

**TITLE:** Antibiotics for asthma attacks – masking uncertainty

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**Take Home Message:** Despite current guidelines advising against, GPs commonly prescribe antibiotics with steroids for asthma attacks. The uncertainty caused by a symptom-based management paradigm probably drives this. We need a biology guided asthma attack management paradigm.

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**Plain Language Summary:** A report in this issue of the journal shows that we continue to overestimate infection and overuse antibiotics in asthma attacks. Studying more than 200,000 patients with asthma, Murray and colleagues report that half of these are treated with a combination of corticosteroids and antibiotics, contrary to current guidelines. In this real-world dataset, the utility of the additional antibiotic component is marginal and not clinically significant. The current paradigm for symptom-based management needs to be challenged. We propose that treatment decisions be guided by biomarkers accessible to primary care physicians. This may be the key to better identify patients who might benefit from antibiotics in acute asthma and withholding the prescription in those who would not.

## **Abbreviations**

COPD: chronic obstructive pulmonary disease

CRP: C-reactive protein

FeNO: fractional exhaled nitric oxide

GINA: global Initiative for Asthma

OCS: oral corticosteroids

OPCRD: Optimum Patient Care Research Database

PCR: polymerase chain reaction

POCT: point of care test

## Introduction

The role for antibiotics in acute asthma has been historically overestimated [1]. From a mechanistic point of view, multiplex polymerase chain reaction (PCR) testing and conventional microbiological techniques show that >50-80% of events are associated by viral infections, with the remaining proportion presumed to be due to allergies and irritants, and less than 20% associated with evidence of bacterial infection [2]. Consequently, antibiotics are not expected to work in most asthma attacks and their routine use is not recommended. This stance is supported by a Cochrane review, which found inconsistent data to support antimicrobial use [3] and a good quality retrospective cohort study, which associated the combination of antibiotics and oral corticosteroids (OCS) with a longer hospital length of stay, higher hospital cost, and similar risk of treatment failure compared to matched patients treated only with OCS alone [4].

Despite this evidence and guidelines discouraging antibiotic use, real world data sets show that 22 to 44% of patients are treated with antibiotics as well as oral corticosteroids (OCS) [4–6]. There is similar overuse of antibiotics in primary care [7, 8].

In this issue of the journal, Murray *et al.* provide some new information on the use of antibiotics to treat asthma attacks [9]. They use routinely collected data from the Optimum Patient Care Research Database (OPCRD) to assess if the addition of antibiotics to oral corticosteroids reduced the likelihood of requiring a repeat consultation with asthma/wheeze at 2 weeks. In 22,005 adults and 6,632 children, the addition of antibiotics to the initial prescription of OCS reduced the absolute incidence of repeat consultations at 2 weeks by 3% (20 vs 22.9% for adults; 19.6 vs 22.8% for children). In other words, 33 patients will need to be treated with antibiotics and OCS at day 0 for

their asthma attack to prevent 1 additional asthma consultation at 2 weeks, compared to OCS alone. Penicillins – not macrolides – had a slight advantage in this respect. Nevertheless, when repeat prescriptions of OCS were assessed as an outcome, there was no difference between children treated with OCS and antibiotics or OCS alone at time of their initial asthma attack. In adults, there was no difference at 2 weeks, but there was an increased risk of a repeat OCS prescription at 6 weeks if they were treated with OCS and antibiotics. Overall, the results are consistent with the previous literature.

We also note the authors' exploratory analysis assessing the utility of a random blood eosinophil count to predict the effectiveness of the addition of antibiotics to OCS to treat an asthma attack. This analysis showed that a blood eosinophil count, measured at any point during 3 years prior to the asthma attack in question, did not predict the participants who would benefit from the addition of antibiotics for their asthma attack. We argue that a point of care C-reactive protein (CRP) would have predicted the group who would benefit.

Perhaps the strongest conclusion that can be drawn from this study is that primary care clinicians commonly do not follow guideline advice on treatment of asthma attacks. An observational study such as this cannot really tell us much about why different treatment decisions are made, nor can it compare with any degree of precision the outcomes of different treatment regimens since these are not applied at random and there was no standardisation of assessment. Nevertheless, the findings do raise the possibility that there are some patients with acute severe asthma who derive benefit from the addition of antibiotics. Could we do a better job in identifying this group of patients? Might a precision medicine, biomarker guided management approach allow us to target treatment more effectively? Such an approach has revolutionised the management of

severe asthma and we believe that the time is now ripe for a change in the way we manage asthma attacks.

Should we be surprised by the findings of Murray *et al.*? We think not. When a patient with asthma presents to primary care with an increase in asthma symptoms, general practitioners are expected to provide effective and safe care without any additional tests. Physicians, especially primary care physicians, are natural Bayesian thinkers and they tend to be cautious, particularly in an acutely ill patient. We know that the pattern of symptoms and signs, including increased sputum production and/or purulence do not appreciably alter the pre-test probability of bacterial infection [10] so in the absence of additional useful information, the safest and most rational approach [11] is to treat for both infectious and non-infectious causes. Prescribers are mindful of the adverse effects of indiscriminate antibiotic use on (antibiotic resistance particularly) but assess the risk of not using antibiotics to be higher.

