in the United Kingdom in 2007, reported a hemorrhagic incidence of 3.5% on a total of 34.000 tonsillectomies, but only 0.9% of cases required surgical hemostasis (4). Post-adenoidectomy haemorrhages have a lower incidence rate, approximately 0.8%, regardless of the surgical technique used.

The literature also shows that children under six years of age have approximately three times lower bleeding risk than children over six years of age. Males have a 1.3-fold higher hemorrhagic risk rate than females. Furthermore, different diagnoses present a different intrinsic risk: patients undergoing surgery for adenotonsillar hypertrophy have shown a lower hemorrhagic risk compared to patients undergoing surgery for recurrent infections. As far as the surgical technique is concerned, the use of cold instruments is related to a lower bleeding risk (1.2%) than the electrocauterization technique (6%) (5). Table 1 reports the classification of the main complications following surgery.

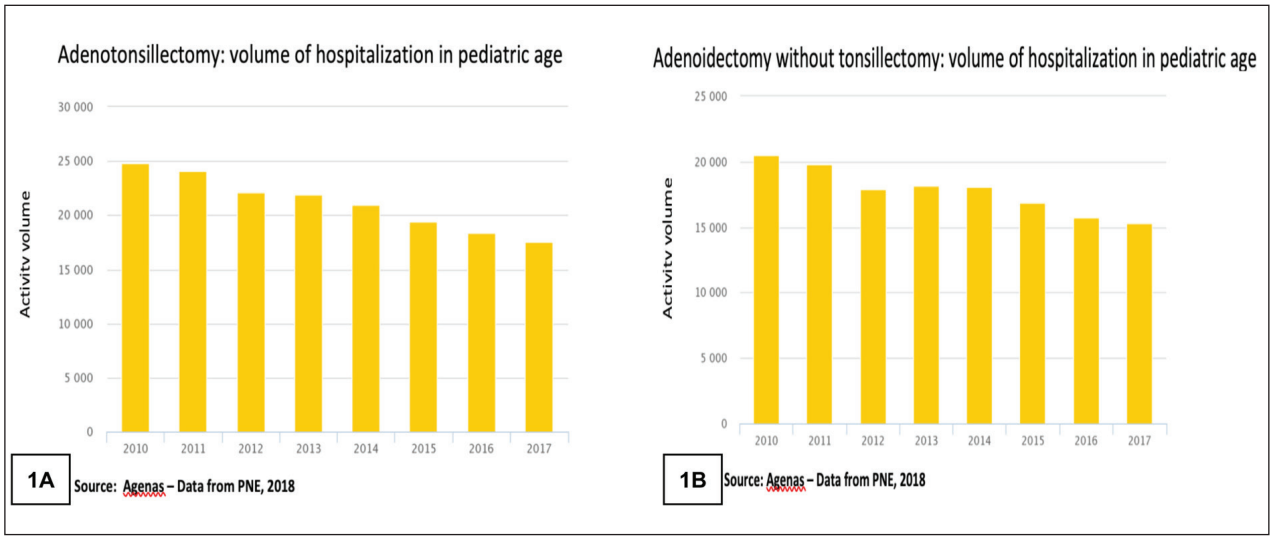

Figure 1.

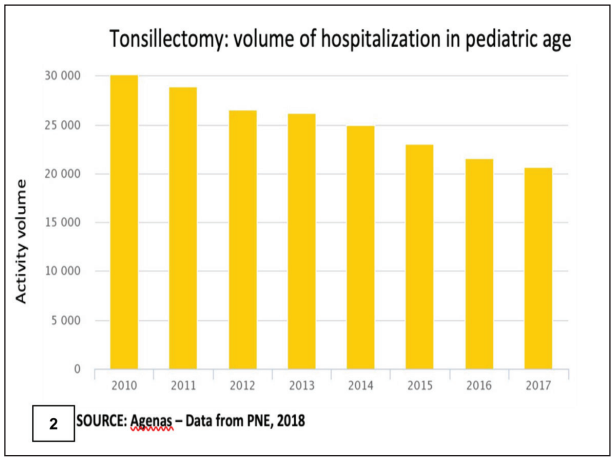

Figure 2.

Hemorrhagic complications

The tonsillar lodge presents a rich vascularization that comes from the external carotid artery (ECA). The main arterial blood supply is provided by the tonsillar artery, which originates from the ascending palatine artery and the ascending pharyngeal artery. These vessels can branch either from the lingual artery at a 90° angle or directly from the ECA. The palatine artery and the ascending pharyngeal artery give rise to the tonsillar arteriolar branches (polar branches), which perforate the pharyngeal constrictor muscle and run towards the tonsillar parenchyma. The veins form a tributary plexus of the pharyngeal plexus. Innervation is supplied by the tonsillar plexus, located on the lateral wall and formed by branches of the lingual nerve and the glossopharyngeal nerve.

Based on the time of onset, postoperative haemorrhages can be divided into:

- immediate
- delayed
- late

or into:

- primary: presenting in the first 24 hours (< 5%)
- secondary: presenting within two weeks, but generally between the 6th and 10th postoperative day; bleeding episodes have been reported in the literature up to 55 days after surgery (6,7).

Immediate haemorrhages are usually complications of ineffective or incongruous intraoperative hemostasis due to inadequate cauterization of a blood vessel, imperfect arterial ligation, accidental detachment of a ligation snare, reduction or loss of the tensile strength of the suture from salivary stagnation, or a hypertensive peak or agitation upon awakening.

In the case of deficiency of coagulation factors or thrombocytopenia, it is important to provide adequate therapy or pre-intraoperative prophylaxis.

Table 1. Complications classified on the time of onset as follows:

Immediate onset	**Medium onset**	**Late onset**
Anesthesiological: 1. Cardiac-circulatory arrest 2. Hypoventilation 3. Intoxication 4. Ab ingestis during haemorrhage 5. Acute pulmonary oedema	Velo-pharyngeal insufficiency: 1. Palatine veil injury 2. Tonsil pillar injury 3. Uvular injury	Chronic pharyngitis
Hemorrhagic: 1. Primary (within 24 h) 2. Secondary (after 24 h)	Voice alterations: 1. Post-surgical pain 2. Vocal resonance apparatus modifications 3. Velo-pharyngeal incontinency	Facial pain and dysphagia due to ossification of the stylohyoid ligament (Eagle's syndrome)
Oral cavity lesions: 1. Uvular oedema 2. Tongue ecchymosis and oedema 3. Dental avulsion 4. Mouth or lip burn 5. Temporomandibular joint dislocation 6. Mandibular condyle fracture	Neurological complications: 1. Dysgeusia 2. Glossopharyngeal nerve palsy 3. Facial nerve palsy 4. Horner's syndrome	
Local infections: 1. Neck lymph node suppuration or phlegmon 2. Paratonsillar cellulitis 3. Retro/parapharyngeal abscess	Compensatory hypertrophy of the remaining lymphatic tissue (lingual tonsil)	
Regional infections: 1. otitis 2. sinusitis 3. epiglottitits 4. pneumonia	Emotional trauma	
Subcutaneous emphysema or pneumomediastinum		
Grisel's syndrome		

Late or secondary haemorrhages, on the other hand, are usually caused by eschar falling, generally occurring between the 6th and the 10th postoperative day, but inappropriate postoperative patient behaviour can also favour this process.

Among the causes, vascular disruptures should be taken into considerations as well. They can be caused by:

- Local necrosis
- Anomalous or aberrant vessels originating from the internal or external carotid artery
- Arterial loops
- Traumatic pseudoaneurysms
- Septic arteritis
- Exposition or rhexis of major vessels (facial artery, lingual artery, ascending palatine artery…)

Although the percentage of hemorrhagic complications is low in the various casuistries, it should not be forgotten that they may represent a dramatic emergency. Besides, recurrent late haemorrhages, albeit mild, should never be underestimated: for this reason, patients presenting even with a low-entity bleeding episode should always be hospitalized (7).

In case of a hemorrhagic event, the measures are

very varied. Depending on the severity of the bleeding, local hemostasis by infiltration with a solution of 1% xylocaine with a vasoconstrictor may be sufficient, or surgical revision of the tonsillar lodge may be required. In the latter case, different procedures might be performed, ranging from ligation of tonsil pillars or tamponade of the tonsillar lodge to ligation of the ECA or embolization of one of its branches (8,9,6,10).

Respiratory complications

In recent years we have also seen an improvement in anaesthesia techniques, which has resulted in greater safety in some procedures, including tonsillectomy. Nonetheless, it should not be forgotten that, in this peculiar situation, the anaesthetist and the Otolaryngology surgeon are to interact on the same surgical field, so it is not infrequent that, during the surgical manoeuvres, the endotracheal tube can be bumped, bent or dislocated, so as to determine hypoventilation or even extubation of the patient (6,7,11,12).

Consequently, respiratory complications can result from hypoxic phenomena and suffocation caused by:

- blood ab ingestis
- irritative laryngeal spasm during haemorrhage
- insufficiency or delays in orotracheal intubations
- severe OSAS
- obesity
- drugs: promethazine, morphine and its derivatives, inducing breath depression, apnea, contractions and eventually cardiac arrest, etc.

Infectious complications

Infectious complications are now a rare occurrence, although data from the literature show an incidence between 6% and 41%, with a higher frequency in children affected by recurrent acute otitis media or recurrent pharyngotonsillitis (13). On the contrary, transient bacteremia is a frequent occurrence. The most commonly isolated pathogen is *Haemophilus influenzae*, but *Streptococcus viridans, Streptococcus pneumoniae,* and *Staphylococcus aureus* have been isolated from blood cultures with a certain frequency, as well. Minor complications reported in the literature include pneumonia and urinary tract infections, whereas, among the major complications, sporadic cases of meningitis (14), cerebral abscess, sepsis and osteomyelitis at distant sites (15) have been described. Cervical osteomyelitis can occur after tonsillectomy or adenoidectomy procedures. It is caused by the spreading of the infectious process either through the cervical planes, the blood vessels or the lymphatic system. The clinical onset is often insidious.

Internal jugular vein thrombosis, known as Lemierre Syndrome, has also been reported. This condition results from an initial thrombosis involving the tonsillar vein with subsequent spreading to the internal jugular vein and, occasionally, also to the cavernous sinus.

Traumatic complications

Traumatic complications, taken as a whole, are more frequent than previously considered. They are mostly due to patient positioning manoeuvres, incongruous tools, defective electrical insulation equipment, direct or inadequate heat transfer, and operator-related errors.

The most frequent complications are:

- Grisel syndrome, i.e., subluxation or displacement of the atlantoaxial joint (C1 on C2). This occurrence is more frequent in children affected by Down's syndrome due to increased ligament laxity (16,17);
- perforation of the posterior tonsil pillar, velar or velopharyngeal injury;
- dental trauma with rupture, dislocation or avulsion of dental elements;
- dislocation of the temporomandibular joint (18);
- hematoma of the tongue;
- pseudoaneurysm of the lingual artery (19) or, more rarely, of the external or internal carotid arteries (20)

The late complications from surgical trauma include:

- rhinolalia;
- velar insufficiency, sometimes accompanied by dysphagia and nasal regurgitation of food (21);
- oropharyngeal stenosis

Other complications

Haematological and metabolic complications are very rare, as well as neurological complications. The latter include the appearance of dysgeusia, and hypoglossal nerve or lingual nerve deficit caused by surgical or anesthesiological manoeuvres (20,21).

However, it is important to be aware of these potential complications as well, to make a timely diagnosis that allows early therapy.

