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Shorter versus longer durations of antibiotic treatment for patients with community-acquired pneumonia: a protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction Community-acquired pneumonia (CAP), frequently encountered in both outpatient and inpatient settings, is the leading cause of infectious disease-related mortality. While equipoise regarding the optimal duration of antimicrobial therapy to treat CAP remains, recent studies suggest shorter durations of therapy may achieve optimal outcomes. We have therefore planned a systematic review and meta-analysis evaluating the impact of shorter versus longer durations of antibiotic therapy for patients with CAP.

Methods and analysis We searched Ovid MEDLINE, Embase, CINAHL and Cochrane Central Register of Controlled Trials from inception to September 2021 for randomised controlled trials evaluating shorter versus longer duration of antibiotics. Eligible studies will compare durations with a minimum difference of two days of antibiotic therapy, irrespective of antibiotic agent, class, route, frequency or dosage, and will report on any patient-important outcome of benefit or harm. Paired reviewers working independently will conduct title and abstract screening, full-text screening, data extraction and risk of bias (RoB) evaluation using a modified Cochrane RoB 2.0 tool. We will perform random-effects modelling for meta-analyses, with study weights generated using the inverse variance method, and will assess certainty in effect estimates using Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology. The Instrument for assessing the Credibility of Effect Modification Analyses (ICEMAN) tool will inform assessments of credibility of subgroup effects based on severity of illness, drug class, duration of therapy, setting of CAP acquisition and RoB.

Ethics and dissemination The results will be of importance to general practitioners and internists managing CAP, and may directly inform international clinical guidance. Where concerns regarding antimicrobial resistance continue to grow internationally, this evidence summary may motivate new recommendations regarding shorter durations of therapy. We intend to disseminate our findings via national and international conferences, and publication in a peer-reviewed journal.

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STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The planned systematic review will summarise all available evidence relevant to antibiotic duration for community-acquired pneumonia, irrespective of setting (outpatient or inpatient) and severity of illness, with a planned subgroup analysis to address possible effect modification by disease severity.
⇒ The review will use a comprehensive search strategy supplemented by reference list screening, will incorporate both published and unpublished data, and will have predefined frameworks for screening, extraction, statistical analysis and subgroup analysis.
⇒ The review will evaluate all patient-important outcomes with available data, and will not be limited to prespecified outcomes of interest.
⇒ The review will use a validated risk of bias tool, GRADE methodology to systematically evaluate certainty in effect estimates, and the ICEMAN tool to evaluate credibility of subgroup effects.
⇒ We have no plans to contact authors about issues of inadequate reporting or confirmation regarding our data abstraction or risk of bias assessments.

INTRODUCTION

Community-acquired pneumonia (CAP) is among the most common illnesses managed in the outpatient setting, frequently requires hospital admission, and constitutes one of the most common indications for antibiotic prescriptions.[1–4] It is the leading cause of infectious disease-related mortality in high-income countries.[5] There remains equipoise regarding the optimal duration of antimicrobial therapy to treat CAP in both inpatient and outpatient settings.

Although CAP has traditionally been treated for at least seven days,[6 7] clinicians are now considering shorter duration of therapy. Guidance from the American Thoracic

Society and Infectious Diseases Society of America published in 2019 provided a strong recommendation, based on moderate-quality evidence, for at least five days of therapy, and continuation of therapy until the patient achieves clinical stability[5] ; guidelines from the American College of Physicians published in 2021 recommended the same.[8] This shift is in keeping with evolving evidence over two decades, which has suggested optimal outcomes may require only five days of therapy.[9–11]

Recent randomised controlled trials (RCTs) have compared three versus eight days of therapy in both outpatients and those requiring hospital admission for CAP, and have reported satisfactory outcomes of clinical improvement and stability, improved adherence and fewer adverse effects in those receiving the shorter duration.[12–20] Whether these trials will motivate a change in recommendations remains uncertain.

Shortened duration of antimicrobial therapy may reduce the emergence of antimicrobial resistance, individual and healthcare system-related costs, antibiotic-related side effects and risk of bacterial superinfection. Short courses may, however, be associated with recurrent or refractory illness, and relatedly greater individual and healthcare system-related costs.[21]

Although previous systematic reviews, and overviews of reviews, have examined shorter versus longer duration of therapy for CAP,[10 11 22–26] they have not evaluated durations less than five days,[11 23 25] or are limited to a comparison of two durations with the same drug across arms.[26] A recent review by Tansarli and colleagues in 2018 found no significant difference in clinical cure, fewer adverse events and lower mortality associated with shorter (≤six days) versus longer courses of therapy (≥seven days), irrespective of patient setting or severity of pneumonia. Subgroup analyses comparing three versus five days of therapy found no significant difference in clinical cure or relapse rates.[10]

An updated synthesis of evidence may motivate a change in evidence-based clinical guidance. We therefore plan to conduct a systematic review and meta-analysis evaluating the impact of shorter versus longer durations of antibiotic therapy for patients with CAP, including recent RCT evidence comparing durations less than five days with longer courses of treatment.

