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Does antibiotic treatment duration affect the outcomes of exacerbations of asthma and COPD? A Systematic Review

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Abstract

**Background**: Asthma and chronic obstructive pulmonary disease (COPD) cause significant morbidity and mortality worldwide, primarily through exacerbations. Exacerbations are often treated with antibiotics but their optimal course duration is uncertain. Reducing antibiotic duration may influence antimicrobial resistance but risks treatment failure.

**Objective**: To review published literature to investigate whether shorter antibiotic therapy duration affects clinical outcomes in the treatment of asthma and COPD exacerbations.

**Methods**: We systematically searched electronic databases (MEDLINE, EMBASE, CINAHL, WHO ICTRP, the Cochrane library and ISRCTN) with no language, location or time restrictions. We retrieved observational and controlled trials comparing different durations of the same oral antibiotic therapy in the treatment of acute exacerbations of asthma or COPD in adults.

**Results**: We found no applicable studies for asthma exacerbations. We included ten placebo-controlled, randomised controlled trials for COPD patients, all from high-income countries. The commonest studied antibiotic class was fluoroquinolones. Antibiotic courses shorter than six days were associated with significantly fewer overall adverse events (risk ratio (RR) 0.84, 95 % confidence interval (CI) 0.75-0.93, p=0.001) when compared with those of 7 or more days. There was no statistically significant difference for clinical success or bacteriological eradication in sputum (RR 1.00, 95% CI 0.88-1.13 and RR 1.06, 95% CI 0.79-1.44 respectively).

**Conclusion**: Shorter durations of antibiotics for COPD exacerbations do not to confer a higher risk of treatment failure, but are associated with fewer adverse events. This is in keeping with previous studies in community acquired pneumonia, but studies were heterogeneous and differed from usual clinical practice. Further observational and prospective work is needed to explore the significance of antibiotic duration in the treatment of asthma and COPD exacerbations.

Key words:

Asthma, COPD, Exacerbation, Antibiotics, Duration, Antimicrobial Resistance

Introduction

Background

Asthma and chronic obstructive pulmonary disease (COPD) are common and are becoming more prevalent globally.[1–4] Exacerbations are a major driver of the morbidity, mortality and cost associated with these chronic airways diseases.[5, 6] The majority exacerbations are thought to be non-bacterial in origin.[7–9] They are, however, frequently treated with antibiotics hence causing a significant antibiotic burden.[10, 11] For example, over eleven years 22 % of 16.1 million asthma presentations to US hospitals received antibiotics, largely against current guidelines.[12]

Antimicrobial resistance is one of the most important public health crises facing the world today. Reduced susceptibility to penicillin or penicillin-resistance in *Streptococcus pneumoniae* exceeds more than 50 % in many countries.[13] The World Health Organisation (WHO) issued a global action plan on antimicrobial resistance in 2015 which called for optimisation of antibiotic prescribing.[14] Use of shorter antibiotic courses may be beneficial to reduce resistance, improve concordance, costs and side effects. However, shorter courses risk treatment failure. Patients in middle and lower income countries are more susceptible to failure due to e.g. reduced susceptibility to penicillins, limited access to follow up, malnutrition and higher risk of abnormal lung architecture caused by air pollution, smoking and industrial exposures.[15–17]

The ideal duration of antibiotic treatment for asthma and COPD exacerbations is uncertain and a prescribing consensus is a priority for providers. The last systematic review on antibiotic duration in COPD exacerbations was published in 2008[18] and none have been published in asthma exacerbations. We therefore undertook an up-to-date review and meta-analysis to investigate whether shorter courses of oral antibiotic treatment for asthma and COPD exacerbations are associated with different outcomes when compared with longer courses.

