ISSN 2222-0682 (online)

World Journal of *Methodology*

World J Methodol 2016 December 26; 6(4): 200-219

Published by Baishideng Publishing Group Inc

World Journal of Methodology

A peer-reviewed, online, open-access journal of methodology

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2016-2019

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World Journal of Methodology

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Quarterly Volume 6 Number 4 December 26, 2016

World Journal of Methodology
Volume 6 Number 4 December 26, 2016

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NAME OF JOURNAL
World Journal of Methodology

ISSN
ISSN 2222-0682 (online)

LAUNCH DATE
September 26, 2011

FREQUENCY
Quarterly

EDITORIAL OFFICE
Xiu-Xia Song, Director
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World Journal of Methodology
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Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: editorialoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
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PUBLISHER
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8226 Regency Drive,
Pleasanton, CA 94588, USA
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E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

PUBLICATION DATE
December 26, 2016

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http://www.wjgnet.com/bpg/gerinfo/204

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World Journal of Methodology

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Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5662/wjm.v6.i4.200

World J Methodol 2016 December 26; 6(4): 200-213
ISSN 2222-0682 (online)

REVIEW

Non-allergic rhinitis in children: Epidemiological aspects, pathological features, diagnostic methodology and clinical management

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Author contributions: All the authors contributed to the manuscript.

Conflict-of-interest statement: The authors report no conflict of interest and have not received any honorarium, grant, or other form of payment to produce it.

Manuscript source: Invited manuscript

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Received: June 9, 2016
Peer-review started: June 14, 2016
First decision: July 29, 2016
Revised: September 18, 2016
Accepted: November 1, 2016
Article in press: November 3, 2016
Published online: December 26, 2016

Abstract

Chronic rhinitis is a very common disease, as the prevalence in the general population resulted to be 40%. Allergic rhinitis has been considered to be the most frequent form of chronic rhinitis, as non-allergic rhinitis has been estimated to account for 25%. However, several evidences suggested that non-allergic rhinitis have been underrated, especially in children. In pediatrics, the diagnostic definition of non-allergic rhinitis has been often limited to the exclusion of an allergic sensitization. Actually, local allergic rhinitis has been often misdiagnosed as well as mixed rhinitis has not been recognized in most cases. Nasal cytology is a diagnostic procedure being suitable for routine clinical practice with children and could be a very useful tool to characterize and diagnose non-allergic rhinitis, providing important clues for epidemiological analysis and clinical management.

Key words: Pediatric chronic rhinitis; Non-allergic rhinitis; Nasal cytology; Local allergic rhinitis

Core tip: This manuscript aims at describing the current evidences regarding non-allergic rhinitis in children, whose diagnosis is probably underrated. Here, we described the epidemiology and the diagnostic definition of non-allergic rhinitis, highlighting also the differences compared

to allergic rhinitis. Moreover, pathophysiological aspects, the emerging evidences on local allergic rhinitis and the growing role of nasal cytology in the diagnostic work-up of pediatric chronic rhinitis are discussed. Finally, insights on the therapeutic approach are provided.

Poddighe D, Gelardi M, Licari A, del Giudice MM, Marseglia GL. Non-allergic rhinitis in children: Epidemiological aspects, pathological features, diagnostic methodology and clinical management. *World J Methodol* 2016; 6(4): 200-213 Available from: URL: http://www.wjgnet.com/2222-0682/full/v6/i4/200.htm DOI: http://dx.doi.org/10.5662/wjm.v6.i4.200

INTRODUCTION

Rhinitis is a general term indicating any inflammatory disease of the nasal mucosa. Clinically, rhinitis is defined by the onset of two or more of the following symptoms: Nasal discharge, sneezing, nasal itching and congestion. According to the duration of nasal symptoms, rhinitis is defined as acute (resolving within 10 d) or chronic (lasting longer than 10 d). Whereas acute rhinitis is usually a viral (more often) and/or bacterial illness, isolate chronic rhinitis (without sinusitis) does not recognize infectious agents as a common etiology. Actually, the superimposition of bacterial or - less frequently - fungal infections has been more often described in the clinical setting of chronic rhino-sinusitis (CRS), however, this topic goes over the aim of this review[1].

Although the most defined group of chronic rhinitis (CR), both in adults and children, is represented by allergic rhinitis (AR), actually those often recognize also other causes, that are attributable neither to allergic factors nor to infectious agents. Such a large portion of CR that cannot be definitively linked to allergy (and to infections) was included in a very heterogeneous "basket", named as non-allergic rhinitis (NAR): Here, several pathological entities have been enclosed and, indeed, NAR have been indicated with a number of terms (vasomotor, occupational, hormonal, atrophic, iatrogenic, idiopathic), according to the dominant clinical and/or pathologic aspects[2,3]. Thus, it is quite evident that NAR is still a very poorly defined medical entity, where several and different causes and mechanisms are supposed, and, as a consequence, it has been often misdiagnosed and/or underrated, especially in the pediatric population[4].

Nowadays, the current definition of NAR merely relies upon the exclusion of an allergic and IgE-mediated mechanism, defining AR. Unfortunately, such a simplistic clinical distinction was complicated by the fact that AR and some forms of NAR share several clinical and pathologic features and, moreover, some patients present aspects that can be consistent with both allergic and non-allergic mechanisms, namely a "mixed" rhinitis[5].

EPIDEMIOLOGY

CR is a very common disease with an increasing incidence, especially in the Western countries, where the actual prevalence in the general population is comprised between 10% and 40%, according to different studies. Despite such an epidemiological burden, CR has been considered mild disorders and that poor consideration contributed to underestimate such a diagnosis and as a consequence, the real prevalence for long time. Actually, a lot of studies focused on AR, representing the most diagnosed type of CR, showed that nasal symptoms often interfere with daily activities and alter the sleep pattern, leading to negative consequences on the social life and intellectual performances. All these aspects make CR be a global health issue characterized with significant direct and indirect costs for the society[6,7].

In general, an allergic etiology, namely AR, can be established only in around half adult cases of CR, which indicates that a significant portion of the problem is represented by NAR. Prevalence studies on adults estimated that NAR could affect almost 20 million people in the United States, 50 million people in Europe and more than 200 million people worldwide[6,8].

However, because of its poor clinical and pathological definition, NAR is often under-considered by clinicians and, as a consequence, the epidemiological burden is also under-estimated, especially in the pediatric age. Actually, the exact prevalence of NAR in children is not known, but the comparative prevalence between NAR and AR was estimated to be to be at least 1:3-4[4,9]. A recent retrospective analysis by Topal *et al*[10] regarding 472 consecutive children evaluated for CR within 1-year period, showed that 76.9% patients were diagnosed with AR and, thus, the remaining 23.1% children had NAR. Previously, another pediatric study by Chiang *et al*[11] enrolling 660 children (aged 1 to 18 year) with CR, provided very similar results, as AR was diagnosed in 75.9% cases and, by exclusion, NAR represented 24.1% of the total.

DEFINITION AND DIAGNOSIS OF AR

AR is caused by the immunologic sensitization to one or more environmental allergens, leading to the production of specific IgE that trigger some inflammatory events responsible of the nasal symptoms. Depending upon the individual sensitization(s), AR can show different temporal patterns of symptoms, but the classical distinction between seasonal and perennial has been completed by the classification of the project Allergic Rhinitis and its Impact on Asthma (ARIA). It considers both the duration and the severity of nasal symptoms. The temporal patterns of AR have been defined by the following definitions: (1) episodic rhinitis, when nasal symptoms are very limited, as those occur if the allergic

individual comes in contact with an allergen exposure that is not a part of the daily environment (*e.g*., a cat at a friend's house); (2) intermittent rhinitis, if symptoms last fewer than 4 d every week or fewer than 4 wk/year; and (3) persistent rhinitis, if symptoms are present for more than 4 d a week and last more than 4 wk/year. The severity of the nasal disease is considered as being moderate to severe, if one or more of the following clinical items are reported, respectively: (1) abnormal sleep; (2) impairment of daily activities, sport and leisure; (3) difficulties at school and/or work; and (4) troublesome symptoms. If no one of these clinical aspects is present, AR is defined as being mild[12,13].

Despite no existing study extensively described the disease-specific pattern of recurrence, duration of symptoms and impact on the quality of life of pediatric NAR, this classification could be suitable anyway and all these aspects must be evaluated in every child complaining of CR, as those are fundamental to achieve a correct diagnosis of AR or NAR. Indeed, the evidence of one or more positive results of skin prick tests and/or serum allergen specific IgE that, by itself, indicates only the allergic sensitization, must be placed into the specific clinical picture, in order to be interpreted correctly and to support a final diagnosis of AR. The diagnosis of AR to one or more environmental allergens can be safely established only if the profile of allergic sensitization(s) displayed by the individual is consistent with the temporal pattern, the persistence and the severity of nasal symptoms[12,14]. Conversely, it is not correct to reach a diagnosis to AR if nasal symptoms and the related temporal pattern, frequency and severity have not resulted to be linked to allergen exposure, although skin prick tests and/or serum of allergen specific IgE are positive for that allergen. In this case, CR is supposed not to be allergic, namely NAR, or to have more pathological components, both allergic and non-allergic, namely mixed rhinitis or overlapped rhinitis, as discussed forward. In conclusion, the nasal anatomy must be always considered too in the diagnostic pathway of CR, as anomalies of turbinates and septum can contribute to the nasal disease; moreover, adenoid hypertrophy must be investigated in children. Finally, the occurrence of superimposed chronic rhinosinusitis (CRS) should be actively excluded in the setting of AR with atypical symptoms and/or when the clinical disease and the pattern of environmental sensitization seem to be mismatching[15].

NAR

Currently, NAR is basically diagnosed by exclusion of AR in the appropriate clinical setting. NAR is a chronic condition of the nasal mucosa showing symptoms of nasal congestion and rhinorrhea with no evidence of allergic sensitization through skin prick tests (SPT) and dosage of serum specific IgE for environmental allergens[16].

According to such a definition, it is estimated that at least a quarter of patients complaining of CR have NAR, but they might be more numerous, considering that some have mixed rhinitis and that NAR are still underrated[17]. According to data from United States National Rhinitis Classification Task Force, which were collected more than 15 years ago, around 17 millions of Americans were affected with NAR and as many people suffered with a combination of non-allergic and allergic nasal disease (mixed rhinitis). As a percentage, AR, NAR and mixed rhinitis affected 43%, 23% and 34% of patients, respectively. Moreover, it was evident that NAR and mixed rhinitis occurred more frequently in adults than in children, were more common in female patients and used to have a perennial rather than seasonal course[18,19]. These observations have been replicated by many other studies and the prevalence of NAR ranged between 17% to more than 50%[20-22].

Although NAR were considered to be more prevalent in adults, actually those could represent a significant burden in the pediatric age, too. Unfortunately, detailed information regarding the prevalence and burden of NAR in children is lacking: That may partially be explained by the few allergen challenges that are performed in young ages[21]. Moreover, the term NAR does not indicate a specific clinical entity and, therefore, includes a number of different forms of CR: As a consequence, several classifications and terminologies generated further imprecisions in the epidemiological evaluations. Indeed, the classification of NAR still relies upon the presence of comorbidities and/or the evidence of triggering factors and/or some pathological features. Unfortunately, most cases of NAR have not been associated to any of the aforementioned conditions and, thus, have been defined as being idiopathic and/or vasomotor[3].

According to the Global Atlas of Allergic Rhinitis and Chronic Rhinosinusitis edited by the European Association of Allergy and Clinical Immunology (EAACI)[23], the following forms of NAR have been recognized: (1) non-allergic rhinitis with eosinophilia syndrome (NARES); (2) hormonal Rhinitis (pregnancy, associated to menstrual cycle, acromegaly, hypothyroidism); (3) rhinitis of the elderly; (4) gustatory rhinitis (hot and spicy foods, alcohol consumption, *etc.*); (5) atrophic rhinitis (primary or secondary to sinus surgery, autoimmune and/or immune-mediated diseases); (6) cold-air induced Rhinitis (triggered by cold and/or windy climate conditions); (7) drug-induced Rhinitis (nasal decongestant "rhinitis medicamentosa"), aspirin, systemic alpha- and beta-adrenergic antagonist, phosphodiesterase inhibitors, calcium channel blockers, neuroleptics, *etc*.); (8) occupational non-allergic rhinitis (irritants, corrosive substances); and (9) idiopathic rhinitis ("vasomotor rhinitis").

The NAR consensus panel of World Allergy Organization (WAO) edited a similar classification, excluding automatically both anatomical/mechanical nose abnormalities and CRS. Moreover, systemic medical conditions (endocrine/metabolic, autoimmune and miscellanea) leading to NAR symptoms have been

Table 1 Classifications of non-allergic rhinitis by World Allergy Organization and european academy of allergy and clinical immunology[23,24]

WAO	EAACI
Drug-induced rhinitis	Drug-induced rhinitis
Local a-adrenergic agonists ("rhinitis medicamentosa": Excessive use of nasal decongestants); systemic a- and b-antagonists; aspirin; phosphodiesterase (PDE) V inhibitors; ACE inhibitors; calcium channel blockers; antipsychotics	
Gustatory rhinitis	Gustatory rhinitis
Anterior rhinorrhea and/or post-nasal drip after eating, especially hot or spicy foods	
Hormonal-induced rhinitis	Hormonal rhinitis
Rhinitis of pregnancy and menstrual cycle-associated rhinitis	
NARES	NARES
Presence of eosinophilia in the nasal secretions	
Occupational rhinitis	Occupational non-allergic rhinitis
Irritant-induced rhinitis and corrosive rhinitis	
Senile rhinitis	Rhinitis of the elderly
Persistent watery rhinorrhea without any identifiable trigger	
Atrophic rhinitis	Atrophic rhinitis
Primary or secondary (extensive surgery, chronic granulomatous disorders, other)	
Non-allergic rhinopathy	Idiopathic rhinitis
Nasal congestion and/or rhinorrhea triggered by irritants and/or weather changes, but also chronic without identifiable triggers	
Cerebral spinal fluid leak	Cold air-induced rhinitis
Persistent rhinorrhea after cranio-facial trauma or facial/sinus surgery	Rhinorrhea and/or nasal congestion and/or burning triggered by cold and/or windy condition

NARES: Non-allergic rhinitis with eosinophilia syndrome; WAO: World Allergy Organization; EAACI: European academy of allergy and clinical immunology.

considered separately. Thus, eight subtypes of NAR have been classified: (1) drug-induced rhinitis; (2) gustatory rhinitis; (3) hormonal-induced rhinitis (including responses to endogenous female hormones, basically the rhinitis of pregnancy); (4) non-allergic rhinitis with eosinophilia; (5) senile rhinitis; (6) atrophic rhinitis; (7) cerebral spinal fluid leak; and (8) non-allergic rhinopathy (corresponding to vasomotor rhinitis and those forms related to climate conditions)[24].