Conclusions

Tonsillectomy is one of the oldest procedures in Otolaryngology: in fact, the first description dates back to 30 BC and is reported in the encyclopedic treatise on the medical art "De Medicina" by Aulus Cornelius Celsus. Despite the refinement and the evolution of surgical and anesthesiological techniques, this procedure should not be considered "banal and risk-free": complications are not so rare and sometimes they can be serious, leading to the death of the patient. Therefore, it is of uttermost importance to assess the indications to tonsillectomy very carefully, using the available guidelines as a reference. The surgical and anesthesiological teams should be well-trained. During the surgical procedure, dissection should be performed carefully, avoiding extensive coagulation and manoeuvres which might result in potential local infectious complications. In case of a hemorrhagic complication, an immediate and correct diagnostic and therapeutic approach is essential; especially, recurrent hemorrhagic manifestations, albeit mild, should not be underestimated. In the end, organizational aspects must not be neglected. The hospitalization regimen in Italy varies from day surgery and one-day surgery to ordinary hospitalization, and the must go beyond the purely economic aspects of DRG (Diagnosis-Related Group) and LEA (Livelli Essenziali di Assistenza) tariffs. Not least the importance of obtaining appropriate Informed Consent, with a written form containing precise and punctual information to be provided to parents by the surgeon. Moreover, information regarding the clinical and surgical process should be addressed directly to the patient even in the case of a minor; such information must be adapted to the age of the young patient.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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Original article

Acute mastoiditis in children

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Abstract. Acute mastoiditis is the most common complication of acute otitis media. Although rare, the disease is carefully studied by otolaryngologists because it usually affects very young children with severe clinical course and sometimes causes serious complications. Most important risk factors are the young age (often>2 years), high fever, alteration of the laboratory findings (very high values of WBC count, absolute neutrophil count and C-reactive protein), while less important are previous antibiotic therapy or previous middle ear infections. The main pathogen of the acute mastoiditis is *Streptococcus pneumoniae*, followed by *Streptococcus piogenes*, *Haemophilus influentiae,* and *Staphylococcus aureus*. The finding of *Pseudomonas aeruginosa* is not uncommon, but often its presence is often considered a contamination or simultaneous infection. The complications can be extracranial (subperiosteal abscess, Bezold's abscess); intratemporal (facial nerve palsy, labyrinthitis) and intracranial (subdural abscess). The complications have often a very serious clinical course and potentially life-threatening. Antibiotic therapy is the main treatment in not complicated forms. Considering the prevalence of *Streptococcus pneumoniae*, cephalosporins are the antibiotic of choice, but they have to be administrated intravenously in hospitalized patients. Combinations with other antibiotic are suggested when multibacterial flora is present. In complicated forms of acute mastoiditis, the antibiotic treatment can be particularly important, in combination with other specific drugs (i.e. anticoagulants and/or corticosteroids). Surgical treatments, such as incision of abscesses, mastoidectomy, and neurosurgical procedures, are sometimes performed in combination with medical therapy in very severe complications. Data from our experience are briefly reported. (www.actabiomedica.it)

Key words: acute mastoiditis, pathogens, antibiotics, surgery

Introduction

Acute mastoiditis (AM) is a serious bacterial infection of the mastoid bone that occurs as a consequence of acute otitis media (AOM). The illness needs to be correctly defined. Given that the middle ear (ME) communicates with the mastoid area through *aditus ad antrum*, a mastoid involvement in infectious acute or chronic diseases of ME is very common; therefore, "otomastoiditis" is the correct definition of all otitis. Instead, AM represents a severe complication of an acute (sometimes chronic) otitis media, favoured by several factors (anatomic condition of the temporal bone, age, bacterial flora, immunological defects, etc).

The main etiopathogenetic factor is represented by the closure of the *aditus ad antrum* due to oedema or granulation tissue which prevents the drainage of the purulent exudate from the mastoid air cells (1). Very common in the pre-antibiotic era (at least 20% of OMA resulted in AM, often complicated by devastating extratemporal and intracranial sequelae), the disease is currently rare but it is often dangerous because it mostly affects very young children, with important clinical course and complications.

OMA is a suppurative infection of mastoid air cells with bone destruction (osteomyelitis); sometimes the process spreads through the periosteum and induces periostitis and subsequent involvement of surrounding structures, in particular, neurological and vascular. So, complications of acute AM are sometimes dramatic and difficult to treat. It is very important to perform a precocious diagnosis and a well-planned and prolonged antimicrobial or surgical treatment to avoid severe complications, sometimes with lethal risks.

In this review, we aim to illustrate a synthetic overview of AM, with some reference to personal experience of the last 15 years.

Incidence

Acute mastoiditis represents the most common complication of an AOM, affecting 1 in 400 cases (0.24%) (2). Its incidence is variously reported in different countries, varying in pediatric age from1.2 to 6.1 per 100,000 children aged 0-14 years, per year (3,4). Dramatically decreased in the antibiotic era, the incidence of AM in pediatric age has consistently increased in the last two decades even in developed countries (5). This event can be attributed to a selection of resistant bacterial strains, more frequently detected over time, due to inadequate antibiotic treatments (abuse or non-specific use) (6,7,8).

Pediatric age is undoubtedly the most prone to mastoid involvement in middle ear infections, due to particular anatomical, immunological and infectious conditions, above all in the first years of life:

In children, the mastoid bone is more pneumatized with thin bone trabeculae and the aditus ad antrum is smaller than in adult's: so, there is a greater predisposition to the accumulation of secretion and osteitic infection. Pediatric age is often characterized by physiological immaturity of the immune system with a peak incidence between the second and third year of life. Particularly in children, non-selected antibiotic therapies can induce a selection of resistant bacterial strains. In a wide casuistry, Groth et al. evidenced differences in the evolution of the AM in different ages: youngest children have more rapid evolution and more serious symptoms of the disease than adults (4).

Our experience confirms the previous studies on the incidence of AM. In our study, most children (27 observed from 2003 to 2017) were < 3 years old; just one case was > 10 years old (Figure 1).

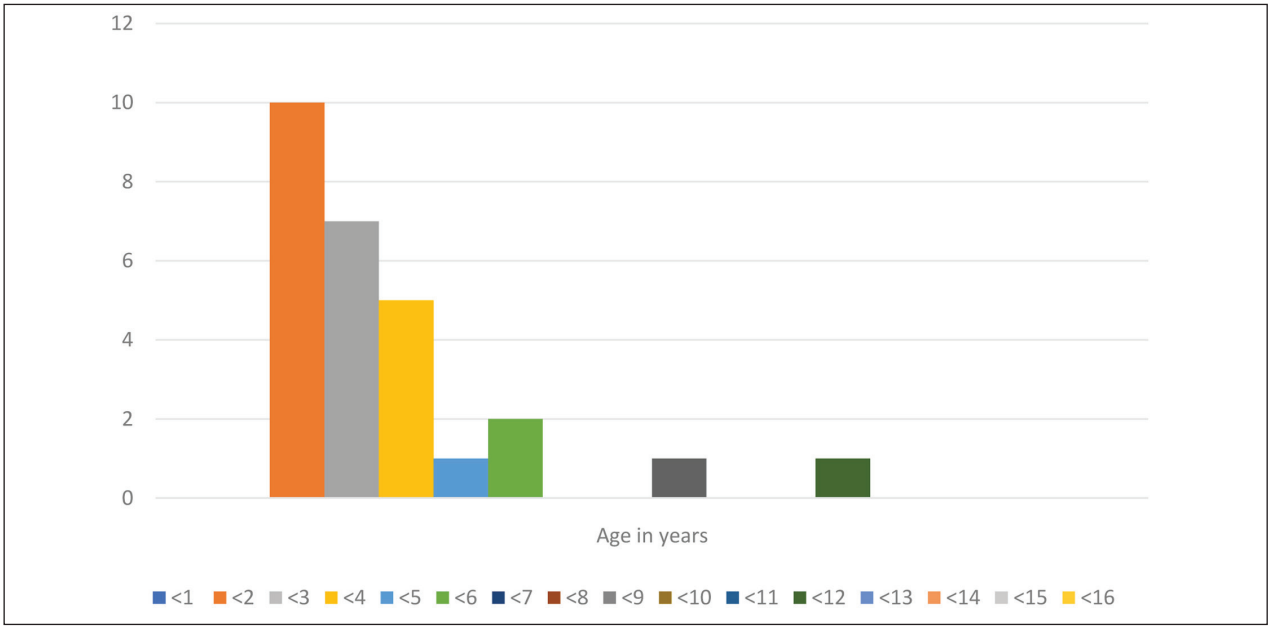

Figure 1. The distribution of ages of the 27 children with acute mastoiditis during the periodo 2003-2017

Complications

If not properly treated, AM can lead to extracranial and intracranial complications, which are sometimes very serious and even life-threatening. Complications are particularly frequent in children younger than 2 years, in which the disease progresses faster and more seriously (9,10). The incidence of complications in AM is variously estimated, depending on interpretation and classification of the complications; intracranial complications range from 4 to 16% (11,12).

The main pathogenetic factor of the AM, and in particular of the complications, is the obstruction of the aditus ad antrum, by edematous mucosa or granulation tissue with inhibition of purulence's drainage from the mastoid. High bacterial virulence and decreased immune defences are also important.

The most frequent complication is the subperiosteal abscess, following the progression of the inflammatory process; periostitis, the release of cytokine with osteoclasts activation and consequent decalcification and bone resorption (coalescent mastoiditis) (1). The clinical picture may include ear pain, persistent high fever, post-auricular tenderness or purulent collection with the displacement of the pinna. Other extracranial complications (facial nerve pulse, labyrinthitis, internal jugular vein thrombosis, periphlebitis of the sigmoid or lateral sinus) are consequent to the involvement of the neurological or vascular structures of the mastoid. Bezold's abscess originates from erosion of the mastoid bone cortex medially to the attachment of sternocleidomastoid muscle (13). The pus extends into the infratemporal fossa and then proceeds along the deep cervical fascia. The main symptoms are fever, severe pain in the perimastoid area, dysphagia, sore throat, and nuchal rigidity. Intracranial complications are not common, but undoubtedly represent very dangerous diseases that can sometimes have a lethal outcome. Symptomatology is mainly neurological and/or septic in case of meningitis, epidural abscesses, encephalitis or thrombosis of the sigmoid or cavernous sinus. The main pathogenetic factors in the complications are the same as those of AM, in particular, the obstruction of the aditus ad antrum, but often associated to high bacterial virulence and decreased immune-defences in very young children (14). In our case history, we had a high number of complications, probably due to a delayed diagnosis of AM (Figure 2).

Complications	Number of cases
SUBPERIOSTEAL ABCESS	11
PERIPHLEBITHIS OF LATERAL SINUS	3
FACIAL NERVE PALSY	2
LABYRINTHITIS	1
BEZOLD'S ABCESS	1
SEPTIC THROMBOSIS OF THE LATERAL SINUS	1
EPIDURAL ABCESS	1
Total:	20

Figure 1. Complications of AM

Bacteriology

In the current opinion, *Streptococcus pneumoniae* is considered the predominant pathogen in children affected by AM. It is undoubtedly the most common and likely cause of the most acute forms of disease and most complications. It has been observed both in the middle ear effusion (spontaneous discharge) and in the purulent collections (15,16,17,18). In lower percentages, *Streptococcus pyogenes, Staphylococcus aureus* and *Hemophilus influenzae* were identified. The role of *Pseudomonas aeruginosa* is still controversial. Some authors consider it a predominant pathogen in AM (19,20). In particular, in the opinion of Butbul et al., it is a leading agent in children > 4 years old, while *S. pneumoniae* is prevalent in patients < 2 years old; moreover, this study evidenced that *P. aeruginosa* is present in mastoiditis resulting from recurrent or chronic otitis media, whereas *S. pneumoniae* is more easily found in isolated episodes of AM (19). Laulajainen et al. found a clear correlation between previous tympanostomy tubes and AM caused by *P. aeruginosa*. Moreover, the study underlined a different course of the disease due to this pathogen, compared to *S. pneumoniae*: the patients had mild signs and symptoms, but all with otorrhea (15). However, most Authors do not consider it a main causative agent of AM. *P. aeruginosa* (as well as *Staphylococcus aureus*, often associated), is present in the external ear canal as

a component of saprophytic flora; so, its presence in the culture obtained from ear canal swab is considered contamination or simultaneous infection (21). Actually, in the cultures coming from the middle ear (via tympanic paracentesis) or from abscesses collections the leading pathogen turns out to be *S. pneumoniae* (22).

