



# The acceptability and tolerability of nasal douching in children with allergic rhinitis: A systematic review



Nelson Gutiérrez-Cardona<sup>a,\*</sup>, Paula Sands<sup>b</sup>, Graham Roberts<sup>b</sup>, Jane S. Lucas<sup>b</sup>,  
Woolf Walker<sup>b</sup>, Rami Salib<sup>a,b</sup>, Andrea Burgess<sup>b</sup>, Hasnaa Ismail-Koch<sup>a,b</sup>

<sup>a</sup> Faculty of Medicine, University of Southampton, Building 85, Life Sciences Building, Highfield Campus, Southampton, SO171BJ, United Kingdom

<sup>b</sup> Southampton Children's Hospital, University Hospital Southampton NHS Foundation Trust, Tremona Road Southampton Hampshire, Southampton, SO16 6YD, United Kingdom

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## ABSTRACT

**Background:** Allergic rhinitis (AR) is a significant issue in children. Treatment options include allergen avoidance, pharmacotherapy and immunotherapy. The use of nasal saline douching (NSD) in children has recently gained acceptability. However, there is limited data regarding the acceptability and tolerability of NSD in children with AR.

**Methods:** A search was conducted using Medline and Embase databases from January 1946 until June 2015 on the use of NSD in children aged 4–12 years with AR. All publications identified that assessed the beneficial effects, acceptability and tolerability were included.

**Results:** 40 studies were analyzed. Data varied considerably in terms of saline solutions used, modality of application, participant numbers, study design, follow up and outcomes. Factors that appear to influence the acceptability and tolerability of NSD include parental and health professionals' preconceptions, and characteristics of the solution.

**Conclusions:** Nasal saline douching appears to be effective, being accepted and tolerated in the majority of children (78–100%). NSD has a significant positive impact on the quality of life in children with allergic rhinitis. When used as an adjunctive treatment having mainly a cleansing property, NSD potentiates the effects and may reduce the dose required of AR medications. Among the principal factors that influence the acceptability and tolerability of NSD are the child's age, delivery system and method, and tonicity. Nasal saline douching provides an accessible, low cost, low morbidity, easy to use treatment in children with allergic rhinitis.

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## 1. Introduction

Allergic Rhinitis (AR) has a significant negative impact on the quality of life of children and their carers. This IgE-mediated inflammation of the nasal lining is characterized by the occurrence of two or more symptoms, including nasal blockage, itching, sneezing and rhinorrhea. The importance of allergic rhinitis is not attributed to a single disease [1,2]. There is an association between

allergic rhinitis and the development and progression of asthma. Other comorbidities related to AR include: conjunctivitis, sleep related disordered breathing, rhinosinusitis, eczema, pollen-food syndrome and impaired hearing [3].

Currently there are no exclusive paediatric AR guidelines. According to the European Academy of Allergy and Clinical Immunology (EAACI) position paper and the Allergic Rhinitis and Its Impact on Asthma (ARIA) guidelines, allergic rhinitis is classified as being intermittent or persistent [3–5] (Fig. 1). Furthermore the ARIA guidance, which primarily focuses on the management of adults, classifies allergic rhinitis according to the severity of symptoms in relation to the effect on quality of life [4,5].

Allergic rhinitis affects up to 40% of the global population. It is present in more than 20% of people in the United Kingdom, and denotes a major cause of morbidity that affects the quality of life of individuals. The prevalence of AR in Europe is highest in Belgium

\* Corresponding author. Present address: Carrera 14b # 118–79, Bogotá DC, Colombia.

E-mail addresses: [nag1e14@southampton.ac.uk](mailto:nag1e14@southampton.ac.uk) (N. Gutiérrez-Cardona), [P.Sands@soton.ac.uk](mailto:P.Sands@soton.ac.uk) (P. Sands), [g.c.roberts@soton.ac.uk](mailto:g.c.roberts@soton.ac.uk) (G. Roberts), [j.lucas1@soton.ac.uk](mailto:j.lucas1@soton.ac.uk) (J.S. Lucas), [Woolf.Walker@uhs.nhs.uk](mailto:Woolf.Walker@uhs.nhs.uk) (W. Walker), [R.J.Salib@soton.ac.uk](mailto:R.J.Salib@soton.ac.uk) (R. Salib), [Andrea.Burgess@uhs.nhs.uk](mailto:Andrea.Burgess@uhs.nhs.uk) (A. Burgess), [Hasnaa.Ismail-Koch@uhs.nhs.uk](mailto:Hasnaa.Ismail-Koch@uhs.nhs.uk) (H. Ismail-Koch).

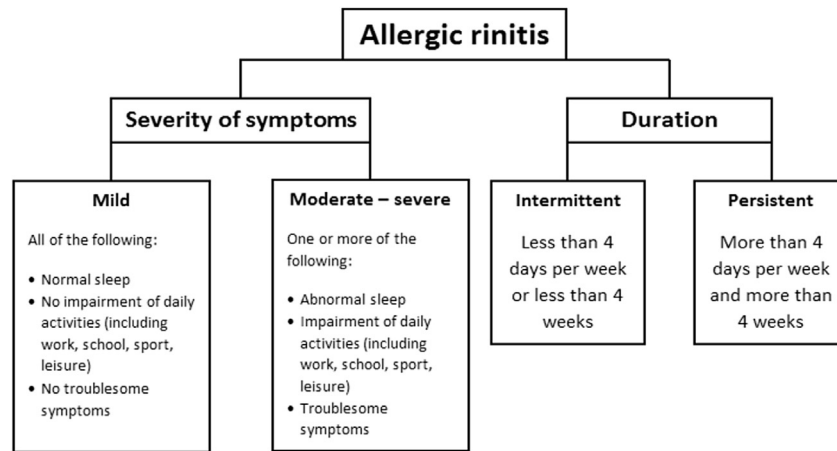


Fig. 1. The Classification of Allergic Rhinitis. Adapted from Bousquet et al. *Allergy* 2008(63).