Taking in account what stated above, it is evident that a systematic classification of NAR based upon pathological mechanisms is still distant (Table 1). Therefore, rather than trying to find some correspondences of the aforementioned categories of NAR in the pediatric population, it seems to be more useful to discuss some specific aspects of NAR, such as the emerging evidence on local allergic rhinitis (LAR), the growing interest on nasal cytology for the possibility of defining the features of NAR inflammation and the pathogenic role of some noxious agents for the nose, such as environmental pollutants.

LAR

LAR is a type of CR showing the same phenotypic characteristics as AR, actually without any remarkable positivity of environmental skin-prick tests (SPT) and/or serum specific IgE. In specific studies, LAR is characterized by an allergen-related nasal hyper-reactivity, despite the absence of specific systemic atopy, as could be evidenced though specific nasal provocation tests (NPT), performed by administering intra-nasally a set of purified airborne allergens. In this clinical setting, the positive response to specific NPT suggested the presence LAR, which could be confirmed by recovering also allergen-specific IgE in the nasal mucosa[25,26]. Indeed, LAR and AR have been demonstrated to have similar patterns of inflammation, sustained by Th2 polarized immune responses: Probably, different initiating immunological events and mechanisms converging to a final common pathway of nasal inflammation may exist[27,28].

The local production of IgE in the nasal mucosa has been largely demonstrated in patients with AR, where the allergen exposure directly drives the antibody class switch recombination[29,30]. The presence of IgE specific to house dust mite in the nasal mucosa of patients with CR displaying negative SPT, but positive specific NPT, was reported in 1975 by Huggins *et al*[31]. Starting from 2000, Carney and Powe published a series of studies investigating nasal allergy due to the local production of IgE, defined as "entopy". They were able to demonstrate the presence of mast cells, eosinophils and IgE+ cells in a selection of archival samples of nasal mucosa from patients affected with idiopathic CR: In addition to an increased number of mast cells, some showed a positive staining for IgE specific to grass pollen[32]. Eventually, Rondón *et al*[33] and Wise *et al*[34] described a cohort of NAR patients manifesting positive response to specific NPT to house dust mite: That result was reported in around 50% cases and, interestingly, specific IgE were detected in the nasal lavage of more than 10% of those.

Poor SPT technique and/or quality of allergen preparations or a cover allergy, namely the sensitivity to not tested allergens, have been suggested to explain some cases of apparent entopy. Additional pathological mechanisms, such as non-IgE mediated hypersensitivity and other tissue-specific immune responses could be considered in patients showing specific nasal hyperreactivity, but not local IgE[35].

Epidemiologically, LAR might affect more than 40% people diagnosed with NAR currently. In a study including 428 patients with chronic rhinitis, Rondón *et al*[36] diagnosed AR, LAR and NAR in 63%, 26% and 11% of patients, respectively. Importantly, in addition to highlighting the epidemiological importance of LAR among chronic rhinitis, this study noticed that 36% of patients with LAR had rhinitis since childhood. Moreover, some authors suggested that LAR might be the first step of the natural history of AR, especially in polysensitized and young patients[37]. Indeed, some studies showed that children could develop systemic atopy to grass pollen only in the second or third season of nasal symptoms[38]. However, such a hypothesis upon LAR as an initial stage of AR needs to be tested adequately and immune processes might differ according to allergens. So far, the most prevalent allergen sensitizations identified in

patients with LAR have been house dust mite, grass and olive pollen, but other allergens, including molds, animal dander and occupational substances, have not been completely investigated yet and might have a role[39,40].

However, that LAR is not only an adult disease and can arise from the pediatric age was evident also in the large follow-up study by Rondón *et al*[41,42] at least 35% of patients diagnosed with LAR and followed-up were 14-20 years old, confirming that the diagnosis should be considered in children too. Actually, this study showed also that the rate of conversion of LAR to "systemic" AR, namely displaying positive SPT and/or serum specific IgE, was only 6.8% and was similar to the percentage observed in healthy controls. Thus, these observations seemed to support the concept that LAR and AR could be different pathological entities. The first pediatric study assessing specific nasal hyper-reactivity and mucosal IgE was carried out by Fuiano *et al*[43] who analyzed 192 children aged 3-15 years and showing at least one positive SPT for aeroallergens (among house dust mite, grass pollen, olive pollen, Parietaria and Alternaria): Of those, 67.6% were symptomatic and 34.6% were asymptomatic. Between these two groups, a striking difference in nasal IgE was found, being 77% *vs* 13%, respectively. This study suggested a major role of nasal IgE in determining symptoms in children sensitized to environmental allergen, but also highlighted the presence of other mechanisms than or in addition to the production mucosal IgE, being able to suppress its activity (in asymptomatic children positive for nasal IgE) or to replace it (in symptomatic children negative for nasal IgE)[44]. The same authors replicated similar analysis in children suffering from chronic rhinitis during the period when Alternaria spores can be present in the environment. Interestingly, they found that most children (64.3%) had negative SPT for Alternaria, but were positive for nasal specific IgE; only 16.1% were positive to both tests and the remaining 19.6% had a positive SPT without nasal IgE. These results represented the first pediatric evidence that an allergic sensitization manifesting with chronic rhinitis can be mediated by an exclusive production of specific IgE in the nasal mucosa. Unfortunately, current evidences on pediatric LAR are insufficient to draw any consistent conclusion, as appropriate prospective studies are still lacking[45].

PATHOPHYSIOLOGICAL ASPECTS

According to the findings of studies including nasal cytology, AR can display different forms and severity of inflammation according to the allergic sensitization and, possibly, the season. Similarly, NAR can be classified through several inflammatory patterns. These observations supported the concept that several immune-pathological mechanisms could be involved in both AR and NAR. Moreover, nasal cytology also demonstrated that AR and NAR coexist in some patients, leading to so-called overlapped rhinitis: Thus, more mechanisms seem to interplay or, perhaps, some of those could be shared between AR and NAR[46]. Importantly, some studies showed synergistic interactions in the inflammatory nasal responses between the specific IgE-mediated component of AR and the superimposition of non-specific irritation induced by environmental pollutants (*e.g.,* diesel exhaust particulate, ozone, *etc.*), maybe in a bidirectional way[5].

By definition, AR and LAR are sustained by an IgE-mediated inflammation and are mainly associated to a Th2 immune response. However, among seasonal and perennial forms of AR, nasal cytology evidenced different features of the inflammatory infiltrate into the nasal mucosa, which suggested some substantial differences in the pathophysiological immune cascade anyway. On the contrary, by exclusion, NAR included all that is not promoted by an IgE-mediated pathogenesis. A series of non IgE-mediate immune responses are plausible, considering the heterogeneity of NAR, as evidenced by the nasal cytology and by the clinical observation. Unfortunately, most pathophysiological aspects of NAR have not been unveiled yet. Moreover, in addition to immune-mediated mechanisms, several evidences showed that some neurogenic responses seem to play a fundamental role in the development of NAR inflammation and, probably, are involved in AR, too[47-49].

Non IgE-mediated immune mechanisms could take place in several classified forms of NAR. In occupational rhinitis, lymphocytic infiltrates have been described, in association to epithelial desquamation and glandular hypertrophy. In atrophic rhinitis, different inflammation patterns can be seen, including granulomatous lesions. Conversely, inflammatory changes are less evident in other forms of NAR: For instance, in gustatory rhinitis, rhinitis medicamentosa or idiopathic (vasomotor) rhinitis, the nasal symptoms mainly resulted from the increased glandular secretion and the mucosal edema due to a local transudate, rather than from the presence of exudate and abundant inflammatory cells. Indeed, some authors preferred to refer these forms as rhinopathy, rather than rhinitis[3,24,50].

Therefore, in addition to pure immunologic mechanisms, actually a complex series of neuroendocrine pathways have been proposed to explain the pathophysiology of several forms of NAR and, in some extent, those could be involved in AR too. Probably, both immune and neuroendocrine systems interact in the nasal mucosa of subjects suffering from chronic rhinitis, but those might have a different importance according to the type of NAR. Some evidences supported the involvement of autonomic neural responses in the pathophysiology of NAR. The neural regulation of upper airways relies upon sympathetic (adrenergic) and parasympathetic (cholinergic) fibers, which regulate the activity and the trophism of epithelial, vascular and glandular components of the nasal mucosa. Sympathetic neuromediators, being mainly norepinephrine and neuropeptide Y, cause local vascular constriction; however, in a lesser extent, those innervate also the glandular structures, decreasing the nasal secretions. Conversely, parasympathetic fibers, through the secretion

of acetylcholine and some neuropeptides (particularly, vasoactive intestinal peptide), stimulate nasal glands and induce vasodilation. Actually, the neural system of the nasal mucosa includes also the sensory innervation supplying the septum, the lateral walls, the anterior parts of nasal floor and the inferior meatus. Among these nerves, non-adrenergic and non-cholinergic nervous fibers have been demonstrated in the human nasal mucosa. Predominantly, those resulted to be sensory unmyelinated C-fibers and have been demonstrated to be involved in the realization of several protective nasal responses (such as sneezing, mucus production and mucosal congestion) against potential noxious stimuli entering in the nasal cavities. The activation of these unmyelinated sensory C-fibers leads to the release of several neuropeptides [Substance P (SP), calcitonin gene related peptide (CGRP) and neurokinins] in the human nasal mucosa, through an antidromic conduction, in response to a large variety of stimuli[50,51].

Thus, this neurogenic reactivity seems to be dominant in those forms of NAR where the cellular inflammation resulted to be poorly expressed. However, some evidences suggested that the neural factors could play a role also in AR and in other forms of NAR anyway. Interestingly, a denser innervation of sensory C-fibers in the nasal mucosa was demonstrated in different forms of NAR, including idiopathic rhinitis, occupational rhinitis and some drug-induced rhinitis. Moreover, this hyperinnervation was associated to an increased expression of some neuropeptides (SP and CGRP, in particular) in the mucosal nerve fibers and, importantly, this finding was observed also in patients with AR ~~too~~, where some neuroinflammatory mechanisms might worsen the clinical expression of AR and/or promote the occurrence of overlapped rhinitis. Indeed, further investigations might determine whether overlapped rhinitis could be part of a continuum between AR and NAR, where immunologic responses (both IgE-mediated and non IgE-mediated), inflammatory/irritant responses upon exposure to chemicals and/or particulate matter and neurogenic factors develop over the time starting from an initial trigger[52-54]. In fact, non specific nasal hyperreactivity, being an abnormal or excessive reaction of the nasal tissue (in term of glandular activity, mucosal inflammation and vascular leakage) after the exposure to a non allergenic stimulus that is usually innocuous to most people, have been demonstrated in patients with both NAR and AR. Such a nasal hyper-reactivity seemed to result mainly from the impaired balance of the activity of the aforementioned neural local reflexes. Indeed, several inflammatory mediators have been demonstrated to interact with sensory nerve endings in the nasal mucosa, which resulted to release several neurotrophins, in addition to the aforementioned neuropeptides. The formers would be responsible of the hyperinnervation seen in chronic rhinitis, both AR and NAR, whereas the latters would contribute to up-regulate the local inflammation by promoting the transcription of pro-inflammatory cytokines, in addition to eliciting the vascular and glandular responses causing nasal symptoms[55,56].

DIAGNOSIS OF NAR IN CHILDREN

Pediatric NAR is poorly defined: The available information is quite heterogeneous and most concepts have been derived from NAR in adults. Indeed, there are no pediatric studies recognizing the categories of NAR, as classified by EAACI or WAO, as those classifications were tailored for the adult population: By instance, hormonal, atrophic and occupational rhinitis are related to adult diseases or activities, as well as drugs involved in the occurrence of NAR are not used in the pediatric age and food causing gustatory rhinitis are not usually given to children. Therefore, the current diagnostic work-up of pediatric CR is often limited to the identification of AR, NAR (in general) and mixed rhinitis[4,21]. Such a diagnostic limitation is partially due to the fact that investigational techniques being useful to evaluate nasal obstruction (*e.g.,* rhinomanometry) and nasal hyperreactivity (*e.g.,* nasal provocation test) cannot be applied to children so easily as to adult people, where those have been considered as important diagnostic tools, in order to define objectively the entity and the trigger factors of chronic rhinitis[57].

