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Are antibiotics a safe and effective additional treatment for asthma exacerbations?

Background to the question

Asthma is a common long-term breathing condition that affects adults and children worldwide. Individuals may experience short-term worsening of their symptoms, often known as exacerbations (or asthma attacks). Exacerbations are usually treated by stepping up a person's medication (e.g. giving steroid tablets for a few days). Sometimes exacerbations can be triggered by infections such as viruses. Occasionally, a bacterial infection in the lungs or airways might cause an exacerbation. Symptoms of a bacterial infection include crackles on the chest, fever, and coughing up large volumes of discoloured sputum. Bacterial infections can be confirmed by laboratory tests, for example, blood tests; however, these are not always available in primary care (at the GP). Bacterial infections may require treatment with antibiotics.

In this review, we wanted to find out whether or not antibiotics are helpful and safe for people having asthma exacerbations. Part of the motivation for this review is a concern that antibiotics may be over-prescribed for people with asthma exacerbations.

Study characteristics

We looked for studies that compared a group of people given any type or dose of antibiotic with a group of people not given an antibiotic for an exacerbation. We included only studies in which it was decided by chance who would get an antibiotic. We included studies in adults and children carried out at any time and anywhere in the world.

Key results

We found six studies that included 681 adults and children with asthma. Two of these studies were carried out over 35 years ago.

Overall, we found a small amount of evidence suggesting that antibiotics may improve symptoms and breathing test results compared with no antibiotic. We are not very sure about these results because only a small number of studies and people were included in our review. One of our primary outcomes - admission to intensive care unit/high dependence unit (ICU/HDU) - was not reported.

We also cannot be sure if people given antibiotics have more or fewer adverse events (side effects). Only 10 people (5 given antibiotics and 5 given placebo/no antibiotic) out of 502 had a serious adverse event.

We did not find much evidence about other important outcomes, such as admission to hospital or another exacerbation during the study follow-up period.

The most recent study found it difficult to recruit people with asthma because so many of them had already been given an antibiotic and so could not take part.

Quality of the evidence

Overall, we have low confidence in the evidence presented in this review. We think it is possible that some studies of antibiotics for asthma exacerbations have been carried out but not published because we were able to find so few studies about such an important question. We were also worried about how well study findings apply to all people with asthma attacks because most of the studies that we found recruited only

people in hospitals and emergency departments. Also, two of the studies were old, and asthma treatment has changed a lot in 30 years. Because we found only a few studies, in some cases we cannot tell if antibiotics are better than, worse than, or the same as no antibiotic. Finally, we had some concerns about the ways in which studies were carried out, for example, in one study both patients and study staff knew who was getting an antibiotic and who was not; this might have affected how patients or staff behaved.

Conclusions

We found very limited evidence that antibiotics may help people having asthma attacks, and we are still very unsure. In particular, we did not find much information about important outcomes such as hospital admissions or side effects. However, serious side effects were very rare in the studies that we found.

Authors' conclusions:

We found limited evidence that antibiotics given at the time of an asthma exacerbation may improve symptoms and PEFR at follow-up compared with standard care or placebo. However, findings were inconsistent across the six heterogeneous studies included, two of the studies were conducted over 30 years ago and most of the participants included in this review were recruited from emergency departments, limiting the applicability of findings to this population. Therefore we have limited confidence in the results. We found insufficient evidence about several patient-important outcomes (e.g. hospital admission) to form conclusions. We were unable to rule out a difference between groups in terms of all adverse events, but serious adverse events were rare.

Read the full abstract...

Background:

Asthma is a chronic respiratory condition that affects over 300 million adults and children worldwide. It is characterised by wheeze, cough, chest tightness, and shortness of breath. Symptoms typically are intermittent and may worsen over a short time, leading to an exacerbation. Asthma exacerbations can be serious, leading to hospitalisation or even death in rare cases. Exacerbations may be treated by increasing an individual's usual medication and providing additional medication, such as oral steroids. Although antibiotics are sometimes included in the treatment regimen, bacterial infections are thought to be responsible for only a minority of exacerbations, and current guidance states that antibiotics should be reserved for cases in which clear signs, symptoms, or laboratory test results are suggestive of bacterial infection.

