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TOPICALLY ADMINISTERED HYALURONIC ACID IN THE UPPER AIRWAY: A SYSTEMATIC REVIEW

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Abstract:	Backgroud: Hyaluronic acid (HA) plays a role in controlling inflammatory airway processes and mucociliary clearance, and is also involved in tissue healing and remodelling. Some studies have tested the effectiveness of topically administered HA in patients with upper airway diseases and those who have undergone nasal or sinonasal surgery with positive preliminary results. Objective: To describe the use of topically administered HA in patients with upper airway disorders. Study appraisal and synthesis methods: Pertinent studies published between January 2000 to October 2016 were selected by means of a MEDLINE search (accessed via PubMed) using the following terms: "hyaluronic acid" and "otolaryngology", "otitis", "pharyngitis", "tonsillitis", "rhinitis", "rhinosinusitis", and "nose". Results: Twelve of the 19 initially identified papers were selected, including three papers performed exclusively on pediatric patients, and nine on adult patients corresponding to 902 patients as a whole. Conclusions and implications: There is some evidence that topically administered HA is effective or moderately effective in different otolaryngological conditions, as it improves the global subjective and clinical status of patients with inflammation of the nasopharyngeal and oto-tubaric complex, those with rhinitis or rhinosinusitis, and those who have undergone nasal and sinonasal surgery. However, these findings should be viewed cautiously as they are based on a limited number of studies, some of which were probably under-powered because of their small patient samples.

TITLE PAGE

TITLE

TOPICALLY ADMINISTERED HYALURONIC ACID IN THE UPPER AIRWAY: A SYSTEMATIC REVIEW

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ABSTRACT

Backgroud: Hyaluronic acid (HA) plays a role in controlling inflammatory airway processes and mucociliary clearance, and is also involved in tissue healing and remodelling. Some studies have tested the effectiveness of topically administered HA in patients with upper airway diseases and those who have undergone nasal or sinonasal surgery with positive preliminary results.

Objective: To describe the use of topically administered HA in patients with upper airway disorders.

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Results: Twelve of the 19 initially identified papers were selected, including three papers performed exclusively on pediatric patients, and nine on adult patients corresponding to 902 patients as a whole.

Conclusions and implications: There is some evidence that topically administered HA is effective or moderately effective in different otolaryngological conditions, as it improves the global subjective and clinical status of patients with inflammation of the nasopharyngeal and oto-tubaric complex, those with rhinitis or rhinosinusitis, and those who have undergone nasal and sinonasal surgery. However, these findings should be viewed cautiously as they are based on a limited number of studies, some of which were probably under-powered because of their small patient samples.

Key words: Hyaluronic acid; otitis media; rhinosinusitis; adenoiditis; rhinitis.

INTRODUCTION

Hyaluronic acid (HA) is a high-molecular-weight (HMW) and ubiquitously endogenous non-sulfated glycosaminoglycan consisting of polyanionic disaccharide units of glucuronic acid and N-acetyl-glucosamine that acts as a component of many extra-cellular matrices and organic fluids. It can be found in connective tissue, synovial fluid, skin, vitreous humor, respiratory epithelia, nasal and tracheobronchial mucosa, airway secretions, and gland serous cells. [1]

HA acts as a lubricant of airway surfaces, and is involved in tissue healing and remodelling as it induces fibroblast proliferation and angiogenesis, and modulates inflammatory responses. [2,3] It also plays a role in regulating vascular tone and mucous gland secretion by acting on endothelin-1,[4] and is thought to regulate airways inflammation by acting on the migration and aggregation of polymorphonuclear leukocytes and monocytes.[5] Its immunomodulant effect seems to be due to the balanced and opposite actions exerted by the low- (LMW) and high- (HMW) molecular weight fragments released during the inflammation-mediated breakdown of HA.[6] The LMW fragments enhance chemotaxis and activate trans-cellular signals from impaired tissue, whereas the HMW fragments induce immune suppression and prevent excessive inflammatory exacerbations. [6] The combined effect of both is also involved in regulating upper respiratory tract mucociliary clearance: [7] in the presence of the inflammatory molecules and free radicals, the released HA fragments induce intra-cellular calcium accumulation and modulate the receptors for HA-mediated motility and the subsequent increase in ciliary beat frequency.[8] Furthermore, it has been reported that HA can exert *in vitro* anti-infective and anti-biofilm effects by promoting the phagocytosis of *S. pyogenes*[9,10] and preventing bacterial adhesion.[11]

