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Risk of aspiration pneumonia in paediatric patients with dysphagia who were found to have laryngeal penetration on the instrumental swallow evaluation: a systematic review protocol

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ABSTRACT

Introduction Dysphagia affects several children in USA and around the globe. Videofluoroscopic Swallow Study (VFSS) and Fiberoptic Endoscopic Evaluation of Swallowing (FEES) are the most objective studies to define swallowing function. The presence of tracheal aspiration during VFSS or FEES in children with dysphagia is associated with an increased risk of aspiration pneumonia. However, the association of laryngeal penetration with aspiration pneumonia remains unclear. This systematic review aims to assess the risk of aspiration pneumonia in children with dysphagia with laryngeal penetration on VFSS/FEES and compare it with children with tracheal aspiration and children with neither tracheal aspiration nor laryngeal penetration.

Methods and analysis This study will be a systematic review and meta-analysis. Systematic electronic searches will be conducted on PubMed, EMBASE, Web of Science, CINHAL, Scopus, Cochrane CENTRAL, LILACS and WHO Global Index Medicus. We will include studies published through 6 October 2021. Primary outcome will be the incidence of aspiration pneumonia. Secondary outcomes will be incidence of hospitalisation, paediatric intensive care unit admission, enteral tube requirement, growth, symptoms improvement and mortality. The Cochrane Risk of Bias In Non-Randomised Studies of Interventions tool will be used to assess the risk of bias. Meta-analysis will be used to pool the studies. We will pool dichotomous outcomes to obtain an odd ratio (OR) and report with 95% CI. Continuous outcomes will be pooled to obtain mean difference and reported with 95% CI. Overall grade of evidence will be assessed using Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria, and findings will be presented in a summary of findings table.

Ethics and dissemination This study is a systematic review without contact with patients. Therefore, IRB approval is not required. Authors consent to publishing this review. Data will be kept for review by editors and peer reviewers. Data will be available to general public on request.

Strengths and limitations of this study

- An exhaustive electronic search on multiple databases will be used for systematic review and meta-analysis.
- The study will offer clarification about the risk of aspiration pneumonia in children who have laryngeal penetration on Videofluoroscopic Swallow Study or Fiberoptic Endoscopic Evaluation of Swallowing.
- We will use the Grading of Recommendations Assessment, Development and Evaluation approach to assess evidence quality.
- The studies included in the systematic review may not report all the outcomes of interest, which is a potential limitation.

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INTRODUCTION

About 500 000 children are affected by dysphagia in the USA.[1] Clinical evaluation of children with dysphagia involves obtaining a history, performing a physical examination and additional studies such as a Videofluoroscopic Swallow Study (VFSS) and Fiberoptic Endoscopic Evaluation of Swallowing (FEES). The VFSS is the most objective study to evaluate the swallow function in a child. VFSS gives objective data about chewing, the progression of the bolus from the oral cavity to the pharynx and information about laryngeal penetration and tracheal aspiration.[2] Laryngeal penetration is defined as the passage of material into the larynx without passing the vocal cords. In contrast, tracheal aspiration is defined as the passage of material below the

vocal cords into the trachea.[3] The finding of tracheal aspiration on VFSS in children with dysphagia is associated with a threefold increase in the risk of aspiration pneumonia.[4] Aspiration is among the most common diagnoses in infants who present with apparent life-threatening events.[5] While tracheal aspiration is strongly associated with aspiration pneumonia in children,[6] the association of laryngeal penetration with aspiration pneumonia remains unclear.[7 8] Some retrospective studies have shown an increased incidence of aspiration pneumonia in children with laryngeal penetration,[9 10] whereas others did not find a significant correlation.[11 12] To the best of our knowledge, there are no studies that have systematically reviewed the published data on the association of laryngeal penetration and the risk of aspiration pneumonia in children with dysphagia.

Objective

To assess the risk of aspiration pneumonia in children with dysphagia with laryngeal penetration on VFSS or FEES, compare it with children with tracheal aspiration and children who have neither tracheal aspiration nor laryngeal penetration.

