EDITORIAL

Antibiotic Treatment for Inpatient Asthma Exacerbations
What Have We Learned?

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An extensively revised, retracted, and replaced article by Stefan et al[1] in this issue of *JAMA Internal Medicine* assesses outcomes associated with antibiotic treatment in adults hospitalized for asthma exacerbations. About half of such patients are treated with antibiotics (primarily macrolides and quinolones) without a clear clinical indication. Stefan et al[1] found that while treatment with antibiotics on day 1 of hospitalization was associated with slightly increased length of stay and costs, it was associated with a statistically significant 1.1% (95% CI, 0.2% to 1.9%) absolute reduction in the risk of treatment failure (7.1% vs 8.2%), defined as initiation of mechanical ventilation, transfer to the intensive care unit after hospital day 1, in-hospital mortality, or readmission for asthma exacerbation within 30 days of discharge. They conclude that their results "highlight the need to perform randomized clinical trials to determine the role of antibiotic prescribing among patients hospitalized for asthma exacerbation."[1]

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Because both the risks and benefits of antibiotic therapy in individual patients without apparent infections are small, large sample sizes are needed to quantify them. This makes observational studies of the sort reported by Stefan et al[1] appealing: a large randomized clinical trial to address this question would be expensive and time consuming. However, the design and analysis of observational studies as alternatives to randomized clinical trials can be challenging, as illustrated by the change in the conclusions between the original and revised versions of this article. In the original version, the authors had stated that their findings "lend strong support to current guidelines that recommend against the use of antibiotics in the absence of concomitant infection," rather than highlighting the need for randomized clinical trials to answer the question. (Note: the original version is available in Supplement 2 to the corrected replacement article.[1])

What happened? In their original report, the authors highlighted a highly clinically and statistically significant median 1-day increased length of stay among patients treated with antibiotics. However, their original definition of antibiotic exposure required at least 2 days of inpatient exposure to antibiotics and did not require that the antibiotic therapy be started on day 1. As a result, patients started on antibiotic therapy and then discharged before they had received 2 days of antibiotics were excluded from the exposed group, rather than counted as exposed patients with short stays. In contrast, in the unexposed group, there was no minimum length of inpatient stay.

Although mortality was not the outcome in this study, the resulting bias is called *immortal time bias* because of its similarity to a bias that arises when study participants are given credit for surviving during a period of time when the study design or analysis makes it impossible for them to die.[2,3] In this case, the outcome was discharge from the hospital (which defines the length of stay), rather than mortality, but the problem is the same: patients eligible to be in the antibiotic group could not have been discharged until they had received at least 2 days of inpatient antibiotics. When the authors changed their definition of exposure to being started on antibiotic therapy on day 1, with no minimum duration, the immortal time bias went away, taking with it most of the difference in length of stay.

Most readers know that a major advantage of randomized clinical trials is that they are the best way to minimize confounding (ie, differences between treated and untreated participants other than treatment that might account for differences in outcome). However, another benefit of randomized clinical trials is that they establish a clear starting point (randomization) at which to begin counting outcome events.

Hernán et al[4] suggest that a good way to prevent "immortal time bias and other self-inflicted injuries in observational analyses" is to design a randomized clinical trial to answer the research question addressed by the observational study. They call this the *target trial*. Investigators should then design the observational study to emulate this target trial as closely as possible.

In a randomized clinical trial of antibiotics for asthma exacerbations, patients would be randomized to antibiotic treatment and control groups soon after the decision to admit. Patients would then be analyzed according to the group assigned (intention-to-treat analysis) regardless of whether some participants who had started antibiotic therapy were discharged before remaining on the treatment for 2 days or some participants who were originally assigned to the control group started antibiotic therapy later.

The definition of antibiotic exposure in the revised article by Stefan et al[1] emulates such a randomized clinical trial much more closely than the original because it requires only that antibiotic therapy be initiated on day 1. The change in exposure definition to reduce the risk of immortal time bias had the predicted effect on the primary outcome: length of stay. However, unexpectedly, the investigators now report a benefit of early initiation of antibiotic therapy on treatment failure. It is not clear why the change in exposure definition would lead to the uncovering of this previously missed beneficial outcome. One possibility, offered by the authors, is that patients may have been started on antibiotic therapy late because they were deteriorating; these patients were included in the

exposed group in the previous analysis but not in the revised analysis.

The take-home message for many readers may be to be skeptical of reports of observational studies of treatments based on claims databases. I support that conclusion. On the other hand, the good news is that critical readers can often identify or suspect errors missed by investigators and editors, and this can lead to corrections, or in this case, a retraction and replacement.[5] The simple step of considering a target trial can help prevent or identify some of these self-inflicted injuries.

ARTICLE INFORMATION

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