HA is widely used in various branches of medicine, including orthopedics, otolaryngology, aesthetic medicine and plastic surgery, gastroenterology, and pneumology,[12-15] and new topical formulations have been developed in order to deliver it to the upper airways by means of a nebulised, micronised nasal douche. A number of studies have shown the effectiveness and safety of topically administered HA in adults and children with upper airway tract infections or inflammation, and in those who have undergone nasal surgery.[3,7,16-28]

This systematic review describes the use of topically administered HA in patients with upper airway disorders.

METHODS

According to the review protocol, pertinent studies published between January 2000 to October 2016 were selected by ST on November 2016 by means of a MEDLINE search (accessed via PubMed) using the following terms: “hyaluronic acid” and “otolaryngology”, “otitis”, “pharyngitis”, “tonsillitis”, “rhinitis”, “rhinosinusitis”, and “nose”.

We only considered English language papers describing randomised and controlled trials (RCTs) involving otherwise healthy children or adults with a single and well-defined otolaryngological condition (e.g. inflammation of the nasopharyngeal and oto-tubaric complex; rhinitis and rhinosinusitis; previous nasal and sinonasal surgery) undergoing treatment with topically administered HA that had been published in peer-reviewed journals. When the full text of a paper was not available on line, an e-mailed request was sent to the corresponding author; if this was not answered, the paper was excluded, as were any studies of invasive HA administration or its use in the form of nasal packing or dressing.

The reference lists were subsequently reviewed in order to ensure that all of the selected papers were truly relevant and identify any possibly overlooked and pertinent papers.

RESULTS

Twelve of the 20 initially identified papers were included in this review, corresponding to 902 patients (Fig. 1). Three papers were performed exclusively on pediatric patients, while the remaining ones on adult patients. Table 1 shows their main results and Table 2 summarizes the evidence gathered regarding the efficacy of topically administered HA in the previously defined conditions.

Inflammation of the nasopharyngeal and ototubaric district

Two RCTs[19,20] have investigated the efficacy of topically administered HA in children with chronic adenoiditis and middle ear diseases, including recurrent acute otitis media (RAOM) and otitis media with effusion (OME). In the first, Torretta *et al.*[19] documented a significant reduction in the mean number of all episodes of acute otitis media (AOM; 0.8±0.4 episodes/ month), and in the mean number of AOM episodes without spontaneous tympanic membrane perforation (0.6±0.3 episodes/month) in 54 patients receiving HA (9 mg of sodium hyaluronate [SH] diluted in 3 mL of isotonic saline solution, administered once daily for 15 days a month for three consecutive months), whereas there was no reduction in the 49 children receiving isotonic saline solution alone. HA proved to be effective in improving all of the assessed endoscopic outcomes (the degree of adenoidal hypertrophy, the presence of turbinate hypertrophy, nasal secretion, nasal mucosal dyschromia or swelling, and obstruction of the Eustachian tube orifice), only a few of which were improved into the control group. The second study showed that the same therapeutic protocol reduced the mean number of patients with impaired otoscopy and tympanometry, conductive hearing loss and moderate hearing impairment, and globally improved the mean auditory threshold of 58 children with OME and/or RAOM and chronic adenoiditis, whereas no significant improvement was observed in children receiving isotonic saline solution alone.[20]

