

BMJ Open Conservative and surgical modalities in the management of paediatric parapneumonic effusion and empyema: a protocol for a living systematic review and network meta-analysis

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ABSTRACT

Introduction Parapneumonic effusion and empyema are common complications of paediatric pneumonia. Acceptable treatment modalities for large parapneumonic effusions include antibiotics alone or in conjunction with surgical interventions. Clear guidelines on the best treatment approach are lacking and mostly based on evidence prior to widespread pneumococcal conjugate 13-valent vaccination (PCV-13).

Methods and analysis A living systematic review and network meta-analysis will be performed comparing the five treatment modalities: (1) antibiotics alone; (2) chest tube drainage without fibrinolytics; (3) chest tube drainage with fibrinolytics; (4) video-assisted thoracoscopic surgery and (5) open thoracotomy. The review protocol is reported following the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols guidelines. Eligible studies are randomised controlled trials comparing any pair of interventions in paediatric patients with empyema or parapneumonic effusion. The following databases will be searched: Ovid MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, LILACS and Google Scholar. Citation screening and data extraction will be completed using a validated crowdsourcing methodology using InsightScope. To assess the risk of bias, we will use the revised Cochrane risk of bias tool for randomised trials. The primary outcome of the study is the length of stay. Secondary outcomes are (1) periprocedural complications and (2) need for re-intervention. A frequentist network meta-analysis design will be implemented with a random-effects model comparing different interventions. In a subgroup analysis, studies and patients will be stratified by the size of pleural effusion and the date of trial (pre/post-PCV-13). Eligible citations and available results will be uploaded to an online database, hosted on Open Science Framework. The database will be updated at least every 4 months with any newly published research.

Ethics and dissemination No ethics review is required for this study. Results will be published in a peer-reviewed journal. Data will be available as part of an online database summarising the evidence of this living systematic review.

PROSPERO registration Pending peer review.

Strengths and limitations of this study

- This systematic review will compare different intervention modalities in the treatment of paediatric empyema.
- Network meta-analysis will allow us to synthesise direct and indirect data to generate a comprehensive comparison of each intervention pair, including those not studied in a head-to-head trial.
- This living review will maintain an up-to-date summary of evidence in the field and incorporate any ongoing trials.
- Crowdsourcing steps of the systematic review process will facilitate the broadening of the search strategy and reduce the time to incorporate primary literature into the living review.
- As published trials in the field are small, the quality of the generated summary of evidence might be low.

BACKGROUND

Pneumonia continues to be the leading cause of morbidity and mortality in the paediatric population globally.¹ The introduction of widespread pneumococcal conjugate 13-valent vaccination (PCV-13) programmes has led to a significant reduction in the incidence and mortality of community-acquired pneumonia (CAP).^{2,3} However, this disease's burden remains high, accounting for 15% of deaths in young children worldwide.⁴ Approximately 12% of cases progress to severe illness, with parapneumonic effusion and pleural empyema being the most common complications.⁵ For simplicity, this paper will use the term 'effusion' to refer to parapneumonic effusion and pleural empyema.

The presence of effusion leads to a prolonged length of stay (LOS), escalation of care, morbidity and increased healthcare resources utilisation.^{6–10} Management of the

effusion is controversial.^{6 7} Accepted treatment modalities include antibiotics alone, chest tube drainage with or without fibrinolytics, video-assisted thoracoscopic surgery (VATS) and open thoracotomy (OT) with decortication. In general, guidelines around complicated pneumonia management agree that small and most moderate-sized effusions can be managed with antibiotics alone.^{9–13} Meanwhile, drainage is suggested for large effusions and effusions associated with a high degree of respiratory distress. Despite these guidelines, there is significant variability in clinical practice among physicians in managing parapneumonic effusions and empyema in children.^{14–16}

Additionally, published guidelines are mostly based on pre-PCV-13 studies. The global introduction of PCV-7 and PCV-13 has led to significant changes in paediatric pneumonia's clinical presentation. While the overall incidence of CAP has decreased in the past couple of decades,¹⁷ there was a notable increase in the incidence of empyema post-PCV-7.^{17–20} With the emergence of pneumococcal strains not included in the vaccine, there have been significant changes in the epidemiology and pathogenesis of CAP post-PCV-13. Given these changes, the current applicability of these guidelines is unclear.