Rhinomanometry is a technique allowing an objective estimation of nasal airway obstruction and, therefore, should be also an essential part in the setting of nasal challenge procedures[58]. Whereas some nasal symptoms, like rhinorrhea and sneezing, are clinically evident, actually nasal blockage could be difficult to be assessed subjectively: The individual perception of nasal obstruction can be influenced by several factors and could mismatch with objective measurements of nasal patency. Indeed, available pediatric studies on the correlation between subjective scores and objective techniques for estimating nasal obstruction provided conflicting results[59,60]. Recently, a pediatric study including 284 children aged 6-14 years showed that a major part of children under-estimate or over-estimate their nasal obstruction and concluded that an objective measurement of nasal patency could improve the clinical management[61]. Here, children were evaluated by anterior active rhinomanometry that provides an accurate evaluation of nasal obstruction or resistance through the measurement of nasal airflow generated by a known pressure gradient[61,62]. An alternative technique is represented by acoustic rhinometry, which is basically based upon the amplitude and temporal analysis of the reflections of incident sound waves on the nasal cavities, calculating the cross-sectional area at different depths[63]. However, both techniques require considerable standardization to obtain reproducible results and experience to interpret those. Actually, Peak Nasal Inspiratory Flow could represent a simple, reproducible and inexpensive technique, but it is effort dependent and, thus, could be difficult to apply to the pediatric population[57].

Another important tool in the differential diagnosis of NAR should be the nasal provocation test (NPT) and, ideally, the objective measurement of nasal obstruction should be used to assess the results, in addition to symptom scores. Specific NPT consists of triggering a nasal allergic response by administering a standardized allergenic extract locally in the nose. Non Specific NPTs have been used to evidence non-allergenic nasal hyper-reactivity, namely an abnormal nasal reaction upon the exposure to several physical (*e.g.,* cold air) or chemical (*e.g.,* methacholine, mannitol, distilled water, *etc.*) agents being innocuous for most people. However, their use has been often limited to the research field and more studies are needed to evaluate the clinical usefulness and to standardize the methodology[56,58].

Specific NPT was primarily introduced in order to evaluate the clinical significance of a specific allergen sensitization in multi-sensitized patients. In the clinical setting of NAR, specific NPT could be useful to diagnose LAR, through the positive response to specific allergens in the setting of a chronic rhinitis without evidence of systemic atopy. Unfortunately, as discussed above, both techniques for estimating nasal patency objectively and NPT are difficult to be used in the routine allergy practice in children[64,65]. Indeed, the daily clinical experience in the pediatric allergy clinic includes children showing a clinical history consistent with AR in absence of positive findings at SPT and/or serum specific IgE. Here, the potential alternative to the complicated execution of NPT and/or rhinomanometry might be the detection of allergen specific IgE in the nasal mucosa[45]. Marcucci *et al*[66] described a method to detect nasal IgE in children, by placing into the nostril (in contact with the septum nasal mucosa) a paper strip whose surface had been covalently coupled with a specific allergen. Recently, Fuiano *et al*[44] recalled this method and carried out some pediatric studies by using nasal strips where a colorimetric reaction provided a semi-quantitative evaluation of the presence of specific nasal IgE. The authors sought nasal IgE specific to some aeroallergens (Alternaria, house dust mites, Grass Pollen, Olive pollen and Parietaria) in 192 children with positive SPT for one or more aeroallergens. A significant association between the presence of specific nasal IgE and nasal symptoms was observed in systemically sensitized children. Eventually, another study showed that measuring nasal IgE could be useful to unveil local allergic rhinitis to *Alternaria* and to avoid a misdiagnosis of NAR[66]. Alternatively, specific nasal IgE have been measured in the nasal secretions by immunoassay: Rondón *et al*[67] described a detection rate of specific nasal IgE to grass pollen of around 30%-35% in their cohort of LAR patients (defined by the positivity to specific NPT), which suggested a limited sensitivity of their method or perhaps the involvement of other immunologic mechanisms.

In summary, the testing of nasal specific IgE still needs to be improved and standardized and there are no available studies regarding the diagnosis of LAR in children through the evaluation of nasal IgE and/or specific NPT[45]. Recently, Gómez *et al*[68] proposed a role for basophil activation test (BAT) in the diagnosis of LAR: They found a sensitivity of around 50% in patients diagnosed with LAR to house dust mite, but that remains an isolated experience till now.

Thus, the diagnostic work-up of NAR in children is still limited to its definition by exclusion of AR in most cases, as further diagnostic investigations cannot routinely performed in children (*e.g.,* specific NPT, rhinomanometry, acoustic rhinometry) or showed no acceptable sensitivity and/or standardization (nasal specific IgE, BAT). However, a simple and inexpensive method to investigate patients (including children) with chronic rhinitis is represented by nasal cytology that might allow the description and classification of nasal diseases according to the inflammatory features. Moreover, a number of studies regarding nasal cytology have been performed also in the pediatric age ~~too~~ and, therefore, a specific section will be dedicated.

NASAL CYTOLOGY

Nasal cytology consists of the microscopic analysis of surface cells of nasal mucosa. The suitable biological sample can be collected through a sterile swab or by scraping and is usually obtained by anterior rhinoscopy in order to reach the middle portion of the inferior turbinate. Thus, the material must be placed on a glass slide and, after it is fixed by air-drying, it can be stained according to May-Grunwald-Giemsa method. This simple staining allows identifying correctly all the normal cellular components of the nasal mucosa, the inflammatory cells and also bacteria and fungi, if those are present. Therefore, nasal cytology is endowed with several aspects allowing a routine use in allergy daily practice, including the pediatric setting: It is non-invasive, easy to perform, non-time-consuming and inexpensive[69].

The result of nasal cytology is the rhinocytogram that, in healthy controls, shows only ciliated cells and mucous-secreting cells of the pseudo-stratified epithelium of the nasal mucosa, in addition to sparse neutrophils. On the contrary, the presence of more abundant neutrophils and/or other inflammatory cells (eosinophils, mast cells, lymphocytes), as well as the presence of bacteria and fungi, represents a sign of nasal pathology. Nasal cyto-pathology has been studied in several nasal diseases and it might be a promising diagnostic tool for allergic and non-allergic rhinitis[70].

AR can be caused by several environmental allergens, differing as regards the immunological properties and the presence during the year. AR caused by indoor allergens, such as house dust mite, are usually perennial, as the patients complain of nasal symptoms all over the year and, accordingly, the rhinocytogram is characterized with a persistent infiltration of neutrophils and, in a lesser extent, of eosinophils, describing a pathological pattern of "minimal persistent inflammation". Seasonal AR is often triggered when the pollens are present in the atmosphere and, therefore, the nasal symptoms are

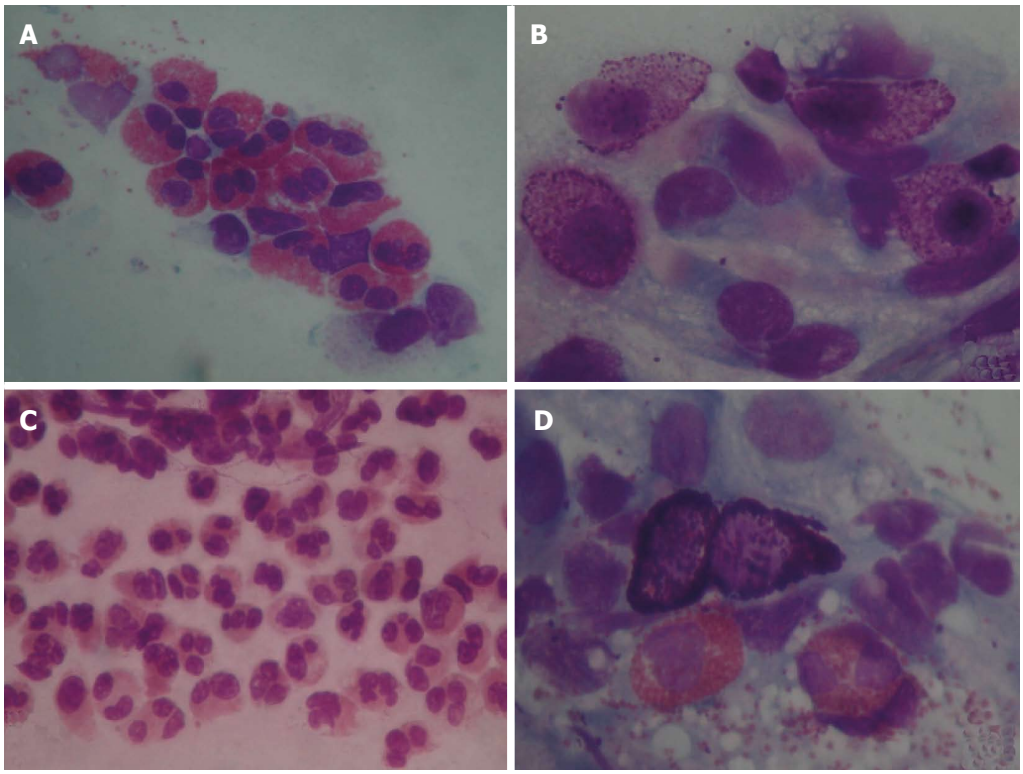

Figure 1 Nasal cytology of non-allergic rhinitis. A: NARES; B: NARMA; C: NARNE; D: NARESMA. NARES: Non-allergic rhinitis with eosinophilia syndrome; NARMA: NAR with mast cells; NARNE: NAR with neutrophils; NARESMA: NAR with eosinophils and mast cells.

limited within a specific period of the year. In this setting, the rhinocytogram is very rich of all inflammatory cells, including neutrophils, lymphocytes, eosinophils and mast cells; by contrast, the cytological aspect of nasal mucosa can be completely normal outside the pollen season[71].

Interestingly, nasal cytology provided a heterogeneous landscape of non-allergic rhinitis, both in adults and children, but EAACI and WAO classifications considered only non-allergic rhinitis with eosinophilia syndrome (NARES), as a separated cyto-pathological entity of NAR[3]. That should include those patients having the same clinical features as AR, but not positive SPT and/or serum specific IgE, namely LAR[72]. Under this limited perspective, all the other variants of NAR could be defined as non-NARES. Actually, nasal cytology suggested that the situation is more complex than two variants of NAR[73]; moreover, very recent evidences suggested that also NARES might recognize immunological mechanisms other than entopy[74]. Gelardi *et al*[73] described at least four cytological patterns of NAR (Figure 1): (1) NAR with eosinophils (NARES); (2) NAR with mast cells (NARMA); (3) NAR with neutrophils (NARNE); and (4) NAR with eosinophils and mast cells (NARESMA).

These authors tried defining the incidence, the clinical aspects and the prognosis of these different cytological forms of "cell-mediated non-allergic rhinitis". NARES and NARNE resulted to be the most abundant forms among children, as those were recognized in 46.5% and 40.6% cases, respectively. NARMA has been detected in 10.5% cases and NARESMA in the remaining 2.6%. On the contrary, in adulthood the relative proportions among all these forms of NAR seem to be more balanced and, particularly, NARESMA has been reported as affecting around 25%-30%, like NARES. Importantly, these two types resulted to be associated to the most severe clinical manifestations, such as non-allergic asthma, nasal polyposis and aspirin intolerance. Particularly, NARESMA was described as leading to the worst complications, including major respiratory disturbances (sleep-apnea and severe asthma). Significant respiratory symptoms and complications were almost absent in children with NARMA: Thus, the presence of eosinophils in the nasal mucosa resulted to be most important determinant for the severity of the clinical disease. Despite the significant portion of NARES in the pediatric population, actually respiratory severe symptoms have not been seen as in adults, as those probably require a number of years of rhinopathy to develop. The other prevalent form of NAR in children resulted to be NARNE, as described above. NARNE was associated to cystic fibrosis, but it is supposed to have a multifactorial etiology and, particularly, it has been linked to the exposure to a number of irritants, including air pollution and cigarette smoke[73,75-77].

A large series of pollutants and chemicals have been reported to be involved in the etiopathogenesis of "environmental" NAR. Many of those have been related to occupational exposures (*e.g.*, volatile organic compounds, paper dust, acetic acid, *etc.*), but

others became common environmental pollutants[78]. A significant difference of inflammatory changes in the nasal cytology specimens was observed between people living in highly polluted urban areas and rural residents[79].

Environmental tobacco smoke, including sidestream or second-hand tobacco smoke exposure, has been demonstrated to have detrimental effect on several organs, especially in children. A wide variety of tobacco smoke effects have been described on the immune system and, of course, respiratory airways - and nose as first - are particularly exposed. Effects on immune cells functions and cytokines production have been reported in nasal mucosa and adenoidal tissue of children exposed to passive smoke[80]. Another important irritant for the respiratory system is ozone, whose concentration in the ground-level atmosphere increases in polluted areas. Experimental studies showed that ozone induces epithelial abnormalities and inflammatory responses of the nasal mucosa. A pediatric study reported a significant association between outdoor ozone concentration and levels of leukocytes in the nasal secretions[81]. Similarly, the particulate matter of the urban environment and, particularly, particles derived from diesel exhaust, have been described to increase the expression of inflammatory cells and molecules at several level of the respiratory system, including the nasal mucosa. Also fine particulate matter (PM $\leqslant$ 2.5 μm) was shown to increase significantly the percentage of eosinophils and several inflammatory mediators in the nasal lavage fluid of asthmatic children, but not in healthy children[82]. Thus, environmental pollution could exacerbate allergic inflammation and/or promote the development of new allergic sensitization at the respiratory level, especially in children, leading to mixed patterns of allergic and non allergic rhinitis in some cases[83,84].