METHODS AND ANALYSIS

We followed the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols guidelines for reporting the protocol and will follow the same guidelines for reporting the main review.

Study type

We will include observational studies, including both cohort and case–control studies. We will exclude case series, case reports and observational studies that did not have a comparison group.

Population

Population will include paediatric patients (<18 years) with dysphagia who have been evaluated with VFSS or FEES. We will consider studies that include a mixed population with and without anatomical problems. We will also include studies where the anatomical problem was not known before performing VFSS. However, we will exclude studies that focused exclusively on patients with a particular anatomical anomaly of the aerodigestive tract (eg, cleft palate) or a particular medical diagnosis (eg, myasthenia gravis, poststroke); the results from those studies may not be generalisable to the population of interest.

Intervention/exposure

Our primary exposure of interest is laryngeal penetration on VFSS or FEES in paediatric patients with dysphagia. We will exclude studies in which the VFSS or FEES was not done. We will consider exposure as yes or no (any laryngeal penetration vs no laryngeal penetration for any consistency) and also consider the degrees of laryngeal penetration. The degree of laryngeal penetration will be categorised using the eight point aspiration penetration scale as follows[3]:

1. Material does not enter airway.
2. Material enters the airway, remains above the vocal folds and is ejected from the airway.
3. Material enters the airway, remains above the vocal folds and is not ejected from the airway.
4. Material enters the airway, contacts the vocal folds and is ejected from the airway.
5. Material enters the airway, contacts the vocal folds and is not ejected from the airway.
6. Material enters the airway, passes below the vocal folds and is ejected into the larynx or out of the airway.
7. Material enters the airway, passes below the vocal folds and is not ejected from the trachea despite the effort.
8. Material enters the airway, passes below the vocal folds and no effort is made to eject.

We will also consider categorising the exposure based on mild/none versus moderate versus deep laryngeal penetration. The definition of none/mild versus moderate versus deep laryngeal penetration will be based on definitions given in reference[8]: none/mild laryngeal penetration: penetration of contrast medium under the tip of the epiglottis; moderate penetration: entry of contrast medium into the upper two-thirds of the laryngeal vestibule and remaining above the arbitrary plane that extends from the top of the arytenoids to the top of the thyroid cartilage and; deep laryngeal penetration: entry of contrast medium into the lower one-third of the laryngeal vestibule below the arbitrary plane that extends from the top of the arytenoids to the top of the thyroid cartilage; this level of laryngeal penetration may or may not result in the coating of the vocal cords. We will consider the penetration score discussed above: score 0–3 as mild/none, score 4: moderate and score 5: deep laryngeal penetration.

Comparison

We will compare the exposure group with patients with tracheal aspiration, that is, the passage of material below the vocal folds, and patients with neither penetration nor aspiration on VFSS. We will exclude studies that did not have a comparison group.

Outcomes

Primary outcome

Incidence of aspiration pneumonia (any severity): Dichotomous outcome measured at 3 months, 6 months and at the longest follow-up.

We will use the WHO definition to define pneumonia in children between 2 and 59 months of age as cough and/or difficulty breathing with tachypnoea and/or chest indrawing. ‘Severe pneumonia’ will be defined as pneumonia with general danger signs, including not being able to drink, persistent vomiting, convulsions, lethargy or unconsciousness, stridor in a calm child or severe malnutrition.[13]

Secondary outcomes

- Incidence of hospitalisation: Dichotomous outcome measured at 3 months, 6 months and at the longest follow-up.
- Incidence of paediatric intensive care unit (PICU) admission: Dichotomous outcome measured at 3 months, 6 months and at the longest follow-up.
- Enteral tube requirement: Dichotomous outcome measured at 3 months, 6 months and at the longest follow-up.
- Mortality: Dichotomous outcome measured at 3 months, 6 months and at the longest follow-up.
- Weight for age (kg or Z scores): Continuous outcome measured at 3 months, 6 months and at the longest follow-up.
- Height for age (cm or Z scores): Continuous outcome measured at 3 months, 6 months and at the longest follow-up.
- Body mass index (BMI) for age (kg/m^2 or Z scores): Continuous outcome measured at 3 months, 6 months and at the longest follow-up.
- Changes in feeding practices (thickening or slowing): Dichotomous outcome measured at 3 months, 6 months and at the longest follow-up.
- Adverse events: Dichotomous outcome.