In addition, Varricchio *et al.*[18] found that the efficacy of topical antibiotic therapy with 125 of thiamphenicol could be improved by adding 4 ml of SH 0.2% plus xylitol 5%, as shown by the greater effect on symptom perception and nasal neutrophilic and bacterial counts in 51 children with acute bacterial rhinopharyngitis

Rhinitis and rhinosinusitis

Two studies published by Gelardi *et al.*[17,22] assessed the effectiveness of two compounds containing HA in patients with allergic and non-allergic rhinitis. In the first,[17] nebulised SH 9 mg diluted in 3 mL of isotonic saline solution plus mometasone furoate nasal spray 100 µg/day and oral desloratadine 5 mg (39 patients) was compared with 6 mL of nebulised isotonic saline solution plus mometasone furoate nasal spray 100 µg/day and oral desloratadine 5 mg (39 patients). It was found that, in comparison with the controls, the patients in the treatment group had a significantly lower

number of nasal neutrophils as assessed by means of nasal cytology; they also experienced a significant improvement in nasal symptoms (sneezing, rhinorrhea and nasal congestion) and showed a reduction in endoscopic evidence of nasal exudate. In the second, an intranasal ointment containing lysine hyaluronate, thymine and sodium chloride (LHT) was used in 48 patients with allergic, non-allergic and mixed rhinitis[22] in addition to intranasal mometasone furoato 100 µg/day and oral rupatadine fumarate. It was found that intranasal LHT significantly reduced the number of patients with subjective symptoms, the number of inflammatory intranasal cells, and the endoscopic features of nasal impairment in comparison with baseline, and in comparison with the control treatment (intranasal isotonic saline solution plus intranasal corticosteroid and oral antihistamine).

Topically administered HA has also been successfully used to treat chronic rhinosinusitis with or without nasal polyps:[23,27] Cassandro *et al*.[27] conducted an open-label trial involving 80 patients with chronic rhinosinusitis with nasal polyposis and found a significant improvement in nasal symptoms, endoscopic appearance, radiological score, rhinomanometry, and saccharine clearance in those receiving mometasone furoato nasal spray 400 µg/day with or without nebulised SH 9 mg diluted in 2 mL of isotonic saline solution in comparison with baseline, and in comparison with patients receiving nebulised isotonic saline solution alone. Moreover, the patients in the treatment groups resorted to oral steroid consumption less frequently than the controls. Casale *et al.*[23] found that nebulised HA (SH 3 mL dissolved in 2 mL of isotonic saline solution) significantly reduced ostiomeatal edema and secretion, and improved the quality of life of 21 adults with chronic rhinosinusitis and nasal polyposis, whereas no change was observed in 18 patients receiving nebulised isotonic saline solution alone.

Nasal and sinonasal surgery

We found five RCTs assessing the effect of topically administered HA after nasal or sinonasal surgery,[3,7,21,24,26] four of which involved patients who had undergone functional endoscopic sinus surgery (FESS),[3,7,21,26] and one patients who had undergone turbinoplasty.[24]

The trials conducted by Macchi,[3] Gelardi,[7] and Cantone[26] compared the effects of nebulised SH 9 mg diluted in isotonic saline solution with those of nebulised isotonic saline solution alone in patients who had undergone FESS because of chronic rhinosinusitis with nasal polyposis and for the purpose of rhino-sinusal remodelling. Of the 202 patients in the three trials, 104 received topically administered SH and 98 received nebulised isotonic saline solution. All three studies showed that SH had a positive clinical effect on subjective and objective parameters, including symptom scores evaluated by means of visual analogue scales and standardised SNOT-22 and SF-36 questionnaires, endoscopic appearance, and cytological measures. In particular, it was reported that the patients receiving nebulised SH experienced a significantly greater improvement in nasal

dyspnea, impaired nasal secretion and ciliar motility, and a reduction in the presence of nasal mycetes and biofilm.[3]

Cantone *et al*.[26] compared topically administered SH with nebulised isotonic saline solution in a double-blind trial involving 124 patients and found that, in comparison with the controls, SH significantly improved the patients' post-operative quality of life not only in terms of sinonasal status, but also in terms of general health as assessed on the basis of physical functioning, social/emotional role functioning, bodily pain, vitality, and mental health.

