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Efficacy of Intranasal Corticosteroid Sprays in Relieving Clinical Signs of Eustachian Tube Dysfunction: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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ABSTRACT

Objective. Eustachian tube dysfunction (ETD) is prevalent in both pediatric and adult populations. Current clinical guidelines recommend observation over topical intranasal corticosteroids (INCS) for ETD management, which remains controversial. This study aimed to systematically review randomized controlled trials (RCTs) assessing topical INCS efficacy in ETD, and analyze impact through tympanometric normalization.

Methods. PubMed, EMBASE, Web of Science, and Cochrane Library databases were searched. All RCTs assessing INCS in adult or pediatric ETD were included. A meta-analysis of proportions was used to evaluate tympanogram normalization.

Results. Of 330 results, 8 RCTs met inclusion criteria and underwent qualitative data synthesis and risk-of-bias analysis. Meta-analysis of tympanometry data from 4 eligible trials (n=512 ears) revealed no significant difference in tympanometric normalization between INCS and control (OR 1.21, 95% CI 0.65–2.24).

Conclusion. Study results do not strongly support INCS for ETD. Data were limited, emphasizing the need for larger, higher-quality RCTs.

Keywords.

Otitis Media with Effusion, Corticosteroids, Otology, Eustachian Tube, Systematic Review

INTRODUCTION

Eustachian tube dysfunction (ETD) refers to the failure of the eustachian tube to adequately protect, ventilate, or drain secretions and pathogens away from the middle ear[9,10]. Insufficient drainage of the middle ear can result in otitis media with effusion (OME), defined as middle ear fluid accumulation without signs/symptoms of acute infection[11]. An inability of the eustachian tube to equilibrate pressures within the middle ear space and the nasopharynx results in negative middle ear pressure (NMEP)[12-14]. Signs of these common ETD sequelae include middle ear effusion, retraction/reduced mobility of the tympanic membrane (TM), or a flat or left-shifted tympanogram[10,14]. Tympanometry is a highly sensitive (84-93%) tool for ETD diagnosis[15]. ETD is prevalent in both children and adults, particularly those of lower socioeconomic status[16-19].

Concerning management, reduction of edema around the eustachian tube opening through topical intranasal corticosteroids (INCS) theoretically may improve the dysfunction[19-25]. Yet, conclusions from prior clinical trials of INCS impact on ETD have been conflicting, and it remains unclear whether patients without comorbid nasal symptoms would benefit from INCS[26-27]. Current international guidelines for OME advise against pharmacological therapies as the risk/benefit ratio is uncertain, particularly in children[11]. Despite this, across specialties INCS remain one of the most prescribed treatments for ETD patients, with or without additional nasal symptoms[28].

Globally, management of ETD continues to be controversial. To our knowledge, no systematic review and meta-analysis study has previously assessed randomized controlled trials (RCTs) on the specific impact of INCS in both pediatric and adult ETD patients. The present

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study aims to 1) systematically review international literature for RCTs evaluating the ability of INCS to alleviate OME and NMEP in ETD and 2) conduct a meta-analysis of available data.

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METHODS

Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRIMSA) guidelines, a systematic review was undertaken for investigation of this topic. A protocol was produced and registered on PROSPERO (CRD42021264211).

Search strategy

A standardized search query was created using the search items ("Eustachian Tube" or "Eustachian Tube Dysfunction") crossed with ("Flonase" or "Fluticasone" or ("Nasal steroid" AND "Administration, Intranasal")) within the following electronic databases: PubMed, EMBASE, Web of Science, and The Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials (CENTRAL))(Appendix I). No study design filters, nor date limitations were applied to the search. References of included studies were scanned to identify any additional relevant records.

Eligibility assessment

RCTs assessing the effect of topical INCS sprays on at least one of the stated primary outcomes in adult and children of any age clinically diagnosed with ETD were included. As otitis media with effusion (OME) is a common complication of ETD, clinical diagnoses of OME or middle ear effusion (MEE) were also accepted. No restrictions were set for control treatment. Studies that were non-RCTs, non-English, still unpublished, or that focused on the incorrect patient population (e.g., patulous ETD, acute otitis media, rhinosinusitis) or intervention (e.g., orally administered corticosteroids) were excluded.