Literature search

Systematic electronic searches will be conducted on multiple electronic databases, including PubMed, EMBASE, Web of Science, CINHAL, Scopus, Cochrane CENTRAL, LILACS and WHO Global Index Medicus. We will include studies published through 6 October 2021. We will also search the website ClinicalTrials.gov to look for ongoing studies. No restrictions will be applied to the searches based on language, outcomes, publication status or publication date. We will also search for the reference sections of previously published studies to look for eligible studies. We have two librarians on our team who will help with the literature searches. A proposed search strategy is shown in online supplemental appendix 1.

Data extraction and synthesis

Selection of studies

The selection of studies will proceed by a three-stage process. Two authors will first screen the titles to identify potentially eligible studies. Any studies determined to be eligible at this step will proceed to the second stage of screening for a full-text review. Lastly, any studies retained after the full-text review will proceed to the third step of full data extraction. The software Covidence will be used to help with the screening and data extraction.[14]

If a study is only available in abstract form, we will contact the authors to obtain complete details. If a study is available in another language, we will use local resources for translation. If a study is published in multiple publications, that study will be counted as one, and data will be extracted from all available sources.

Data extraction

We will design and use a data extraction sheet to collect information from selected studies. Two authors (VA and LR) will independently use the data extraction sheets and compare their findings. Any incongruence or question will be resolved by discussion and with the help of the senior author on the team. We will extract the information for the study site, study year, study population, exposure (laryngeal penetration, tracheal aspiration), comparison, outcomes, risk of bias and confounding factors.

The authors of the included studies may not follow a uniform definition of pneumonia. We will assess the definition of pneumonia in each of the included studies and see if they followed the WHO definition. If a study does not follow the WHO definition, we will note that but still include the data from that study as reported by the authors. If the authors report the data on pneumonia based on severity (like mild, moderate and severe), and these categories are mutually exclusive. In that case, we will combine these categories to make one outcome (pneumonia, yes or no).

Assessment of risk of bias in included studies

The Cochrane risk of bias in non-randomised studies of interventions tool will be used to assess the risk of bias in studies. This tool will evaluate each study as a hypothetical randomised trial and will cover domains through which bias may be introduced. We will address five domains of 'signalling questions,' including bias due to confounding, bias in the selection of participants into the study, bias due to missing data, bias in the measurement of outcomes and bias in selecting the reported result. Each domain will receive a judgement regarding the risk of bias—low, moderate, serious or critical. The highest risk of bias in one domain will determine the overall risk of bias from a study, regardless of lower risks in other domains.[15]

Data synthesis

Findings from all included studies will be reported in a narrative synthesis. We will also conduct meta-analyses to quantitatively synthesise evidence across studies if data are available from more than one study and there is clinical and methodological homogeneity. Dichotomous outcomes will be combined to obtain ORs and will be reported with 95% CI. Continuous outcomes will be combined using mean difference and will also be reported with their 95% CI. We will use the random effect models to pool the data using the generic inverse variance method of meta-analysis. The software RevMAN[16] and STATA-16[17] will be used for statistical analysis.

We will include the occurrence of aspiration pneumonia, incidence of hospitalisations, PICU admission, enteral tube requirement, mortality and changes in feeding practices as dichotomous values and adverse events (yes/no). For these dichotomous outcomes, the total number of participants for each group and the number of participants experiencing an event will be extracted. In addition, we will include weight for age, height for age and

Table 1 GRADE method for rating up or down the quality of evidence[20]

Study design	Quality of evidence	Lower if	Higher if
Randomised trial →	High	Risk of bias ► 1 Serious ► 2 Very serious Inconsistency ► 1 Serious ► 2 Very serious Indirectness ► 1 Serious ► 2 Very serious Imprecision ► 1 Serious ► 2 Very serious Publication bias ► 1 Likely ► 2 Very likely	Large effect +1 Large +2 Very large Dose response +1 Evidence of a gradient All plausible confounding +1 Would reduce a demonstrated effect or +1 Would suggest a spurious effect when results show no effect
	Moderate		
Observational study →	Low		
	Very low		

GRADE, Grading of Recommendations Assessment, Development and Evaluation.