To summarise currently available evidence, we will systematically review the existing literature for management of parapneumonic effusion and empyema. The primary aim of this systematic review is to identify which of antibiotics alone, chest tube drainage with/without fibrinolytics, VATS or OT leads to a shortened LOS in children with empyema. These five treatment arms were selected as they are well documented in the literature and are recommended therapies by guidelines. Given the heterogeneity of empyema staging, it is essential to compare outcomes between comparable group of patients. Limiting the systematic review to randomised controlled trials (RCTs) would minimise the potential for confounding. Furthermore, a subgroup analysis will allow us to stratify patients by the size of the stage of parapneumonic effusion and the date of trial (pre/post-PCV-13). As this is an active research field with multiple ongoing studies,^{21 22} we will undertake a living systematic review methodology. This will allow us to update our review findings with new evidence regularly. The network meta-analysis (NMA) will enable us to synthesise direct and indirect data to generate a comprehensive comparison of all possible pairwise comparisons available in the network.

METHODS AND ANALYSIS

The protocol of this study is reported following the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines (online supplemental file 1),²³ and will be prospectively registered on PROSPERO (pending peer review). The final review will be reported in accordance with the PRISMA extension for NMA.²⁴

Search strategy and selection criteria

The search is aimed to identify all citations relevant to empyema/parapneumonic effusion AND pediatric/children AND randomized controlled trials AND intervention/treatment/management/surgery/efficacy, with no filtering of search by language or date. Cochrane search filter was used to identify RCTs.²⁵ A draft Ovid MEDLINE search strategy is provided in online supplemental file 2. This will be peer reviewed by another librarian using the PRESS Evidence-Based Checklist, and then translated to the other databases.²⁶ The following databases will be searched: Ovid MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science Core Collection, LILACS and Google Scholar. In addition, a comprehensive grey literature search will be undertaken: clinicaltrials.gov, WHO International Clinical Trials Registry Platform, Papers First (via WorldCat), Proceedings (via WorldCat), Networked Digital Library of Theses and Dissertations, ProQuest Dissertations and Theses Global and OAister (narrowing to theses/dissertations; via WorldCat). The reference list of any included study or relevant systematic review will be searched for other potentially eligible studies.

Eligibility criteria

Studies will be included if they are RCTs and targeted patients under 18 years of age with parapneumonic effusion or pleural empyema as complications of pneumonia. Parapneumonic effusion is defined as any collection of pleural fluid associated with an underlying pneumonia.²⁷ Empyema is defined as the presence of grossly purulent pleural fluid. We will retain studies in English, French, Arabic, Chinese, German, Italian, Polish, Portuguese, Russian or Spanish. Trials must include at least one of the following therapeutic interventions:

1. Antibiotics alone.
2. Chest tube drainage without fibrinolytics.
3. Chest tube drainage with fibrinolytics.
4. VATS.
5. OT.

The interventions mentioned above are restricted to primary therapy rather than secondary interventions following failed treatments (eg, salvage VATS following a failed chest tube drainage). Studies that included only patients who experienced failure of primary therapy will be excluded. There is no restriction on antibiotic or fibrinolytic therapy's nature/details, such as the type of antibiotic/fibrinolytic, dosage or frequency, compliance level or the treatment setting. No restriction is applied on the presented outcomes. Studies will be excluded if they did not have any patients below 18 years of age, or were limited to the following populations: chronic lung diseases (including cystic fibrosis and ciliary dyskinesia), pre-existing cardiac or neurological disease, immunodeficiency, malignant effusions, post-cancer chemotherapy or children receiving home mechanical ventilation. If a trial included eligible patients under 18 years of age as

well as adults, results would be included if the data for the eligible age group were presented separately.

Crowdsourcing of study selection

Citation screening will be completed on InsightScope, a platform designed for crowdsourcing systematic reviews.²⁸ A recruitment email will be sent out to registered crowd members and disseminated through paediatric interest groups, research interest groups, undergraduate societies across Canada and the Cochrane task exchange platform. The crowd is mostly comprised of students with post-secondary training (undergraduate/medical/graduate students).^{29 30}

Two of the expert reviewers will screen 10% of citations. A draft of screening criteria is prepared as part of this protocol (online supplemental file 3). Screening criteria will be reviewed and amended if there is a disagreement between the two experts. From this set of citations, a qualification set of randomly selected 50 citations (containing at least five eligible ones) will be used as the reference standard to which the crowd members are compared. Crowd members will need to demonstrate acceptable performance with citation screening on the qualification set (sensitivity $\geq 80\%$ and specificity $\geq 70\%$). Reviewers with sensitivity between 80% and 90% will receive further training before participating in the full review.

To improve sensitivity, each abstract will be screened independently in triplicate, with an expert resolving conflicts.³⁰ At the full-text stage, the crowd will upload the full-text articles and screen the full citations similarly. The final list of retained citations by the crowd will be screened by an expert to confirm eligibility.

Data extraction

A draft data extraction form was prepared as part of this protocol (online supplemental file 4). This will be piloted by two independent experts on five eligible citations. Conflicts will be discussed and the crowd will use a refined extraction form. Data will be extracted independently by two crowd members and verified by one of the expert investigators. The extraction form includes the following: (1) study identification; (2) methodological characteristics and (3) risk of bias assessment (as detailed below). The following data are to be collected separately for patients who received one of the four treatment arms: (1) description of the population; (2) completed investigations; (3) treatment course (details on antibiotic management as well as the intervention of interest) and (4) outcomes (as detailed below).