(29%) [6]. Rhinoconjunctivitis symptoms are higher in high vs low income nations [7] (Fig. 2). In England, 10% of children aged 6 and 7 years and 15–19% of 13 and 14 year olds have allergic rhinitis. The International Study of Asthma and Allergies in Childhood (ISAAC study) stated an average prevalence of allergic rhinitis in 8.5% (1.8–20.4%) of 6–7 year olds and 14.6% (1.4–33.3%) in children aged between 13 and 14 years [3]. The likelihood of receiving a diagnosis of AR progresses with age in younger individuals but declines in the mid-20s.

Allergic rhinitis globally is on the rise in most areas with few exceptions. According to the World Allergy Organization, Australia, New Zealand and the United Kingdom are countries with a very high prevalence of AR. Conversely, countries with a very low prevalence include Albania, Indonesia, Georgia, Romania and Greece [8].

Allergic rhinitis may be triggered by both seasonal and perennial allergens; the commonest are house dust mite, animals' dander, pollens and molds [4].

The diagnosis of AR is primarily based on the history, clinical features and the duration of symptoms. A comprehensive longitudinal history and anterior rhinoscopy are frequently sufficient to make the diagnosis. Allergy tests help and are a valuable adjunct to validate the diagnosis [3,7,9]. Sensitization to foreign proteins in the environment is present in up to 40% of the population [10]. The presence of sensitization in children is considered as a major risk factor for AR [3]. Awareness that similar symptoms may be present with other upper respiratory tract conditions; such as chronic adenoiditis, adenoidal hypertrophy, nasal foreign bodies, nasal polyps/tumors, primary ciliary dyskinesia, etc., is fundamental.

Currently, the scope of treatment modalities for allergic rhinitis include; allergen avoidance, pharmacotherapy, immunotherapy and other treatment adjuncts (Fig. 3). The ARIA guidelines provide a treatment algorithm for patients, which when followed is successful in the vast majority of cases. There is no clear consensus concerning the effectiveness of allergen avoidance in the management of allergic rhinitis [5]. However, reducing exposure to

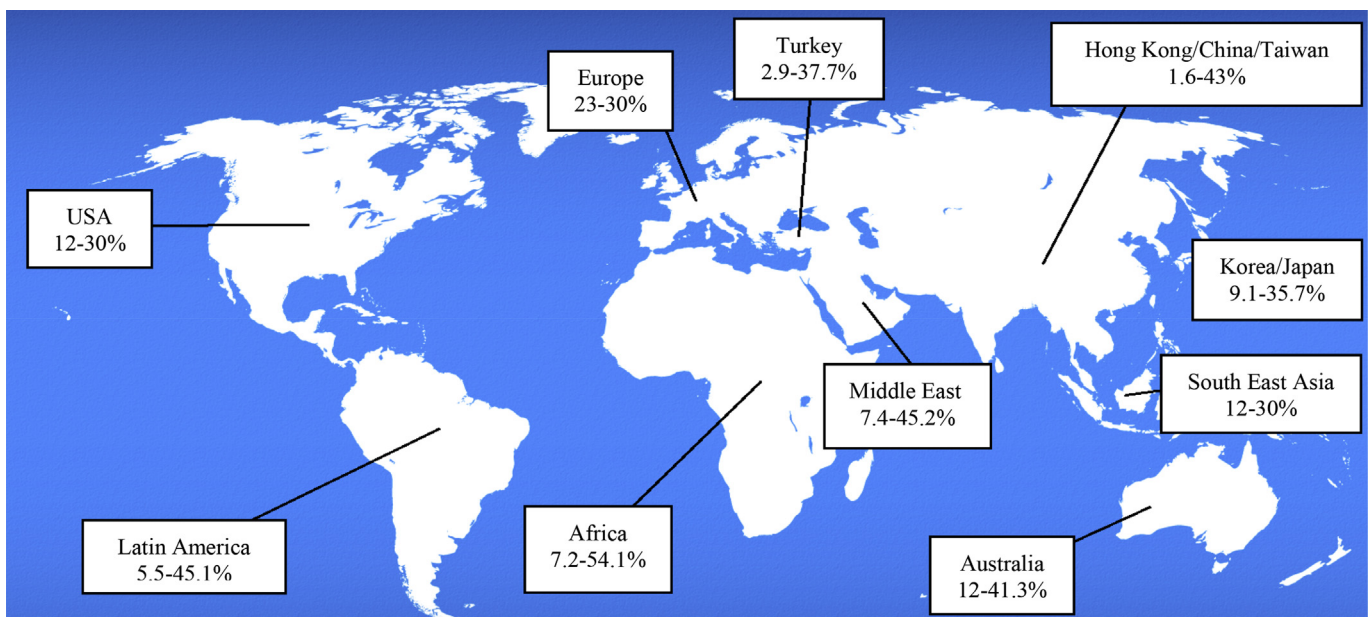


Fig. 2. Prevalence of allergic rhinitis in different regions of the world, according to the Global Atlas of allergic rhinitis and chronic rhinosinusitis. Adapted from Akdis et al. *European Academy of Allergy and Clinical Immunology* 2015.

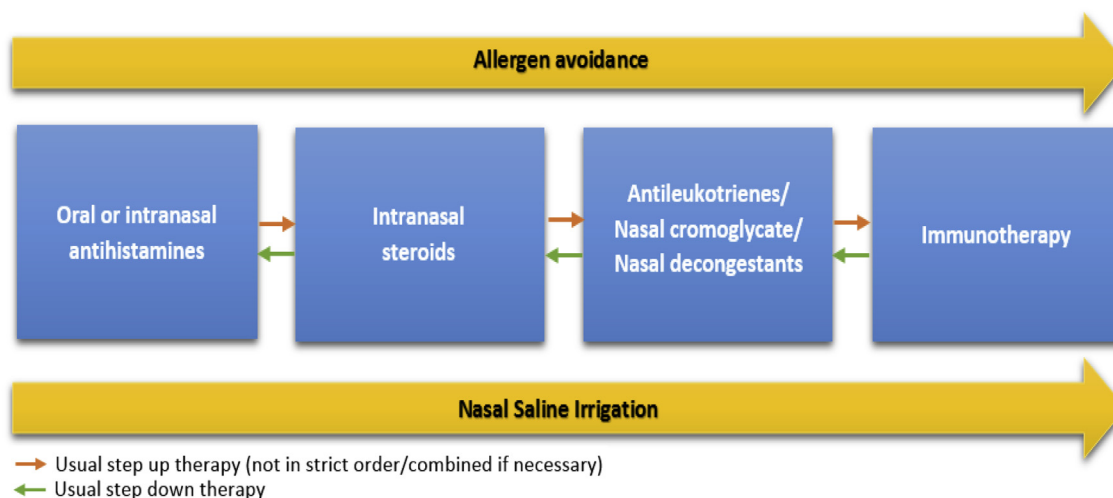


Fig. 3. The therapeutic algorithm for Allergic Rhinitis. Progressive escalation of treatment regimen. Adapted from Bousquet et al. *Allergy* 2008(63).