Finally, some Authors evidenced no growth flora, probably due to previously administered antibiotic therapy; in these cases, a statistically significant higher complication rate was verified (18,23).

In our experience, *S. pneumoniae* was the predominant bacterium (21-77%), followed by *Streptococcus pyogenes* (9-33%), *Hemophilus influenzae* (6-22%) and *Pseudomonas aeruginosa* (2-7%). Association of two or more pathogens was found in 9 (40%) cases; no growth flora in 5 (18%) cases. In the study, the bacteriological examination was performed almost always on the purulent exudate taken from the middle ear, by aspiration or from the retro-auricular purulent collection, never from the external ear canal. The low presence of the *P. aeruginosa* confirms the hypothesis that this pathogen is often a contaminant element of the external ear canal, sometimes simultaneously infected.

Diagnosis

In non-complicated AM the diagnosis is mainly clinical, considering in particular two factors: clinical picture and risk factors for the involvement of the mastoid bone in an acute or chronic middle ear infection.

Signs and symptoms of a non-complicated AM generally do not differ from those of AOM (fever, earache, otorrhea, etc.) but are often more serious, with spontaneous or pressure pain in the mastoid area, sometime with tense, red and swollen retro-auricular skin, even in the cases where there is still not complete erosion of the cortical bone or purulent collection.

Risk factors for AM are frequently highlighted in the literature. Particularly interesting is the analysis performed by Garcia et al (Figure 3) which evidenced that the main suspected factors for an acute mastoid involvement during AOM, are the age (< 24 months), high values of C-reactive protein and previous surgical treatment for otitis. High values of Leucocyte count are also important but less so. Furthermore, the same predisposing factors to AM seem also to be implicated in its complications (16,22). Instead, significantly less important predisposing factors to AM and its complications are the previous otolaryngology diseases (in particular, chronic otitis media or recurrent AOM and adenoids) and previous antibiotic treatments (22). So, most authors agree that the uncomplicated forms of AM can be diagnosed only based on a clinical observation: when in very young children affected by AOM, high fever, compromised general condition and particularly altered laboratory findings are present. In these cases, more detailed and specific examinations (CT scan, MRI, angiography, angio-MR) can be avoided, while they are essential in the intratemporal, vascular and intracranial complications (23-26). However, different opinions have been expressed by some Authors who consider it essential to perform at least a CT SCAN in any case of suspected AM for early recognition of complications not yet clinically evident and for a treatment adequate to the severity of the illness (22, 27).

Treatment

In the uncomplicated forms of AM, antibiotic therapy is the main treatment. Most studies underline the necessity of carrying out in every case a middle ear culture for a more specific choice of antibiotic. Considering the high incidence of *S. pneumoniae* and its specific sensitivity to cephalosporins (less frequently to penicillins), this antibiotic, in particular, Ceftriaxone sodium, is widely used in the treatment of AM, always administered intravenously in hospitalized patients. The treatment with different antibiotics (amoxicillin, amoxicillin-clavulanate, erythromycin, etc), orally administrated, often proves to be ineffective and may even predispose to complications (4,18,28). The use of antibiotics other than cephalosporins can be justified only by a specific response of the bacteriological examination and antibiogram (i.e. antipseudomonal agent if *P. aeruginosa* infection is established). The association of 2 o 3 specific antibiotics is often opportune in polymicrobial infections (18,22). Also, antibiotic therapy with amoxicillin-clavulanate (less frequently other antibiotics) should continue for at least 10 days after recovery to avoid recurrences or long-term sequelae of AM, which are sometimes observed (recurrent otorrhea, recurrent AOM, persistent OM with effusion,

tympanic membrane perforation, etc) (18,28,29).

The introduction of the pneumococcal conjugate vaccine (PCV7) in 2000, subsequently replaced by a polyvalent version (PCV13), has certainly reduced the incidence of pneumococcal infections and consequently of AOM (15,23). Surprisingly, no decrease has been reported in the incidence of AM after vaccination, probably due to a possible pneumococcal serotype replacement. However, pneumococcal vaccination is always recommended in young children to avoid at least recurrent AOM, of which AM is the main consequence (30).

Many studies agree on the need for a myringotomy ± tympanostomy tube placement, above all in the cases of AM without spontaneous TM perforation (most often verified in children < 24 months) or AM of children with recurrent AOM or EOM (6,10,28,29,31).

The importance of this simple surgical procedure is enhanced by two studies, which demonstrate its validity even in some complications of AM, i.e. subperiosteal abscess. The Authors evidenced that myringotomy ± tympanostomy tube placement, combined with a simple retro-auricular puncture of the abscess and antibiotics (29) or retro-auricular incision and antibiotics (23) (conservative treatment), obtained the same results observed in patients treated with mastoidectomy and antibiotics (operative treatment). Conservative treatment was adopted even in some cases of more serious neurological or vascular complications (intracranial abscesses or lateral sinus thrombosis), in which the medical treatment with broad-spectrum intravenous antibiotic agents, anticoagulants and/or corticosteroids are often effective. However current opinion suggests that more aggressive surgical procedures, such as mastoidectomy, neurosurgical procedures, etc, are undoubtedly indicated in more important complications, in particular when intratemporal, endocranial or vascular structures are seriously involved (32, 33).

In our patients, antibiotic treatment was carried out in the cases of uncomplicated AM and in some cases of complications in which CT scan did not highlight serious mastoid osteomyelitis (2 cases of periphlebitis and 1 of thrombophlebitis of the lateral sinus); in these two cases antibiotics associated with anticoagulants and/or corticosteroids were effective. In all cases of the unperforated tympanic membrane (TM) was immediately performed with the suction of the secretion to allow better drainage and a bacterial examination without contamination of the bacterial flora in the ear canal. For this reason, an accurate toilet of the middle ear by suction was performed also in spontaneous perforation of MT cases. More important surgical procedures ("operative treatment": mastoidectomy with toilet and/or an enlargement of *aditus ad antrum*, tympanoplasty, abscesses incisions, etc) were adopted in most complications and in all cases in which CT scan showed a serious impairment of the mastoid bone. In just 2 cases of subperiosteal abscess, we performed a "conservative treatment" (tympanic paracentesis and abscess incision) associated with medical therapy.

Our therapeutic strategy allowed in all cases healing of the AM and its complications. No cases required further surgical treatment.

Conclusions

Despite the increasingly effective antibiotic and vaccine treatments, the AM is still a worrying disease that even seems to be growing in pediatric age due to ever-increasing antibiotic resistances. The severity of the complications of AM suggests careful clinical observation in all cases of OMA in which the symptoms are particularly severe, especially when they occur in very young children. In these cases, specific laboratory findings are certainly useful in diagnostic assessment. An early, specific and well-planned antibiotic therapy is fundamental for the resolution of the disease and the prevention of complications, that often require conservative or demolitive surgical treatments, sometimes dangerous in very young children.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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Original article

Foreign bodies in the pediatric age: the experience of an Italian tertiary care hospital

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Abstract. Foreign bodies in pediatric age represent an extremely frequent pathological condition and can undergo fearsome complications. Within the ENT area, foreign bodies in the pediatric age can be found in various districts such as external auditory canal, nasal passages, oral cavity, pharynx, larynx and trachea. They can be various and shape; generally, the main ones are buttons, beads, small parts of toys, caps of pens, pebbles, fragments of food bolus and others. As described in the literature, the main localizations are the external auditory canal and nasal cavities. Laryngeal and tracheal localization is infrequent but can be fatal. The aspiration of foreign bodies, mainly small parts of toys, occurs more frequently under three years age and mainly-especially in males. The experience of the ENT Department of the San Camillo-Forlanini Hospital in Rome, in the period between January 2007 and December 2018, consists a total of 1443 patients, aged between 0 and 14, who arrived in the emergency room with a foreign body diagnosis; of these, 613 (42.5%) were found with foreign body in the external auditory canal, 458 (31.7%) in nasal fossa, 298 (20.5%) in pharynx, 64 (4.4%) in oropharynx, and 10 (0.7%) in larynx and trachea. Treatment was in 1255 (87%) removal in the emergency room and home discharge, 79 (5.4%) with outpatient discharge, 40 (2.7%) need for hospitalization and surgery, 64 (4.4 %) refusal of hospitalization and 1 case (0.07%) died in the emergency room. (www.actabiomedica.it)

Key words: foreign body, children, otorhinolaryngology

Introduction

Foreign bodies in pediatric age represent an extremely frequent pathological condition. Within the ENT area, foreign bodies in the pediatric age can be found in various districts such as external auditory canal, nasal passages, oral cavity, pharynx, larynx and trachea. Foreign bodies can be various and shape, the main ones being buttons, beads, small parts of toys, caps of pens, pebbles, fragments of food bolus, and others. The symptoms depend largely on the location and size of the foreign body. In particular, the most important complications are related to the characteristics of the foreign body to which particular attention must be paid for the therapeutic choice (1). Several authors report a mortality rate of 4% to 7% (2,3). Mechanical obstruction of the respiratory tract due to inhalation or aspiration of foreign bodies is the primary source of fatal accidents in children under the age of one year and represents a major cause of death in children aged 1 to 4 years (4). It represents one of the main causes of sudden death.

Personal experience

The experience of the ENT Department of San Camillo-Forlanini Hospital in Rome, in the period between January 2007 and December 2018, consists of 1443 patients aged between 0-14 years, arrived in the emergency room with a foreign body diagnosis. Of these 613 (42.5%) with foreign body in the external auditory canal, 458 (31.7%) in nasal fossa, 298 (20.5%) in pharynx, 64 (4.4%) in oropharynx and 10 (0.7%) in larynx and trachea. The treatment adopted was 1255 (87%) removal in the emergency room and home dis-

charge, 79 (5.4%) with outpatient discharge, 40 (2.7%) need for hospitalization and surgery, 64 (4.4 %) refusal of hospitalization and 1 case (0.07%) died in the emergency room. In conclusion, we can affirm that in our casuistry, as well as in literature, the most documented incident is the foreign body in the external auditory canal, followed by those in nasal cavities.

Discussion

The site of greatest localization of foreign bodies in children is represented by the external auditory canal and the objects can be various, mainly inorganic. They may remain silent, if not referred to by the child, or manifest themselves instead with aurication, otorrhea, otorrhagia, and otodinia. The complications are represented by otitis externa, perforation of the tympanic *membran*e and dislocation of the ear chain. The diagnosis is based on otoscopy and otomicroscopy which allow to identify the type of foreign body, size, shape and to plan treatment. The extraction manoeuvres are based on the aid of chamfered hooks or pliers, in case of objects with irregular surfaces and prehensile edges. It is important to avoid gripping with unsuitable forceps, especially in case of rounded objects, due to the danger of pushing them deep, with the possibility of hesitating in complications. Sometimes the manoeuvre, based on the characteristics of the patient, is preferable to be performed in narcosis. The second most frequent location is represented in the nasal cavities. Also, in this case, they can remain silent if not reported by the child, in particular in case of objects with a smooth and non-irritating surface. Also, reflex phenomena can occur, including tearing, sneezing, serous rhinorrhea and headache, as well as pain in case of objects with sharp or pointed surfaces. Furthermore, whatever the nature or shape of the foreign body, unilateral nasal obstruction can occur with the possibility of mucopurulent rhinorrhea and blood streaks.