Gelardi *et al*.[21] recently published a paper describing an open-label trial of intranasal LHT ointment involving 83 patients who had undergone FESS, septoplasty and turbinoplasty and found that, in comparison with isotonic saline solution nasal lavages, the treatment significantly reduced symptom severity, and improved endoscopic and nasal cytological features.

Casale *et al*.[24] studied the effect of nebulised HA (SH 3 mL dissolved in 2 mL of isotonic saline solution) in 22 patients who had undergone radiofrequency surgery because of chronic inferior turbinate hypertrophy, and found that, in comparison with 35 patients receiving nasal irrigation with isotonic saline solution, the patients in the treatment group experienced a significant post-operative improvement in nasal respiration as assessed by means of subjective scores and the reduction in nasal crusting.

DISCUSSION

The few published studies of topically administered HA in patients with otolaryngological disorders suggest that it is effective compound as ancillary treatment in children with recurrent or chronic middle ear inflammation and chronic adenoiditis, in adult patients with rhinitis or chronic rhinosinusitis, and those who have undergone sinonasal surgery.

Nebulised HA seems to act positively on the endoscopic appearance of the sinonasal and nasopharyngeal district, as shown by the significant reduction in nasal exudate and inflammatory cells, and the improvements in mucociliary clearance, microbiological status and nasal respiratory patency. This leads to a decrease in the number of AOM episodes and a global improvement in audiological outcomes and the otoscopic appearance of the tympanic membrane in otitis-prone children, and the better control of respiratory symptoms and inflammatory events in patients with recurrent or chronic nasal or sinonasal disease.

Some of the reviewed RCTs show that topically administered HA can significantly improve sinus ostial patency and reduce the presence of nasal crusting and secretions, thus allowing a prompt mucosal recovery and greater comfort in patients who have undergone FESS or turbinoplasty. This is probably due to its positive effect on the healing process and mucosal trophism.[2]

Our review also indicates that nebulised HA is safe as it was well-tolerated and no untoward effects were reported.

CONCLUSIONS

There is some evidence that topically administered HA improves the global subjective and clinical status of patients with inflammation of the nasopharyngeal and oto-tubaric complex, those with rhinitis or rhinosinusitis, and those who have undergone nasal and sinonasal surgery. However, these findings should be viewed cautiously as they are based on a limited number of studies (including only three involving children), some of which were probably under-powered because of their small patient samples.

CONFLICT OF INTEREST STATEMENT: None declared.

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FIGURE LEGEND

Figure 1: Flow-chart of article selection.

302

Table 1: Results of the included studies.