Nasal cytology provided another important contribution under this perspective, as introduced the concept of mixed of "overlapped" rhinitis, namely the simultaneous presence of different forms of inflammatory rhinopathies in the same patient[85]. Particularly, there are patients (including children) diagnosed with AR, but that diagnosis actually is not fully consistent with the nasal symptoms and/or the related temporal pattern. In these cases, including both seasonal and perennial forms of AR, the superimposition of a form of NAR could be suspected and nasal cytology could provide fundamental clues. By instance, there are children suffering with a pollen-related AR who have nasal symptoms during the winter, when the rhinocytogram can show the presence of eosinophils, as well as there are children with house dust mite AR who have an abnormal clinical course and whose rhinocytogram can display mast cells and/or eosinophils, in addition to the pattern of minimal persistent inflammation (showing usually a preponderance of neutrophils). Those are typical examples of patients where an overlapped rhinitis should be suspected. Gelardi M and Landi M proposed some clinical and cytological criteria, in order to evaluate the likelihood of the presence of an overlapped rhinitis. Schematically, cytological features of overlapped rhinitis could be the finding of eosinophilia > 20% and/or mast cells > 10% in the rhinocytogram of patients with perennial CR and of patients with seasonal CR outside the pollen period corresponding to the personal allergic sensitization[78,86].

The possibility to unveil an overlapped rhinitis through nasal cytology might ameliorate the clinical and therapeutic management of these patients and also could have implications in the epidemiological analysis of pediatric chronic rhinitis and their complications (*e.g.,* asthma, nasal polyposis, chronic rhinosinusitis, *etc.*). Adult studies suggested that the presence of inflammation ad the type of inflammatory cells in NAR influences the clinical features and the risk of comorbidities[52,76].

Indeed, AR and NAR could be overlapping condition in a greater number of cases than previously thought. Distinguishing isolated AR and overlapped rhinitis might improve the clinical management, as those recognize different clinical presentation, comorbidities and therapeutic responses. However, in order to achieve a better correlation between cyto-pathological patterns and clinical features of CR, a systematic application of nasal cytology and further studies are needed, both in adults and children. That might lead to a wider understanding of nasal pathophysiology, to a better classification of nasal diseases and, finally, to a rational therapeutic approach.

THERAPEUTIC MANAGEMENT

Once the diagnosis of AR has been established, the therapeutic approach includes the avoidance of allergen exposure, whether it is practicable, and the control and/or prevention of nasal symptoms by local or systemic anti-histamine drugs, intra-nasal steroids, leukotriene-receptor antagonists and, in a lesser extent, intra-nasal cromones and decongestants. Among those drugs, intra-nasal steroids have been demonstrated to be able to produce the greatest relief, as those mainly improve the nasal obstruction. Unfortunately, all these drugs control the symptoms, but cannot cure the allergic disease[87].

According to the "allergic/atopic march" hypothesis and to the "united airways disease" concept, AR can be associated to lung function test abnormalities and/or anticipate the onset of asthma. Thus, an important aim of the therapy of AR with identifiable allergenic triggers should be also prevention of the progression to asthma or other respiratory diseases, in addition to ameliorating patient's life quality. Such a goal may be reached through the inclusion of specific immunotherapy (SIT) in the early treatment of AR: Indeed, SIT - unlike symptomatic drugs - has been demonstrated to modulate the immune mechanisms underlying the allergic disease and, therefore, it is the only treatment that currently could modify the natural history of allergic diseases[88]. SIT has been administered by two main ways: Subcutaneously (SCIT) or sublingually (SLIT). In

many European countries, SCIT is still the most common way to administer allergy immunotherapy; however, sublingual immunotherapy (SLIT) has been gaining success, especially in the pediatric population, where it could be preferred because it is easily accepted and it is basically lacking of systemic and life-threatening adverse reactions[89,90]. Moreover, several systematic reviews supported the specific use of SLIT in the treatment of AR in children, as well as the EAACI position paper on pediatric rhinitis did. Recent analyses inferred a moderate strength and general evidence that SLIT improves pediatric AR and conjunctivitis, ameliorating symptoms and/or decreasing the drug consumption[12,91-93]. This evidence resulted to be stronger for grass pollen SLIT in the treatment of isolated AR, whereas the evidence for house dust mite SLIT effectiveness is still considered "of moderate-low quality", as resulted from few available randomized controlled trials. Anyway, some indirect beneficial effects, as the prevention of asthma development and the reduction of respiratory infections, must be considered[94,95]. Moreover, as discussed previously, it must be reminded that the importance of a correct diagnostic definition of pediatric chronic rhinitis might affect these conclusions on the efficacy of SLIT. By instance, NAR sustained by the exposure to environmental pollutants producing similar nasal inflammatory changes and disease as house dust mite AR might could affect the outcome analysis of SLIT, by worsening the nasal inflammation due to allergy or by misleading the correct diagnosis. So far, very few studies faced this topic, but an interesting study showed that the exposure to passive smoke significantly reduced the clinical response to SLIT in children affected with AR due to house dust mite[96].

On the contrary, achieving a diagnosis of LAR in patients affected with NAR could have a major impact on the therapeutic management. Indeed, the cornerstone therapy of AR produced a good clinical response in patients with LAR and, particularly, those could receive further important benefit from SIT too. Rondón *at al*[97] reported a significant improvement of symptom and medication scores in 20 patients affected with LAR sensitized to grass pollen after receiving SCIT. However, so far there no pediatric studies regarding drug therapy and SIT in LAR.

As regards the treatment of NAR, the list of drugs basically includes most of molecules used in the management of AR. Unfortunately, patients with NAR resulted to be less responsive to the pharmacological therapy than patients affected with AR, in general[98].

Antihistamines have been largely used for the treatment of NAR. Compared to AR, non-sedating second generation molecules have not resulted to be so effective, whereas some benefits have been observed with first generation antihistamines, probably due to the greater anticholinergic activity. Actually, several studies supported the effectiveness of topical antihistamines in NAR, especially azelastine. Nasal spray containing azelastine have been approved for use in children aged six years and older, but there are no pediatric studies assessing its efficacy in children with NAR[98-100]. The association of azelastine with an intranasal corticosteroid, usually fluticasone propionate, resulted even more effective in the treatment of adult NAR. Similarly, that association was approved for use in children older than five years; however, the available studies on this drug included children aged 12 years and older, which suggested a similar efficacy in AR and NAR[101,102].

Thus, antihistamines and/or topical steroids are the mainstay of the general treatment of NAR. Additional drugs have been used with specific indications. By instance, topical anticholinergic medications, containing ipratropium bromide, could be recommended for patients having rhinorrhea as isolate or dominant nasal symptom, namely vasomotor rhinitis. Specific studies addressing the efficacy of ipratropium nasal spray in pediatric NAR are lacking; however, it has been studied in children complaining of rhinorrhea because of allergy or common cold and resulted to be easy to be administered, safe and effective also in children as young as 2 years[103,104]. In children saline nasal irrigation is considered the first step and the basic tool in every therapy for rhinitis and, indeed, resulted to be useful in the management of NAR, too. This procedure resulted to improve nasal symptoms, relieving post-nasal drip, nasal congestion and also sneezing. Nasal irrigation with isotonic saline irrigation seemed to ameliorate the mucociliary clearance, promoting the removal of allergens, biofilms and inflammatory mediators[6,105].

Finally, several adjunctive therapies have been proposed in adults, such as topical capsaicin, anti-leukotrienes and oral/intranasal decongestants. Unfortunately, there is no experience in the pediatric field at all[99,106]. However, some recommendations (based upon personal observations) have been reported in Table 2, according to the inflammatory pattern recovered by the nasal cytology.

CONCLUSION

Chronic rhinitis is a very common medical issue in children, as its incidence was estimated to be 40% in Western countries. Allergic rhinitis is considered to be the most frequent form of chronic rhinitis in children, whereas non-allergic rhinitis resulted to account for at least 25% of cases, according to few available pediatric studies. Actually, pediatric non-allergic rhinitis is poorly defined and is likely to be underrated. Indeed, although local allergic rhinitis is often misdiagnosed as being non allergic, a lot of chronic rhinitis do not receive the appropriate attention after an allergic cause has been excluded. Moreover, cases of non-allergic rhinitis could be lost because of a misdiagnosis of allergic rhinitis or because of its coexistence with allergic rhinitis, defined as mixed or overlapped rhinitis. Currently, the diagnostic definition of pediatric non-allergic rhinitis is often limited to the exclusion of allergy, as several investigations, such as nasal provocation tests and objective measurement of nasal patency, are not suitable for routine

Table 2 Recommendation for the treatment of pediatric non-allergic rhinitis, according to nasal cytology

	NARES	NARESMA	NARMA	NARNE
Topical anti-histamines	1	1	1	2
Systemic anti-histamines	1	1	1	2
Topical corticosteroids	1	1	1	1
Systemic corticosteroids	1	1	1	2
Ipratropium bromide	2	2	2	2
Anti-leukotrienes	1	1	1	2
Cromones	3	3	3	2
Nasal decongestant	3, 4	3, 4	3, 4	3, 4
Nasal saline irrigation	1	1	1	1

1: Recommended; 2: Not recommended; 3: Uncertain recommendation; 4: Permitted in children younger than 12 years, according to the dosage and for no more than 10-14 d. NARES: Non-allergic rhinitis with eosinophilia syndrome; NARMA: NAR with mast cells; NARNE: NAR with neutrophils; NARESMA: NAR with eosinophils and mast cells.

clinical practice with children. Actually, important clues could come through the growing application of nasal cytology in the diagnostic approach of children complaining of chronic rhinitis. That might lead to a better definition and classification of pediatric non-allergic rhinitis and, as a consequence, to an appropriate clinical management.

REFERENCES

1 **Dykewicz MS**, Hamilos DL. Rhinitis and sinusitis. *J Allergy Clin Immunol* 2010; **125**: S103-S115 [PMID: 20176255 DOI: 10.1016/j.jaci.2009.12.989]

2 **Scadding GK**. Non-allergic rhinitis: diagnosis and management. *Curr Opin Allergy Clin Immunol* 2001; **1**: 15-20 [PMID: 11964664 DOI: 10.1097/00130832-200102000-00004]

3 **Settipane RA**, Kaliner MA. Chapter 14: Nonallergic rhinitis. *Am J Rhinol Allergy* 2013; **27** Suppl 1: S48-S51 [PMID: 23711042 DOI: 10.2500/ajra.2013.27.3927]

4 **Berger WE**, Schonfeld JE. Nonallergic rhinitis in children. *Curr Allergy Asthma Rep* 2007; **7**: 112-116 [PMID: 17437681 DOI: 10.1007/s11882-007-0008-0]

5 **Bernstein JA**. Allergic and mixed rhinitis: Epidemiology and natural history. *Allergy Asthma Proc* 2010; **31**: 365-369 [PMID: 20929601 DOI: 10.2500/aap.2010.31.3380]

6 **Tran NP**, Vickery J, Blaiss MS. Management of rhinitis: allergic and non-allergic. *Allergy Asthma Immunol Res* 2011; **3**: 148-156 [PMID: 21738880 DOI: 10.4168/aair.2011.3.3.148]

7 **Blaiss MS**. Allergic rhinitis: Direct and indirect costs. *Allergy Asthma Proc* 2010; **31**: 375-380 [PMID: 20929603 DOI: 10.2500/aap.2010.31.3329]

8 **Bousquet J**, Fokkens W, Burney P, Durham SR, Bachert C, Akdis CA, Canonica GW, Dahlen SE, Zuberbier T, Bieber T, Bonini S, Bousquet PJ, Brozek JL, Cardell LO, Crameri R, Custovic A, Demoly P, van Wijk RG, Gjomarkaj M, Holland C, Howarth P, Humbert M, Johnston SL, Kauffmann F, Kowalski ML, Lambrecht B, Lehmann S, Leynaert B, Lodrup-Carlsen K, Mullol J, Niggemann B, Nizankowska-Mogilnicka E, Papadopoulos N, Passalacqua G, Schünemann HJ, Simon HU, Todo-Bom A, Toskala E, Valenta R, Wickman M, Zock JP. Important research questions in allergy and related diseases: nonallergic rhinitis: a GA2LEN paper. *Allergy* 2008; **63**: 842-853 [PMID: 18588549 DOI: 10.1111/j.1398-9995.2008.01715.x]

9 **Settipane RA**. Rhinitis: a dose of epidemiological reality. *Allergy Asthma Proc* 2003; **24**: 147-154 [PMID: 12866316]

10 **Topal E**, Bakirtas A, Yılmaz O, Karagöl IH, Arslan U, Arga M, Demirsoy MS, Turktas I. Predictive factors to differentiate between allergic and nonallergic rhinitis in children. *Int Forum Allergy Rhinol* 2014; **4**: 447-452 [PMID: 24574308 DOI: 10.1002/alr.21312]

11 **Chiang WC**, Chen YM, Tan HK, Balakrishnan A, Liew WK, Lim HH, Goh SH, Loh WY, Wong P, Teoh OH, Goh A, Chay OM. Allergic rhinitis and non-allergic rhinitis in children in the tropics: prevalence and risk associations. *Pediatr Pulmonol* 2012; **47**: 1026-1033 [PMID: 22628118 DOI: 10.1002/ppul.22554]

12 **Roberts G**, Xatzipsalti M, Borrego LM, Custovic A, Halken S, Hellings PW, Papadopoulos NG, Rotiroti G, Scadding G, Timmermans F, Valovirta E. Paediatric rhinitis: position paper of the European Academy of Allergy and Clinical Immunology. *Allergy* 2013; **68**: 1102-1116 [PMID: 23952296 DOI: 10.1111/all.12235]

13 **Brozek JL**, Bousquet J, Baena-Cagnani CE, Bonini S, Canonica GW, Casale TB, van Wijk RG, Ohta K, Zuberbier T, Schünemann HJ. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. *J Allergy Clin Immunol* 2010; **126**: 466-476 [PMID: 20816182 DOI: 10.1016/j.jaci.2010.06.047]