triggers of any source, including pollens, animal dander, molds and house dust mites, may be beneficial for managing AR in children [3–5].

Medications are similar to those used in adults, with the adjustment of dosages in children, in order to avoid side effects [1]. Depending on the severity of disease, the drug scheme employed in children is gradual and progressive [8]. Mild intermittent allergic rhinitis is treated initially with a non-sedating H1-blocker, either oral or topical, with the addition of an oral or nasal decongestant (for less than 10 days). For moderate to severe intermittent symptoms, a topical nasal steroid and/or an anti-leukotriene/local cromone is added [11,12]. Evidence demonstrating the effectiveness of medications in the treatment of allergic rhinitis during childhood is limited. The data is specifically reduced when assessing non-widely standardized treatments. Although several studies have been performed to extrapolate the doses for children from adults, it is important for healthcare professionals to bear in mind that altered cognitive function (antihistamines) and minimal growth impairment (intranasal steroids) are side effects [1]. The treatment regimen is tailored to the individual child and in accordance with available guidelines.

Alternative therapies described include nasal saline douching (NSD), which although commonly accepted, has not been incorporated into any treatment algorithms [13].

### 1.1. Nasal saline douching

Nasal irrigation is an inexpensive method of cleaning and clearing the nose of potential allergens. Saline nasal douching reduces mucosal edema, decreases inflammatory mediators, promotes mucociliary function and may reduce the medication requirement [7].

Nasal saline douching has been used since ancient times in the Hindu practice of Ayurveda [13]. In sinonasal disease, which includes allergic rhinitis, chronic rhinosinusitis and viral upper respiratory tract infections, NSD is performed as an adjunctive treatment. It is of proven efficacy in the treatment of chronic rhinosinusitis [2]. In children with AR, NSD has mainly been used as a homeopathic therapy but lately has gained acceptability [14].

Revyakina et al. (2010), demonstrated that children with allergic rhinitis were predominantly colonized by *Staphylococcus aureus* (54.4%) and *Streptococcus pneumoniae* (17.5%) [15]. Nasal douches are considered to clear pathogens and other irritants from

the nasal lining membranes, through different mechanisms, rather than having an anti-inflammatory effect [1,14]. Intranasal irrigation with isotonic or slightly hypertonic salt water has been associated with the reduction of the need for intranasal steroids and antihistamines in children [14,16,17].

The main functions of NSD are:

- Moisturization and humidification of the nasal mucosa
- Clearance of mucus and reduction of crust formation
- Promotion of healing through effector molecules of innate immunity in the nasal lining, inducing wound repair [18,19].
- Improvement of mucociliary transit time; related to carrying elements in a gradual flow (1 cm/min approx.); elements include bacteria, viruses, dust and particles of pollution inhaled from the rhino-pharynx and swallowed
- Decrease of both the concentration of inflammatory mediators and in mucosal edema [20].

In general, the role of NSD is limited to the nasal lining membranes, and more specifically to the mucociliary layer. This layer provides a defense mechanism that consists of columnar ciliated epithelial cells and goblet cells, bathed in mucus. The action of mucociliary cells is to propel the entire mucus layer out of the sinuses and into the nasopharynx [21].

The NSD recipe varies according to the healthcare service group treating the AR. Generally for a hypertonic solution, one pint of previously boiled water cooled to body temperature is sufficient. One teaspoon of salt is added to the solution, with the same amount of bicarbonate of soda, until dissolved [22]. Table salt is not recommended. Pickling salt or sea salt are preferred as neither contains any other additives (anti-caking agents). A small amount of baking soda is used as a buffer to adjust the pH value to that of the body. A teaspoon of sugar may also be added [12]. According to the British Society of Allergy and Clinical Immunology (BSACI) an isotonic solution contains 240 mL of cooled boiled water, ¼ teaspoon of salt and ¼ teaspoon of bicarbonate of soda [22].

Delivery systems used in nasal douching may include devices such as syringes, pots, canisters (e.g. NeilMed® Nasal Mist, Sterimar® Spray) and squeeze bottles with a low-pressure, high-volume system (e.g. NeilMed® SinuRise) [22].

The purpose of this systematic review is to assess the available evidence in order to establish whether nasal saline douching is beneficial, acceptable and tolerable in the treatment of children

with AR. As a low cost, low morbidity treatment the potential efficacy, acceptability and tolerability needs to be evaluated. Currently no reviews exist in the literature and this comprehensive review provides a summary of the available evidence on the use of NSD in AR in children. Furthermore this review provides a platform from which other related research may be undertaken. It may also add strength to the case for the inclusion and standardization of NSD in treatment protocols for children with AR.

## 2. Materials and methods

### 2.1. Participants

The population selected were generally children aged 4 to 12, suffering from allergic rhinitis (seasonal or perennial). However some of the studies selected not only included children of this age range but children older than 12 years of age, whom participated in the studies. This age range was selected as nasal saline douching with high-volume low-pressure systems is recommended from the age of 4 years. The upper age limit was selected, as in those older than 12 years adult doses and volumes are recommended. Compliance may also be better in those older than 12 years. The diagnosis of allergy did not require conformation by positive skin prick tests and/or specific IgE to allergens. Patients diagnosed with nasal polyposis or other airway conditions were excluded from the analysis.