Methods

1. Data Sources and Search Strategy

We conducted systematic searches of bibliographic databases including MEDLINE, EMBASE and CINAHL through NHS library services. We also ran a search of the WHO International Clinical Trial Registry Platform, the Cochrane library and ISRCTN and used search engines on their own websites. All databases were searched from inception until 29th February 2016. There was no restriction of publication language. We removed duplicate references using reference management software (Endnote X7, Thomson Reuters). The search strategy is described below. The reference lists of earlier reviews on the same topic and abstracts of the European Respiratory Society and American Thoracic Society conferences from the previous year (2015) were hand-searched and titles included if the inclusion criteria were fulfilled.

2. Study Selection

We included observational and controlled trials of adults (≥ 18 years) with a clinical diagnosis of asthma or COPD exacerbation. We only included original studies with explicitly different durations of the same oral antibiotic therapy. We excluded studies of pneumonia treatment and prophylactic antibiotics.

We reviewed the list of titles to exclude publications which were clearly not contributory on this basis, and duplicate titles. Two investigators screened the eligible abstracts independently. We obtained full text articles of selected papers via University of Liverpool library, NHSlibrary and inter-library loans. Two investigators reviewed the full texts for eligibility independently. Any disagreement was resolved by a third investigator.

3. Data Extraction

Two authors extracted data using a pre-set data extraction form which included details of the study’s publication, authorship and funding; study characteristics (design and location); participants (sample size, method of recruitment, selection and demographics); outcome measures; interventions; data analysis and reporting; confounding adjustments; and the main findings. Disagreements were resolved by discussion. We used RevMan 5.3 (Cochrane Collaboration) and Endnote X7 software in the collection and management of data from abstracts and papers.

4. Quality and Risk of Bias Assessment

We assessed the studies’ accuracy and risk of bias using the Cochrane Handbook for Systematic Reviews of Interventions criteria.[19] Controlled trials were additionally analysed using the Cochrane Collaboration’s tool for assessing risk of bias.

5. Analysis

We combined intention to treat population data from comparable studies in quantitative analyses. We pooled data using fixed effect model in RevMan 5.3.[20] We used the Mantel-Haenszel method, presenting data as risk ratio with 95 % confidence intervals (CI). We used statistical significance of p < 0.05 and assessed the degree of heterogeneity using the I2 statistic.

Results

Asthma

We identified 1604 individual titles through database searches (figure 1). No additional studies were identified by hand-searching. The commonest reason for non-inclusion into abstract screening was a lack of an asthma diagnosis for all participants (1304 records). We reviewed 29 abstracts. The commonest reason for not progression to full text review were missing explicit antibiotic duration (8 studies), with other reasons demonstrated in figure 1. The one full text analysed assessed antibiotics for one duration only and was hence excluded.

[Insert Figure 1 – PRISMA flow diagram of systematic search for asthma studies]

COPD

We identified 1762 individual titles in COPD from database searches, 32 from hand-searching of recent reviews and two from conference abstracts (figure 2).[18, 21] The commonest reason for non-inclusion in abstract screening were lack of COPD diagnosis (951 studies) and not assessing oral antibiotic treatment (603 studies). We screened 160 abstracts. The commonest reasons for exclusion at this stage were not assessing one antibiotic with two different durations (67 studies) or not comparing specific antibiotic durations (26 studies). 33 full texts were eligible for analysis and ten full texts were included in the final meta-analysis. One text in Polish was translated but was not applicable.

[Insert figure 2 – PRISMA flow diagram of systematic search for COPD studies]

Characteristics and definitions of COPD studies

a) Design, participants and setting

All ten studies included in the meta-analysis were placebo-controlled, randomised controlled trials (table 1). Nine studies considered “chronic bronchitis” but included individuals with airflow limitation and a smoking history: their design would have predated the global use of the term “COPD”.[22] Eight studies reported smoking status. The youngest enrolled participant was 18 years old. Four studies recruited from outpatients, three from hospital admissions, one from primary care and two from primary care and outpatients. Two multi‑centre studies included patients in the developing world (Latin America; Pakistan, Philippines)[23, 24], the rest were based in Europe or North America. Where documented all exacerbations were diagnosed clinically, one study additionally used microscopically confirmed purulent sputum.[25] There was a range of exacerbation severities from “mild” in outpatients to inpatients not needing critical care or ventilation.[25, 26] Eight studies characterised the severity of the underlying lung disease.