14 **Rotiroti G**, Roberts G, Scadding GK. Rhinitis in children: common clinical presentations and differential diagnoses. *Pediatr Allergy Immunol* 2015; **26**: 103-110 [PMID: 25616224 DOI: 10.1111/pai.12339]

15 **Chawes BL**. Upper and lower airway pathology in young children with allergic- and non-allergic rhinitis. *Dan Med Bull* 2011; **58**: B4278 [PMID: 21535990]

16 **Kaliner MA**. Nonallergic rhinopathy (formerly known as vasomotor rhinitis). *Immunol Allergy Clin North Am* 2011; **31**: 441-455 [PMID: 21737036 DOI: 10.1016/j.iac.2011.05.007]

17 **Rolla G**, Guida G, Heffler E, Badiu I, Bommarito L, De Stefani A, Usai A, Cosseddu D, Nebiolo F, Bucca C. Diagnostic classification of persistent rhinitis and its relationship to exhaled nitric oxide and asthma: a clinical study of a consecutive series of patients. *Chest* 2007; **131**: 1345-1352 [PMID: 17317733 DOI: 10.1378/chest.06-2618]

18 **Settipane RA**, Lieberman P. Update on nonallergic rhinitis. *Ann Allergy Asthma Immunol* 2001; **86**: 494-507; quiz 507-508 [PMID: 11379801 DOI: 10.1016/S1081-1206(10)62896-7]

19 **Settipane RA**, Charnock DR. Epidemiology of rhinitis: allergic and nonallergic. *Clin Allergy Immunol* 2007; **19**: 23-34 [PMID: 17153005]

20 **Mølgaard E**, Thomsen SF, Lund T, Pedersen L, Nolte H, Backer V. Differences between allergic and nonallergic rhinitis in a large sample of adolescents and adults. *Allergy* 2007; **62**: 1033-1037 [PMID: 17578499 DOI: 10.1111/j.1398-9995.2007.01355.x]

21 **Erwin EA**, Faust RA, Platts-Mills TA, Borish L. Epidemiological analysis of chronic rhinitis in pediatric patients. *Am J Rhinol Allergy* 2011; **25**: 327-332 [PMID: 22186247 DOI: 10.2500/ajra.2011.25.3640]

22 **Bhargava D**, Bhargava K, Al-Abri A, Al-Bassam W, Al-Abri R. Non allergic rhinitis: prevalence, clinical profile and knowledge gaps in literature. *Oman Med J* 2011; **26**: 416-420 [PMID: 22253950 DOI: 10.5001/omj.2011.106]

23 **Togias A**. Nonallergic rhinitis. In: Akdis CA, Hellings PW, Agache I, editors. Spain: Global Atlas of Allergic Rhinitis and Chronic Rhinosinusitis, 2015: 234-236

24 **Kaliner MA**. Classification of Nonallergic Rhinitis Syndromes With a Focus on Vasomotor Rhinitis, Proposed to be Known henceforth as Nonallergic Rhinopathy. *World Allergy Organ J* 2009; **2**: 98-101 [PMID: 24229372 DOI: 10.1097/WOX.0b013e3181a9d55b]

25 **Rondón C**, Campo P, Togias A, Fokkens WJ, Durham SR, Powe DG, Mullol J, Blanca M. Local allergic rhinitis: concept, pathophysiology, and management. *J Allergy Clin Immunol* 2012; **129**: 1460-1467 [PMID: 22516477 DOI: 10.1016/j.jaci.2012.02.032]

26 **Jang TY**, Kim YH. Nasal provocation test is useful for discriminating allergic, nonallergic, and local allergic rhinitis. *Am J Rhinol Allergy* 2015; **29**: e100-e104 [PMID: 26163237 DOI: 10.2500/ajra.2015.29.4214]

27 **Khan DA**. Allergic rhinitis with negative skin tests: does it exist? *Allergy Asthma Proc* 2009; **30**: 465-469 [PMID: 19843399 DOI: 10.2500/aap.2009.30.3265]

28 **Powe DG**, Huskisson RS, Carney AS, Jenkins D, McEuen AR, Walls AF, Jones NS. Mucosal T-cell phenotypes in persistent atopic and nonatopic rhinitis show an association with mast cells. *Allergy* 2004; **59**: 204-212 [PMID: 14763935 DOI: 10.1046/j.1398-9995.2003.00315.x]

29 **Durham SR**, Gould HJ, Hamid QA. Local IgE production in nasal allergy. *Int Arch Allergy Immunol* 1997; **113**: 128-130 [PMID: 9130501 DOI: 10.1159/000237525]

30 **Takhar P**, Smurthwaite L, Coker HA, Fear DJ, Banfield GK, Carr VA, Durham SR, Gould HJ. Allergen drives class switching to IgE in the nasal mucosa in allergic rhinitis. *J Immunol* 2005; **174**: 5024-5032 [PMID: 15814733 DOI: 10.4049/jimmunol.174.8.5024]

31 **Huggins KG**, Brostoff J. Local production of specific IgE antibodies in allergic-rhinitis patients with negative skin tests. *Lancet* 1975; **2**: 148-150 [PMID: 49744 DOI: 10.1016/S0140-6736(75)90056-2]

32 **Powe DG**, Jagger C, Kleinjan A, Carney AS, Jenkins D, Jones NS. 'Entopy': localized mucosal allergic disease in the absence of systemic responses for atopy. *Clin Exp Allergy* 2003; **33**: 1374-1379 [PMID: 14519143 DOI: 10.1046/j.1365-2222.2003.01737.x]

33 **Rondón C**, Romero JJ, López S, Antúnez C, Martín-Casañez E, Torres MJ, Mayorga C, R-Pena R, Blanca M. Local IgE production and positive nasal provocation test in patients with persistent nonallergic rhinitis. *J Allergy Clin Immunol* 2007; **119**: 899-905 [PMID: 17337294 DOI: 10.1016/j.jaci.2007.01.006]

34 **Wise SK**, Ahn CN, Schlosser RJ. Localized immunoglobulin E expression in allergic rhinitis and nasal polyposis. *Curr Opin Otolaryngol Head Neck Surg* 2009; **17**: 216-222 [PMID: 19417663 DOI: 10.1097/MOO.0b013e32832ad23d]

35 **Powe DG**, Jones NS. Local mucosal immunoglobulin E production: does allergy exist in non-allergic rhinitis? *Clin Exp Allergy* 2006; **36**: 1367-1372 [PMID: 17083346 DOI: 10.1111/j.1365-2222.2006.02593.x]

36 **Rondón C**, Campo P, Galindo L, Blanca-López N, Cassinello MS, Rodriguez-Bada JL, Torres MJ, Blanca M. Prevalence and clinical relevance of local allergic rhinitis. *Allergy* 2012; **67**: 1282-1288 [PMID: 22913574 DOI: 10.1111/all.12002]

37 **Sennekamp J**, Joest I, Filipiak-Pittroff B, von Berg A, Berdel D. Local allergic nasal reactions convert to classic systemic allergic reactions: a long-term follow-up. *Int Arch Allergy Immunol* 2015; **166**: 154-160 [PMID: 25871862 DOI: 10.1159/000380852]

38 **Hatzler L**, Hofmaier S, Papadopoulos NG. Allergic airway diseases in childhood - marching from epidemiology to novel concepts of prevention. *Pediatr Allergy Immunol* 2012; **23**: 616-622 [PMID: 23106446 DOI: 10.1111/pai.12022]

39 **Gómez F**, Rondón C, Salas M, Campo P. Local allergic rhinitis: mechanisms, diagnosis and relevance for occupational rhinitis. *Curr Opin Allergy Clin Immunol* 2015; **15**: 111-116 [PMID: 25961385 DOI: 10.1097/ACI.0000000000000150]

40 **De Schryver E**, Devuyst L, Derycke L, Dullaers M, Van Zele T, Bachert C, Gevaert P. Local immunoglobulin e in the nasal mucosa: clinical implications. *Allergy Asthma Immunol Res* 2015; **7**: 321-331 [PMID: 25749769 DOI: 10.4168/aair.2015.7.4.321]

41 **Rondón C**, Campo P, Zambonino MA, Blanca-Lopez N, Torres MJ, Melendez L, Herrera R, Guéant-Rodriguez RM, Guéant JL, Canto G, Blanca M. Follow-up study in local allergic rhinitis shows a consistent entity not evolving to systemic allergic rhinitis. *J Allergy Clin Immunol* 2014; **133**: 1026-1031 [PMID: 24332860 DOI: 10.1016/j.jaci.2013.10.034]

42 **Rondón C**, Campo P, Blanca-López N, Torres MJ, Blanca M. More research is needed for local allergic rhinitis. *Int Arch Allergy Immunol* 2015; **167**: 99-100 [PMID: 26202337 DOI: 10.1159/000436970]

43 **Fuiano N**, Fusilli S, Incorvaia C. A role for measurement of nasal IgE antibodies in diagnosis of Alternaria-induced rhinitis in children. *Allergol Immunopathol* (Madr) 2012; **40**: 71-74 [PMID: 21641712 DOI: 10.1016/j.aller.2011.03.010]

44 **Fuiano N**, Fusilli S, Passalacqua G, Incorvaia C. Allergen-specific immunoglobulin E in the skin and nasal mucosa of symptomatic and asymptomatic children sensitized to aeroallergens. *J Investig Allergol Clin Immunol* 2010; **20**: 425-430 [PMID: 20945610]

45 **Arasi S**, Pajno GB, Lau S, Matricardi PM. Local allergic rhinitis: A critical reappraisal from a paediatric perspective. *Pediatr Allergy Immunol* 2016; **27**: 569-573 [PMID: 27098888 DOI: 10.1111/pai.12577]

46 **Gelardi M**, Russo C, Fiorella ML, Fiorella R, Canonica GW, Passalacqua G. When allergic rhinitis is not only allergic. *Am J Rhinol Allergy* 2009; **23**: 312-315 [PMID: 19490808 DOI: 10.2500/ajra.2009.23.3320]

47 **Canakcioglu S**, Tahamiler R, Saritzali G, Alimoglu Y, Isildak H, Guvenc MG, Acar GO, Inci E. Evaluation of nasal cytology in subjects with chronic rhinitis: a 7-year study. *Am J Otolaryngol* 2009; **30**: 312-317 [PMID: 19720248 DOI: 10.1016/j.amjoto.2008.06.015]

48 **Gelardi M**, Passalacqua G, Fiorella ML, Quaranta N. Assessment of biofilm by nasal cytology in different forms of rhinitis and its functional correlations. *Eur Ann Allergy Clin Immunol* 2013; **45**: 25-29 [PMID: 23678556]

49 **Wang ZY**, Jiang MJ, Zhang Y, Cheng Y, Pang XJ, Xie YQ, Zhong NS, Wang QP, Chen W. Classification of non-allergic rhinitis based on inflammatory characteristics. *Int J Clin Exp Med* 2015; **8**: 17523-17529 [PMID: 26770343]

50 **Baroody FM**. Nonallergic Rhinitis: Mechanism of Action. *Immunol Allergy Clin North Am* 2016; **36**: 279-287 [PMID: 27083102 DOI: 10.1016/j.iac.2015.12.005]

51 **Bernstein JA**, Singh U. Neural Abnormalities in Nonallergic Rhinitis. *Curr Allergy Asthma Rep* 2015; **15**: 18 [PMID: 26130469 DOI: 10.1007/s11882-015-0511-7]

52 **de Corso E**, Battista M, Pandolfini M, Liberati L, Baroni S, Romanello M, Passali GC, Fetoni AR, Sergi B, Di Nardo W, Paludetti G. Role of inflammation in non-allergic rhinitis. *Rhinology* 2014; **52**: 142-149 [PMID: 24932626 DOI: 10.4193/Rhin]

53 **Kavut AB**, Kalpaklıoğlu F, Atasoy P. Contribution of neurogenic and allergic ways to the pathophysiology of nonallergic rhinitis. *Int Arch Allergy Immunol* 2013; **160**: 184-191 [PMID: 23018649 DOI: 10.1159/000339739]

54 **Undem BJ**, Taylor-Clark T. Mechanisms underlying the neuronal-based symptoms of allergy. *J Allergy Clin Immunol* 2014; **133**: 1521-1534 [PMID: 24433703 DOI: 10.1016/j.jaci.2013.11.027]

55 **Van Gerven L**, Boeckxstaens G, Hellings P. Up-date on neuro-immune mechanisms involved in allergic and non-allergic rhinitis. *Rhinology* 2012; **50**: 227-235 [PMID: 22888478 DOI: 10.4193/Rhino11.152]

56 **Lluch-Bernal M**, Dordal MT, Antón E, Campo P, Colás C, Dávila I, Del Cuvillo Bernal A, Fernández-Parra B, González R, González ML, Matheu V, Montoro J, Panizo C, Rondón C, Sánchez MC, Valero A, Vega F, Velázquez E, Navarro A. Nasal Hyperreactivity: Nonspecific Nasal Provocation Tests. Review by the Rhinoconjunctivitis Committee of the Spanish Society of Allergy and Clinical Immunology. *J Investig Allergol Clin Immunol* 2015; **25**: 396-407 [PMID: 26817136]

57 **Scadding GK**, Scadding GW. Diagnosing Allergic Rhinitis. *Immunol Allergy Clin North Am* 2016; **36**: 249-260 [PMID: 27083100 DOI: 10.1016/j.iac.2015.12.003]

58 **Dordal MT**, Lluch-Bernal M, Sánchez MC, Rondón C, Navarro A, Montoro J, Matheu V, Ibáñez MD, Fernández-Parra B, Dávila I, Conde J, Antón E, Colás C, Valero A. Allergen-specific nasal provocation testing: review by the rhinoconjunctivitis committee of the Spanish Society of Allergy and Clinical Immunology. *J Investig Allergol Clin Immunol* 2011; **21**: 1-12; quiz follow 12 [PMID: 21370717]

