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Are intra-pleural bacterial products associated with longer survival in adults with malignant pleural effusions? A systematic review

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ABSTRACT

Background: Intra-pleural bacteria are effective pleurodesis agents in malignant pleural effusions. However, their relationship with survival is unclear.
Objectives: We undertook a comprehensive, structured evaluation of survival outcomes in adults with malignant pleural effusions treated with intra-pleural bacterial products.
Data sources: Medline, Embase, Cochrane library, Clinical Trials Registers and Open Grey.
Study eligibility criteria, participants, and interventions: Randomised controlled trials and non-randomised comparative studies were included, if the population included adults with malignant pleural effusions. Interventions of interest were any intra-pleural bacterial product, compared with placebo, alternative intra-pleural drug, or no treatment. Survival outcomes were collected.

Study appraisal and synthesis methods: Two reviewers independently screened studies for eligibility, assessed papers for risk of bias and extracted data. Narrative synthesis was performed as high heterogeneity between studies precluded meta-analysis.
Results: 631 studies were identified, of which 14 were included. All were at high or unclear risk of bias in at least one domain. Six studies reported a survival benefit associated with intra-pleural bacterial products, whilst 8 reported no difference. Non-randomised studies and studies published prior to 2000 were more likely to report survival benefits.
Limitations: There was high heterogeneity between studies, which limited the generalisability of findings. Publication bias may have affected the review as five full-text papers were unobtainable, and survival outcomes were missing in a further five.
Conclusions: There is a lack of high quality evidence regarding the relationship between intra-pleural bacterial products and survival.

Implications of key findings: Well-designed, prospective randomised trials are needed, to determine whether intra-pleural bacterial products can improve survival in pleural malignancy.
PROSPERO registration number: CRD42017058067.

1. Background

Malignant pleural effusions (MPE) arise as a result of primary pleural tumours, i.e. malignant pleural mesothelioma (MPM), or metastatic spread from distal tumours, most commonly lung cancer [1]. The presence of MPE usually reflects advanced or metastatic disease, and consequently treatment is primarily palliative, with fluid management a priority [2–4].

Administering an inflammatory agent into the pleural space to achieve pleurodesis is an effective way of controlling fluid and improving breathlessness, but has no effect on the underlying disease process. [1,3,5,6], Historically, pleurodesis was undertaken using bacterial products such as *Corynebacterium*] parvum, and in certain countries these products are still used [7–10]. Some clinicians believed these products exerted an anti-tumour effect alongside their pleurodesis properties [11–13]. The hypothesis was based on evidence that MPE were associated with local immune inhibition, and that survival correlated with the ability to maintain intra-pleural immune activity [14–19]. Bacterial products were recognised as potent stimulators of the immune response, and hence an early theory of immunotherapy was developed. This was supported by observational studies that suggested pleural infection was associated with longer survival following

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surgery for lung cancer [20–22].

The concept evolved through the 1970 s with clinical trials evaluating the role of intra-pleural BCG after lung cancer surgery. Trial data were conflicting, and the practice was not adopted into routine care [23–27]. However, BCG found a role as an intra-vesical treatment for bladder cancer, suggesting some anti-neoplastic activity [28].

Recently, interest in immunotherapy has resurfaced, and several systemic immunotherapy products have been adopted into routine use for other cancer types [29–35]. Interest in intra-pleural bacterial products has also risen, with agents such as *Staphylococcus* superantigen, *Lactobacillus* casei and streptococcal preparations undergoing investigations in clinical studies [36–38].

To date, the literature on intra-pleural bacterial products and their relationship with survival has not been systematically reviewed. We aimed to undertake a comprehensive evaluation of the evidence, with meta-analysis of RCT data if possible, to answer the question "Are intra-pleural bacterial products associated with longer survival in adults with MPE?"

2. Methods

2.1. Registration

The review was registered on PROSPERO International Prospective Register of Systematic Reviews, registration CRD42017058067. A summary of the protocol is available at https://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42017058067.