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Initial pooled results underwent screening for duplicates and title/abstract eligibility, and eligible papers underwent a full text review to yield the final included references. Records were managed within the software Zotero (version 6.0.13). Screening and eligibility assessment were performed independently in a blinded, standardized manner through the website application Rayyan by 2 reviewers (TN, CT) using standardized eligibility forms[29] (Appendix II). Disagreements between reviewers were resolved by consensus. Consultation of third author was planned if warranted but was not found to be necessary.

Outcome measures

Primary outcomes included changes in middle ear fluid and negative middle ear pressure (NMEP) severity (assessed through tympanometry and/or otoscopy), as well as ETD symptomatology.

Additional outcomes of interest included pure tone audiometry, adverse events, ability to delay procedural treatment, cost-effectiveness, quality of life, and nasopharyngoscopy, although analysis of these outcomes was not a requirement for study inclusion.

Data extraction

A slightly modified version of Cochrane's data collection form for RCTs was piloted and used to extract data on these outcomes (Appendix II). One review author (TN) extracted data from included studies, and a second author (CT) checked extracted data for accuracy. Data from studies with multiple publications were planned to be extracted into one form and reported as a single study. The extraction form structure included collection of general information on the

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study, as well as data on study methods, participant characteristics, comparison and intervention characteristics, description of study outcomes, and summary of data and analysis (**Table I**).

Quantitative data synthesis and statistical analysis

A meta-analysis was planned for one or more of the outcomes of interest, conditional on the clinical and methodological heterogeneity of included studies[30]. Narrative synthesis was to be implemented if extracted data was found to be overall insufficient for rigorous quantitative analysis.

Data was available from 4 RCTs to conduct a meta-analysis of proportions using R (version 4.1.3). The outcome measure was tympanogram *normalization*, defined as proportion of study group (by ear) recovering completely on tympanometry (i.e., from Type B/C at baseline to Type A immediately upon completion of the intervention schedule).

Tympanometry data from 512 ears with baseline ETD were pooled. A random-effects model was implemented based on the computed I^2 value for included studies (I^2=53.8% [0.0%; 84.7%], moderate statistical heterogeneity). Comparison of normalization rates between study arms was expressed as an odds ratio (OR) with 95% confidence interval (CI), where OR >1 favors INCS treatment over control intervention. Subgroup analyses were planned to assess INCS impact on ETD by characteristics such as INCS type and dosage schedule, patient age, and patient comorbidities, however this was limited by the lack of available data. Due to significant heterogeneity in the collection and reporting of data for the other outcomes across the included references, a quantitative analysis was not feasible for other primary or additional outcomes of interest.

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Qualitative data synthesis

Narrative synthesis was employed to report the tympanometry data from additional included studies not eligible for quantitative analysis, for which collected data contained high methodological and clinical heterogeneity. For qualitative synthesis, a broader measure of treatment impact, tympanogram *improvement*, was reported. This outcome was defined as proportion of study group (by subject) found to experience any post-intervention improvement on tympanogram – either partial resolution (i.e., from Type B at baseline to Type C post-intervention) or complete resolution (i.e., from either Type B or C at baseline to Type A post-intervention).

Quality Assessment

A standard critical appraisal tool, the Cochrane revised risk-of-bias form for randomized trials (RoB 2)[31], was used to assess for outcome-specific risk of bias in the tympanometry results of all eligible studies (Appendix III). Randomization process, deviations from intended interventions, missing outcome data, measurement of outcome, and selection of reported results were individually assessed. Disagreements were planned to be resolved by consensus, although was not found to be necessary. RoB assessment results were summarized using the *robvis* tool[32].

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RESULTS

Description of included studies

Study characteristics. Initial pooled results (n=330) underwent title/abstract screening, and full reports were sought for potentially eligible papers (n=21). Fifteen reports underwent full text review, as detailed in **Figure I**. Based on study characteristics, eight RCTs (nine publications) were eligible for data synthesis (**Figure II)**. Study publication dates ranged from 1982 to 2020, and trials ranged in size from 59 to 217 participants. The majority were conducted internationally (n=6), while two studies were carried out within the United States. Of the eight eligible, four studies, performed between 1982 and 2011 and randomizing 312 subjects, reported data with clinical and methodological homogeneity that allowed for pooling and subsequent meta-analysis (highlighted in **Figure II**).