59 **André RF**, Vuyk HD, Ahmed A, Graamans K, Nolst Trenité GJ. Correlation between subjective and objective evaluation of the nasal airway. A systematic review of the highest level of evidence. *Clin Otolaryngol* 2009; **34**: 518-525 [PMID: 20070760 DOI: 10.1111/j.1749-4486.2009.02042.x]

60 **Priftis KN**, Drigopoulos K, Sakalidou A, Triga M, Kallis V, Nicolaidou P. Subjective and objective nasal obstruction assessment in children with chronic rhinitis. *Int J Pediatr Otorhinolaryngol* 2006; **70**: 501-505 [PMID: 16154642]

61 **Occasi F**, Duse M, Vittori T, Rugiano A, Tancredi G, De Castro G, Indinnimeo L, Zicari AM. Primary school children often underestimate their nasal obstruction. *Rhinology* 2016; **54**: 164-169

[PMID: 26874896 DOI: 10.4193/Rhin15.120]
62 **Zapletal A**, Chalupová J. Nasal airflow and resistance measured by active anterior rhinomanometry in healthy children and adolescents. *Pediatr Pulmonol* 2002; **33**: 174-180 [PMID: 11836796 DOI: 10.1002/ppul.10066]
63 **Clement PA**, Gordts F. Consensus report on acoustic rhinometry and rhinomanometry. *Rhinology* 2005; **43**: 169-179 [PMID: 16218509]
64 **Litvyakova LI**, Baraniuk JN. Human nasal allergen provocation for determination of true allergic rhinitis: methods for clinicians. *Curr Allergy Asthma Rep* 2002; **2**: 194-202 [PMID: 11918860 DOI: 10.1007/s11882-002-0019-9]
65 **Akarcay M**, Miman MC, Erdem T, Oncel S, Ozturan O, Selimoglu E. Comparison of clinical differences between patients with allergic rhinitis and nonallergic rhinitis. *Ear Nose Throat J* 2013; **92**: E1-E6 [PMID: 24057906]
66 **Marcucci F**, Sensi L. A new method for IgE detection in nasal mucosa. *Clin Exp Allergy* 1989; **19**: 157-162 [PMID: 2752318 DOI: 10.1111/j.1365-2222.1989.tb02358.x]
67 **Rondón C**, Doña I, López S, Campo P, Romero JJ, Torres MJ, Mayorga C, Blanca M. Seasonal idiopathic rhinitis with local inflammatory response and specific IgE in absence of systemic response. *Allergy* 2008; **63**: 1352-1358 [PMID: 18782115 DOI: 10.1111/j.1398-9995.2008.01695.x]
68 **Gómez E**, Campo P, Rondón C, Barrionuevo E, Blanca-López N, Torres MJ, Herrera R, Galindo L, Mayorga C, Blanca M. Role of the basophil activation test in the diagnosis of local allergic rhinitis. *J Allergy Clin Immunol* 2013; **132**: 975-6.e1-975-6.e5 [PMID: 24001803 DOI: 10.1016/j.jaci.2013.07.016]
69 **Meltzer EO**, Jalowayski AA. Nasal cytology in clinical practice. *Am J Rhinol* 1988; **2**: 7-54 [DOI: 10.2500/105065888781693212]
70 **Bogaerts PA**, Clement PA. The diagnostic value of a cytogram in rhinopathology. *Rhinology* 1981; **19**: 203-208 [PMID: 7323622]
71 **Gelardi M**, Incorvaia C, Passalacqua G, Quaranta N, Frati F. The classification of allergic rhinitis and its cytological correlate. *Allergy* 2011; **66**: 1624-1625 [PMID: 22029868 DOI: 10.1111/j.1398-9995.2011.02741.x]
72 **Powe DG**, Groot Kormelink T, Sisson M, Blokhuis BJ, Kramer MF, Jones NS, Redegeld FA. Evidence for the involvement of free light chain immunoglobulins in allergic and nonallergic rhinitis. *J Allergy Clin Immunol* 2010; **125**: 139-145.e1-3 [PMID: 19818484 DOI: 10.1016/j.jaci.2009.07.025]
73 **Gelardi M**, Maselli del Giudice A, Fiorella ML, Fiorella R, Russo C, Soleti P, Di Gioacchino M, Ciprandi G. Non-allergic rhinitis with eosinophils and mast cells constitutes a new severe nasal disorder. *Int J Immunopathol Pharmacol* 2008; **21**: 325-331 [PMID: 18547476]
74 **Becker S**, Rasp J, Eder K, Berghaus A, Kramer MF, Gröger M. Non-allergic rhinitis with eosinophilia syndrome is not associated with local production of specific IgE in nasal mucosa. *Eur Arch Otorhinolaryngol* 2016; **273**: 1469-1475 [PMID: 26342925 DOI: 10.1007/s00405-015-3769-4]
75 **Maselli Del Giudice A**, Barbara M, Russo GM, Fiocca Matthews E, Cassano M. Cell-mediated non-allergic rhinitis in children. *Int J Pediatr Otorhinolaryngol* 2012; **76**: 1741-1745 [PMID: 22939589 DOI: 10.1016/j.ijporl.2012.08.013]
76 **Gelardi M**, Luigi Marseglia G, Licari A, Landi M, Dell'Albani I, Incorvaia C, Frati F, Quaranta N. Nasal cytology in children: recent advances. *Ital J Pediatr* 2012; **38**: 51 [PMID: 23009215 DOI: 10.1186/1824-7288-38-51]
77 **Gelardi M**, Iannuzzi L, Quaranta N, Landi M, Passalacqua G. NASAL cytology: practical aspects and clinical relevance. *Clin Exp Allergy* 2016; **46**: 785-792 [PMID: 27009397 DOI: 10.1111/cea.12730]
78 **Shusterman D**. Nonallergic Rhinitis: Environmental Determinants. *Immunol Allergy Clin North Am* 2016; **36**: 379-399 [PMID: 27083110 DOI: 10.1016/j.iac.2015.12.013]
79 **Pacini S**, Giovannelli L, Gulisano M, Peruzzi B, Polli G, Boddi V, Ruggiero M, Bozzo C, Stomeo F, Fenu G, Pezzatini S, Pitozzi V, Dolara P. Association between atmospheric ozone levels and damage to human nasal mucosa in Florence, Italy. *Environ Mol Mutagen* 2003; **42**: 127-135 [PMID: 14556220 DOI: 10.1002/em.10188]
80 **Marseglia GL**, Avanzini MA, Caimmi S, Caimmi D, Marseglia A, Valsecchi C, Poddighe D, Ciprandi G, Pagella F, Klersy C, Castellazzi AM. Passive exposure to smoke results in defective interferon-gamma production by adenoids in children with recurrent respiratory infections. *J Interferon Cytokine Res* 2009; **29**: 427-432 [PMID: 19514840 DOI: 10.1089/jir.2008.0108]
81 **Kopp MV**, Ulmer C, Ihorst G, Seydewitz HH, Frischer T, Forster J, Kuehr J. Upper airway inflammation in children exposed to ambient ozone and potential signs of adaptation. *Eur Respir J* 1999; **14**: 854-861 [PMID: 10573233 DOI: 10.1034/j.1399-3003.1999.14d22.x]
82 **Nikasinovic L**, Just J, Sahraoui F, Seta N, Grimfeld A, Momas I. Nasal inflammation and personal exposure to fine particles PM2.5 in asthmatic children. *J Allergy Clin Immunol* 2006; **117**: 1382-1388 [PMID: 16751001 DOI: 10.1016/j.jaci.2006.03.023]
83 **Higgins TS**, Reh DD. Environmental pollutants and allergic rhinitis. *Curr Opin Otolaryngol Head Neck Surg* 2012; **20**: 209-214 [PMID: 22487789 DOI: 10.1097/MOO.0b013e3283534821]
84 **Kim BJ**, Hong SJ. Ambient air pollution and allergic diseases in children. *Korean J Pediatr* 2012; **55**: 185-192 [PMID: 22745642 DOI: 10.3345/kjp.2012.55.6.185]
85 **Gelardi M**. "Overlapped" rhinitis: a real trap for rhinoallergologists. *Eur Ann Allergy Clin Immunol* 2014; **46**: 234-236 [PMID: 25398169]
86 **Gelardi M**, Iannuzzi L, Tafuri S, Passalacqua G, Quaranta N. Allergic and non-allergic rhinitis: relationship with nasal polyposis, asthma and family history. *Acta Otorhinolaryngol Ital* 2014; **34**: 36-41 [PMID: 24711681]
87 **Benninger M**, Farrar JR, Blaiss M, Chipps B, Ferguson B, Krouse J, Marple B, Storms W, Kaliner M. Evaluating approved medications to treat allergic rhinitis in the United States: an evidence-based review of efficacy for nasal symptoms by class. *Ann Allergy Asthma Immunol* 2010; **104**: 13-29 [PMID: 20143641 DOI: 10.1016/j.anai.2009.11.020]
88 **Morjaria JB**, Caruso M, Rosalia E, Russo C, Polosa R. Preventing progression of allergic rhinitis to asthma. *Curr Allergy Asthma Rep* 2014; **14**: 412 [PMID: 24408536 DOI: 10.1007/s11882-013-0412-6]
89 **Kim JM**, Lin SY, Suarez-Cuervo C, Chelladurai Y, Ramanathan M, Segal JB, Erekosima N. Allergen-specific immunotherapy for pediatric asthma and rhinoconjunctivitis: a systematic review. *Pediatrics* 2013; **131**: 1155-1167 [PMID: 23650298 DOI: 10.1542/peds.2013-0343]
90 **Marseglia GL**, Incorvaia C, La Rosa M, Frati F, Marcucci F. Sublingual immunotherapy in children: facts and needs. *Ital J Pediatr* 2009; **35**: 31 [PMID: 19852795 DOI: 10.1186/1824-7288-35-31]
91 **Pleskovic N**, Bartholow A, Skoner DP. Sublingual immunotherapy in children: the recent experiences. *Curr Opin Allergy Clin Immunol* 2014; **14**: 582-590 [PMID: 25188717 DOI: 10.1097/ACI.0000000000000112]
92 **Licari A**, Castagnoli R, Bottino C, Marseglia A, Marseglia G, Ciprandi G. Emerging drugs for the treatment of perennial allergic rhinitis. *Expert Opin Emerg Drugs* 2016; **21**: 57-67 [PMID: 26733401 DOI: 10.1517/14728214.2016.1139082]
93 **Ciprandi G**, Marseglia GL, Castagnoli R, Valsecchi C, Tagliacarne C, Caimmi S, Licari A. From IgE to clinical trials of allergic rhinitis. *Expert Rev Clin Immunol* 2015; **11**: 1321-1333 [PMID: 26358006 DOI: 10.1586/1744666X.2015.1086645]
94 **Poddighe D**, Licari A, Caimmi S, Marseglia GL. Sublingual immunotherapy for pediatric allergic rhinitis: The clinical evidence. *World J Clin Pediatr* 2016; **5**: 47-56 [PMID: 26862501 DOI: 10.5409/wjcp.v5.i1.47]
95 **Licari A**, Marseglia A, Caimmi S, Ricci A, Rundo B, Poddighe D, Verrotti A, Marseglia GL. EMERGING AND FUTURE THERAPIES FOR ALLERGIC RHINITIS. *J Biol Regul Homeost Agents* 2015; **29**: 38-46 [PMID: 26634586]
96 **Marogna M**, Massolo A, Colombo F, Isella P, Bruno M, Falagiani P. Children passive smoking jeopardises the efficacy of standard anti-allergic pharmacological therapy, while sublingual immunotherapy withstands. *Allergol Immunopathol* (Madr) 2011; **39**: 60-67 [PMID: 21216083 DOI: 10.1016/j.aller.2010.05.002]

97 **Rondón C**, Blanca-López N, Aranda A, Herrera R, Rodriguez-Bada JL, Canto G, Mayorga C, Torres MJ, Campo P, Blanca M. Local allergic rhinitis: allergen tolerance and immunologic changes after preseasonal immunotherapy with grass pollen. *J Allergy Clin Immunol* 2011; **127**: 1069-1071 [PMID: 21277626 DOI: 10.1016/j.jaci.2010.12.013]

98 **Lieberman PL**, Smith P. Nonallergic Rhinitis: Treatment. *Immunol Allergy Clin North Am* 2016; **36**: 305-319 [PMID: 27083104 DOI: 10.1016/j.iac.2015.12.007]

99 **Banov CH**, Lieberman P. Efficacy of azelastine nasal spray in the treatment of vasomotor (perennial nonallergic) rhinitis. *Ann Allergy Asthma Immunol* 2001; **86**: 28-35 [PMID: 11206234 DOI: 10.1016/S1081-1206(10)62352-6]

100 **Lieberman PL**, Settipane RA. Azelastine nasal spray: a review of pharmacology and clinical efficacy in allergic and nonallergic rhinitis. *Allergy Asthma Proc* 2003; **24**: 95-105 [PMID: 12776442]

101 **Price D**, Shah S, Bhatia S, Bachert C, Berger W, Bousquet J, Carr W, Hellings P, Munzel U, Scadding G, Lieberman P. A new therapy (MP29-02) is effective for the long-term treatment of chronic rhinitis. *J Investig Allergol Clin Immunol* 2013; **23**: 495-503 [PMID: 24654314]

102 **Carr W**, Bernstein J, Lieberman P, Meltzer E, Bachert C, Price D, Munzel U, Bousquet J. A novel intranasal therapy of azelastine with fluticasone for the treatment of allergic rhinitis. *J Allergy Clin Immunol* 2012; **129**: 1282-1289.e10 [PMID: 22418065 DOI: 10.1016/j.jaci.2012.01.077]

103 **Greiner AN**, Meltzer EO. Overview of the treatment of allergic rhinitis and nonallergic rhinopathy. *Proc Am Thorac Soc* 2011; **8**: 121-131 [PMID: 21364230 DOI: 10.1513/pats.201004-033RN]

104 **Kim KT**, Kerwin E, Landwehr L, Bernstein JA, Bruner D, Harris D, Drda K, Wanger J, Wood CC. Use of 0.06% ipratropium bromide nasal spray in children aged 2 to 5 years with rhinorrhea due to a common cold or allergies. *Ann Allergy Asthma Immunol* 2005; **94**: 73-79 [PMID: 15702820 DOI: 10.1016/S1081-1206(10)61289-6]

105 **Chirico G**, Quartarone G, Mallefet P. Nasal congestion in infants and children: a literature review on efficacy and safety of non-pharmacological treatments. *Minerva Pediatr* 2014; **66**: 549-557 [PMID: 25336097]

106 **Gevorgyan A**, Segboer C, Gorissen R, van Drunen CM, Fokkens W. Capsaicin for non-allergic rhinitis. *Cochrane Database Syst Rev* 2015; **(7)**: CD010591 [PMID: 26171907 DOI: 10.1002/14651858.CD010591]

P- Reviewer: Ciuman R, Murdaca G, Unal M **S- Editor**: Qiu S
L- Editor: A **E- Editor**: Lu YJ

World Journal of Methodology

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Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5662/wjm.v6.i4.214

World J Methodol 2016 December 26; 6(4): 214-219
ISSN 2222-0682 (online)

ORIGINAL ARTICLE

Clinical Trials Study

Radiological clinical trials: Proposal of a problem-finding questionnaire to improve study success

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Institutional review board statement: All studies included in this work were already approved by the respective Ethical Committee.