BMI as continuous values. For continuous outcomes, the data will be pooled to obtain a mean difference. This will be reported with a 95% CI. If the data are reported in different units (eg, some studies report weight in kg and others in Z scores), the standardised mean difference will be used and reported with a 95% CI. If a study does not report the SD for a continuous outcome, we will contact the authors to obtain the data. If the authors do not have the SD data available, we will use SD from a similar study with a similar study population.

Dealing with missing data

Attrition will be noted during data extraction. We will contact authors if data are missing for some cases or if reasons for dropout are not reported. If a study does not report SD and we cannot retrieve these values from authors, we will find another study with a similar sample size that reports the same data and uses the SD values reported in this study. If the data is missing for the key variables, we will write to the authors to request additional data.

Assessment of heterogeneity

Heterogeneity is defined as any variability among studies in a systematic review. Clinical heterogeneity is described as variability among participants, interventions and outcomes studied. Methodological heterogeneity is variability in study design, outcome measurement tools and risk of bias. Lastly, statistical heterogeneity is defined as the variability in the intervention effects being evaluated in different studies, resulting from clinical or methodological heterogeneity.[18] Statistical heterogeneity will be assessed using the I^2 statistics and χ^2.[19] Low, moderate and high levels of heterogeneity are defined with upper limits of 25%, 50% and 75% for I^2, respectively. Calculated values are considered to be significant for heterogeneity when the I^2 value is >50% or the p <0.1. Subgroup analyses will be performed to determine the reasons for any statistically significant heterogeneity.

Assessment of reporting bias

Small study effects and publication bias in meta-analysis will be interpreted with funnel plots. If funnel plot asymmetry is present, weighted linear regression (Egger) tests will be used to determine the presence of bias when there are more than ten studies in the meta-analysis.

Subgroup analysis and investigation of heterogeneity

1. Study population: age: infants (<1 year of age) versus children (1–5 years of age).
2. Study population: neurological comorbidity: children with central nervous system (CNS) anomalies versus children with no known CNS anomalies.
3. Study population: syndromic comorbidity: children with a syndromic diagnosis versus children with no syndromic diagnosis.
4. Study population: anatomic anomalies of airway or gastrointestinal tract: children with anatomical anomalies versus children with no anatomical anomalies.
5. Exposure: Aspiration scale score: Scores of 0–2 vs 3–5 vs 6–8.
6. Exposure: laryngeal penetration: none/mild versus moderate versus deep penetration.

Exposure: consistency of food: thin liquid versus thick liquid versus puree versus solid food.

Exposure: severity of impairment of swallow reflex initiation:[8] normal versus mild, moderate versus severe versus profound.

We will use the following definitions for the severity of impairment of swallow reflex initiation[8]:

Normal: swallow reflex initiated at the back of the tongue with no hesitation as the bolus moves from the back of the tongue into the pharynx.

Mild: swallow reflex initiated in the mid-pharynx (vallecular spaces) after a brief hesitation.

Moderate: swallow reflex initiated in the lower pharynx (pyriform sinuses) after a brief hesitation.

Severe: swallow Reflex initiated in the lower pharynx (pyriform sinuses) after prolonged pooling.

Profound: absent swallow reflex.

These subgroup analyses will be considered based on subgroup effects reported in studies based on individual patient features

Sensitivity analysis

1. Meta-analysis without studies with a high risk of bias
2. Random versus fixed effect model.
3. WHO definition of pneumonia versus non-WHO/non-standard definition of pneumonia.