Patient characteristics. All studies included patients with clinically diagnosed manifestations of ETD. Most studies evaluated only children (n=7), with varying age restrictions, while one study evaluated both children and adults[3]. The mean age of included patients ranged between 3.8[5] – 41.7 years[3].

In two of the eight studies, all[6]/nearly all (83.3%)[2] pediatric patients had an additional comorbidity of adenoidal hypertrophy.

Intervention and control characteristics. INCS sprays assessed were mometasone [2,5,6,8], beclomethasone[1,4,7], and triamcinolone acetonide[3]. Duration of treatment ranged from 4 weeks to 24 weeks. In the majority of the included RCTs, INCS intervention was assessed alone in comparison to placebo[2,3,4,6,8].

However, two of the included studies instead assessed INCS in comparison to no treatment (with[1] or without[5] underlying co-intervention administered to both intervention and

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comparison groups). In another included study, two control groups were assessed – one group provided with no treatment and one group provided with a placebo nasal spray[7]. For this study, data was available only for both groups combined; therefore, comparison data was extracted for both control groups (no treatment and placebo) in conjunction.

Quantitative Analysis of Results – Tympanometric Normalization

Tympanometry data from four of the included trials were eligible for meta-analysis of odds ratios (OR) for post-intervention rate of complete tympanometric normalization by ear[1,3,4,7] (**Figure III**).

In 512 pooled ears, there was no significant difference in the overall proportion of patients that recovered from Type B/C tympanogram at baseline to Type A tympanogram post-intervention (OR 1.21, 95% CI 0.65–2.24) when comparing ETD patients receiving INCS to those receiving control treatment. Tympanometry data obtained from included studies were not adequate for sub-group analysis.

Qualitative Synthesis of Results

Tympanometric Improvement. Eight RCTs were determined eligible for analysis through the systematic review screening, and a qualitative analysis was conducted in which tympanometry data from all eight studies (n = 771 subjects) were compiled regardless of heterogeneity in data measurement and reporting[1-8] **(Figure IV).**

Only five of the eight studies reported a statistical comparison between INCS and control arms for post-intervention tympanometric data[3,4,5,6,8]. Of these, only one study reported a significant difference (comparison between INCS and placebo saline spray, $p = 0.0002$)[6].

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Qualitatively, it seemed that neither studies with the oldest participants[3] nor those with the youngest participants[5] found INCS to be more effective in treating ETD, at least in terms of tympanometric improvement.

Adverse events. Of the eight studies, six discussed adverse events that emerged during the course of treatment, while two did not discuss this outcome[1,5]. There were overall minimal differences in adverse events between INCS and control groups.

Qualitative Synthesis of Additional Outcomes. A number of studies discussed changes in reported symptoms[2, 3, 6, 7, 8], otoscopy[1, 2, 7], and pure tone audiometry[2, 4, 6, 8]. Very few studies reported on quality of life[2,8], cost-effectiveness[8], and nasopharyngoscopy[2]. None contained discussion of INCS ability to postpone or reduce need for surgical management (e.g., tympanostomy tube placement).

Risk of Bias Assessment

Risk of Bias assessment was performed for the outcome of tympanometry across all included studies, though five domains (**Figure V)**. Three studies were assessed as low risk of bias[2,3,8].

Five of the trials were found to have some concerns in the assignment of intervention (Domain 2), either due to a lack of specification about analysis on an intent-to-treat basis, or due to lack of clarity on the awareness of participants and outcome assessors regarding intervention allocation[1,4,5,6,7].