METHODS AND ANALYSIS

This protocol adheres to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)-Protocols standards. We will adhere to the PRISMA checklist for reporting our systematic review and meta-analysis (online supplemental material 1). Our protocol has been registered on PROSPERO (CRD42021283990).

Search strategy

With the aid of a medical librarian, we have conducted a systematic search of the published literature in four electronic databases from inception to present: Ovid MEDLINE (1946–September 2021), Embase (1947–September 2021), CINAHL (1982–September 2021) and the Cochrane Central Register of Controlled Trials (1991–September 2021).

Search terms include a combination of keywords and medical subject heading terms: “duration of therapy”, “vs”, “days”, “extended”, “limited”, “shorter”, “longer”, “pneumonia, “respiratory tract infection”, “antibiotic”, “randomized controlled trial” (online supplemental material 2). We did not apply language restrictions in our search.

We will supplement our search by reviewing bibliographies of review articles and eligible trials for additional studies not identified by the electronic searches.

Eligibility criteria

We will include parallel arm RCTs or quasi-randomised studies.

Studies including adults aged 18 years of age or older with a diagnosis of CAP will be eligible. We will accept investigator-defined definitions of CAP, including clinical (confirmed based on signs and symptoms) and radiologically established diagnoses. All severities of CAP will be eligible, including mild, moderate, severe and critical illness. We will not limit eligibility to ‘uncomplicated’ or ‘complicated’ pneumonia, regardless of definition. Studies undertaken in the outpatient setting, and those in hospitalised patients, will both be eligible. Studies involving patients with immunocompromise or other comorbidities will be eligible. We will not limit to specific implicated organisms, and will include both typical and atypical pneumonias and both empirical and pathogen-directed therapies. Pneumonia acquired in other congregate settings such as long-term care facilities and retirement homes will be eligible.

We will exclude studies addressing hospital-acquired pneumonia and those enrolling only patients with Pneumocystis pneumonia. We will include studies enrolling patients we do not consider eligible (eg, under 18 years, having Pneumocystis pneumonia) if the proportion of such patients is 20% or less, or if authors report separately on our population of interest.

We will include studies with at least one arm with antibiotics for a shorter duration, compared with at least one arm with antibiotics for a longer duration. Eligible studies will involve a minimum difference of two days in duration of therapy between two or more arms, without requirement that the shorter and longer duration arms use the same antibiotic regimens, and without restriction regarding frequency, dosage or route of administration.

Eligible studies will report at least one patient-important outcome including, but not limited to, clinical cure or response, overall and pneumonia-related mortality, need for and duration of hospitalisation, need for and duration of intensive care unit admission, hospital readmission, invasive ventilation, relapse, serious adverse events leading to discontinuation and all adverse events.

We will include articles meeting eligibility criteria, irrespective of publication status; specifically, we will include grey literature and conference abstracts.

Study selection

Paired reviewers will independently conduct title and abstract and full-text screening using pretested, standardised screening forms with accompanying instructions. Reviewers will resolve disagreements by discussion; as necessary, a third reviewer (AA) will adjudicate. We will use Covidence (https://covidence.org/) for screening.

Data extraction and risk of bias

Paired reviewers will independently extract data and evaluate risk of bias using pretested, standardised extraction forms with accompanying instructions, resolving disagreements by discussion; if necessary, a third reviewer (AA) will adjudicate.

We will extract data on population, interventions, comparators and outcomes of interest. For population, extracted data will include: setting (outpatient vs admission to hospital at baseline); initial severity of illness (mild vs moderate vs severe vs critical); cointerventions; antibiotic administered; dosing, route of administration and frequency; compliance with therapy; radiographic findings and sputum culture positivity.

We will evaluate risk of bias using the modified Cochrane risk of bias 2.0, with judgements classified as 'low', 'probably low', 'probably high' or 'high' for the following domains: bias due to randomisation, bias due to deviations from the intended intervention, bias due to missing outcome data, bias in measurement of the outcome, bias in selection of the reported result and bias due to competing risks. We will assess risk of bias by outcome.