Corresponding authors of eligible studies will be contacted to obtain any missing data and confirm whether they are aware of any additional published or ongoing trials.

Outcomes

The primary outcome of the study is the LOS. Secondary outcomes defined ad hoc are (1) periprocedural complications and (2) need for re-intervention. If a study

presented other outcomes, these will be assessed in an exploratory analysis. For periprocedural complications, we will include pain, bleeding, secondary infections or any other treatment-related adverse events reported by the investigative teams.

Risk of bias assessment

To assess the risk of bias, we will use the revised Cochrane risk of bias tool for randomised trials.³¹ Each citation will be independently assessed by two crowd members and conflicts resolved by an expert investigator.

Network meta-analysis

The five treatment arms described above will be compared in an NMA. We will evaluate all eligible RCTs involving any head-to-head comparisons. We will not differentiate based on the type of fibrinolytic. If a sufficient number of trials compared different types of fibrinolytics, this will be explored further in a secondary analysis. A network diagram will be generated and modelled within a frequentist NMA design. A random-effects model will be implemented to account for potential heterogeneity between study populations. A mean difference will be used in the meta-analysis for combining continuous data such as LOS, and OR will be used for binary outcomes such as incidence of periprocedural complications and need for re-intervention. If there are no multiarm trials, we will use meta-regression to synthesise direct and indirect evidence. In the case of multiarm trials, we will use the approach of multivariate meta-analysis. We will estimate rankings of interventions using ranking probability, calculated based on the joint distribution of relative efficacy estimates.

Assumptions made in NMA include homogeneity, similarity and consistency. Studies will be assessed for consistency of design, and influence analysis will be performed to evaluate the assumption of homogeneity. Heterogeneity of treatment effects will be explored visually using a forest plot and statistically using I^2 based on the Cochran's Q test. We will compare data generated via the random-effects model with a fixed-effect model in a sensitivity analysis.

Results from direct and indirect comparisons of the same two treatment interventions will be reviewed for consistency. Consistency will be addressed using node splitting via a network meta-regression model. Node splitting will assess that the relative effect of two treatments based on direct comparisons is comparable with the same effect based on indirect comparisons. Assessment of transitivity will be carried out by comparing the distribution of effect modifiers across the different comparisons. Assessment of incoherence will be evaluated with the Separating Indirect from Direct Evidence technique. This would entail obtaining the statistical incoherence factor by measuring the absolute difference between direct and indirect summary estimates for the pairwise comparisons. The potential for publication bias will be investigated visually using a funnel plot.

Grades of Recommendation, Assessment, Development and Evaluation will be used to evaluate the overall quality of evidence, through consideration of five domains: risk of bias, inconsistency, indirectness, imprecision and publication bias. These provide an overall quality of the evidence rated as high, moderate, low or very low.³² We will use CINeMA to assess the confidence in NMA (<http://cinema.ispm.ch/>).

Data analysis

Data analysis will be conducted in R (V.4.0.0). In a subgroup analysis, studies and patients will be stratified by the stage of parapneumonic effusion and the date of trial (pre/post-PCV-13). Parapneumonic effusions and empyema will be classified based on the American College of Chest Physicians staging system^{27 33}:

- ▶ Stage I: minimal uncomplicated parapneumonic effusion (<10 mm on lateral decubitus).
- ▶ Stage II: small-to-moderate uncomplicated parapneumonic effusion (>10 mm and less than half of the hemithorax).
- ▶ Stage III: complicated parapneumonic effusion (large effusion greater than half of the hemithorax, loculated effusion, or effusion with a positive gram stain or culture).
- ▶ Stage IV: empyema (grossly purulent effusion).

We will use 2010 as a cut-off to distinguish between pre-PCV-13 and post-PCV-13 studies.³⁴ Studies that span both periods will be excluded from the subgroup analysis.

Living systematic review

Eligible citations and available results will be uploaded to an online database, hosted on Open Science Framework. New citations will be screened and extracted, similar to the original review. The database will be updated at least every 4 months with any newly published research. The synthesis of available evidence will also be updated to reflect the most up-to-date estimates of the measured outcomes.

Patient and public involvement

No patients or public will be involved in this systematic review.

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Contributors All authors conceptualised and designed the protocol, critically revised the manuscript, approved the final draft and agreed to be accountable for all aspects of the work. In addition, EA drafted the initial manuscript and developed the planned data collection and analysis; NN developed the living systematic review process and data analysis; MI designed the network meta-analysis; CP designed

the search strategy; and MW and MC provided content expertise and supervised the project.

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