[Insert table 1 – Characteristics of included full text studies]

b) Interventions and outcomes

Fluoroquinolones were the most commonly examined antimicrobial class (five studies). Two studies assessed grepafloxacin, and two assessed co-amoxiclav. The shortest antibiotic treatment was three days, the longest ten days. One study included the potential administration of intravenous antibiotic in the first three days of treatment.[26] Follow up duration varied from 0-3 days after final treatment to one year after. All studies reported clinical responses (based on sputum production and appearance) and adverse effects. Nine studies assessed changes in sputum microbiology. Spirometry and inflammatory markers were assessed by a smaller number of studies. No studies compared outcomes in high versus low or middle income countries.

c) Risk of bias

One study had low risk of bias across all domains (table 2).[25] One study had a high risk of bias due to not considering smoking as a confounding factor.[27] Two studies did not recruit enough patients for the primary endpoint, based on their power calculations.[26, 28]

Those with unclear risk of bias lacked information on blinding of participants, personnel and outcome assessments (8 of 10 studies). All studies were commercially funded, one additionally received non-commercial funding.[26] We did not detect publication bias.

[Insert table 2 – Table of risk of bias and study analysis methods]

Analysis

Combining the populations of the ten included studies, 1990 patients received short antibiotic courses (fewer than six days) and 1989 patients long courses (seven or more days).

a) Clinical response

Nine studies used the resolution of clinical signs or symptoms of acute exacerbations as their primary outcome. Bennett et al [28] used the absence of mucoid sputum in isolation and was hence excluded from meta-analysis for this outcome. Some studies reported outcomes at multiple time points so we presented clinical success as early (within 6 days of treatment completion), middle (7-14 days after treatment completion) or late (more than 20 days after treatment completion). Two studies assessed outcomes at 7‑17 days and 17‑23 days after treatment completion - they were excluded from this analysis.[29, 30]

There was no statistically significant difference between shorter and longer antibiotic courses in early clinical success (risk ratio (RR) 1.00, 95 % CI 0.96‑1.03) in the five studies that considered this (figure 3).

[Insert Figure 3 - Forest plot of early clinical success, within 6 days of treatment completion, < 6 versus ≥ 7 days antibiotic duration]

There was no statistically significant difference in medium (RR 1.08, 95 % CI 0.91‑1.27; 5 studies; figure 4) or late clinical success (RR 1.00, 95 % CI 0.99‑1.11; 6 studies; figure 5).

[Insert Figure 4 – Forest plot of medium clinical success, 7-14 days after treatment completion, < 6 versus ≥ 7 days antibiotic duration]

[Insert Figure 5 – Forest plot of late clinical success, > 20 days after treatment completion, < 6 versus ≥ 7 days antibiotic duration]

b) Adverse events

Nine studies reported overall adverse events (1882 and 1877 patients for the shorter and longer duration respectively). There was a statistically significant lower risk of developing adverse events in the shorter treatment group compared with the longer treatment group (RR 0.84, 95 % CI 0.75‑0.93, p=0.001; figure 6). For nausea the risk was statistically significantly lower in the shorter treatment group (RR 0.71, 95 % CI 0.52-0.98, p=0.04; 8 studies; supplementary data). No significant difference was found for diarrhoea (RR 1.03, 95 % CI 0.82‑1.29; 7 studies; supplementary data).