Diagnosis is based on anterior rhinoscopy and, eventually, rhinofibroscopy in case of posterior localization. The extraction manoeuvres are based on the aid of chamfered hooks or pliers, in case of objects with irregular surfaces and prehensile edges. It is essential to avoid gripping with unsuitable forceps, especially in the case of round objects due to the danger of pushing them deeper with the possibility of inhaling or swallowing the foreign body.

Based on the location in the nasal fossa and on the patient's collaboration, it is possible to define the possibility of performing the procedure under local anaesthetic or in narcosis. The third most frequent location of foreign bodies in pediatric age is in the oropharynx, mainly represented by small objects, toys or food. They usually occur in moments of distraction during the game or while watching television and they must be removed immediately, as they can become complicated with ingestion or inhalation. In literature, it is reported that FB aspiration is observed mainly in children under 3 years of age and males (5,6). When the diagnosis of foreign body aspiration is delayed, the risk of complications and death is increased (7). In particular, a delay of more than 24 hours is associated with a risk of complication 2.5 times higher than an early diagnosis (8).

The location of arrest, the nature, and the degree of obstruction of the foreign body affect the children's clinical picture and the possible complications. Minor site of localization of foreign bodies is represented by the larynx, with extremely important and potentially fatal complications. Endoscopic surgery is often not possible due to lack of time.

The diagnosis and localization of the foreign body can be confirmed by radiography, in cases of radiopaque foreign bodies and by direct laryngoscopy with the diagnostic and therapeutic value being able to allow the removal of the foreign body. In cases where the foreign body is localized to the level of the bronchial tree, spontaneous attenuation or remission of the symptomatology can occur, with a free interval that can last months or years.

Late complications, in this case, are manifested by atelectasis, pulmonary abscesses, bronchiectasis that can occur even years later.

The unblocking manoeuvre is represented by the Heimlich manoeuvre. Possible therapeutic options are based on endoscopic removal with a flexible instrument, but more often with a rigid bronchoscope. Rigid bronchoscopy under general anaesthesia represents the best diagnostic and therapeutic method (5). It provides safe ventilation, better exposure to the foreign body and allows different sizes of pliers to be used. It must be

Our experience from 2007-2018

AZIENDA OSPEDALIERA SAN CAMILLO FORLANINI

LOCATION		HOME DISCHARGE	OUTPATIENT DISCHARGE	RECOVERY	REFUSES ADMISSION	TRASFER TO ANOTHER STRUCTURE	DECEASED IN THE EMERGENCY ROOM
EAR	613 (42,5%)	521	62	14	16	o	0
NASAL CAVITIES	458 (31,7%)	398	10	15	35	0	0
PHARYNX	298 (20,5%)	271	7	4	12	4	0
LARYNX/ TRACHEA	10 (0,7%)	7	0	2	0	0	1
ORAL CAVITY	64 (4,4%)	58	0	5	1	0	0
TOTAL (N)	1443 (100%)	1255 (87%)	79 (5,4%)	40 (2,7%)	64 (4,4%)	4 (0,2%)	1 (0,07%)

Figure 1. Total number of foreign bodies at the ENT Department San Camillo-Forlanini, Rome, from 2007 to 2018

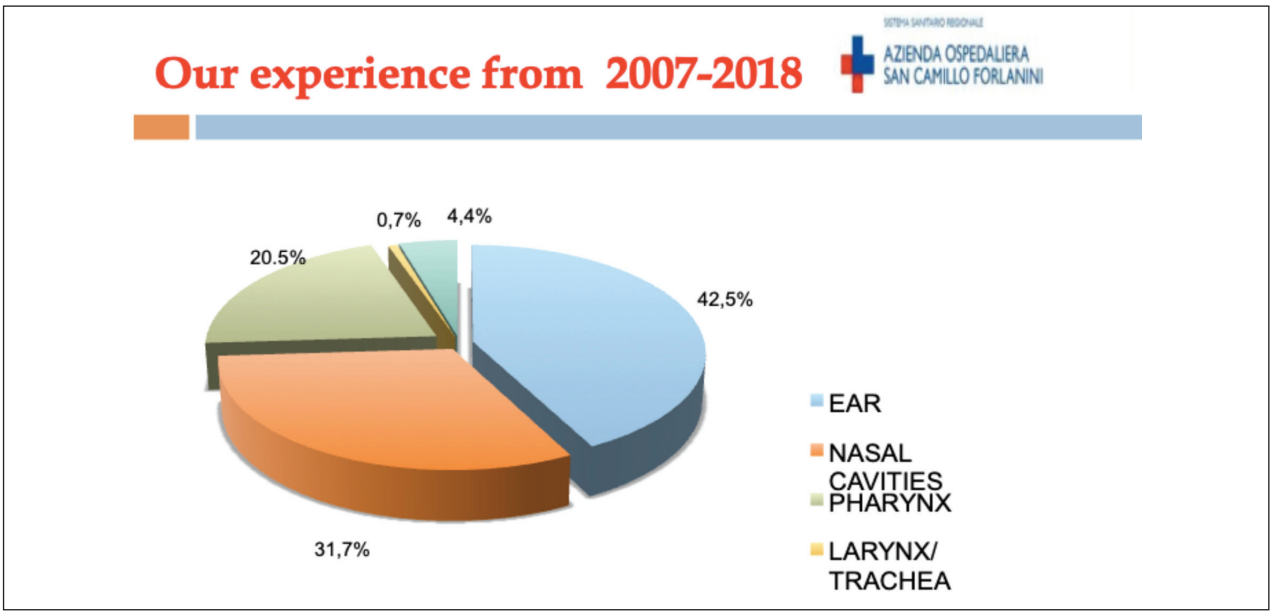

Figure 2. Percentage of foreign bodies at the ENT Department, San Camillo-Forlanini, Rome, from 2007 to 2018

performed without delay by qualified staff, appropriate tools and a period of fasting, except in emergencies (5,9). Due to the high risks and complications of this pathological condition, "The Susy Safe project" has been created, which aims to establish a register of cases of foreign body injuries in children aged 0-14 (10).

Collect relevant, up-to-date, representative, accurate and systematic information relating to foreign

body injuries. This is a project co-funded by DG SANCO that collects data on foreign body injuries in all countries the EU and beyond and was established to create surveillance systems for choking injuries capable of providing a risk analysis profile for each of the products that cause the injury (11).

The main results showed: 16,878 foreign body injuries were recorded in children aged 0 to 14 in the SUSY SAFE databases; 8,046 cases were reported by countries outside the EU. Almost a quarter of cases involve very young children (less than one-year-old) with a foreign body located in the bronchial tract, which represented a serious threat to their health. In older children, the most common locations are ears and nose. The type of foreign body was specified in 10,564 cases. Food items represented 26% of cases, while non-food items were the remaining 74%. Among the food items, the most common were bones, nuts, and seeds, while for non-food items pearls, balls and marbles were more commonly observed (29%). The coins were involved in 15% of the non-food injuries and the toys accounted for 4% of the cases. In conclusion, this represents a data collection system that should be taken into account when calculating the risk of injury, to provide the European Commission with all relevant estimates of foreign body injuries (10).

Inhalation from foreign bodies as described represents an extremely frequent and formidable condition, which is why numerous studies are present in the literature on the risks and complications related to the introduction of foreign bodies in pediatric age in the upper aerodigestive tracts. A study conducted by the European Study group on Foreign Body Injuries (ESFBI), conducted in the main pediatric hospitals of 19 European countries, aims to evaluate the characteristics of the foreign body (shape, volume, consistency), age and sex, location, details of hospitalization and onset of complications.

Between 2000 and 2003, a total of 2,094 foreign body injuries were recorded in children aged 0 to 14 years. Of these, 121 (5.8%) were due to toys (mainly toy parts) and 95 (4.5%) occurred in the aero-digestive tract; 58 children needed hospitalization. It has been assessed that the first determining factor of the damage that requires hospitalization is the rigidity of the object (11).

A further study, conducted by the same working group reports data from the Siriraj hospital, in Thailand, from June 2006 to 2010, compared with four other countries, such as Finland, Slovenia, Sweden, and Turkey. The results of this study: 172 cases were collected from the Siriraj hospital in Bangkok (Thailand) compared to the other centres, respectively Finland, Sweden, Slovenia, and Turkey, with a sample size of 307, 235, 104, and 196 cases respectively. All countries showed a higher male than female prevalence and lesions occurred more frequently in children younger than 3 years. The most frequent place of recovery was the digestive system (oesophagus) in Thailand (97 cases, 56.40% of the cases), while the European cases most frequently concerned the nose in Slovenia (58.65%), Finland (37.79 % of cases), and Sweden (54.47%). In the Turkish case series, the highest prevalence of cases involved the airways. In the Thai and Finnish case series, the main types of foreign bodies were bones (66 cases, 38.37%, and 48 cases, 15.64% respectively), while pearls, beads, and marble were the most frequent foreign bodies both in Slovenia (16.35%) and Sweden (35.32%). The case series in Turkey had nuts, seeds, and cereals as prevalent foreign matter (29%). In conclusion, it can be said that the nature of foreign bodies varies from country to country and depends on different cultural, social, religious and economic factors that include parental attitudes, eating habits, availability and types of potentially dangerous objects and prevention strategies (12).

Furthermore, an evaluation conducted by the same group assessed the impact in terms of direct costs of injuries in children caused by foreign bodies in the upper air and digestive tract. 2105 cases were collected from 2000 to 2002 in 16 European hospitals, one hospital for each participating country and referred to children aged 0 to 14 years with a foreign body diagnosis. The costs were based on the procedure of extraction of the foreign body and the duration of the hospitalization, based on the DRG. It has been found that the major cost of treating foreign body injuries is covered by ENT departments, which are usually the first choice of reference, directly by patients. The children had an average duration of stay (LOS) of 2.13 days (95% of C.I. 1.99-2.29). The treatment of the foreign body was associated with an average cost of 1017.37

euros (95% C.I. 963.27-1073.51). In the multivariate analysis, the highest costs are related to the method of arrival at the hospital on foot, the site of the lesion (ICD-933, ICD-934, ICD-935 in particular) and the use of surgery in the removal of the foreign body.

The results obtained show that lesions from foreign bodies represent a great threat not only about the clinical aspects but also from public health because their treatment is associated with high costs, in particular when surgery is required (13).

Conclusions

Our experience and literature show that most foreign bodies are of an inorganic nature and the risk of complications is highly related to the type of foreign body, such as rigid or semi-rigid objects or with sharp edges; they present a greater risk of perforation and laceration of the aerodigestive pathways, while small round-shaped objects increase the likelihood of inhalation. Most choking episodes occur during meal or play and generally occur under adult supervision (76.8%) (5).

The high presence of adults during the aspiration of foreign bodies shows that primary prevention plays a fundamental role. The need to develop primary prevention strategies is crucial, implementing educational programs aimed at parents and school collaborators, to emphasize the importance of children eating food and playing with toys that are suitable for their age (14).