### 2.2. Studies

Studies that were identified comprised clinical trials, case reviews, conference abstracts, letters to the editor and surveys assessing the quality of life, acceptability and/or tolerability of NSD or nasal saline irrigation (NSI) in children with allergic rhinitis.

### 2.3. Interventions

All trials identified were analyzed regardless of treatment duration, dosage, tonicity and nature of the nasal douche (e.g. nebulizers, sprays, irrigations and drops). Studies comparing different nasal saline solution concentrations, buffered versus non-buffered saline solutions, different methods of delivery, with or without concomitant therapy were evaluated.

### 2.4. Outcome measures

#### 2.4.1. Primary outcomes

- 2.4.1.1. Acceptability and tolerance of nasal douches, in children where NSD treatment was implemented.
- 2.4.1.2. Symptom control; which was assessed from studies in which symptom scores were recorded.
- 2.4.1.3. Quality of Life Scores; collected from studies in which the quality of life was documented.

Preference was given to validated symptom score questionnaires wherever possible (e.g. Paediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ), Total Nasal Symptom Score).

#### 2.4.2. Secondary outcomes

- 2.4.2.1. Efficacy of nasal douching, according to the tonicity of the solution, mode of delivery, quantity, technique and frequency of administration.
- 2.4.2.2. Patient diary: Visual Analogue Scales where studied.

### 2.5. Search strategy

A systematic search for studies which complied with the selection criteria was conducted. Studies that were in the English language were evaluated. The search of online databases was not restricted by date. The search included all the available literature fulfilling the selection criteria from January 1946 and up to and including the third week of June 2015. There were no restrictions on publication type, publication year and duration of subject follow up for the study.

#### 2.5.1. Electronic search

One reviewer performed a search of the following electronic databases: MEDLINE (Medical Literature Analysis and Retrieval System Online), and EMBASE (Excerpta Medica Database). All publications identified that complied with the selection criteria were analyzed for the review. The following combination of terms with variations and/or tags (e.g. text word or tw, adjective or adj., etc.) were used: children, allergic rhinitis, and nasal douche combined using the Boolean operators "AND" and "OR" (Table A1). Additionally, only studies with human participants were included in the search.

#### 2.5.2. Other resources

The reference lists of the identified publications were scanned for further potential applicable studies and information. Further literature was found whilst reviewing the selected articles. TRIP-database and Google scholar were used to retrieve existing evidence.

#### 2.5.3. Data collection

The research route was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and its four-phase flow diagram, including the stages of identification, screening, eligibility and inclusion (Fig. 4) [23].

### 2.6. Selection of studies

Initially, 892 records were identified using MEDLINE (490) and EMBASE (402). There were 5 more publications considered relevant for the review. All of the five additional publications were incorporated into the review after performing the literature review described above, when the databases did not include the publication.

After excluding 279 registers of duplicates, 614 publications remained. Subsequently, articles were screened by two reviewers according to the paper title (231 excluded by title) and abstract (338 excluded by abstract) (Fig. 4). Following this process 569, records which did not fulfil the selection criteria were excluded. Thus, 45 publications were preliminarily selected, however, 10 were excluded as the full article was not in the English language. Only 40 references (35 following the above pathway, in addition to the 5 additional articles from the search of reference lists of articles) were identified and included that complied with the selection criteria and/or were of relevance with respect to their contents.

#### 2.6.1. Data extraction

The data were extracted using a detailed form created by the first author specifically for the purposes of the review. The results were documented according to the evaluated outcome measure. The information documented in the form included qualitative data (Table B1).

#### 2.6.2. Assessment of risk of bias

Two reviewers performed quality assessment of clinical trials

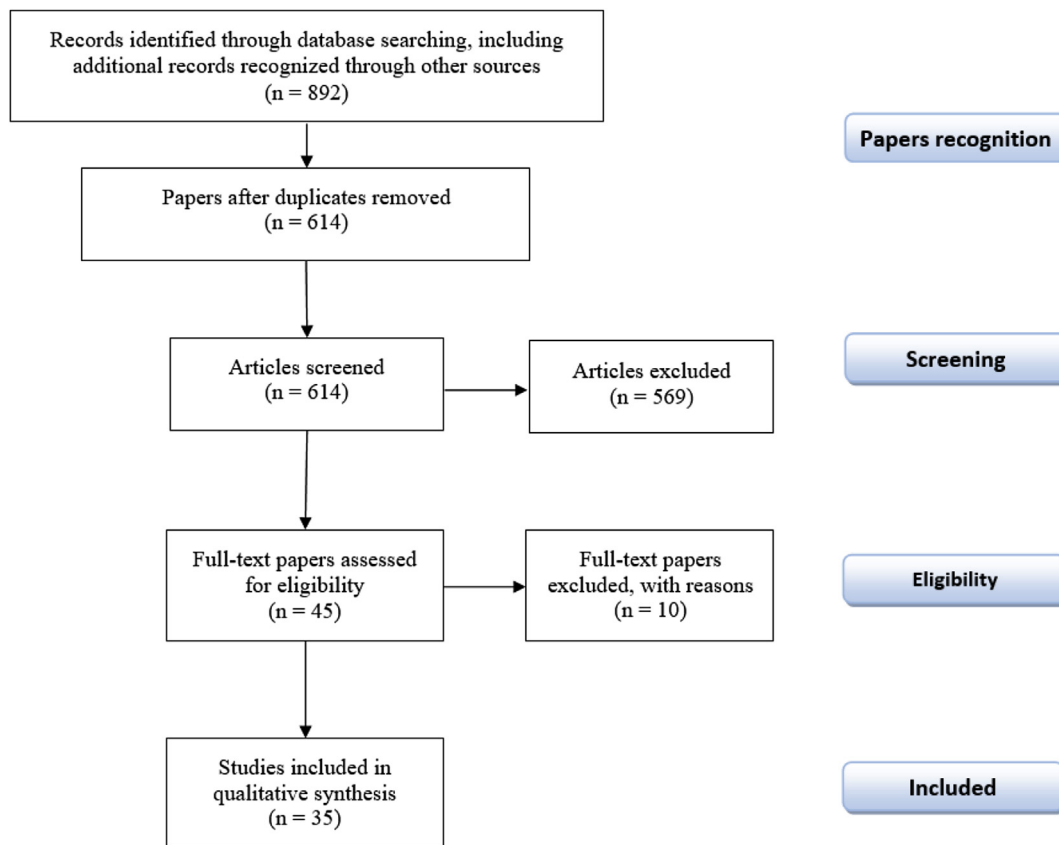


Fig. 4. Research route. Adapted from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, 2009.

according to the Jadad scale. A score of 3 or more was required for the inclusion of the study [24]. In addition, case reviews, conference abstracts, letter to editors, and surveys were included and evaluated using the Critical Appraisal Skills Programme (CASP) criteria [25]. These resources were considered useful regarding the limited evidence about the studied topic.