2.2. Data sources

An electronic literature search was undertaken using MEDLINE (1946 to Present), EMBASE (1974–2017 week 09), Cochrane Database of Systematic Reviews, Cochrane CENTRAL Register of Controlled Trials, International Clinical Trials Registry (ISRCTN), EU Clinical Trials Register, US NIH Clinical Trials Register and Open Grey (System for Information on Grey Literature in Europe – SIGLE).

Once the initial electronic search was complete, a manual search was undertaken to review the references of included papers and systematic reviews, to ensure all relevant papers were captured.

2.3. Search strategy

The search strategy for each database is shown in Appendix A. The strategy included exploded MeSH headings for MPE, combined with keyword or title word searches for intra-pleural bacteria, immunotherapy and specific products. The initial search was performed on 28/02/17 and was repeated on 22/02/18 to identify studies published in the intervening year.

2.4. Eligibility criteria

2.4.1. Types of study

RCTs were included, as were non-randomised comparative studies. Non-randomised studies included case-control studies, comparative cohort studies and matched case series, prospective or retrospective. Studies with no comparison group were excluded, as were informal review articles, editorials, conference abstracts, animal or in vitro studies and studies where no abstract was available. Systematic reviews were included and used to identify potentially eligible studies not identified by the search.

Clinical trials registers were searched. If the timelines suggested the trial had been completed but not reported, the authors were contacted and asked to provide the data.

Research papers in all languages were included. Foreign language papers were translated into English using an online translation service. No date limitations were placed on the search.

2.4.2. Types of participants

Studies were eligible if they included adults with MPE due to any underlying tumour. Studies were excluded if they included a mixed population of benign and malignant effusions, unless there was a clear distinction in reporting the results for the two groups. Similarly, studies that included participants with other effusions (e.g. ascites) were excluded unless the results were reported separately for each effusion type. Studies that included a surgical cohort were excluded as pleural involvement is usually a contra-indication for cancer surgery.

2.4.3. Types of interventions

The intervention was intra-pleural delivery of any bacterial product including, but not limited to, *Corynebacterium* parvum, BCG, *Staphylococcus* superantigen, *Lactobacillus* casei, OK432 and lipopolysaccharides. Studies in which bacterial preparations were delivered via other methods were excluded. Studies assessing viral vectors, vaccine therapy, fungal extracts or synthetic immunotherapies were excluded.

2.4.4. Types of comparators

Comparators included no treatment, placebo or alternative non-bacterial intra-pleural product.

2.4.5. Types of outcomes

The outcome of interest was survival. Outcomes relating to pleural effusion size, pleural effusion control or pleurodesis were not collected as this data has been reviewed in a recent Cochrane meta-analysis [6]. If an article referred to unpublished data that may have met the eligibility criteria, the authors were contacted and asked to provide raw data.

2.4.6. Screening & study selection

The titles and abstracts of studies identified by the search were screened for eligibility and potential studies obtained in full-text format and reviewed.

2.4.7. Assessment of risk of bias

Included studies were assessed using the Cochrane risk of bias tool [39].

2.4.8. Data extraction

Data were extracted from included studies using the form shown in Appendix B. If a study stated in its methodology that data relevant to the PICO criteria was collected, but did not report this data, the authors were contacted and asked to provide the data.

Abstract screening, full-text review, risk of bias assessment and data extraction were undertaken by two reviewers, independently. Discrepancies were resolved by discussion, or by consultation with a third party.

2.4.9. Data analysis

Odds ratios were calculated with 95% confidence intervals (95% CI) for proportional outcomes, where possible. Hazard ratios (and 95% CI) were extracted for time to event data, or calculated using Cox Proportional Hazards Model if sufficient data were available. Where comparative statistics could not be calculated, simple descriptors were reported with measures of variance as reported in the original studies.

Meta-analysis was planned if two or more RCTs were identified with low risk of bias in the randomisation domain, provided the data were comparable. Heterogeneity was expected to be high, therefore a random effects model was planned. Heterogeneity would be assessed visually with Forest plots, and using the I2 statistic [40]. Where insufficient data were available for meta-analysis, and for studies with a high risk of bias, narrative synthesis was performed.

Univariable meta-regression and Fishers exact test for heterogeneity were used to explore the relationship between study design, year of publication, patient population and bacterial product studied and the