Furthermore, primary prevention must also be extended to producers and consumer associations, to provide rigorous regulation on the production, packaging, quality control and marketing of dangerous objects.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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Original article

A comparison between mometasone furoate nasal spray and intranasal glycyrrhetic acid in patients with allergic rhinitis: a preliminary study in clinical practice

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Abstract. Allergic rhinitis (AR) is caused by an IgE-mediated inflammatory reaction consequent to the exposure to the causal allergen. Glycyrrhetic acid (GlyAc) is a natural compound extracted from the liquorice that exerts anti-inflammatory activity. This real-life study compared intranasal GlyAc, present in a medical device containing also glycerol and mannitol, with mometasone furoate nasal spray (MFNS) in 50 adult outpatients with AR. Both treatments lasted 2 months. Endoscopic signs, perception of symptom severity, assessed by VAS, and nasal function measured by rhinomanometry were evaluated at baseline (T0), after one (T1) and two (T2) months. The intergroup analysis showed that at T1 there was no significant difference between groups about the use of decongestants and antihistamines, turbinate hypertrophy and pale mucosa, perception of olfaction and snoring. At T2 there was no significant difference between groups about use of relievers, all endoscopic signs, and perception of nasal discomfort, nasal obstruction, olfaction, and snoring. The intragroup analysis showed that in MFNS group there was a significant change during the entire period of treatment for all parameters except watery rhinorrhea (sign) and ocular discomfort; in GlyAc group there was a significant change during the entire period of treatment for all parameters. In conclusion, this preliminary study, conducted in clinical practice, evidenced that intranasal CysAC plus mannitol was able to significantly improve nasal endoscopic signs, perception of symptoms, and nasal function in patients with AR. Therefore, GlyAc could be a reasonable therapeutic option to control allergic inflammation. (www.actabiomedica.it)

Key words: glycyrrhetic acid, mannitol, mometasone furoate, allergic rhinitis, topical treatment, clinical practice

Introduction

Allergic rhinitis (AR) is caused by a type 2 inflammation characterized by functional defect of allergen-specific T regulatory cells, T helper 2 cell polarization, and eosinophilic mucosal infiltration (1). Also, AR is frequently associated with comorbidity, such as conjunctivitis and asthma (2). Allergic inflammation causes typical AR symptoms, including itching, sneezing, watery rhinorrhea (anterior and posterior), and nasal obstruction. In particular, nasal obstruction is a very bothersome symptom that may also induce nasal discomfort, reduced olfaction and disturbed sleep, and, lastly, significantly impairs quality of life (QoL) and daily activities (3, 4).

As allergic inflammation is the mainstay of AR symptoms, anti-inflammatory drugs are the most effective treatment option (5). Intranasal corticosteroids

are widely used with effective and safe outcomes (6). In this regard, mometasone furoate nasal spray (MFNS) is one of the most used intranasal corticosteroids, as a matter of fact MFNS quickly reduces allergic inflammation and relieves AR symptoms (7). Even though the safety profile of intranasal corticosteroids is substantially fair, there is popular dislike of them, the so-called corticosteroid phobia (8). Therefore, non-steroidal anti-inflammatory drugs have been developed to remedy this disappointment. In this regard, it has been discovered that a natural compound, derived from the *Glycyrrhiza glabra*, exerts anti-inflammatory activity, inhibiting extracellular high mobility group protein box 1 (HMGB1), such as an alarmin involved in inflammation (9). Glycyrrhizin is a glycoside alkaloid present in *Glycyrrhiza glabra* roots and is composed of one molecule of glycyrrhetic acid (GlyAc), the active component, and two molecules of glucuronic acid. GlyAc has no cytotoxicity, even at high concentration, and good pharmacological tolerance (10). GlyAc significantly reduced HMGB1 levels in nasal lavage fluid of AR children and HMGB1 *in vitro* release from cultured eosinophils, and increased eosinophilic apoptosis (11). These anti-inflammatory effects resulted in improved mucociliary clearance as demonstrated in patients with CRSwNP (12). GlyAC also improved nasal symptoms in children with AR and adults with nasal congestion (13, 14). GlyAc is presently available as a multicomponent medical device containing also mannitol, effective anti-edema osmotic molecules.

On the basis of this background, the current study compared MFNS with GlyAc in patients with AR in clinical practice.

Patients and methods

The present study was conducted as prospective and randomized study. Globally, 50 outpatients (27 males; mean age 37.9 ± 10.72 years) suffering from AR were enrolled. AR diagnosis was performed, according to validated criteria (15). Briefly, nasal symptom history had to be consistent with documented sensitization, i.e. allergic symptoms should occur after exposure to the sensitizing allergen.

Inclusion criteria were: i) age range between 18 and 65 years, ii) both genders, iii) AR diagnosis, iv) presence of nasal symptoms since at least one month, documented by a run-in period, and v) written informed consent. Exclusion criteria were: i) presence of concomitant chronic nasal diseases, ii) any acute upper respiratory tract infections, iii) presence of massive occlusive nasal polyposis, iv) diagnosis of cystic fibrosis or Kartagener syndrome, v) immune diseases and/or immunodeficiency (congenital or acquired), vi) clinical conditions (systemic diseases or other) that may interfere with the evaluation of the safety and efficacy of the products under investigation.

The primary endpoint was the demonstration of non-inferiority of GlyAc in comparison with MFNS about the perceived symptoms (including nasal discomfort, nasal obstruction, rhinorrhea, itching, sneezing, post-nasal drip, olfaction, snoring, bronchial and ocular discomfort, quality of life, quality of sleep, and impact on daily activities) measured by a standard Visual Analogue Scale (VAS).

The secondary endpoints were the changes of: i) the nasal endoscopy findings (including turbinate hypertrophy, watery rhinorrhea, post-nasal drip, and pale mucosa), ii) the nasal airway resistance assessed by Active Anterior Rhinomanometry (AAR) in basal condition and after decongestant test (3), iii) the impact of the treatment on the quality of life, quality of sleep and ability to perform daily activities, iv) the tolerability and the compliance, and v) any possible adverse event.

Patients were randomly (1:1 ratio) subdivided in two groups: MFSN Group (2 puffs for nostril once daily for 60 days) and GlyAc Group (2 puffs for nostril twice a day for 60 days). The patients were evaluated at baseline (T0), after 30 (T1) and 60 (T2) days.

Patients could take as rescue medication intranasal decongestants and/or systemic antihistamines, their use was recorded and assessed.

The study protocol was approved by the Ethics Committee of the Clinical Republican Hospital of Chisinau.

Statistical analysis

Continuous variables were given as means with standard deviations and categorical variables as num-

ber of subjects and percentage values. Turbinate hypertrophy, watery rhinorrhea, and post-nasal drip were dichotomised as absent or present.

To evaluate the statistical significance of the clinical characteristics across the three time-point (T0, T1, and T2), an intra-group analysis was performed. In particular, continuous variables were analysed using Friedman's test, while categorical variables were analysed by the Cochran's Q test. Thereafter to decide which groups are significantly different from each other, the post-hoc tests were performed using the Wilcoxon or the McNemar test for continuous or categorical variables, respectively.

An inter-group analysis was performed comparing data between the two treatment groups of patients at the three time-point. In particular, the Wilcoxon test and the Pearson's Chi-squared Test (Fisher's Exact test where appropriated) were used for continuous and categorical variables, respectively.

Owing to the exploratory design of this study, adjustment for multiple testing was performed using Bonferroni method only in the post-hoc tests. Differences, with a p-value less than 0.05, were selected as significant and data were acquired and analysed in R v3.6.2 software environment.

Results

All outpatients completed the study. The compliance was good in all patients. The tolerability was good in 79% of MFNS patients and 92% of GlyAc patients. No clinically relevant adverse events were reported.

Inter-group analysis

The descriptive statistics of demographic and clinical variables in the two groups is reported in Table 1.

At baseline, the two groups were not homogeneous for two endoscopic signs, post-nasal drip and pale mucosa (both more frequent in GlyAc group), for the nasal resistances (higher in GlyAc group), and for the perceived symptom of ocular discomfort (more severe in GlyAc group).

At T1, there was no significant difference between groups about the use of decongestants and antihistamines, turbinate hypertrophy and pale mucosa, perception of olfaction and snoring. Patients in MFNS group had significantly less frequently watery rhinorrhea, post-nasal drip, and lower resistances, than patients treated with GlyAc.

At T2, there was no significant difference between groups about use of relievers, all endoscopic signs, and perception of nasal discomfort, nasal obstruction, olfaction, and snoring. Patients treated with MFNS had significantly lower resistances, and lower perception of symptom severity of rhinorrhea, itching, sneezing, post-nasal drip, ocular discomfort, quality of life, quality of sleep, and impact on daily activities, than patients in GlyAc group.

Intra-group analysis

MFSN group: there was a significant change during the entire period of treatment for all parameters except watery rhinorrhea (sign) and ocular discomfort (Table 2). The post-hoc analysis showed that there were some parameters that did not significantly change at T1 and/or T2 in comparison with baseline values as reported in detail in Table 2.

GlyAc group: there was a significant change during the entire period of treatment for all parameters (Table 3). The post-hoc analysis showed that there were some parameters that did not significantly change at T1 and/or T2 in comparison with baseline values as reported in detail in Table 3.

Discussion

Type 2 inflammation sustains signs, symptoms and functional impairment in AR patients. For this reason, intranasal corticosteroids are an effective therapeutic option as are able to improve clinical feature and restore nasal function. The International guidelines state that intranasal corticosteroids are usually safe (15). However, many doctors, and also patients, discourage a prolonged use for potential side effects. GlyAc could be a promising alternative to corticosteroids as has been demonstrated to be effective and safe (10-14). A previous study compared GlyAc with intranasal budesonide (11). The findings showed that

Table 1: Demographic data and inter-group analysis at the three time points. Characteristic: variable taken into account; p-value: test p-value (see the text for abbreviations and further details)

Characteristic	Time T0			Time T1			Time T2		
	Treatment		P-value	Treatment		P-value	Treatment		P-value
	MFSN	*GlyAc*		*MFSN*	*GlyAc*		*MFSN*	*GlyAc*	
Age	37.98 (9.34)	37.83 (12.03)	0.7932						
Gender *Male*	11 (45.83%)	16 (61.54%)	0.4070						
Female	13 (54.17%)	10 (38.46%)							
Decongestants use	9 (37.5%)	8 (30.77%)	0.7666	2 (8.33%)	4 (15.38%)	0.6688	1 (4.17%)	3 (11.54%)	0.6105
Systemic antihistamines use	7 (29.17%)	7 (26.92%)	0.9999	2 (8.33%)	3 (11.54%)	0.9999	0 (0%)	2 (7.69%)	0.4906
SIGNS									
Turbinate Hypertrophy	24 (100%)	26 (100%)	0.9999	24 (100%)	26 (100%)	0.9999	14 (58.33%)	14 (53.85%)	0.7827
Watery Rhinorrhea	14 (58.33%)	21 (80.77%)	0.1239	11 (45.83%)	21 (80.77%)	**0.0176**	7 (29.17%)	10 (38.46%)	0.5592
Post-nasal Drip	12 (50%)	21 (80.77%)	**0.0359**	11 (45.83%)	20 (76.92%)	**0.0404**	7 (29.17%)	10 (38.46%)	0.0996
Pale mucosa	18 (75%)	25 (96.15%)	**0.0451**	15 (62.5%)	21 (80.77%)	0.2109	7 (29.17%)	8 (30.77%)	0.9999
NASAL AIRFLOW									
Inspiratory Resistance	0.96 (0.33)	1.3 (0.25)	**0.0001**	0.55 (0.27)	1.04 (0.18)	**<0.0001**	0.39 (0.16)	0.64 (0.18)	**<0.0001**
Expiratory Resistance	1.05 (0.34)	1.49 (0.16)	**<0.0001**	0.61 (0.26)	1.14 (0.21)	**<0.0001**	0.46 (0.17)	0.65 (0.21)	**0.0001**
Nasal Decongestant Test Insp.	0.59 (0.27)	0.95 (0.1)	**<0.0001**	0.41 (0.18)	0.74 (0.16)	**<0.0001**	0.34 (0.16)	0.42 (0.17)	**0.0285**
Nasal Decongestant Test Exp.	0.66 (0.28)	1.03 (0.1)	**<0.0001**	0.44 (0.18)	0.79 (0.15)	**<0.0001**	0.38 (0.15)	0.46 (0.2)	**0.0489**
SYMPTOMS									
VAS Nasal Discomfort	5.29 (3.79)	6.34 (2.74)	0.5264	2.74 (2.63)	3.82 (2.02)	**0.0456**	0.95 (1.66)	1.67 (2.3)	0.2801
VAS Nasal Obstruction	7.3 (2.28)	7.36 (1.57)	0.9534	2.65 (1.61)	3.85 (1.51)	**0.0030**	0.85 (1.38)	1.54 (1.99)	0.1413
VAS Rhinorrea	5.47 (3.52)	6.88 (1.98)	0.2171	1.78 (1.9)	3.54 (1.57)	**0.0006**	0.37 (0.8)	1.77 (1.96)	**0.0009**
VAS Itching	3.74 (3.83)	4.71 (3.36)	0.3959	0.9 (1.48)	2 (1.82)	**0.0165**	0.01 (0.04)	0.88 (1.17)	**<0.0001**
VAS Sneezing	5.17 (3.48)	5.7 (2.86)	0.5588	1.1 (1.68)	2.72 (2.11)	**0.0055**	0.04 (0.18)	1.36 (1.67)	**0.0001**
VAS Post-nasal Drip	3.93 (3.56)	6.02 (2.11)	0.0682	1.54 (1.53)	3.15 (2.14)	**0.0033**	0.27 (0.66)	1.55 (1.86)	**0.0005**
VAS Olfaction	2.48 (2.67)	1.33 (2.22)	0.0892	0.93 (1.29)	0.62 (1.11)	0.3006	0.38 (0.75)	0.22 (0.49)	0.5625
VAS Snoring	1.92 (2.48)	1.32 (2.35)	0.3841	0.8 (1.2)	0.87 (1.67)	0.5656	0.25 (0.53)	0.37 (0.84)	0.7580
VAS Bronchial Discomfort	0.58 (1.53)	1.01 (2.41)	0.9152	0.55 (1.4)	1.05 (2.52)	0.9152	0.34 (1.06)	0.9 (2.19)	0.9394
VAS Ocular Discomfort	0.9 (2.16)	2.28 (2.64)	**0.0246**	0.3 (1.03)	0.98 (1.53)	**0.0414**	0 (0)	0.34 (0.81)	**0.0265**
VAS Quality of Life	7.78 (2.35)	6.9 (2.11)	0.1320	2.3 (1.74)	3.79 (1.76)	**0.0021**	0.82 (1.4)	1.78 (1.97)	**0.0179**
VAS Quality of Sleep	7.97 (2.23)	7.05 (2.06)	0.0756	2.33 (1.97)	3.69 (1.75)	**0.0030**	0.8 (1.42)	1.67 (1.92)	**0.0318**
VAS Impact on Daily Activities	7.82 (2.44)	6.57 (2.24)	0.0644	1.98 (1.83)	3.33 (1.87)	**0.0056**	0.69 (1.29)	1.63 (2.12)	**0.0481**