### 2.6.3. Data synthesis

This systematic review includes the analysis of the extracted information that was considered relevant to the topic. A wide range of measuring scales and scoring systems were employed by the article authors for presenting both primary and secondary outcomes. The publications were assessed regardless the heterogeneity across studies in terms of delivery method, tonicity, buffering, treatment duration, and pharmacotherapy combination.

## 3. Results

40 studies were analyzed. All evidence found, published until the third week of June 2015 was included in the study. Data were diverse in relation to saline solutions used, modality of application, numbers of participants, study design, follow up, and measures made.

### 3.1. Acceptability and tolerability

The acceptability and tolerability of nasal saline douches in children suffering from allergic rhinitis principally appeared to be related to parental preconceptions in relation to the administration of this therapy, child age, delivery system, tonicity, pH and buffering of the solution.

#### 3.1.1. Parental and healthcare professional concerns

In terms of acceptability, parental and healthcare professional concerns may influence children's perception of NSD therapy [26]. The study from Jeffe et al. (2012), found that only 28% of parents thought that NSD would be tolerated by their children. Conversely, 86% of children were able to tolerate the nasal douches [26]. This study demonstrated that the majority of children, regardless of age, tolerated the nasal saline irrigation. The greatest barrier to nasal douching in children was both parental and physician preconceptions that the child would not be able to tolerate the therapy. This was particularly applicable in the cases of younger children ( $\leq 5$  years) [26]. Jeffe et al. (2012) stated that the parental perception of NSD therapy importantly showed a trend towards parents of older children being more likely to think that their child would be able to tolerate the treatment [26]. However, a significant difference between the initial parental perception and the real tolerance of nasal saline irrigation ( $p < 0.001$ ) could be found. This phone survey showed that it is possible to create a habit of usage of NSD in the majority of patients resulting in symptom relief.

#### 3.1.2. Child age

Another factor that would be expected to influence the acceptability of NSD is the child's age. Chirico et al. (2010) showed good compliance and tolerance in children regardless of age [19,26]. A study from Jeffe, et al. (2012), which comprised 61 children divided into three age groups according to their school year levels; pre-kindergarten ( $\leq 5$  years), elementary school (6–12 years) and high school ( $\geq 13$  years), showed that all three groups tolerated and accepted the treatment of nasal rinsing twice a day (100 cm<sup>3</sup> of isotonic saline irrigated through each nostril) [26]. Children with persistent nasal congestion and rhinorrhea

secondary to sinusitis, chronic rhinitis or allergic rhinitis were reviewed. They found that there was no statistically significant difference in tolerance between the three age groups ( $p = 0.51$ ) [19,26]. However this study showed a tendency that the treatment was more accepted in children <12 years when compared with older children [26].

### 3.1.3. Delivery system

Existing data suggest that the delivery system or method of administration may influence the acceptability [27,28]. Šlapak and co-workers (2008) studied 390 children aged 6–10 years, during 3 follow up visits [28]. They found that a fine spray of the saline solution was more convenient in terms of acceptability; reporting higher comfort levels during and after therapy [27,28]. Tolerability complaints were related to a medium strength flow [28]. Furthermore, some authors suggest that increased pressure of delivery of the saline solution to the nose does not show improved efficacy [28]. There was a general consensus in the literature that the role of NSD was to remove allergens, inflammatory mediators and other particles from the nasal lining membranes, leaving the nasal lining intact, regardless of the mode of administration.

### 3.1.4. Tonicity

Garavello et al. (2005), reported that concentrations above 5.4% may result in pain, nasal blockage and rhinorrhea in a dose-dependent manner; which may subsequently interfere with the acceptability of the NSD. However mucociliary clearance is similar when comparing isotonic and 3.0% hypertonic saline solutions [29]. In their study, Marchisio, and co-workers (2012), enrolled 220 children aged 5–9 years with allergic rhinitis [27]. The children were randomly assigned into one of three groups in this single blinded (investigator-blinded) randomized controlled trial. Hypertonic solution (2.7% sodium chloride) was prescribed for 80 children, 80 were prescribed normal saline (0.9%) and 60 children acted as the control group without any NSD treatment. Data were collected from May 2010 and 2011. The doctor assessed nasal symptoms including rhinorrhea, sneezing, nasal obstruction and itching were reported by the children themselves or their parents (if < 8 years). Improvements in all parameters were achieved with the hypertonic solution, whereas in the normal saline group only rhinorrhea and sneezing were significantly reduced. Compliance with treatment was very good, regardless of the solution implemented for the procedure [27]. No immediate or late side effects, parental satisfaction issues and no significant statistical differences were found in terms of difficulty, unpleasantness and duration of use, between normal and hypertonic solution groups. Treatment with NSD was well tolerated, and seemed to be effortlessly accepted by this group of children with seasonal allergic rhinitis and their carers [27].

### 3.1.5. pH

Satdhabudha and co-workers (2012) assessed the tolerability of nasal douching in a group of 81 children aged 6–15 years, with symptomatic allergic rhinitis who had Total Nasal Symptom Score (TNSS)  $\geq 4$ . Normal saline or Buffered Hypertonic Saline (BHS) were administered [17]. Buffered hypertonic saline of pH 8, was found to be superior to normal saline solution [17]. Parents and children's satisfaction of nasal saline irrigation was graded according to a Likert scale. Sensations and feelings during the treatment with NSD were documented. Thirty five percent of children reported nasal burning and irritation after the first irrigation. This sensation decreased by the second and third follow up visits [17]. Tolerability improved as the treatment advanced [17,28]. The authors reported that BHS was effective, safe, comfortable and well tolerated; positively impacting on adherence to therapy [17].