Of these five trials, one was found to be at high risk of bias due to missing outcome data beyond that accounted for by loss to follow-up[4] (Domain 3). The remaining four trials were not found to have high-risk characteristics. However, due to the aforementioned concern, as well as

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additional concerns about the randomization process and data reporting (Domains 1 and 5), these were judged as "some concerns" for bias[1,5,6,7]. Two of these four trials did not compare INCS to placebo, and instead conducted a comparison to no treatment[1,5]. This may be of concern, as INCS must be administered as a spray intranasally, and lack of treatment was likely an indicator to study participants and outcome assessors as to how the intervention was allocated. This poor allocation concealment may have compromised the benefits of randomization for these trials, and potentially lowered reliability of each study's conclusions.

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DISCUSSION

The aim of this study was to systematically review randomized controlled trials evaluating the ability of INCS to alleviate clinical signs (OME, NMEP) in patients with ETD and conduct a meta-analysis of available data. Study results do not provide supportive evidence for the use of INCS to reverse sequelae of ETD in children and adults. On the basis of complete tympanometric normalization, neither INCS nor control interventions were favored to a statistically significant degree when pooling tympanometric data from ETD patients in four RCTs[3,4,7].

Corticosteroids have also failed to demonstrate benefit for treatment of ETD sequelae in previous systematic reviews and meta-analyses[9, 33-34]. However, two of these studies focused on treatment of only adult ETD patients (≥18 years[9]; ≥ 16 years[33]), and assessed a wide range of medical management types, with very little data compiled specifically regarding INCS efficacy alone. The third of these previous studies assessed the use of steroids in children (≤12 years) diagnosed with OME, however the majority of outcome data characterized oral steroid treatment rather than INCS[34]. Based on these data, current clinical guidelines have recommended against medical management for ETD. Continued observation is recommended instead, with tympanostomy tube placement for at risk patients (unilateral or bilateral OME persisting for ≥3 months and/or type B tympanogram)[11].

Generally, conservative medical management reduces both risk and cost relative to procedural treatments. However, previous data have shown that intranasal corticosteroids are one of two medical management strategies with the highest adult-ETD associated direct costs[28]. All studies except one[5] demonstrated less than ideal rates of spontaneous resolution in the control group (16.7%-52.3%), despite evaluation over long periods of time (up to 24 weeks[2]). In

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pediatrics patients, ETD persistence without treatment can interfere with behavioral development and impairments in learning, language, and speech[11,17,35]. Given that INCS are not definitively effective, an investigation of alternative interventions is warranted.

Compared to INCS, a one-time tympanostomy tube placement may be more effective for ETD as it requires no daily action and is more resistant to variability in compliance. For many patients, tympanostomy tube placement may only require a brief outpatient procedure. Notably, one of the senior authors performs myringotomy as an anecdotal predictor of response to tympanostomy. Additional interventions such as eustachian tube insufflation and eustachian tube balloon dilation may also be effective, however more conclusive data are needed on these options.

Of note, this study primarily focused on studies of patients without comorbid nasal symptoms. Patients experiencing nasal symptoms would presumably benefit from use of INCS to treat their comorbid nasal condition, but the decision to start INCS is less clear for patients without comorbid symptoms. Therefore, while there may be an association with nasal comorbidities and ETD, a strength of this study is that it may better address patients who experience ETD without comorbid nasal symptoms.

Further discussion.

INCS may be effective in pediatric ETD with a primarily adenoidal pathogenesis. In 2 of the 4 studies which reported INCS to be an effective treatment, a significant proportion (all[6] or nearly all (83.3%)[2]) of pediatric patients had the additional comorbidity of adenoidal hypertrophy. While neither study was entered in the meta-analysis, the high rate of comorbid adenoid hypertrophy found in these studies may suggest a relationship between pediatric ETD

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and adenoid hypertrophy. Adenoidal hypertrophy is the most common entity causing eustachian tube obstruction in children, and inflammation of the adenoid pads is a theorized etiology for ETD. In children with nasal pathology, such as inflamed or enlarged adenoids, INCS efficacy may be more related to reductions in adenoidal inflammation, which may improve eustachian tube function.