Table 2. Intra-group analysis in MFSN group at the three time points. Characteristic: variable taken into account; p-value: test p-value (see the text for abbreviations and further details)

Characteristic	Time T0	Time T1	Time T2	p-value	Post-hoc analysis		
					T0 vs T1	T1 vs T2	T0 vs T2
Compliance				0.9999			
good		24 (100%)	24 (100%)				
Tolerability				0.9999			
good		22 (91.67%)	19 (79.17%)				
fairly good		2 (8.33%)	5 (20.83%)				
Decongestants use	9 (37.5%)	2 (8.33%)	1 (4.17%)	**0.0008**	**0.0469**	0.9999	**0.0234**
Systemic antihistamines use	7 (29.17%)	2 (8.33%)	0 (0%)	**0.0076**	0.3750	0.9999	**0.0469**
SIGNS							
Turbinate Hypertrophy	24 (100%)	24 (100%)	14 (58.33%)	**<0.0001**	0.9999	**0.0059**	**0.0059**
Watery Rhinorrhea	14 (58.33%)	11 (45.83%)	7 (29.17%)	0.0581			
Post-Nasal Drip	12 (50%)	11 (45.83%)	3 (12.5%)	**0.0013**	0.9999	0.0645	**0.0352**
Pale Mucosa	18 (75%)	15 (62.5%)	7 (29.17%)	**0.0010**	0.9999	**0.0234**	**0.0103**
NASAL AIRFLOW							
Inspiratory Resistance	0.96 (0.33)	0.55 (0.27)	0.39 (0.16)	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**
Expiratory Resistance	1.05 (0.34)	0.61 (0.26)	0.46 (0.17)	**<0.0001**	**0.0001**	**<0.0001**	**0.0001**
Nasal Decongestant Test Insp.	0.59 (0.27)	0.41 (0.18)	0.34 (0.16)	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**
Nasal Decongestant Test Exp.	0.66 (0.28)	0.44 (0.18)	0.38 (0.15)	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**
SYMPTOMS							
VAS Nasal Discomfort	5.29 (3.79)	2.74 (2.63)	0.95 (1.66)	**<0.0001**	0.0848	0.0794	**0.0013**
VAS Nasal Obstruction	7.3 (2.28)	2.65 (1.61)	0.85 (1.38)	**<0.0001**	**0.0262**	**0.0143**	**<0.0001**
VAS Rhinorrhea	5.47 (3.52)	1.78 (1.9)	0.37 (0.8)	**<0.0001**	**0.0157**	0.8538	**0.0001**
VAS Itching	3.74 (3.83)	0.9 (1.48)	0.01 (0.04)	**<0.0001**	**0.0035**	**<0.0001**	**<0.0001**
VAS Sneezing	5.17 (3.48)	1.1 (1.68)	0.04 (0.18)	**<0.0001**	**0.0074**	0.0724	**<0.0001**
VAS Post-nasal Drip	3.93 (3.56)	1.54 (1.53)	0.27 (0.66)	**<0.0001**	**0.0051**	0.7815	**<0.0001**
VAS Olfaction	2.48 (2.67)	0.93 (1.29)	0.38 (0.75)	**<0.0001**	**0.0121**	0.4667	**<0.0001**
VAS Snoring	1.92 (2.48)	0.8 (1.2)	0.25 (0.53)	**0.0001**	**0.0392**	0.0828	**<0.0001**
VAS Bronchial Discomfort	0.58 (1.53)	0.55 (1.4)	0.34 (1.06)	**0.0498**	**0.0001**	**<0.0001**	**<0.0001**
VAS Ocular Discomfort	0.9 (2.16)	0.3 (1.03)	0 (0)	0.0545			
VAS Quality of Life	7.78 (2.35)	2.3 (1.74)	0.82 (1.4)	**<0.0001**	**<0.0001**	**0.0085**	**0.0037**
VAS Quality of Sleep	7.97 (2.23)	2.33 (1.97)	0.8 (1.42)	**<0.0001**	**<0.0001**	**0.0067**	**0.0030**
VAS Impact on Daily Activities	7.82 (2.44)	1.98 (1.83)	0.69 (1.29)	**<0.0001**	**0.0001**	**0.0088**	**0.0003**

Table 3. Intra-group analysis in GlyAc group at the three time points. Characteristic: variable taken into account; p-value: test p-value (see the text for abbreviations and further details)

Characteristic	Time T0	Time T1	Time T2	p-value	Post-hoc analysis		
					T0 vs T1	T1 vs T2	T0 vs T2
Compliance				0.9999			
good		26 (100%)	26 (100%)				
Tolerability				0.9999			
good		24 (92.31%)	24 (92.31%)				
fairly good		2 (7.69%)	2 (7.69%)				
Decongestants use	8 (30.77%)	4 (15.38%)	3 (11.54%)	0.1482			
Systemic antihistamines use	7 (26.92%)	3 (11.54%)	2 (7.69%)	**0.0150**	0.1365	0.9519	0.0760
SIGNS							
Turbinate Hypertrophy	26 (100%)	26 (100%)	14 (53.85%)	**<0.0001**	0.9999	**0.0016**	**0.0016**
Watery Rhinorrhea	21 (80.77%)	21 (80.77%)	10 (38.46%)	**<0.0001**	0.9999	**0.0029**	**0.0029**
Post-Nasal Drip	21 (80.77%)	20 (76.92%)	9 (34.62%)	**<0.0001**	0.9999	**0.0029**	**0.0015**
Pale Mucosa	25 (96.15%)	21 (80.77%)	8 (30.77%)	**<0.0001**	0.3750	**0.0029**	**<0.0001**
NASAL AIRFLOW							
Inspiratory Resistance	1.3 (0.25)	1.04 (0.18)	0.64 (0.18)	**<0.0001**	**0.0025**	**<0.0001**	**0.0025**
Expiratory Resistance	1.49 (0.16)	1.14 (0.21)	0.65 (0.21)	**<0.0001**	**0.0162**	**<0.0001**	**0.0061**
Nasal Decongestant Test Insp.	0.95 (0.1)	0.74 (0.16)	0.42 (0.17)	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**
Nasal Decongestant Test Exp.	1.03 (0.1)	0.79 (0.15)	0.46 (0.2)	**<0.0001**	**0.0001**	**<0.0001**	**0.0001**
SYMPTOMS							
VAS Nasal Discomfort	6.34 (2.74)	3.82 (2.02)	1.67 (2.3)	**<0.0001**	0.9999	**0.0055**	**<0.0001**
VAS Nasal Obstruction	7.36 (1.57)	3.85 (1.51)	1.54 (1.99)	**<0.0001**	0.9999	**0.0055**	**<0.0001**
VAS Rhinorrhea	6.88 (1.98)	3.54 (1.57)	1.77 (1.96)	**<0.0001**	0.9999	**0.0015**	**<0.0001**
VAS Itching	4.71 (3.36)	2 (1.82)	0.88 (1.17)	**<0.0001**	0.9737	**0.0052**	**0.0006**
VAS Sneezing	5.7 (2.86)	2.72 (2.11)	1.36 (1.67)	**<0.0001**	0.6531	**0.0424**	**0.0001**
VAS Post-nasal Drip	6.02 (2.11)	3.15 (2.14)	1.55 (1.86)	**<0.0001**	0.999	**0.0043**	**<0.0001**
VAS Olfaction	1.33 (2.22)	0.62 (1.11)	0.22 (0.49)	**<0.0001**	**0.0163**	**<0.0001**	**0.0008**
VAS Snoring	1.32 (2.35)	0.87 (1.67)	0.37 (0.84)	**<0.0001**	**0.0203**	**<0.0001**	**0.0005**
VAS Bronchial Discomfort	1.01 (2.41)	1.05 (2.52)	0.9 (2.19)	0.1266			
VAS Ocular Discomfort	2.28 (2.64)	0.98 (1.53)	0.34 (0.81)	**<0.0001**	1.0000	0.2238	**<0.0001**
VAS Quality of Life	6.9 (2.11)	3.79 (1.76)	1.78 (1.97)	**<0.0001**	**0.0014**	0.9999	**<0.0001**
VAS Quality of Sleep	7.05 (2.06)	3.69 (1.75)	1.67 (1.92)	**<0.0001**	**0.0010**	0.9999	**<0.0001**
VAS Impact on Daily Activities	6.57 (2.24)	3.33 (1.87)	1.63 (2.12)	**<0.0001**	**0.0050**	0.9999	**<0.0001**

both treatments significantly improved clinical parameters and reduced inflammatory biomarkers, namely HMGB1.

The present study was designed to compare GlyAc with another popular intranasal corticosteroid, such as MFNS, in a real-life setting, such as in outpatients visited at a rhinologic clinic.