Objectives:

To determine the efficacy and safety of antibiotics in the treatment of asthma exacerbations.

Search strategy:

We searched the Cochrane Airways Trials Register, which contains records compiled from multiple electronic and handsearched resources. We also searched trial registries and reference lists of primary studies. We conducted the most recent search in October 2017.

Selection criteria:

We included studies comparing antibiotic therapy for asthma exacerbations in adults or children versus placebo or usual care not involving

an antibiotic. We allowed studies including any type of antibiotic, any dose, and any duration, providing the aim was to treat the exacerbation. We included parallel studies of any duration conducted in any setting and planned to include cluster trials. We excluded cross-over trials. We included studies reported as full-text articles, those published as abstracts only, and unpublished data.

Data collection and analysis:

At least two review authors screened the search results for eligible studies. We extracted outcome data, assessed risk of bias in duplicate, and resolved discrepancies by involving another review author. We analysed dichotomous data as odds ratios (ORs) or risk differences (RDs), and continuous data as mean differences (MDs), all with a fixed-effect model. We described skewed data narratively. We graded the results and presented evidence in 'Summary of findings' tables for each comparison. Primary outcomes were intensive care unit/high dependence unit (ICU/HDU) admission, duration of symptoms/exacerbations, and all adverse events. Seconday outcomes were mortality, length of hospital admission, relapse after index presentation, and peak expiratory flow rate (PEFR).

Main results:

Six studies met our inclusion criteria and included a total of 681 adults and children with exacerbations of asthma. Mean age in the three studies in adults ranged from 36.2 to 41.2 years. The three studies in children applied varied inclusion criteria, ranging from one to 18 years of age. Five studies explicitly excluded participants with obvious signs and symptoms of bacterial infection (i.e. those clearly meeting current guidance to receive antibiotics). Four studies investigated macrolide antibiotics, and two studies investigated penicillin (amoxicillin and ampicillin) antibiotics; both studies using penicillin were conducted over 35 years ago. Five studies compared antibiotics versus placebo, and one was open-label. Study follow-up ranged from one to twelve weeks. Trials were of varied methodological quality, and we were able to perform only limited meta-analysis.

None of the included trials reported ICU/HDU admission, although one participant in the placebo group of a study including children with status asthmaticus experienced a respiratory arrest and was ventilated. Four studies reported asthma symptoms, but we were able to combine results for only two macrolide studies of 416 participants; the MD in diary card symptom score was -0.34 (95% confidence interval (CI) -0.60 to -0.08), with lower scores (on a 7 point scale) denoting improved symptoms. Two macrolide studies reported symptom-free days. One study of 255 adults authors reported the percentage of symptom-free days at 10 days as 16% in the antibiotic group and 8% in the placebo group. In a further study of 40 children study authors reported significantly more symptom-free days at all time points in the antibiotic group compared with the usual care group. The same study reported the duration in days of the index asthma exacerbation, again favouring the antibiotic group. One study of a penicillin including 69 participants reported asthma symptoms at hospital discharge; the between-group difference for both studies was reported as non-significant.

We combined data for serious adverse events from three studies involving 502 participants, but events were rare; the three trials reported only 10 events: five in the antibiotic group and five in the placebo group. We combined data for all adverse events (AEs) from three studies, but the effect estimate is imprecise (OR 0.99, 95% CI 0.69 to 1.43). No deaths were reported in any of the included studies.

Two studies investigating penicillins reported admission duration; neither study reported a between-group difference. In one study (263 participants) of macrolides, two participants in each arm were reported as experiencing a relapse, defined as a further exacerbation, by the six-week time points. We combined PEFR endpoint results at 10 days for two macrolide studies; the result favoured antibiotics over placebo (MD 23.42 L/min, 95% CI 5.23 to 41.60). One study in children reported the maximum peak flow recorded during the follow-up period, favouring the clarithromycin group, but the confidence interval includes no difference (MD 38.80, 95% CI -11.19 to 88.79).

Grading of outcomes ranged from moderate to very low quality, with quality of outcomes downgraded for suspicion of publication bias, indirectness, imprecision, and poor methodological quality of studies.

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