Clinical trial registration statement: The ASTOUND study is registered at https://clinicaltrials.gov/ct2/show/NCT02066142, and the registration identification number is NCT02066142; the TAM01 study is registered at https://clinicaltrials.gov/ct2/show/NCT01357772?term=tam01&rank=1, and the registration identification number is NCT01357772.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: None declared.

Data sharing statement: No additional data are available.

Manuscript source: Invited manuscript

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Received: May 30, 2016
Peer-review started: June 2, 2016
First decision: July 5, 2016
Revised: November 28, 2016
Accepted: December 1, 2016
Article in press: December 1, 2016
Published online: December 26, 2016

Abstract

AIM

To develop a survey to help define the main problems in radiological clinical trials.

METHODS

Since 2006, we have managed seven different radiological clinical trials recruiting patients in academic and non-academic centres. We developed a preliminary questionnaire using a four-round Delphi approach to identify problems occurring in radiological clinical trials run at our centre. We investigated the recruitment experience, involvement of all multi-disciplinary team members and main obstacles to completing the projects. A final round of Delphi processes elucidated solutions to the identified problems.

RESULTS

Among 19/20 (95%) respondents, 10 (53%) were young physicians (under 35 years old), and the respondents included non-faculty members, fellows, residents, and undergraduate students. Ninety-four percent (18/19) of respondents showed interest in conducting clinical trials. On a scale of 1 to 10, the problems with higher/worse scores (8-9) were related to technical or communication problems. The most frequent problems across all studies were technical problems related to clinical trial equipment, insufficient willingness to participate, obstacles to understanding the design of electronic-case report form and extra work.

CONCLUSION

The developed questionnaire identified the main recurring problems in radiological clinical trials as perceived by end-users and helped define possible solutions that are mostly related to having dedicated clinical trial research staff.

Key words: Clinical trials; Data management; Magnetic resonance imaging; Mammography; Ultrasonography

Core tip: Clinical data management (CDM) is important for efficiently managing and completing a clinical trial. CDM is the process of controlling, processing, validating and querying data generated in a clinical study. In this paper, we developed a questionnaire identifying the main recurring obstacles in radiological clinical trials as perceived by end-users. We tried to define possible solutions that are mostly related to having dedicated clinical trial research staff. This topic is relatively well-known by clinicians, while it is less well-known by radiologists and could be useful for radiological centres that are currently involved or will be involved in conducting or participating in radiological clinical trials. For this reason, we suggested a problem-solving questionnaire and reported our experience in managing seven multi-centre national and international radiological clinical trials.

Valdora F, Bignotti B, Calabrese M, Houssami N, Tagliafico A. Radiological clinical trials: Proposal of a problem-finding questionnaire to improve study success. *World J Methodol* 2016; 6(4): 214-219 Available from: URL: http://www.wjgnet.com/2222-0682/full/v6/i4/214.htm DOI: http://dx.doi.org/10.5662/wjm.v6.i4.214

INTRODUCTION

Clinical data management (CDM) is important for efficiently managing and completing a clinical trial. CDM is the process of controlling, processing, validating and querying data generated in a clinical study. Recommendations indicate that a specialized research unit may be useful for conducting clinical trials[1-3]. As indicated by Farrell *et al*[3], the success of a clinical trial depends on the presence of an efficient trial team consisting of various experts with different roles and responsibilities. In addition, it is important to have the resources to manage the study workflow stages, as defined by the coordinating centre. The presence of a dedicated trial manager is also important to collecting high-quality clinical data in healthcare studies. Indeed, the collection of poor quality data or the collection of a lower level of data than expected may contribute to underpowered, inconclusive or misleading results.

A good study design and efficient CDM Plan (CDMP) are important for taking full advantage of research project budgets, especially in multi-centre and international collaborative trials. The essential components of a CDMP include the following: Details of study personnel involved in the study and data access roles assigned to each, database design and database location, data entry procedure, methods of data collection - paper or electronic-case report form (e-CRF), data preparation before entry into the electronic system, and data flow and tracking to ensure optimal data completion and facilitate reporting.

The efficiency of the CDMP is crucial to optimizing patient recruitment and follow-up, increasing the percentage of completed e-CRFs, and using processes ensuring that high-quality data are collected with minimal or no missing data. As recently reported[4-6], investigators conducting randomized controlled trials (RCTs) use different strategies to avoid biases in data collection. However, many trials do not recruit sufficient participants, limiting the use of research results and translation of research findings into practice[7-9]. Additionally, an audit is necessary to regularly monitor the randomization process[10,11]. Standardized procedures are necessary to handle errors or problems in the randomization process and data acquisition, which is crucial to the overall trial quality.

The medical literature lacks a structured description of the main problems affecting clinical trials that specifically deal with imaging and are led by a radiological unit[12]. Imaging in research is increasingly involved. The use of imaging data in clinical research can provide many scientific benefits, but it can result in additional complexities that contribute to risks, biases and errors[13]. As indicated by Erickson *et al*[14], the use of imaging data in clinical trials may be a part of the solution for reducing the cost and increasing the efficiency to conduct a timely clinical trial. A frequent problem with a radiological clinical trial consists of the quality of the clinical trial data; multi-centre clinical trials need reproducible, quality assured data with post-processing methods supported by an operational infrastructure.

In the hospital, the medical subject's imaging data are managed in the clinical picture archiving and communication system (PACS) *via* the digital imaging and communications in medicine (DICOM) protocol. Clinical PACS could be separate from the research PACS.

PACS is extremely limited in its support for research imaging. The system is DICO-centric and generally does

not support the alternative file formats used in research. It is essential to guarantee the high quality of the entire process that images for clinical trials are collected using uniform image acquisition and measurement methods to minimize the variability.

To address this knowledge gap, we performed a survey-based study to identify the main problems in conducting radiological clinical trials and to help find solutions, including roles for staff dedicated to ongoing radiological clinical trials. The aim of this study was to identify potential barriers to conducting clinical trials in imaging.

This work is a pilot study. The survey was performed as an internal questionnaire survey at our centre, which is involved in several multi-centre clinical trials, and the preliminary results could help all centres involved in radiological clinical trials find solutions to the main problems and improve the progress and outcomes of future radiological clinical trials.

MATERIALS AND METHODS

Clinical trials

Data for this study were derived from staff involved in seven different radiological national and international multi-centre clinical trials employing cancer imaging. The clinical trials are listed as indicated in the Supplementary Information. The first study was performed in 2006 and the most recent in 2015[15-18].

All studies included in this work were already approved by the respective Ethical Committee and all participants signed a written informed consent form before enrolment. The studies were performed according to the principles outlined in the Declaration of Helsinki.

The studies codified as ASTOUND[15], Tomo-micro[16], BP-US[17] and BP-MRI[18] in the Supplementary Information were already published.

Development of the survey

The survey was developed using a 4-step consensus approach by the Delphi method[19,20]. The personnel of the University Hospital and all teams that participated in the seven radiological trials were invited to respond to the survey and participate in the Delphi method. The Delphi method is based on the premise that collective beliefs are more trustworthy than the beliefs of a single person; therefore, it is considered an efficient procedure to generate thematic knowledge[20]. By this method, opinions, expertise and critical thinking are systematized. Individual feedback on a topic, the judgment of the group's work, and opportunities to change opinion were given in an anonymous form[19]. The questionnaire focused on the key issues identified by the personnel directly involved in the trials to reduce the influence of department chairs.

The first step consisted of a review of the existing literature up to July 2015 and the development of the first draft of the survey. The subsequent three steps each included a Delphi round to develop the final survey. A series of discussions (face-to-face meeting and e-mails) among the participants was performed. The survey investigated several stages of clinical trials, including the recruitment experience, effective involvement of all multi-disciplinary teams (MDTs), the main obstacles faced in clinical trials, and the background of each team member. After the survey, critical issues were identified and summarized; then, possible solutions were suggested by the same Delphi method.

The questionnaire consisted of 12 items that were written in English, as indicated in Supplementary Figure 1.

We have classified each issue of the survey given to the participants with a score of 0 to 10 (1 = no problems observed, 10 = several problems can negatively affect the results and induce the participants to quit). The characteristics are listed in Table 1.

Survey participants

The survey involved investigators who were participants belonging to the MDT, including personnel of the University Hospital and of all teams who took part in the seven radiological trials as described above. They were asked to complete the questionnaire, highlighting the main problems faced during clinical trials.

The survey was sent to all clinical team members, including the principal investigators (PIs), research nurses, nursing staff, and technicians. The anonymous questionnaire had to be returned to the identified PI's delegate to record the responses, as normally done in a Delphi process. We performed further rounds of Delphi processes to solve all encountered difficulties.

Statistical analysis

The mean experience of team members in radiological clinical trials as well as the percentage of questionnaires returned was recorded. Group agreement with the clinical condition under consideration was defined as total cumulative agreement > 67% after the second or third Delphi round. Group consensus was defined if the consensus level of agreement (CLA) was > 90% for each issue of the survey. The results are presented as the total cumulative agreement after the last Delphi round by a four-point simplified Likert scale (agree, agree with minor reservation, agree with major reservation, and disagree).

RESULTS

Characteristics of survey participants

Nineteen of 20 team members (95%) returned the questionnaires. Ten of nineteen of survey participants were young physicians and non-faculty members (fellows, resident and undergraduate students). The other members (9/19) were staff-doctors, principal investigators, and co-investigators. Additionally, 18/19 of respondents showed interest in conducting clinical trials. Among these, a large proportion of physicians with previous clinical trial experience (14/18) and many residents, data managers, and nurses without clinical trial experience expressed high interest in conducting clinical trials. Only one participant

Table 1 List of main issues and problems identified when conducting clinical trials[1]

Problem	Score (mean ± SD) among respondents	Effect on clinical trial conduction	Suggested solution	No. of surveys scored from 19 completed surveys
Principal investigator	9 ± 0.5	Lack of team consistency and participation	The principal investigator should be PERSONALLY involved and have a pro-active approach to the study	15/19
Administrative impediments (ethics committee, insurance) affect the beginning of clinical trials	6 ± 0.37	Delay in starting the study	Employ a coordinator from administrative staff with no clinical burden	13/19
Technical problems with instruments used in the study	6 ± 0.62	Delay in conducting the study	Identify a key person to regularly check instrumentation	12/19
Insufficient willingness to be part of a team and to collaborate in the trial	7 ± 0.41	Lack of interest and enthusiasm and inability to progress or finish in time	Organise frequent investigator meetings, conference calls and study checks	15/19
Slightly different clinical practices of the involved centres	7 ± 0.42	Risk of missing or non-standardized data	Discuss and standardize practical, methodological data-related aspects of the study	14/19
Difficulties to complete a complex e-CRF	7 ± 0.46	Incomplete e-CFR and missing data	Simplify the e-CRF	17/19
Perform quantitative evaluations	8 ± 0.38	Delay in quantitative radiological data acquisition	Have dedicated trained personnel and workstations	18/19
Extra work required to comply with study inclusion criteria	9 ± 0.32	Loss of patients potentially eligible for the study	Check inclusion criteria in advance by available patient data review	18/19

[1]The score system ranges from 1 (no problem) to 10 (serious problem). e-CRF: Electronic-case report form.

was involved in a clinical trial that had terminated before the completion of the present survey.

Main problems encountered

The main barriers faced in conducting a radiological clinical trial (with a score of 8-9) were the time commitment to perform quantitative evaluations of radiological exams that are already reported and the extra work required to comply with the clinical trial's inclusion criteria. A score of 6, reflecting a significant but not severe problem, was the need to deal with administrative impediments, such as the need to prepare all the documents for the local ethics committee and insurances for research studies. Indeed, these problems can delay the beginning of the radiological clinical trial. A low score of 6 was also due to a technical problem with the instruments (for example, new software applications) needed in a study and the lack of organized support from the hospital facilities. A score of 7 indicated a possible lack of interest to conduct the clinical trial and several difficulties to complete the e-CRF. From participating in multinational clinical trials, 15/19 of respondents assigned a score of 8 or 9 for the PI, indicating that the role of the PI is crucial to conducting a radiological clinical trial. After problem identification, possible solutions suggested from the final Delphi round are reported in Table 1.