Age does not seem to play a role in INCS efficacy. The mean age of included patients ranged between 3.8[5] – 41.7 years[3]. This includes pediatric patients on both sides of the threshold (around 7 years of age) for morphological maturity of the eustachian tube, as well as adults[36]. Qualitatively, in terms of tympanometric improvement, it seemed that neither studies with the oldest participants[3] nor those with the youngest participants[5] found INCS to be more effective in treating ETD. Of note, RCTs assessing the impact of INCS in ETD in adults are scarce. Only one study including the adult population was found for systematic review inclusion, identifying a clear deficit in current clinical evidence around this problem.

Limitations. Data regarding differences in adherence to the nasal spray regimen between placebo and intervention groups were only available for two of the 8 included studies[7,8]. INCS are most effective when used consistently. While studies that reported on adherence found no significant difference between treatment groups, for other studies consistently the administration schedule was followed.

Additionally, it is unspecified how included ETD patient diagnoses were distributed between acute (signs/symptoms <3 months) versus chronic (signs/symptoms ≥3 months) for all included studies except one[7]. While management is similar between acute and chronic ETD, patients with acute symptoms may have been more likely to self-resolve during treatment in both placebo and

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intervention groups[10]. The impact of this limitation was likely small in the context of this study, however may be important to keep in mind for future studies in this topic.

Overall, available data obtained through systematic review was small in quantity, extremely heterogenous, and on average mediocre in quality. This precluded any planned quantitative subgroup analysis, and lessens the predictive power and generalizability of our findings. Trends in efficacy by study size, participant age distribution, INCS type, and/or treatment duration were only able to be assessed qualitatively. Existing systematic review and meta-analyses, in conjunction with the current study, provide evidence that a significant gap remains in the literature. Larger, higher quality RCTs are needed with thorough subgroup data collection to more rigorously address this still unresolved contention in ETD medical management.

Conclusions.

Study results do not provide supportive evidence for the use of INCS in ETD. Neither INCS nor control interventions were favored to a statistically significant degree when pooling tympanometric normalization rates from ETD patients in four RCTs[1,3,4,7]. As study results do not provide supportive evidence for the use of INCS in ETD, current clinical recommendations of avoiding INCS for treatment of ETD sequela remain acceptable, and further investigation of alternative interventions is warranted.

The precise mechanism of action of INCS on ETD remains unclear. Larger, higher quality randomized controlled trials are needed to more rigorously identify potential variations in INCS efficacy among ETD patient subgroups. Authoritative clinical data is particularly lacking in the adult ETD patient population as well as in comparing ETD patients with comorbid nasal

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conditions (e.g., allergic and non-allergic rhinitis, inflammation of the adenoids) to those with alternative ETD etiologies.

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Précis

- Eustachian tube dysfunction (ETD) is multifactorial and leads to insufficient drainage and pressure regulation of the middle ear cavity, which can significantly impact quality of life in adult and pediatric populations.
- Topical administration of anti-inflammatory corticosteroids is theorized to improve ETD, however conclusions from prior clinical trials on the subject have been conflicting.
- Current international guidelines advise against intranasal corticosteroids for ETD and its common sequelae, yet many providers continue to prescribe intranasal corticosteroids for this condition.
- To our knowledge, no systematic review and meta-analysis study has previously assessed randomized, controlled trials on the specific impact of intranasal corticosteroids in both pediatric and adult ETD patients, the aim of the present study.

- We found that current evidence on this topic is of mediocre quality and does not support the use of intranasal corticosteroids in ETD.

- This validates previous clinical guidelines and reveals a need for higher quality, more rigorous clinical trials studying this issue, particularly in how INCS efficacy may vary in adults and with differences in ETD etiology.