## 3.2. Symptom control and medications' use

Nasal douching with saline water is considered to be a positive adjunctive treatment option and may achieve the effectiveness of an intranasal steroid at a low dose [1]. Chen and co-workers (2014), in their randomized study, recruited 61 children whom were allocated into one of three treatment arms; intranasal steroid, nasal saline douche or a combined treatment group of NSD and topical nasal steroid [1]. Eosinophilic count decreased in each treatment group. Children treated with NSD and intranasal steroids (reduced dose) had a better clinical response, with much improved nasal obstruction in particular, over a 12-week period [1]. Nasal hypertonic saline administration in a twice or three times daily regimen in children with seasonal AR has been associated with a reduced consumption of antihistamines [7]. The clinical response appears to be more pronounced following the third week of treatment. Chirico et al. (2010), hypothesized that the real effect of NSD may be related to a direct and physical cleansing action, reducing the use of antibiotics [19]. This cleansing action results in removing particles, allergens, mucus, crusts and inflammatory mediators (e.g. histamine, leukotrienes, prostaglandins) from the nasal cavity. In concordance with these findings, Li et al. (2009), in a study of 26 children with mean age of 11 years, showed an improvement in mucociliary clearance and decreased expression of the soluble intercellular adhesion molecule (sICAM-1) in epithelial cells. Therefore NSD appears to be beneficial in controlling allergic rhinitis, resulting in the decreased use of topical steroids [30].

## 3.3. Quality of life

In an 8 week follow up randomized controlled trial Chairattananon et al. (2013), showed that NSD improved the quality of life in thirty children aged 5 to 15, who used this treatment for 3 or more weeks [31]. There was a significant reduction ( $p < 0.05$ ) in the combined daily total nasal and medication score (CSM). There was also improvement in the Rhinoconjunctivitis Quality of Life Questionnaire score (RQLQ) and the Visual Analogue scale (VAS) [31]. Moreover, in an investigation of 190 patients, Jan (2013), demonstrated that applying a nasal saline aerosol purging method for 3 consecutive days, could improve the TNSS, particularly in children under 12 years ( $p = 0.035$ ) [32]. Manole (2013), subjectively and objectively measured the effects of AR on children's lives. Nasal discharge, nasal obstruction and sneezing were evaluated through a diary of symptoms. Additionally, nasal endoscopy was performed before treatment and at weeks 4 and 8 of NSD therapy. Children ( $n = 63$ ) were divided into three groups. The first group were managed with nasal hypertonic saline irrigation twice a day, the second group with intranasal steroids and the third group with a combination of intranasal steroids and nasal irrigation twice a day. Total nasal symptoms improved in groups 2 and 3. This difference was statistically significant ( $p < 0.001$ ) [33]. These findings are in agreement with other publications by the same author, regarding the effectiveness of hypertonic NSD [33,34].

Factors influencing adherence to NSD treatment are summarized in Table 1.

## 4. Discussion

Nasal saline douching represents an inexpensive, easy to use and accessible treatment modality in AR. However data regarding the role of NSD in children with AR is limited.

The benefits and efficacy of NSD have been extensively demonstrated. According to Solelhac et al. (2014), a 27% improvement in quality of life, 62% reduction in medicine consumption, 31% acceleration of mucociliary clearance time and 27% improvement in nasal

**Table 1**  
Comparative of studies addressing acceptance and tolerance of Nasal Saline Irrigation for children with Allergic Rhinitis.

| Study authors                              | Probable factors associated with acceptability and tolerability                                           | Type of solution, delivery method and duration                                               | N° of evaluated patients  | Assessment method – Results                                                                                                                                                                                                                                                                                                                 |
|--------------------------------------------|-----------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------|---------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Chairattananon C, et al. (Thailand - 2013) | Delivery method and tonicity                                                                              | Osmolality, tonicity and pH not fully described; positive pressure device; 8 weeks follow up | 30 children (5–15 years)  | Combined symptom and medication score (CSM), The Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) and the Visual Analog Scale (VAS). Improvement in all parameters                                                                                                                                                                  |
| Chen J, et al. (China - 2014)              | Delivery method and tonicity                                                                              | Seawater; spray; 12 weeks follow up                                                          | 61 children (2–15 years)  | Nasal signs and symptoms record by patients and their parents. All symptoms of allergic rhinitis improved, in combination with intranasal steroids                                                                                                                                                                                          |
| Garavello W, et al. (Italy - 2005)         | Delivery method, pH and tonicity                                                                          | Hypertonic saline; spray; 7 weeks follow up                                                  | 44 children (<16 years)   | Daily symptom score of rhinoconjunctivitis. Improvement of nasal symptoms. Effectiveness of NSD reported 100% improvement in symptoms                                                                                                                                                                                                       |
| Jeffre J, et al. (USA - 2012)              | Delivery method, child's age, tonicity and parental/healthcare professional preconceptions of the therapy | Isotonic nasal saline; rinses; within 2 and 4 months of being prescribed the treatment       | 61 children (<18 years)   | Phone survey. Parental questionnaire. Regardless of age, the majority of children tolerated the nasal saline douching (NSD). Assumption of both physicians and carers that children were not be able to tolerate the therapy, particularly if the child was young. Improvement in nasal symptoms. Therapy acceptability between 78 and 100% |
| Marchisio P, et al. (Italy - 2012)         | Delivery system and tonicity                                                                              | Isotonic or hypertonic saline; syringe; 4 weeks of follow up                                 | 220 children (5–9 years)  | Symptom score. Improvement in all nasal symptoms with the hypertonic solution whereas with normal saline group only rhinorrhea and sneezing were significantly reduced                                                                                                                                                                      |
| Satdhabudha A, et al. (Thailand–2012)      | Delivery system, pH and tonicity                                                                          | Buffered hypertonic and normal saline; syringe; 4 weeks of follow up                         | 81 children (6–15 years)  | Total nasal symptom score. Thai allergic rhinoconjunctivitis patients' questionnaire. Improvement in nasal symptoms and quality of life                                                                                                                                                                                                     |
| Šlapak I, et al. (Czech Republic - 2008)   | Delivery system, pH and tonicity                                                                          | Seawater; medium jet flow and spray; 12 weeks of follow up                                   | 401 children (6–10 years) | Child's health status qualitative scale. Sensations and feelings during and after application. Improvement in nasal symptoms; higher acceptability for the spray                                                                                                                                                                            |