Might there be a feasible way to reduce the risk/benefit ratio for antibiotic use in acute asthma (Figure 1)? In chronic obstructive pulmonary disease (COPD), guidelines are clear on the reasons to ask for a sputum culture [12], and antibiotic therapy for acute exacerbations were reduced from 77 to 57% by point of care CRP testing with no evidence of harm [13]. Moreover, a randomised trial has shown that a multiplex PCR for respiratory viruses can reduce antibiotic use compared to routine clinical care in airways disease [14]. Both tests could be offered at the point of care in a community setting and we suggest that it is time to assess a biomarker directed personalised treatment approach for asthma attacks (Figure 1B) [15, 16].

This thinking could also be applied to the use of OCS. There is much wider acceptance of the universal treatment of significant asthma attacks with systemic corticosteroids. However, this practice is based on small and old studies carried out in patients who by and large were not treated with inhaled corticosteroids (ICS). The benefits are not large: a systematic review showed that 10 asthma attacks need to be treated with OCS to prevent 1 relapse [17] and this effect would be predicted to be less in a population who are treated with ICS. The positive effects of OCS need to be considered alongside increasing evidence of treatment associated morbidity, even with a short course of OCS [18]. We and others [15, 16] argue that precision, biomarker directed OCS use might also allow us to improve the risk/benefit ratio of OCS use. Blood eosinophil directed OCS use looks very promising in the setting of COPD attacks and there is no reason to suppose that this would be different in asthma. Recently, the MEX trial [19] found that fractional exhaled nitric oxide measurements (FeNO) was a very effective way of discriminating asthma attacks occurring on mepolizumab that are associated with high and low sputum eosinophil count, potentially aiding physicians' choice to prescribe OCS.

On a final and more ambitious note, might it be time to think about a new taxonomy of asthma attacks? The GINA guidelines define asthma exacerbations as events that lead to a change in symptoms and lung function sufficient to warrant additional treatment [20]. Dr Murray and colleagues revert to defining an asthma attack by need for OCS prescription. Doing this, they disregard the possibility that some asthma attacks are treated without OCS, like attacks treated with antibiotics alone. They also define treatment failure as a GP visit with an asthma/wheeze read code, excluding other respiratory consultations. While we applaud the author's efforts to also use the repeat prescription of OCS and/or antibiotics at different time points as a robust measure of

treatment failure, a consensus decision is needed to define treatment failure. When does one asthma attack end and another begin? How long after initial treatment is the next event a relapse? In clinical trials, an OCS prescription at any time, even days after an asthma attack would be counted as another attack. Most patients and physicians would disagree, instead considering it delayed recovery from the previous event. A recent COPD expert Delphi survey [21] showed that there is indeed consensus amongst COPD experts on the definition of treatment failure and the timeline to stability after an attack. A similar expert consensus is needed for asthma.

## **Conclusion**

To summarise, we agree and commend Murray *et al.* for pointing out that a weak statistically positive finding for reduced cough/wheeze consultations in the 2 weeks following an initial prescription of OCS plus antibiotics does not justify the routine use of antibiotics for asthma attacks. The surprisingly widespread use of antibiotics should nevertheless challenge our perceptions of acute asthma. In chronic asthma, we know that different biological subtypes have different treatment responsiveness. This knowledge needs to be extended to asthma attacks in primary and secondary care. We owe our patients more confident decision making, guided by accessible biomarkers, when choosing to prescribe antibiotics for asthma attacks.

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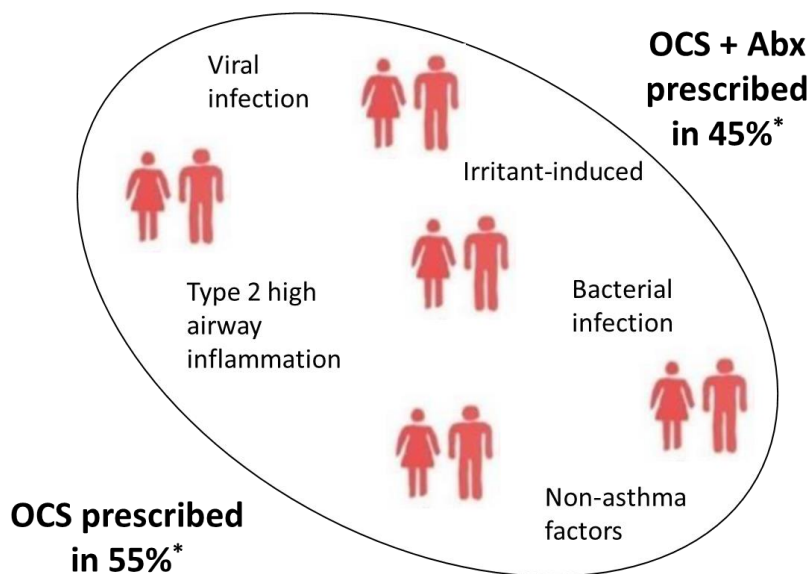
## FIGURE LEGENDS

**FIGURE 1.** Two different approaches to asthma attacks. **A.** In the current paradigm for symptom-based management of asthma, we prevent and treat all acute events equally or randomly, at least with an oral corticosteroid (OCS) and often with antibiotics (Abx). **B.** Our goal is to better inform both our preventive and therapeutic decisions with objective evidence of the underlying biology using accessible biomarkers – many of which are available as point of care tests (+). CRP = C-reactive protein, Eos = eosinophils, FeNO = fractional exhaled nitric oxide PCR = polymerase chain-reaction, Sx = symptoms. \*Data reported by Murray *et al.* in this issue of the journal [9].

Figure 1 A and 1 B

### A. Current paradigm:

Symptom-based prevention and management



### B. Goal:

Biomarker-guided prevention and management