DISCUSSION

Clinical trials have rapidly evolved during the past decade. As we discussed above, radiological clinical trials can be affected by different types of bias concerning imaging technology and recruitment strategies. Bias can result from differences in the methods in which information is collected or in the manner in which data are obtained during the recruitment process. In the past, radiologists have had limited direct patient interaction and have depended on other specialists to refer patients for enrolment; in this way, inadequate approaches to patient recruitment could introduce bias. The main strategies for recruitment were flyer distribution, brochure pick-up, internet posting-ads or poster distributions without direct patient contact. Current technology has allowed us to take a different approach, directly interact with the patients, and monitor the follow-up or response.

In this work, we developed a preliminary survey to elucidate knowledge on obstacles or problems in running radiological clinical trials from all participating in various radiological studies at our centre, and we hoped that the acquired information could improve the conduct of radiological clinical trials. We observed that several obstacles (related to administrative, technical/equipment, or resourcing issues) could hamper the development of relatively feasible radiological clinical trials. Using the same survey-based/Delphi process, we also sought to define possible solutions to the main problems that had to be overcome during several radiological clinical trials.

We tried to differentiate serious problems from less serious or minor problems. It is not surprising that the majority of problems that received a high score were related to the lack of resourcing and, specifically, to the lack of dedicated research personnel without a clinical

burden. Indeed, busy daily radiological clinical practices have limited time for the additional work generated by conducting or contributing to a clinical trial. In our survey, the highest scores ("bigger problems") were assigned to issues that typically go well beyond the radiological report, such as performing a quantitative evaluation on radiological images as part of the research protocol, or becoming familiar, and complying with the study inclusion criteria (patient eligibility). Indeed, for prospective trials, respecting the inclusion criteria of the study is crucial for several reasons, such as reaching the required number of patients and collecting reliable and unbiased data. Consequently, the suggestion given by the last Delphi round was to have dedicated clinical trial personnel who are not involved in the clinical routine undertake the role of checking and ensuring compliance with the inclusion criteria.

In larger multicentre studies requiring that data are gathered from different centres, even minor differences in the population, culture, nomenclature and medical practice can be causes of variability. As indicated by Willis-Shattuck *et al*[21] in a systematic review facing the issues related to recruitment in developing countries, the authors reviewed all studies investigating the link between motivation and retention of health workers in developing countries. The authors concluded that motivational factors are influenced by the context, and the successful completion of a study depends on the number of available resources.

It is commonly thought that the public health sectors of many countries suffer from a surplus of workers who are not particularly productive because they have not received adequate training. In fact, a survey presented at RSNA 2013 by Rehani *et al*[22] confirms that radiologists in developing countries need an accurate training program.

Indeed, in a single country, multi-centre trial, there can be variability and bias, but some of the possible sources of bias can be controlled with an appropriate trial design. An important result of our survey is that standardized trial planning and the identification of a key figure managing several phases of a radiological clinical trial is very important for ensuring a timely start and correct development of the trial.

Through our experience of being involved in seven different studies on cancer imaging and collaborating with several research groups from different contexts, we investigated how many problems can arise when developing clinical studies. Unfortunately, we did not evaluate the hospital due to a lack of funding.

We found it very useful to monitor monthly enrolment progress by site and permit sites to compare and discuss their progress. We organized collaborative workshops with all investigators from the included studies for all periods of the studies. These meetings were valuable to discuss practical, methodological and data-related aspects of each original study and to build trust among investigators. During these workshops, we discussed and refined the study protocol in advance, examined patient characteristics and information from diagnostic tests that are to be analysed, and agreed on data checking procedures and the main analyses to be performed.

In conclusion, this study could be a valuable preliminary survey that can elucidate the critical key points identified in radiological clinical trials. Obviously, this study does not solve all problems that a radiologist could face during a clinical trial. However, the main problems in oncology clinical trials or in imaging are not very different, and they are in common with what has previously been described as essential to successfully concluding a clinical trial. It is important to identify the crucial role of key people who are capable of connecting different expertise levels and responsibilities. Indeed, each person involved in conducting a trial should be instructed and qualified to tailor his or her respective task(s), taking advantage of previous cultural backgrounds. Our problem-solving approach may improve the organization of radiological clinical trials, especially in non-academic centres.

ACKNOWLEDGMENTS

The authors are very grateful to all our dedicated study staff (technicians and research personnel) for their enthusiasm, recruitment, assistance and retention efforts.

COMMENTS

Background

Clinical data management (CDM) is the process of controlling, processing, validating and querying data generated in a clinical study. Recommendations indicate that a specialized research unit may be useful for conducting clinical trials. The presence of a dedicated trial manager is important for collecting high-quality clinical data in healthcare studies. Indeed, the collection of poor quality data or of a lower level of data than expected may result in underpowered, inconclusive or misleading results. The essential components of a CDM plan (CDMP) include: Details of study personnel involved in the study and data access roles assigned to each, database design and database location, data entry procedures, methods of data collection - paper or e-CRF, data preparation before entry onto electronic system, and data flow and tracking to ensure optimal data completion and facilitate reporting.

Research frontiers

The efficiency of the CDMP is crucial to optimizing patient recruitment and follow-up, increasing the percentage of completed electronic-case report forms, and using processes ensuring that high-quality data are collected with minimal or no missing data. Usually, investigators conducting randomized controlled trials employ different strategies to avoid biases in data collection. Standardized procedures are necessary to handle errors or problems in the randomization process and data acquisition, which is crucial to the overall quality of the trial.

Innovations and breakthroughs

A good study design and an efficient CDMP are important for taking full advantage of research project budgets, especially in multi-centre and international collaborative trials. The information from this study might allow all centres involved in radiological clinical trials to find solutions to the main problems as well as help improve the progress and outcomes of future radiological clinical trials.

Applications

The medical literature lacks a structured description of the main problems that affect clinical trials specifically dealing with imaging in a radiological unit. The aim of this study was to identify potential barriers to conducting clinical trials in imaging.

Peer-review

The authors investigated problems faced when conducting clinical trials. This work clarified the issues for improving the efficiency of clinical research.

REFERENCES

1 **Cataliotti L**, De Wolf C, Holland R, Marotti L, Perry N, Redmond K, Rosselli Del Turco M, Rijken H, Kearney N, Ellis IO, Di Leo A, Orecchia R, Noel A, Andersson M, Audretsch W, Bjurstam N, Blamey RW, Blichert-Toft M, Bosmans H, Burch A, Bussolati G, Christiaens MR, Colleoni M, Cserni G, Cufer T, Cush S, Damilakis J, Drijkoningen M, Ellis P, Foubert J, Gambaccini M, Gentile E, Guedea F, Hendriks J, Jakesz R, Jassem J, Jereczek-Fossa BA, Laird O, Lartigau E, Mattheiem W, O'higgins N, Pennery E, Rainsbury D, Rutgers E, Smola M, Van Limbergen E, von Smitten K, Wells C, Wilson R. Guidelines on the standards for the training of specialised health professionals dealing with breast cancer. *Eur J Cancer* 2007; **43**: 660-675 [PMID: 17276672 DOI: 10.1016/j.ejca.2006.12.008]

2 **Wilson AR**, Marotti L, Bianchi S, Biganzoli L, Claassen S, Decker T, Frigerio A, Goldhirsch A, Gustafsson EG, Mansel RE, Orecchia R, Ponti A, Poortmans P, Regitnig P, Rosselli Del Turco M, Rutgers EJ, van Asperen C, Wells CA, Wengström Y, Cataliotti L. The requirements of a specialist Breast Centre. *Eur J Cancer* 2013; **49**: 3579-3587 [PMID: 23968730 DOI: 10.1016/j.ejca.2013.07.017]

3 **Farrell B**, Kenyon S, Shakur H. Managing clinical trials. *Trials* 2010; **11**: 78 [PMID: 20626885 DOI: 10.1186/1745-6215-11-78]

4 **Brueton VC**, Tierney JF, Stenning S, Meredith S, Harding S, Nazareth I, Rait G. Strategies to improve retention in randomised trials: a Cochrane systematic review and meta-analysis. *BMJ Open* 2014; **4**: e003821 [PMID: 24496696 DOI: 10.1136/bmjopen-2013-003821]

5 **Treweek S**, Lockhart P, Pitkethly M, Cook JA, Kjeldstrøm M, Johansen M, Taskila TK, Sullivan FM, Wilson S, Jackson C, Jones R, Mitchell ED. Methods to improve recruitment to randomised controlled trials: Cochrane systematic review and meta-analysis. *BMJ Open* 2013; **3**: e002360 [PMID: 23396504 DOI: 10.1136/bmjopen-2012-002360]

6 **Singhal R**, Rana R. Intricacy of missing data in clinical trials: Deterrence and management. *Int J Appl Basic Med Res* 2014; **4**: S2-S5 [PMID: 25298936 DOI: 10.4103/2229-516X.140706]

7 **Krishnankutty B**, Bellary S, Kumar NB, Moodahadu LS. Data management in clinical research: An overview. *Indian J Pharmacol* 2012; **44**: 168-172 [PMID: 22529469 DOI: 10.4103/0253-7613.93842]

8 **Lu Z**, Su J. Clinical data management: Current status, challenges, and future directions from industry perspectives. *Open Access J Clinical Trials* 2010; **2**: 93-105 [DOI: 10.2147/OAJCT.S8172]

9 **Kang M**, Ragan BG, Park JH. Issues in outcomes research: an overview of randomization techniques for clinical trials. *J Athl Train* 2008; **43**: 215-221 [PMID: 18345348 DOI: 10.4085/1062-6050-43.2.215]

10 **Richard C**, Bruce YL. Principles and Practice of clinical trial Medicine. London: Elsevier, 2008

11 **Mihojlovic-Madzarevic V**. Clinical trials audit preparation: a guide for Good Clinical Practice (GCP) Inspections. USA: John Wiley & Sons, Inc, 2010 [DOI: 10.1002/9780470572757]

12 **Grand MM**, O'Brien PC. Obstacles to participation in randomised cancer clinical trials: a systematic review of the literature. *J Med Imaging Radiat Oncol* 2012; **56**: 31-39 [PMID: 22339743 DOI: 10.1111/j.1754-9485.2011.02337.x]

13 **Erickson BJ**, Pan T, Marcus DS, CTSA Imaging Project Group. Whitepapers on Imaging Infrastructure for Research. Part 1: General workflow considerations. *J Digit Imaging* 2012; **25**: 449-453 [DOI: 10.1007/s10278-012-9490-6]

14 **Erickson BJ**, Buckner JC. Imaging in clinical trials. *Cancer Inform* 2007; **4**: 13-18 [PMID: 19390660]

15 **Tagliafico AS**, Calabrese M, Mariscotti G, Durando M, Tosto S, Monetti F, Airaldi S, Bignotti B, Nori J, Bagni A, Signori A, Sormani MP, Houssami N. Adjunct Screening With Tomosynthesis or Ultrasound in Women With Mammography-Negative Dense Breasts: Interim Report of a Prospective Comparative Trial. *J Clin Oncol* 2016 Mar 9; Epub ahead of print [PMID: 26962097 DOI: 10.1200/JCO.2015.63.4147]

16 **Tagliafico A**, Mariscotti G, Durando M, Stevanin C, Tagliafico G, Martino L, Bignotti B, Calabrese M, Houssami N. Characterisation of microcalcification clusters on 2D digital mammography (FFDM) and digital breast tomosynthesis (DBT): does DBT underestimate microcalcification clusters? Results of a multicentre study. *Eur Radiol* 2015; **25**: 9-14 [PMID: 25163902 DOI: 10.1007/s00330-014-3402-8]

17 **Tagliafico A**, Succio G, Serafini G, Martinoli C. Diagnostic performance of ultrasound in patients with suspected brachial plexus lesions in adults: a multicenter retrospective study with MRI, surgical findings and clinical follow-up as reference standard. *Skeletal Radiol* 2013; **42**: 371-376 [PMID: 22707095 DOI: 10.1007/s00256-012-1471-9]

18 **Tagliafico A**, Succio G, Serafini G, Martinoli C. Diagnostic accuracy of MRI in adults with suspect brachial plexus lesions: a multicentre retrospective study with surgical findings and clinical follow-up as reference standard. *Eur J Radiol* 2012; **81**: 2666-2672 [PMID: 22071340 DOI: 10.1016/j.ejrad.2011.10.007]

19 **Steurer J**. The Delphi method: an efficient procedure to generate knowledge. *Skeletal Radiol* 2011; **40**: 959-961 [PMID: 21667147 DOI: 10.1007/s00256-011-1145-z]

20 **Jones J**, Hunter D. Consensus methods for medical and health services research. *BMJ* 1995; **311**: 376-380 [PMID: 7640549 DOI: 10.1136/bmj.311.7001.376]

21 **Willis-Shattuck M**, Bidwell P, Thomas S, Wyness L, Blaauw D, Ditlopo P. Motivation and retention of health workers in developing countries: a systematic review. *BMC Health Serv Res* 2008; **8**: 247 [PMID: 19055827 DOI: 10.1186/1472-6963-8-247]

22 **Rehani B**, Schaefer P, Gonzalez R, Shah V, Romero J, Rapalino O, Rosman D, Choy G. Making Imaging around the World Better: Global Survey of Radiologists in 10 Countries. Prsented at Radiological Society of North America 2013 Scientific Assembly and Annual Meeting, December 1 - December 6, 2013, Chicago IL. [accessed 2016 Jul 26]. Available from: URL: http://archive.rsna.org/2013/13027448.html

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