Rating of overall quality of evidence

Using the Grading of Recommendations Assessment, Development and Evaluation approach with the help of the software GradePro, we will assess the overall quality of evidence for the intervention's effect on each outcome.[20] This approach identifies and assesses many different features that affect the certainty of evidence in the review, including the type of study design, statistical heterogeneity, the directness of evidence, within-study risk of bias, risk of publication bias and precision of effect estimates. Using GradePro, we will rate the overall quality of evidence as very low, low, moderate or high. Observational studies begin as low-quality evidence; however, certain factors may lead to a rating up or down (table 1).

Patient and public involvement

There is no direct patient involvement in this study.

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REFERENCES

1 Bhattacharyya N. The prevalence of pediatric voice and swallowing problems in the United States. *Laryngoscope* 2015;125:746–50.
2 Durvasula VSPB, O'Neill AC, Richter GT. Oropharyngeal dysphagia in children: mechanism, source, and management. *Otolaryngol Clin North Am* 2014;47:691–720.
3 Rosenbek JC, Robbins JA, Roecker EB, *et al*. A penetration-aspiration scale. *Dysphagia* 1996;11:93–8.
4 Taniguchi MH, Moyer RS. Assessment of risk factors for pneumonia in dysphagic children: significance of videofluoroscopic swallowing evaluation. *Dev Med Child Neurol* 1994;36:495–502.
5 Duncan DR, Amirault J, Mitchell PD, *et al*. Oropharyngeal dysphagia is strongly correlated with apparent life-threatening events. *J Pediatr Gastroenterol Nutr* 2017;65:168–72.
6 Weir K, McMahon S, Barry L, *et al*. Oropharyngeal aspiration and pneumonia in children. *Pediatr Pulmonol* 2007;42:1024–31.
7 Delzell PB, Kraus RA, Gaisie G, *et al*. Laryngeal penetration: a predictor of aspiration in infants? *Pediatr Radiol* 1999;29:762–5.
8 Friedman B, Frazier JB. Deep laryngeal penetration as a predictor of aspiration. *Dysphagia* 2000;15:153–8.
9 Serel Arslan S, Demir N, Karaduman AA. Both pharyngeal and esophageal phases of swallowing are associated with recurrent pneumonia in pediatric patients. *Clin Respir J* 2018;12:767–71.
10 Gurberg J, Birnbaum R, Daniel SJ. Laryngeal penetration on videofluoroscopic swallowing study is associated with increased pneumonia in children. *Int J Pediatr Otorhinolaryngol* 2015;79:1827–30.
11 Kemps G, Sewitch M, Birnbaum R, *et al*. Contrast pooling in videofluoroscopic swallowing study as a risk factor for pneumonia in children with dysphagia. *Int J Pediatr Otorhinolaryngol* 2015;79:1306–9.
12 Newman LA, Keckley C, Petersen MC, *et al*. Swallowing function and medical diagnoses in infants suspected of dysphagia. *Pediatrics* 2001;108:E106.
13 WHO classification and treatment of pneumonia in children at health facilities: evidence summaries. [Internet], 2014. Available: http://apps.who.int/iris/bitstream/10665/137319/1/9789241507813_eng.pdf?ua=1 [Accessed 21 Dec 2021].
14 Covidence systematic review software VHI, Melbourne, Australia. Available: www.covidence.org
15 Sterne JA, Hernán MA, Reeves BC, *et al*. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016;355:i4919.
16 The Nordic Cochrane Centre TCC. *Review Manager (RevMan) [Computer program]. Version 5.3*. Copenhagen, 2014.
17 StataCorp LLC. *Stata statistical software: release 16*. College Station, TX, 2019.
18 Higgins JPT TJ, Chandler J, Cumpston M, *et al*, eds. *Cochrane Handbook for Systematic Reviews of Interventions version 6.1*. Cochrane, 2020.
19 Melsen WG, Bootsma MCJ, Rovers MM, *et al*. The effects of clinical and statistical heterogeneity on the predictive values of results from meta-analyses. *Clin Microbiol Infect* 2014;20:123–9.
20 Guyatt G, Oxman AD, Akl EA, *et al*. Grade guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 2011;64:383–94.