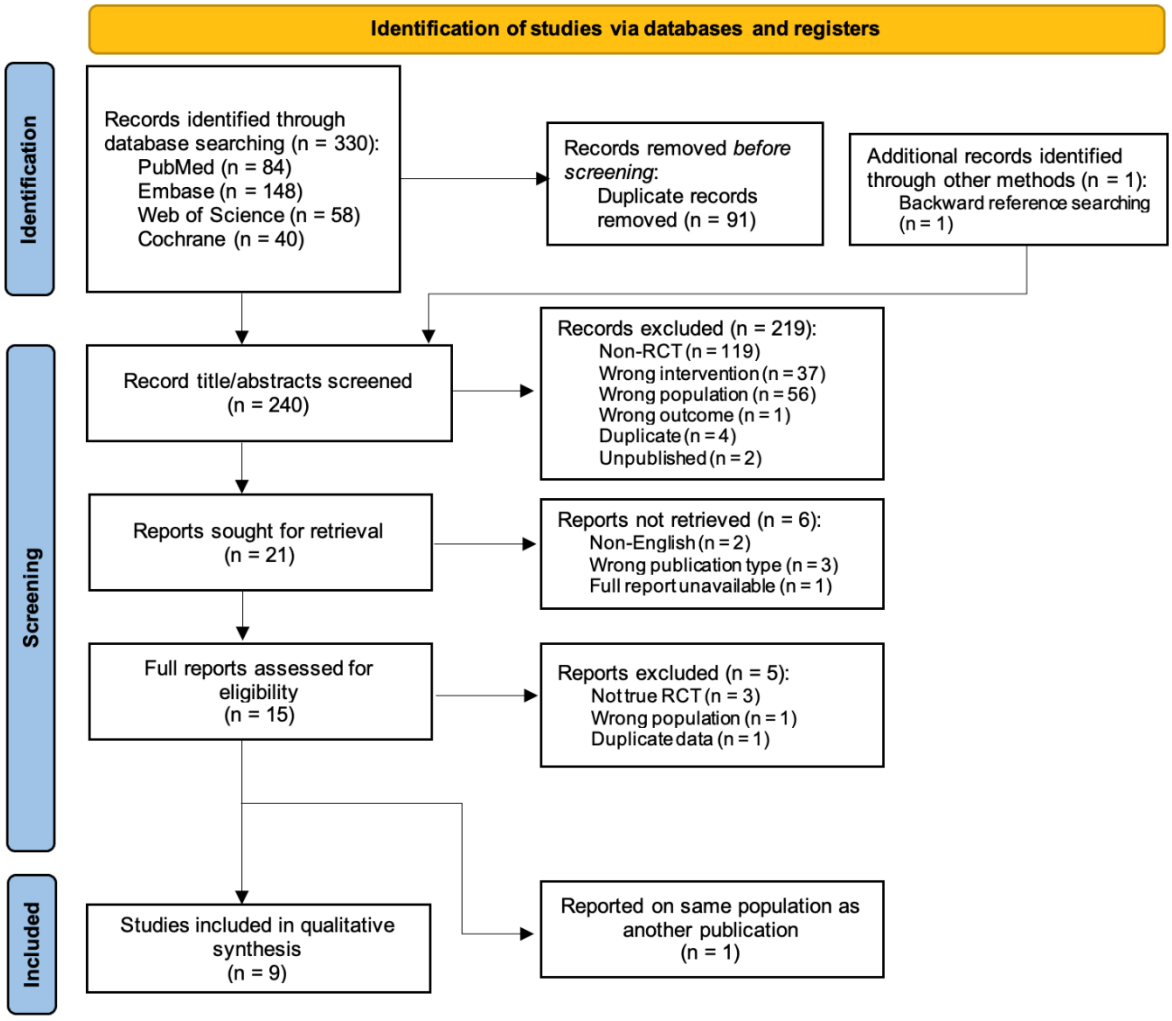

Figure 1. PRISMA flow diagram

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SUMMARY OF KEY STUDY CHARACTERISTICS