Certainty of the evidence

We will consider the overall certainty in evidence for each outcome using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework, based on the following domains: risk of bias, imprecision, inconsistency, indirectness and publication bias. Overall certainty of evidence will be rated as 'very low', 'low', 'moderate' or 'high'. We will consider rating down the certainty of evidence for risk of bias based on lack of blinding for subjective outcomes only.[27–29] We will address missing data as part of risk of bias assessments based on a previously published approach.[30]

Statistical analysis

Given significant variation in patients and interventions may be present, we plan to conduct random-effects modelling for our primary meta-analyses (Cochrane Collaboration, Oxford). In instances where random effects give counterintuitive results, in particular large differences between small and larger studies, we will switch to fixed-effect modelling. All analyses will be performed in RevMan version 5.3 (Cochrane Collaboration, Oxford).

Study weights will be generated using the inverse variance method. We will present dichotomous outcomes as risk ratios, with absolute effects calculated to facilitate interpretation. Baseline risk will be inferred from median values for a given outcome from the control group. We will present continuous outcomes as mean differences or standardised mean differences, all with 95% CIs. We will assume a normal distribution for continuous outcomes, and will convert IQRs to SDs as per guidance from the Cochrane Collaboration. We will assess heterogeneity between studies using the χ^2 test for homogeneity, I^2 measure and visual inspection of the forest plots.

If sufficient data are available, we will plan the following subgroup analyses:

1. Severity of illness: mild versus moderate versus severe versus critical (hypothesis: larger benefit in the longer duration group with increasingly severe disease).
2. Drug class: comparisons in which arms receive agents belonging to the same drug class versus comparisons in which arms receive agents belonging to different drug classes (hypothesis: differences will be greater when the drug classes differ between arms).
3. Shorter durations of therapy: 1 day vs 3 days vs 5 days vs 7 days (all compared with longer durations) (hypothesis: differences will be greater with comparisons involving shorter duration in the shorter duration arm).
4. Setting: nursing home-acquired pneumonia versus pneumonia acquired in other community settings (hypothesis: differences will be greater in studies including patients with nursing home-acquired pneumonia).
5. Risk of bias: low versus high risk of bias studies (hypothesis: differences will be greater in high risk of bias studies).

We will classify patients requiring hospitalisation without intensive care unit-level care as severe illness, and those requiring intensive care unit-level care, vasopressors and/or mechanical ventilation as critical illness.

We will rate the credibility of effect modification analyses using the Instrument for assessing the Credibility of Effect Modification Analyses tool.[31]

Ethics and dissemination

Ethics approval is not required for this systematic review. We plan to disseminate our results through national and international clinical and methods conferences. We also plan to publish our findings in a peer-reviewed journal widely accessed by general practitioners and internists.

Patient and public involvement

The research question was developed with a focus on all patient-important outcomes. Patients and members of the public were not directly involved in the design of this review.

DISCUSSION

The publication of multiple RCTs evaluating three days of antibiotic therapy compared with longer durations

for the treatment of CAP warrants an updated evidence synthesis to inform guideline recommendations and clinical practice.

Our planned systematic review has a number of strengths. First, we will summarise evidence relevant to CAP irrespective of whether treatment is initiated in the outpatient or inpatient setting. Our evaluation will therefore address the effectiveness of shorter versus longer duration across the spectrum of mild to critical illness, with a planned subgroup analysis to address possible effect modification by disease severity. Second, our analysis will account for both interclass and intraclass antibiotic comparisons. Third, we will evaluate all patient-important outcomes and will not limit our analysis *a priori* to specific outcomes, maximising the available information to guide clinical practice. Fourth, we have used a comprehensive search strategy developed with the aid of a medical librarian, have incorporated both published and unpublished data, and have predefined screening, extraction, statistical analysis and subgroup analysis plans. To ensure comprehensive identification of all eligible literature, we will screen the reference lists of previously conducted systematic reviews. We intend to use a validated risk of bias tool and GRADE methodology to systematically evaluate certainty in effect estimates.

In conclusion, this protocol describes the detailed methodology of a planned systematic review and meta-analysis addressing shorter versus longer durations of antibiotic therapy for CAP. The results will be of importance to general practitioners and internists managing CAP, and may directly inform international clinical guidance. Particularly, given growing concerns regarding antimicrobial resistance, should shorter and longer courses prove similar in their impact on patient-important outcomes, the new evidence may result in new recommendations for shorter durations of therapy.

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