Topic	Authors and year	No. of pts.	Mean age±SD (years)	Disease	Treatment	Results
Inflammation of the nasopharyngeal and oto-tubaric district	Varricchio *et al*., 2014 [18]	51	5.9±2.1	Acute bacterial rhinopharyngitis	Nebulised thiamphenicol+SH +xylitol 5% *vs* nebulised thiamphenicol+ISS	Thiamphenicol+SH had a significantly greater effect on subjective symptoms, and nasal neutrophilic and bacterial counts than thiamphenicol+ISS
	Torretta et al., 2016 [19]	103	63.3±18.2 months	Chronic adenoiditis with RAOM and OME	Nebulised SH+ISS *vs* nebulised ISS	SH significantly reduced the mean number of all AOM episodes and AOM episodes without spontaneous tympanic membrane perforation, and significantly improved all endoscopic findings. ISS did not reduce the number of AOM episodes and significantly improved only 3/10 endo-scopic findings
	Torretta et al., 2016 [20]	116	62.9±17.9 months	OME and/or RAOM with chronic adenoiditis	Nebulised SH+ISS *vs* nebulised ISS	SH significantly reduced the number of children with impaired otoscopy and tympanometry, conductive hearing loss, and moderate hearing impairment, and significantly improved the mean auditory threshold. No improvement was found in the ISS group
Rhinitis and rhinosinusitis	Gelardi et al., 2013m [17]	78	21-63 (range)	Allergic and non-allergic rhinitis	Nebulised SH+ISS+ intranasal mometasone spray+oral desloratadine *vs* nebulised ISS+ mometasone intranasal spray+oral desloratadine	SH was significantly more effective than ISS in improving rhinorrhoea and sneezing, and reducing nasal exudate.
	Casale et al., 2014 [23]	39	30-63 (range)	Chronic rhinosinusitis	Nebulised SH+ISS *vs* nebulised ISS	SH significantly improved symptom scores and endoscopic findings; no change was observed in the ISS group.

	Cassandro et al., 2015 [27]	80	38.6±13.1 (NIS) 34.8±17.7 (ICS) 38.7±13.1 (NSH) 38.8±13.3 (ICS+NSH)	CRSwNP	Nebulised ISS (NIS) *vs* intranasal mometasone spray (ICS) *vs* nebulised SH+ISS (NSH) *vs* intransal mometasone spray+nebulised SH+ISS (ICS+NSH)	Nasal symptoms, endoscopic and, radio-logical scores, rhinomanometry, and saccharine clearance test significantly improved in the NSH, ICS, and ICS+NSH groups during treatment. In comparison with NIS, NSH, ICS and ICS+NSH led to significant improvements in all scores during and after treatment, and signifycantly reduced the use of oral steroids.
	Gelardi et al., 2016 [22]	89	36.3±7.1	Allergic, non-allergic rhinitis, and mixed rhinitis	Intranasal ointment containing LHT *vs* nasal lavage with ISS	The active treatment significantly improved symptoms and endoscopic features, and reduced the number of inflammatory nasal cells.
Nasal and nasosinusal surgery	Casale et al., 2013 [24]	57	19-78 (range)	Pts. who had undergone radiofrequency turbinoplasty	Nebulised SH+ISS *vs* nasal irrigation with ISS	SH was significantly more effective than ISS in improving symptoms one and two weeks after treatment, and significantly reduced nasal crusting.
	Macchi et al., 2013 [16]	46	37±14 (SH) 40±15 (ISS)	Pts. who had undergone FESS for rhino-sinusal remodelling	Nebulised SH+ISS *vs* nebulised ISS	SH significantly improved nasal dyspnea, ciliary motility and nasal secretions, and significantly decreased endonasal mycetes in comparison with ISS.
	Gelardi et al., 2013 [7]	36	47±14 (SH) 47±14 (ISS)	Pts. who had undergone FESS because of CRSwNP	Nebulised SH+ISS *vs* nebulised ISS	SH significantly improved mucociliary clearance, rhinorrhoea, nasal obstruction, and nasal exudate in comparison with ISS.
	Cantone et al., 2014 [26]	124	41.4±2.4 (SH) 42.4±1.4 (ISS)	Pts. who had undergone FESS because of CRSwNP	Nebulised SH+ISS *vs* nebulised ISS	SH significantly improved symptoms, and endoscopic, SNOT-22 and SF-36 scores in comparison with ISS
	Gelardi et al., 2016 [21]	83	46.4±6.2	Pts. who had undergone FESS because of CRSwNP, CRSwithoutNP, and for purposes of septoplasty and turbinoplasty.	Intranasal ointment containing LHT vs. nasal lavage with ISS	LTH significantly improved symptoms and endoscopic features, and reduced inflam-matory nasal cells in comparison with controls.