symptoms were found following NSD [35]. The exact mechanism of action of NSD is not fully understood [36,37]. Physical removal (e.g. allergen, inflammatory mediators) and immune response stimulation, through neuronal modifications in the immunologic process appear to be implicated in the patient's clinical response [36,37]. Therefore if the clinical response is improved, it follows that quality of life will improve. This can be explained by the direct correlation that has been established between clinical score and the Paediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ) score, proposed by Juniper [38]. PRQLQ was evaluated in a 7 point response – Likert type – scales [37]. Yuksel et al. (2009), found that the PRQLQ score in children with AR was  $2.5 \pm 0.9$  (higher score = greater impairment), showing the negative impact of AR on the quality of life [38]. It is reasonable to hypothesize that NSD would improve the lives of children with AR.

The beneficial effects of nasal saline douching in children with AR become evident following durations of usage ranging from 3 to 12 weeks [20].

External factors such as parental and healthcare professional perception of therapy and age may also influence adherence to NSD treatment (Table 1). In particular parents of young children seem to be especially skeptical about their child's tolerability of NSD [26]. Surprisingly, no statistically significant difference has been demonstrated for compliance and acceptability of NSD between different age groups [26]. However the same study showed a tendency that older children ( $\geq 13$  years) were less likely to use nasal saline douching [26].

Conversely, Wong et al. (2010), found that when comparing routes of drug administration in children with allergic rhinitis, those aged 7–15 years were more likely to accept the nasal route when compared to those aged 1–6 years (OR 2.9, 95% CI 1.4–6.0) [39]. This research group analyzed 194 children using topical nasal sprays and/or drops [39]. Despite this evidence regarding nasal sprays and drops, there is no conclusive evidence available regarding the acceptability and tolerability of NSD with respect to age in children.

In order to positively influence the clinical response, treatment with NSD needs to be accepted, tolerated, adopted and consequently should ideally fulfil certain specifications. The success of NSD depends on multiple factors including the characteristics of the saline solution (delivery system, tonicity and pH).

There is evidence to support that the mode of delivery may play an important role in the efficacy, tolerability and acceptability of NSD. There are different types of administration methods, such as aerosolized systems, squeezing bottles, motorized devices, cupped hands, gravity pots and inhaling/sniffing devices [16]. A stepwise increase in NSD has been advocated to increase tolerability [26,36]. Devices used to perform nasal douches, require cleaning and/or replacement to achieve the treatment goals [40]. Nasal saline sprays have been reported to be better accepted than nasal saline irrigations [37]. Hermelingmeier et al. (2012), found nasal sprays to be more effective than nasal douches. Improvements in symptom parameters with the spray were achieved in more subjects (23–45%). The use of larger volume NSD (200–400 mL), resulted in improvements in a smaller number of subjects (3.2–45.5%) [37]. Hypertonic and pressurized systems of delivery result in better symptom control [27–29].

Hypertonic solutions appear to be especially effective nasal decongestants, reducing edema due to osmotic pressure, inducing water transport outside the epithelial membrane [12,17]. In comparison, isotonic solutions require more frequent administration [12]. This evidence supports the use of hypertonic solutions for NSD. Conversely, *in vitro* studies have shown that hypertonic saline irrigation may decrease mucociliary transport [41]. The authors of this study suggested that hypertonic solutions could lead to the release of histamine and possibly enhance the release of P substance, triggering pain in patients via stimulation of nociceptive nerves [41]. Consequently an irritating effect on the nasal membranes is observed at different concentrations. This may induce nasal blockage, when the saline solution concentration is 2.7%. Additionally pain and rhinorrhea are present with a 5.4% saline solution concentration, thus affecting

the acceptability and tolerability of the treatment [17,21,41,42].

The pH of the solution may also be linked to the effectiveness of and compliance with therapy. Optimum ciliary action has been reported at a pH of  $7.0 \pm 0.5$  [43]. Respiratory cilia appear to tolerate an alkaline environment rather than an acidic setting [17,43]. Satdhabudha, et al. (2012), found that buffered hypertonic saline (BHS) of pH 8, was superior to normal saline solution and suggested that it may lead to the decreased use of some anti-allergy medications [17]. However no studies have been performed in children with AR comparing the efficacy of and compliance with NSD using solutions of different pH value. In their review, Chirico et al. (2014), reported a study in which three different groups of adults were administered isotonic saline solutions of varying pH value [44]. The middle alkaline solution was the most accepted (pH 7.2–7.4) [44].

Other factors that possibly influence the acceptability and tolerability of NSD are the taste of the solution and the technique used for application [39]. Although, no studies exist evaluating the taste of nasal saline solution, Wong et al. (2010), noted some difficulties experienced during administration of medication. Of the children enrolled in the study, 15% felt an unpleasant aftertaste; and thus this could interfere in the preference towards adopting or continuing the NSD therapy [39]. The technique of application is another aspect that has not been addressed by the majority of authors. Despite a wide range of systems (from motorized devices to cupped hands) that have been suggested to perform nasal saline irrigation, there is no uniform consensus regarding the optimal method. Performing the NSD correctly, whichever method is employed, is crucial in providing positive reinforcement, improved control of AR symptoms and to diminish any potential discomfort.

The tolerability and acceptability of NSD is likely to be related to side effects and pleasantness of the therapy. For instance, if patients experience pain when administering hypertonic saline, this may adversely affect adherence to therapy [27]. There were no immediate or late side effects reported in the majority of the evaluated studies. No statistically significant differences were found in terms of unpleasantness between normal and hypertonic solutions [27].