The inter-group comparison demonstrates that there was no significant difference between corticosteroid treatment and GlyAc about the use of relievers, such as decongestants and antihistamines. This outcome is clinically important as demonstrates that both treatments were able to control AR. Moreover, there was no significant different also for the turbinate hypertrophy, watery anterior and posterior (post-nasal drip) rhinorrhea, such as the visible discharge in the nasal cavity, and pale mucosa: these endoscopic signs mean the intensity of inflammatory reaction. So, these findings establish that both MFNS and GlyAc reduce inflammatory phenomena. On the contrary, there was a significant difference between groups about the effect on nasal resistances, but it has to be noted that these differences were present even at baseline. Consequently, the clinically relevant information may derive only by the intragroup analysis. Concerning the subjective perception of symptom severity, assessed by VAS, MFNS significantly reduced the symptom perception even after one month for many parameters. However, the significant difference disappeared for some symptoms, including nasal discomfort, nasal obstruction, olfaction, snoring, and bronchial discomfort, at the end of the treatment. This outcome depends on the fact that corticosteroids are a fast mechanism of action, but CysAc, even though more slowly than MFNS, has equally an effect on many symptoms that express the allergic inflammation. In particular, nasal discomfort and obstruction are the typical expression of type 2 inflammation as nasal airflow limitation and severity of nasal obstruction very well correlate (16). Moreover, olfaction impairment and snoring are closely linked to nasal inflammation (17, 18). These data confirm that 2-month CysAc treatment can control nasal inflammation as well as intranasal corticosteroids.

The intra-group analysis confirmed that MFNS was, as expected, effective in improving AR signs, symptoms, and nasal function (19). Interestingly, also CysAc significantly improved all the evaluated parameters. This finding depends on the dual mechanism of action of the medical device: the anti-inflammatory activity due to GlyAc and the anti-edema effect due to mannitol (20).

However, there are some limitations of this study: i) the open design, ii) the relatively limited number of treated patients, iii) the absence of inflammatory mediator assessment, and iv) the study was mono-center. Moreover, the two groups were not homogeneous for some parameters, even though it could occur in real-life studies. For these reasons, the findings should be considered preliminary; indeed, a continuation is ongoing.

Conclusions

This preliminary study, conducted in clinical practice, evidenced that intranasal CysAC plus mannitol was able to significantly improve nasal endoscopic signs, perception of symptoms, and nasal function in patients with AR. In addition, there was no significant difference between nasal corticosteroid and GlyAC about the use of relievers, endoscopic signs of inflammation, and perception of nasal obstruction and discomfort. Therefore, GlyAc could be a reasonable therapeutic option to control allergic inflammation.

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Conflict of interest: Nobody of them, but VD employee of DMG, has conflicts of interest in this issue.

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Original article

Oral bacteriotherapy in children with recurrent respiratory infections: a real-life study

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Abstract. Children with recurrent respiratory infections (RRI) represent a social issue for the economic burden and the familiar negative impact. Bacteriotherapy, such as the administration of "good" bacteria, is a new therapeutic strategy that could be potentially effective in preventing infections. The current study tested the hypothesis of preventing RRI by oral Bacteriotherapy in a real-life setting. This open study was conducted in an outpatient clinic, enrolling 51 children (27 males, mean age 4.8 ± 2.6 years) suffering from RRI. Children were treated with an oral spray, containing *Streptococcus salivarius* 24SMB and *Streptococcus oralis*89a (125 x 10^9 CFU/g), 2 puffs per os once/day for 30 consecutive days; this course was repeated for 3 months. The evaluated parameters were: RI number and school absences reported in the current year; these outcomes were compared with those recorded in the past year. The mean number of RI significantly diminished: from 5.17 (2.30) in the past year to 2.25 (2.43) after the treatment ($p<0.0001$). The mean number of school absences significantly diminished (from 3.35 to 1.86; $p<0.0001$). In conclusion, this real-life study suggests that oral Bacteriotherapy with Streptococcus salivarius 24SMB and *Streptococcus oralis*89a could efficaciously and safely prevent RRI in children. (www.actabiomedica.it)

Key words: recurrent respiratory infections, bacteriotherapy, *Streptococcus salivarius* 24SMB, *Streptococcus oralis*89a, oral spray, children

Introduction

The recurrent respiratory infections (RRI) in children constitute an impressive drawback for the family and a significant burden for the Healthcare Service (1-3). Pediatricians and otolaryngologists are, therefore, engaged to counteract this relevant issue in daily practice.

Many factors may cause the RI recurrence, namely early age (because of the relative immaturity of the immune system), early attendance at nursery school, environmental pollution, passive smoking, low socioeconomic level, and allergic disorders (4). Noteworthy, viral infections exert a crucial role as are the most common cause of respiratory infection in childhood (5).

The guidelines state the appropriate use of anti-inflammatory drugs and antibiotics, even though they are really prescribed on an empiric basis in clinical practice and often uselessly (6, 7). Notably, antibiotic overuse/abuse is frequently associated with resistance to many bacteria because multi-resistant microbes are selected by indiscriminate and excessive antibiotic prescriptions. Consequently, to prevent RRI could succeed in reducing antibiotic resistance, complications, medical costs, and the family and social burden. However, many prevention attempts have experimented in the past. Unfortunately, these efforts were frequently expensive, long-lasting, and/or ineffective, and even dangerous. Therefore, to prevent RRI is still an unresolved puzzle.

Respiratory microbioma is currently an intriguing topic that deserves particular attention (8,9). The "normal" nasopharyngeal microbioma counteracts the pathogens. As a consequence, it has been hypothesized that the administration of "good" bacteria (usually saprophytic) could prevent infections contrasting the growth of the pathogens (10). In this regard, it was initially reported that an α-haemolytic strain, obtained from healthy children (*Streptococcus salivarius* 24SMB), and administered as a nasal spray, reduced the recurrence of acute otitis media (AOM) in otitis-prone children (11). A further study showed that *Streptococcus salivarius* 24SMB, associated with *Streptococcus oralis*89a, was effective in preventing recurrent otitis in a real-life setting (12). These findings were confirmed by a study that reported a positive outcome in the prevention of RRI in clinical practice (13).

Recently, this Bacteriotherapy compound has been proposed also as an oral formulation. A first study has been conducted in children with recurrent streptococcal pharyngotonsillitis caused by Group A β-haemolytic *Streptococcus* (14). This study showed that oral spray with *Streptococcus salivarius* 24SMB and *Streptococcus oralis*89a significantly reduced the number of streptococcal infections, the use of antibiotics, and the scholar absences.

Therefore, the current study aimed to extend the potential application of this new oral formulation also in children with RRI.

Materials and Methods

The present experience included 51 children (27 males, mean age 4.8 ± 2.6 years) with a history of RRI in the past year. Inclusion criteria were: i) age ranging between 3 and 10 years, ii) both genders, iii) documented RRI in the past year, iv) written informed consent by parents. Exclusion criteria were: i) severe allergic symptoms (such as able to interfere the assessment of treatments), ii) congenital or acquired immunodeficiency, iii) craniofacial abnormalities, iv) sleep apnoea, v) Down syndrome, vi) chronic disease (including metabolic disorders, cystic fibrosis, cancer, etc.), vii) clinically relevant passive smoking, and viii) previous (last 3 months) or current administration of drugs able to interfere with the study (e.g. immunomodulators, homeopathic therapy, or systemic corticosteroids for at least 2 consecutive weeks).

Study design

The current experience was designed as an open study. Children with RRI were visited by the otolaryngologist for thorough management. Children were treated with a commercially available, class IIa medical device, oral spray containing *Streptococcus salivarius* 24SMB and *Streptococcus oralis*89a (Orogermina, DMG, Rome, Italy). It was administered as 2 puffs *per os* once/day for 30 consecutive days. The suspension consisted of a minimum of 125 x 10^9 CFU/g per bottle. This course was usually administered for 3 consecutive months. As Bacteriotherapy has a preventive activity, the first course usually started in the early autumn.

The number of RI and the number of days of school absence were considered. These variables were evaluated in the past year (T0) and the current year (T1).

Safety

Safety and tolerability were evaluated based on the number and type of adverse events recorded according to the rules of good clinical practice.

Study procedures

RI was diagnosed based on the symptoms reported by the parents, as previously defined (13, 15). The RI diagnosis was made when at least 2 symptoms or fever (axillary temperature ≥38°C), in addition to one other symptom (see below), were present for at least 48 hours. The considered symptoms were: mucopurulent rhinorrhoea, stuffy or dripping nose or both, sore-throat, cough (dry or productive), otalgia (earache), fever, and mucopurulent secretion. RRI diagnosis was performed on history, such as the patient's recall of symptoms.

The children were examined at study entry, and the follow-up re-evaluation (in the late summer). All assessed parameters were regularly recorded on a daily diary card.

Statistical analysis

Continuous variables were given as median with range and categorical variables as the number of subjects and percentage values. To evaluate the statistical significance of RI episode number and number of school days lost differences, the Wilcoxon test for paired samples was performed and then, the adjustment for multiple testing was done using the Bonferroni method. Differences, with a p-value less than 0.05, were selected as significant and data were acquired and analyzed in the R v3.6.2 software environment.

Results

All the children completed the study without any clinically relevant adverse event.

Bacteriotherapy significantly halved the mean number of RI episodes from a median value of 5 (2-10) in the past year (T0) to 2 (0-5) in the current year (T1) (p<0.0001, Figure1A).

Bacteriotherapy also reduced (about 35%) both the number of school days missed from 3 (0-10) at T0 to 1 (0-6) at T1 (p<0.0001), Figure 1B).

Discussion

RI guidelines suggest limiting antibiotic prescription to severe and bacterial infections as most of RI are viral. In clinical practice, antibiotics are often prescribed ignoring guidelines precepts. In this regard, preventing RI could reduce antibiotic overuse/abuse and have important socio-economic outcomes. However, this topic is still debated and argued. In this regard, a placebo-controlled study investigated a 12-month treatment with azithromycin (5 mg/Kg/d) 3 days/week in children with recurrent rhinosinusitis (16, 17). This schedule reduced the number of rhinosinusitis, the medication use, and the severity of the symptoms. However, it is obvious that this preventive proposal is yet long-lasting and could induce resistance to macrolides. Macrolides resistance is an emerging problem in many countries (18). Moreover, long-standing antibiotic therapy is frequently associated with adverse events and antibiotic resistance. Instead, the so-called Bacteriotherapy, such as the administration of "good" bacteria, could be a promising way. The rationale is that some non-pathogenic physiological, mainly saprophytic, strains may protect from pathogens ("bad" bacteria) infections. In particular, *Strep-*

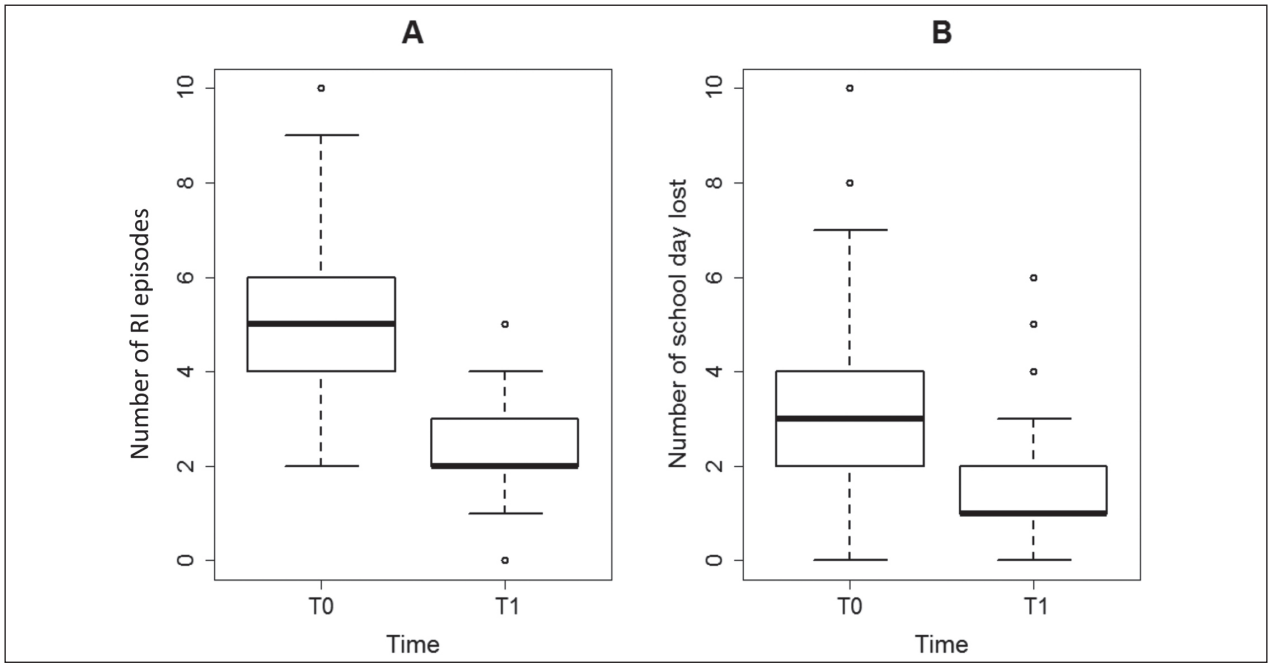

Figure 1. Panel A = number of RI episodes at T0 and T1; Panel B = number of school day lost at T0 and T1

tococcus salivarius 24SMB and *Streptococcus oralis*89a turned attention to this topic as some studies provided promising results (10-14).