Legend:
No.: number;
Pts: patients;
SD: standard deviation;
SH: sodium hyaluronate;
ISS: isotonic saline solution;

ICS intra-nasal corticoid steroid;
RAOM: recurrent acute otitis media;
OME: otitis media with effusion;
AOM: acute otitis media;
FESS: functional endoscopic sinus surgery;
CRSwNP: chronic rhinosinusitis with nasal polyps;
SNOT-22: 22-item Sino-Nasal Outcome Test [29];
SF-36: Italian Short Form-36 questionnaire [26];
LHT: lysine hyaluronate, thymine, and sodium chloride.

Table 2: Overall efficacy of topically administered, according to any otolaryngological condition.

Topic	Overall efficacy
RAOM with or without OME	Moderately effective in prevent AOM episodes
Nasopharyngeal inflammation	Effective
Chronic rhinosinusitis	Moderately effective
CRSwNP	Moderately effective with concomitant ICS
Allergic and non-allergic rhinitis	Moderately effective with concomitant ICS
Nasal and nasosinusal surgery	Effective

Legend:
RAOM: recurrent acute otitis media;
OME: otitis media with effusion;
AOM: acute otitis media;
CRSwNP: chronic rhinosinusitis with nasal polyps;
ICS: intra-nasal corticoid steroid.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	4
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	4

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	4
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	4
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	4
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	5-7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	5-7
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	5-7
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	-
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	5-7
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	5-7
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	8
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	8
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	8
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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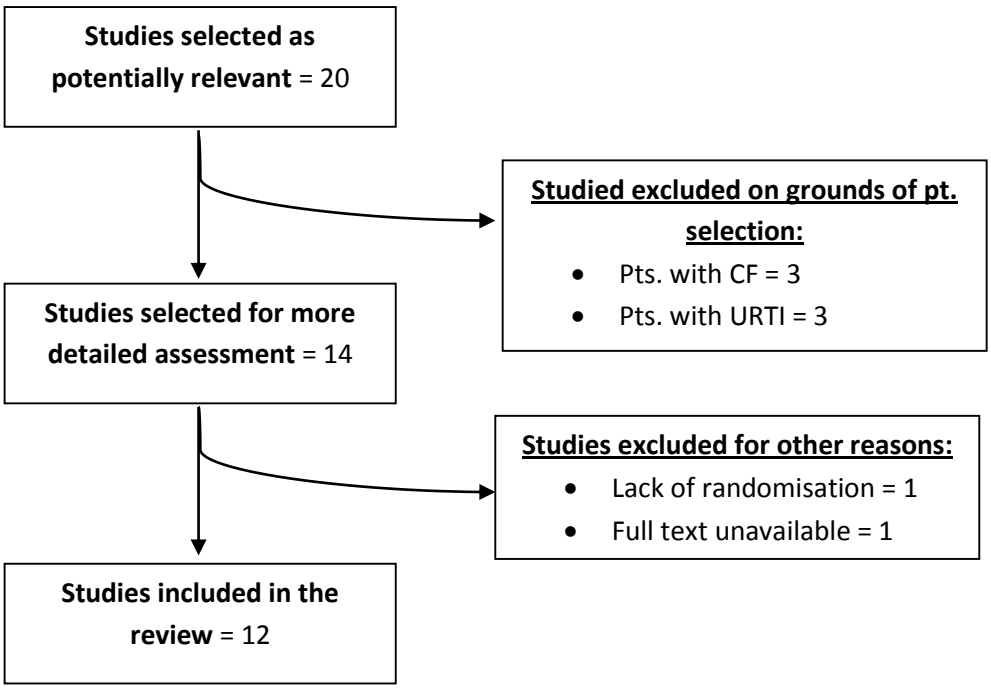
Figure 1: Flow-chart of article selection.



Legend:
Pts: patients;
CF: cystic fibrosis;
URTI: upper respiratory tract infection.