[Insert Figure 6 - Forest plot of overall adverse events, < 6 versus ≥ 7 days antibiotic duration]

c) Bacteriological response in sputum

Eight studies assessed eradication or presumed eradication of pathogens which were present in pre-treatment sputum samples. Presumed eradication was defined as improvement in clinical symptoms without sputum that could be cultured at follow up. All studies used populations that had an identified pre-treatment pathogen in sputum. There was no statistically significant difference between shorter and longer antibiotic treatment 0-6 days after treatment completion (RR 1.08, 95 % CI 0.71-1.65; 3 studies) and 7-23 days after treatment completion (RR 1.08, 95 % CI 0.83-1.39; 7 studies; both in supplementary data).

d) Other outcomes

Two studies considered spirometric change – there was no statistically significant change in either study between shorter and longer durations.[28, 30] One study assessed inflammatory markers, showing no difference between the different durations.[30] One study followed patients up to one year, assessing occurrence and time to new exacerbations, demonstrating no statistically significant differences between the groups.[28] Two studies included patients in the developing world but no sub-group analyses for these was reported.[23, 24]

Discussion

Summary of main findings

The prescription of antibiotics for COPD or asthma exacerbations is a very common clinical activity with serious potential adverse effects. Despite this, we found few studies had investigated optimal antibiotic duration for this indication. There was no difference in clinical success or bacteriological eradication for patients receiving fewer than six or more than seven days of antibiotics for COPD exacerbations. There was, however, a significantly lower risk of side effects overall and specifically nausea in the shorter duration group.

Strengths and limitations

This review was undertaken in a systematically following best practice guidance from the Cochrane Collaboration. Interpretation of our findings should be made in the context of the analysed studies having been largely undertaken at a time of significant variation in the diagnosis and treatment of COPD. The populations were therefore heterogeneous in key aspects such as smoking exposure and airflow obstruction (or did not have these clearly recorded) and by description of exacerbation outcomes. It is plausible that some study participants had other diagnoses such as bronchiectasis and chronic asthma. As many studies were undertaken prior to widespread use of standards for the assessment of COPD, it was not possible to stratify results by severity or GOLD criteria.

A sensitivity analysis without the study where the confounding factor smoking caused a high risk of bias showed no difference in our main findings (supplementary materials).27 Most of the older studies also had an “unclear” risk of bias by current standards. Fluoroquinolones were the commonest antibiotic class studied, but these are not first line treatment for uncomplicated exacerbations in usual clinical practice. This diminishes the external validity of the findings.[31]

Setting in existing literature

Antibiotic courses of five or fewer days were as successful as longer courses for clinical and bacteriological cure for chronic bronchitis and COPD exacerbations in a meta-analysis in 2006. However, this study compared course length regardless of drug (e.g. 10 days of cefuroxime with 5 days of telithromycin).[21] Our study adds to the literature by including a search of the last 10 years of medical publications, and by restricting analyses to consider only whether shorter courses of the same antibiotic are as effective and well tolerated. This reduces bias created by different mechanisms of action irrespective of duration.

Shorter courses of antibiotics have already been found to be as effective as longer courses in community acquired pneumonia and pharyngitis, and our findings are consistent with this.[18, 21, 32–34]

Antibiotics are not routinely recommended for the treatment of asthma exacerbations, and three published studies suggest no benefit above placebo.[7, 10, 35–37] However, antibiotics continue to be prescribed extensively for asthma exacerbations.[10, 12] This discrepancy between observed antibiotic prescribing and limited available evidence highlights the need for further studies.

Implications for future research

This review supports the use of shorter courses of antibiotics for the treatment of COPD exacerbations. However, further research is required to ascertain if these findings hold true in the context of current COPD care, antibiotic use and antibiotic resistance patterns. The development of extensive electronic health record databases of routinely collected data could be used to provide initial evidence in this regard, and could support the design of targeted interventional studies. Future studies in high-income countries are likely to also include biomarker-guided treatment. However, significant challenges exist in lower and middle income countries where antibiotic resistance is prevalent and only fixed duration regimens are currently feasible.

Conclusions

This systematic review highlights the paucity of research evidence relevant to usual clinical practice informing selection of antibiotic duration for asthma and COPD exacerbations. It appears courses of antibiotics of 6 or fewer days are equally as effective as those of one week or longer, but associated with fewer side effects. However, due to the limitations of the published studies, new observational and interventional studies are needed to robustly inform guidelines.

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Conflicts of interest:

None.

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