The current experience real-life reported that *Streptococcus salivarius* 24SMB and *Streptococcus oralis*89a oral spray could reliably prevent RI; of note, no side effects were reported, so the compound was safe and well-tolerated by all treated children. Oral Bacteriotherapy significantly diminished RI and consistently school absences. These outcomes confirmed the previous studies (10-14) and may have a relevant spillover in daily practice.

However, this study has some limitations: i) to be an open study, ii) to be without a control-placebo group, iii) to be based only on clinical outcomes without cultural investigations, and iv) data concerning the past year were retrospectively collected by parents' queries. Thus, further studies should be conducted to correctly define unmet needs.

In conclusion, *Streptococcus salivarius* 24SMB and *Streptococcus oralis*89a oral spray could efficaciously and safely prevent respiratory infections in children.

Conflict of interest: All the authors, but VD employee of DMG, state that have no conflict of interest concerning the present paper.

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Original article

Tonsil volume may predict adenoid size: a real-life study

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Abstract. Tonsil hypertrophy (TH) and adenoid hypertrophy (AH) are very common in children. Adenoid is visible only by endoscopy. This study investigated the possible relationship between the tonsil and adenoid volume and the possible prediction of adenoid size. Globally, 991 children (461 females, 530 males, mean age 6.2 ± 2.3 years), complaining persistent upper airway obstruction, were consecutively visited at an otorhinolaryngological unit. TH was significantly ($p<0.0001$) associated with AH and tonsil volume predicted adenoid size. This outcome could have relevance in clinical practice as adenoid are evaluable only by endoscopy, so tonsil assessment could mirror adenoid volume. (www.actabiomedica.it)

Key words: tonsils hypertrophy, adenoid hypertrophy, nasal endoscopy, children

Introduction

The palatine tonsils and adenoids are part of the lymphoid tissue that surrounds the pharynx: collectively defined as the Waldeyer's ring. Tonsils and adenoids physiologically serve as a defense against inhaled antigens (microbes, pollutants, allergens, etc). Therefore, they are deeply involved in the innate and adaptive immune response because of their peculiar position at the entry of the upper aero-digestive tract. As a consequence of chronic stimulation (the result of prolonged antigenic exposure associated with chronic inflammation), palatine tonsils and adenoids may enlarge so that they may almost fill the space in the oropharynx, limiting the airflow passage. Tonsils hypertrophy (TH) and adenoid hypertrophy (AH) are frequently detected in the general pediatric population and constitute a frequent otorhinolaryngological indication for surgical intervention (1). TH and AH have been associated with recurrent respiratory infections, respiratory dysfunction, and sleep disorders (2).

However, adenoid is visible only during endoscopy assessment. Therefore, the present study investigated the relationship between the tonsil and adenoid volume and the possibility of predicting adenoid size by the tonsil volume in a group of children suffering from nasal obstruction and visited in a real-life setting.

Materials and Methods

Patients: Globally, 991 children (461 females, 530 males, mean age 6.2 ± 2.3 years), complaining persistent upper airway obstruction, were consecutively visited at an otorhinolaryngological unit between 2015 and 2019. They were prospectively enrolled in the study. Inclusion criteria were: i) age between 4 and 12 years; ii) to have complaints of upper airway limitation (mouth breathing, with or without snoring). Exclusion criteria were: i) a craniofacial syndrome, ii) recent facial trauma, iii) significantly deviated septum, iv) concomitant acute rhinosinusitis, v) the previous adenotonsillectomy, and vi) current use of intranasal corticosteroids. The study was approved by the local Review Board and informed consent was obtained by the parents.

Study design: All children were evaluated by clinical visits, nasal endoscopy.

Endoscopy: It was performed with a pediatric rigid endoscope diameter 2.7 mm with a 30° angle of vision (Karl Storz cod 7207 ba). The child lied supine with his-her head bent by about 45°. Some cotton wool soaked with an anesthetic solution (ossibuprocaine 1%) was placed into the nose for 5 minutes. The complete description of the procedure was previously described in detail (3).

Tonsils volume assessment

Tonsils volume was classified according to validated criteria (4) as follows: grade 1: tonsils in the tonsillar fossa barely seen behind the anterior pillar; grade 2: tonsils visible behind the anterior pillar; grade 3: tonsils extended three-quarters of the way to midline; grade 4: tonsils completely obstructing the airway (also known as kissing tonsils).

Adenoids volume assessment

The patients were evaluated by nasal endoscopy for adenoid hypertrophy. The adenoids were graded according to Parikh's classification that was created based on the anatomical relationships between the adenoid tissue and the following structures: vomer, soft palate, and torus tubarius (5). The grading is based on the relationship of the adenoids to adjacent structures when the patient is at rest (i.e. when the soft palate is not elevated). Specifically: grade 1 adenoids are non-obstructive and do not contact any of the previously mentioned anatomic subsites; subsequently, grade 2,3 and 4 adenoids contact the torus tubarius, vomer, and soft palate (at rest) respectively.

Statistical analysis

The Multinomial Logistic regression models were performed to assay the effect of the Tonsillar Hypertrophy on the Adenoid Hypertrophy. The Likelihood Ratio (LR) test was used as a test of statistical significance. The odds ratios associated with the Adenoid Hypertrophy were calculated with their 95% confidence interval from the Multinomial Logistic model. Differences, with a p-value less than 0.05, were selected as significant and data were acquired and analyzed in the R v3.6.2 software environment (6).

Results

The cross-distribution of the tonsil and adenoid volume grades in the visited children is reported in Table 1 and Figure 1. A significant association between the Tonsillar Hypertrophy and the Adenoid Hypertrophy was observed (Table 2: LR test p-value<0.0001).

In particular considering the children with Tonsillar Hypertrophy of grade 1, the probability of having Adenoid Hypertrophy equal to 2 was: 2.6 times more likely in children with Tonsillar Hypertrophy of grade 2 (OR (95%C.I.) = 2.61 (1.55 - 4.42)); 39% less likely in children with Tonsillar Hypertrophy of grade 3 (OR (95%C.I.) = 0.61 (0.37 - 0.99)).

The probability of having Adenoid Hypertrophy equal to 3 was: 7.4 times more likely in children with Tonsillar Hypertrophy of 2 (OR (95%C.I.) = 7.37 (4.48 - 12.14)); 44% less likely in children with Tonsillar Hypertrophy of 4 (OR (95%C.I.) = 0.56 (0.35 - 0.88)).

Table 1. Cross table concerning the distribution of patients according to the tonsil and adenoid volume

	Adenoid Hypertrophy			
	1	*2*	*3*	*4*
Tonsillar Hypertrophy				
1	156 (42.16%)	48 (22.02%)	19 (8.92%)	10 (5.05%)
2	119 (32.16%)	109 (50%)	52 (24.41%)	30 (15.15%)
3	93 (25.14%)	43 (19.72%)	91 (42.72%)	67 (33.84%)
4	2 (0.54%)	18 (8.26%)	51 (23.94%)	91 (45.96%)

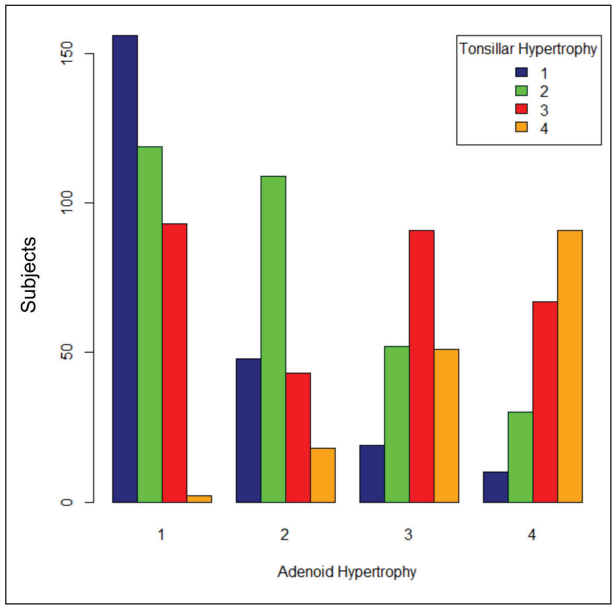

Figure 1.

Finally, the chance of having Adenoid Hypertrophy equal to 4 was: 127 times more likely in children with Tonsillar Hypertrophy of 2 (OR (95%C.I.) = 126.98 (44.58 - 361.72)); 66% less likely in children with Tonsillar Hypertrophy of 3 (OR (95%C.I.) = 0.34 (0.14 - 0.8)).

Discussion

Upper airways symptoms are very common in the pediatric population. Airflow limitation during childhood is frequently attributed to enlarged adenoids. On the other hand, the tonsil volume is frequently related to adenoid volume so that the term "adenotonsillar" hypertrophy is commonly used (8-10). The present study demonstrated that the volume of tonsils was significantly associated with the volume of adenoids. In other words, a large tonsil is predictive of adenoid hypertrophy. This outcome has clinical relevance as adenoid is evaluable only by endoscopy that is usually performed by an otolaryngologist. Therefore, the assessment of tonsil could reasonably mirror the adenoid volume in clinical practice.

The present study was based on a real-life setting, such as the studied cohort was constituted of children complaining upper airways obstruction. They were visited at an ENT office undergoing nasal endoscopy. The main limitations of the present study were: i) the absence of immunological investigation, able to clarify pathogenic mechanisms, ii) the lack of symptoms severity assessment, iii) the selected population, such as complaining nasal obstruction. Therefore, further immunological studies should be performed to address these issues, mainly concerning the impact of symptom severity on the link between TH and AR as well as the possible role of under-treatment on these variables. On the other hand, this study was conducted in a large group of patients and a real-life setting.

Conclusion

This real-life study showed that TH is significantly associated with AH and the assessment of tonsil

Table 2. Summary of the Multinomial Logistic model. Results are expressed as odds ratio (OR) with 95% confidence interval (95%CI); p-value: Likelihood Ratio p-value

Characteristic	**Adenoid Hypertrophy**			**p-value**
	2** versus **1	***3** versus **1***	***4** versus **1***	
Tonsillar Hypertrophy				<0.0001
1	1	1	1	
2	2.61 (1.55 - 4.42)	7.37 (4.48 - 12.14)	126.98 (44.58 - 361.72)	
3	0.61 (0.37 - 0.99)	0.96 (0.6 - 1.56)	0.34 (0.14 - 0.8)	
4	1.2 (0.76 - 1.88)	0.56 (0.35 - 0.88)	1.16 (0.63 - 2.14)	

volume could reasonably predict adenoid size in clinical practice.

Conflict of interest: Nobody of them, but VD employee of DMG, has conflicts of interest in this issue.

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