Study ID	Country	Participant Ages	Size	INCS type	Duration	Comparison	Outcomes Measured	Study Author Conclusion	RoB
Barati 2011[1]	Iran	Children, Age 1-10	92	Beclomethasone*	4 weeks	No treatment (Co-intervention: Antibiotic + Decongestant)	1) Tympanogram normalization 2) Otoscopy 3) Reported symptoms (parent)	**Effective**	Some concerns
Bhargava 2014[2]	India	Children, Age 2-12	62	Mometasone	24 weeks	Placebo	1) OME Resolution (Tympanometry, Otoscopy) 2) Reported symptoms 3) Audiometry	**Effective**	Low
Swain 2020[6]	India	Children, Age 5-10	96	Mometasone	12 weeks	Placebo	1) OME Resolution (Tympanometry, Otoscopy) 2) Reported symptoms 3) Audiometry	**Effective**	Some concerns
Tracy 1998[7]	United States	Children, Age 3-11	59	Beclomethasone*	12 weeks	Placebo (Co-intervention: Antibiotic)	1) Tympanogram normalization 2) Otoscopy 3) Reported symptoms (parent)	**Effective**	Some concerns
Gluth 2011[3]	United States	Adults (≥18 years) Children (6-17 years)	91	Triamcinolone	6 weeks	Placebo	1) Tympanogram normalization 2) Reported symptoms	**Ineffective**	Low
Lildholdt 1982[4]	Denmark	Children, Age 4-14	70	Beclomethasone	4 weeks	Placebo	1) Tympanogram normalization 2) Audiometry	**Ineffective**	High
Rahmati 2017[5]	Iran	Children, Age 2-6	84	Mometasone	4 weeks	No treatment	1) Tympanogram normalization	**Ineffective**	Some concerns
Williamson 2009[8]	United Kingdom	Children, Age 4-11	217	Mometasone	12 weeks	Placebo	1) Tympanogram normalization 2) Reported symptoms 3) Audiometry	**Ineffective**	Low

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Figure 2. Summary of Key Study Characteristics