Another apparent advantageous effect of NSD is the reduction in usage of other medications used to treat AR. Decreased doses of intranasal corticosteroids, oral antihistamines and antibiotics were needed when performing a nasal saline irrigation scheme [1,19,27,30]. Hence, fewer side effects and a reduced economic burden may be present when NSD is instituted. Combinations of nasal saline solution and medications could also be considered, potentially acting synergistically. Wong et al. (2010), proposed a possible enhancement for nasal medications that would take advantage of the benefits of certain molecules [39]. Evidence to support this theory, may include the finding that following NSD, the efficacy of intranasal corticosteroids improves.

There are several limitations to the present systematic review. There are restrictions due to the quantity and quality of the literature available. The heterogeneity of information in existing studies, different methodologies, populations targeted and varying outcome measures further compound this, and thus deductions that can be made. Although there is diverse evidence regarding NSD, the evidence is generally of low quality. Of note, are the small numbers of subjects included in the majority of studies, the lack of documented and appropriate follow up and no exclusive treatment with NSD (i.e. all studies included the addition of antihistamines, intranasal steroids and/or antibiotics during therapy). Few of the publications described a detailed blinding process and the different parameters evaluated to measure the effectiveness of NSD. A wide range of delivery methods were also used making any direct comparisons difficult [16].

No consensus has been reached regarding NSD administration or an ideal saline preparation in terms of tonicity, pH, or even the

source of the solution (e.g. sea water, thermal water etc.); which has demonstrated efficacy in controlling nasal symptoms [45]. Additionally, there are different vehicles, buffering and volumes that have to be considered when making decisions regarding NSD therapy [16]. There are no studies regarding the ideal temperature of the solution or any possible long term negative effects of hypertonic saline water [27].

In summary the available evidence shows that compliance to NSD is particularly controversial among the youngest, but in general it is more accepted in children of  $\leq 12$  years. However parental and physician education and support may alter negative preconceptions; improving compliance with NSD. Cultural factors may play a role in accepting a specific route of administration. This endorses the need for an intervention aimed at both parents and children; entailing education related to the clinical condition and for training regarding how to use the prescribed therapy in order to achieve the treatment goals. Regarding the delivery system, although there are many alternatives on the market, sprays seem to be more convenient, although pressurized delivery devices (high volume, low pressure) appear to be more effective in reducing symptoms. Slightly hypertonic solutions are more beneficial.

A possible product enhancement and improved advertising may have a positive impact on the acceptability and compliance of NSD. Advances in new therapeutic alternative NSD solutions, and the potential development of combinations of medications with the saline solution could be considered. This together with the additional possibility of improved delivery methods, optimal pH, buffering and even improved taste of the solution, could modify the acceptability and tolerability of treatment in children suffering from allergic rhinitis.

Nonetheless, the reported beneficial effects of NSD are consistent throughout the studies included in this review, regardless of the delivery system, solution characteristics, child's age and parental and physician concerns'. However, the levels of acceptance and tolerance differ.

## 5. Conclusions

Nasal saline douching has proven favorable effects in the treatment of allergic rhinitis. It is not only effective in terms of reducing the symptoms of allergic rhinitis but also in potentially reducing the dosage of and maximizing the efficacy of topical nasal and/or systemic medications when used as a treatment adjunct. Although the data is limited and further studies are required, the positive effects, minor side effects, affordability and accessibility of NSD treatment has implications for children with AR, their carers and healthcare professionals worldwide. This management option is often well tolerated and may be effortlessly accepted by children with AR and their carers. As such, NSD should ideally be included in the current treatment guidelines for children with allergic rhinitis.

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## Appendix A

Table A.1 Search strategies.

| MEDLINE                                | EMBASE (Ovid)                          |
|----------------------------------------|----------------------------------------|
| 1 exp Child/                           | 1 child/                               |
| 2 child.tw.                            | 2 child.tw.                            |
| 3 children.tw.                         | 3 children.tw.                         |
| 4 child/                               | 4 p?ediatric*.tw.                      |
| 5 p?ediatric*.tw.                      | 5 exp child/                           |
| 6 1 or 2 or 3 or 4 or 5                | 6 1 or 2 or 3 or 4 or 5                |
| 7 drop*.tw.                            | 7 drop*.tw.                            |
| 8 spray*.tw.                           | 8 spray*.tw.                           |
| 9 nebula?er*.tw.                       | 9 nebula?er*.tw.                       |
| 10 irrigat*.tw.                        | 10 irrigat*.tw.                        |
| 11 douch*.tw.                          | 11 douch*.tw.                          |
| 12 rins*.tw.                           | 12 rins*.tw.                           |
| 13 wash*.tw.                           | 13 wash*.tw.                           |
| 14 7 or 8 or 9 or 10 or 11 or 12 or 13 | 14 7 or 8 or 9 or 10 or 11 or 12 or 13 |
| 15 nose.tw.                            | 15 nose.tw.                            |
| 16 nasal.tw.                           | 16 nasal.tw.                           |
| 17 15 or 16                            | 17 15 or 16                            |
| 18 14 and 17                           | 18 14 and 17                           |
| 19 exp Nasal Lavage/                   | 19 exp Nasal Lavage/                   |
| 20 Therapeutic Irrigation/             | 20 Therapeutic Irrigation/             |
| 21 salin*.tw.                          | 21 salin*.tw.                          |
| 22 19 or 20 or 21                      | 22 19 or 20 or 21                      |
| 23 exp Rhinitis, Allergic/             | 23 exp Rhinitis, Allergic/             |
| 24 (allerg* adj rhiniti*).tw.          | 24 (allerg* adj rhiniti*).tw.          |
| 25 23 or 24                            | 25 23 or 24                            |
| 26 18 or 22                            | 26 18 or 22                            |
| 27 6 and 25 and 26 (402)               | 27 6 and 25 and 26 (490)               |

## Appendix B

Table B.1 Format used for data extraction from selected studies.

| Article title | Authors | Year | Methodology | Abstract | Summary and Comments | Keep? | Reason |
|---------------|---------|------|-------------|----------|----------------------|-------|--------|
|               |         |      |             |          |                      |       |        |

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