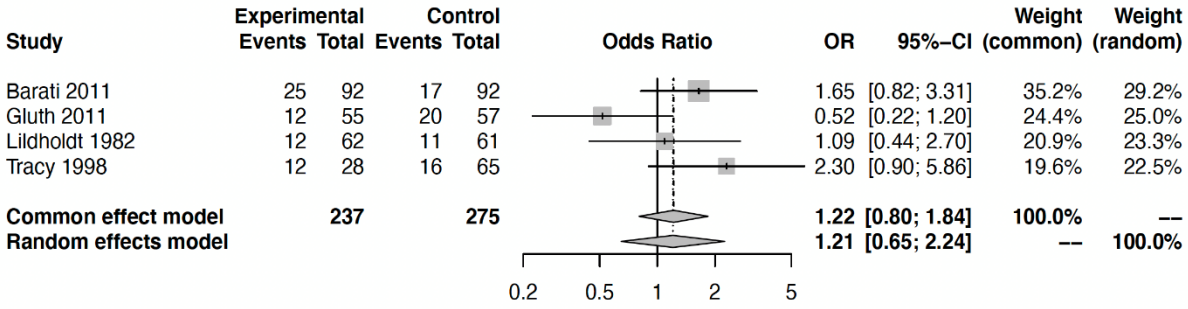

Figure 3. Metaanalysis Pooled OR

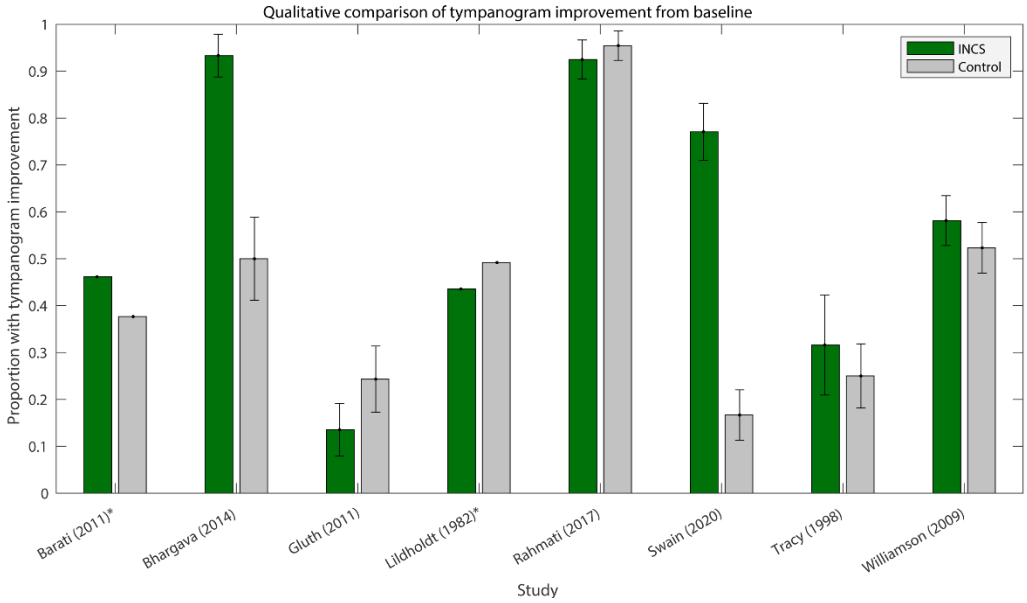

Figure 4. Tymp Improvement Qualitative Agg

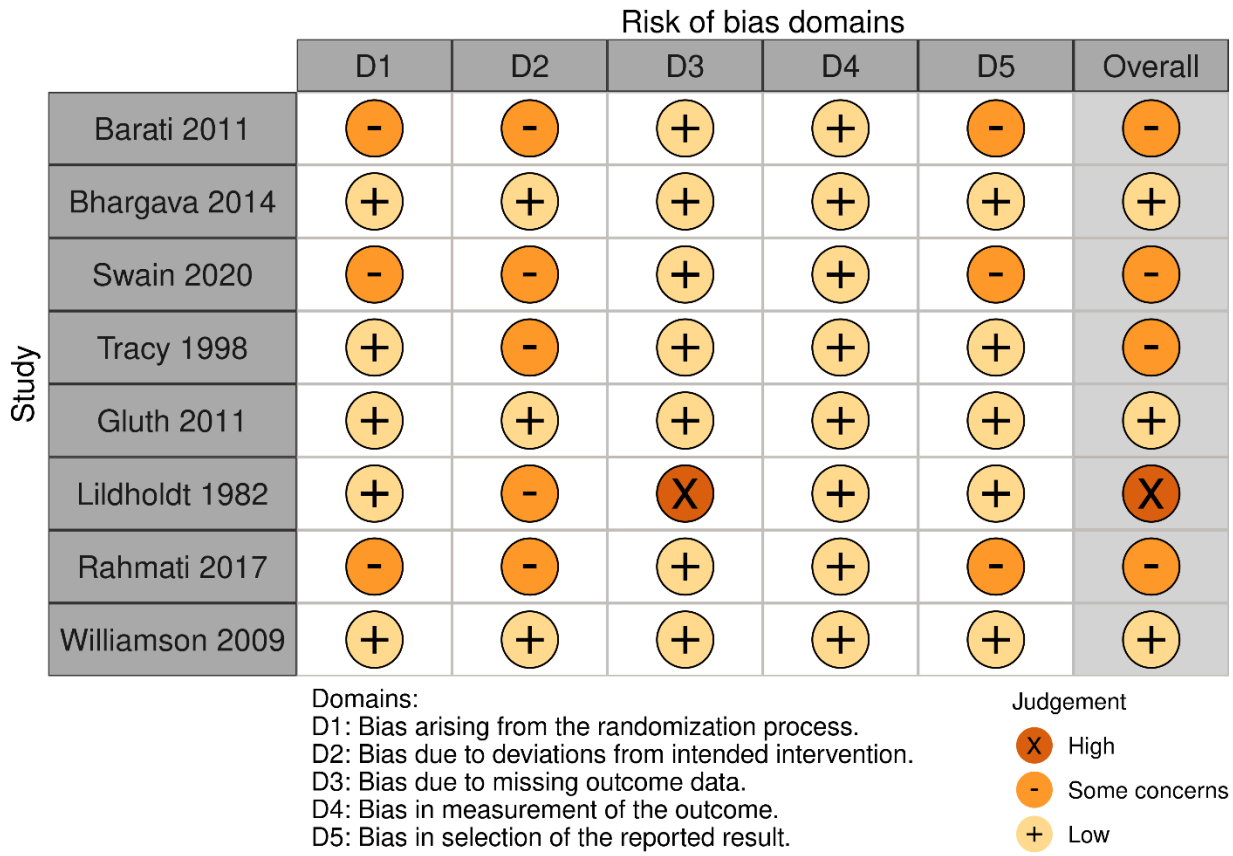

Figure 5. ROB2 figure colorblind friendly

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