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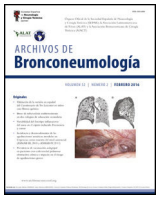

Editorial

The Hidden and Unchecked Judgement Calls When Using Exacerbation History for Managing COPD

Chronic obstructive pulmonary disease (COPD) is one of the most common and debilitating disorders globally. Acute exacerbations of COPD (AECOPD) are a defining feature of the disease and a major source of its burden. Consequently, the prevention of AECOPDs is a cornerstone of modern COPD management strategies. In many guidelines, important disease management decisions, in particular the choice of pharmacotherapy, is based on AECOPD history in the previous twelve months.

While intuitive and parsimonious, this approach has several weaknesses that limit its application in clinical practice. First, this approach produces inherently unstable groups over time. We recently demonstrated in 2 large cohorts that reliance on the patients' AECOPD history often leads to repeated reclassification of patients from year-to-year (from frequent to non-frequent exacerbator phenotype or vice versa) even when the underlying rate of exacerbation remains stable.[1] For example, a patient with a stable underlying AECOPD rate of 2 events per year has a 47% chance of switching between frequent and non-frequent exacerbator in two consecutive years due to chance alone. In this editorial, we highlight a second fundamental weakness of this approach: the "hiddenness" of treatment thresholds.

Treatment threshold at the heart of rational decision making

In their classic paper published more than four decades ago, Pauker and Kassirer applied principles of decision theory to argue that the chance that a patient has a particular disease or is at a risk of a particular event is a crucial factor in the choice of treatment.[2] Because individuals at a high risk of poor outcomes are more likely to benefit from treatments than those at a low risk, there exists a risk 'treatment threshold' at which the benefits and harms of a given treatment are in perfect balance. Above this treatment threshold, the benefits of the treatment outweigh its harms. Below this threshold, the reduction in risk will not offset potential treatment harms.

This treatment threshold approach towards clinical decision making has been widely adopted in some specialties. A leading example is primary prevention of cardiovascular diseases (CVD). For example, the American guidelines on the primary prevention of CVD generally consider a treatment threshold for preventive pharmacotherapies (e.g., statins) to be between 7.5% and 20% with regards to the 10-year risk for acute CVD events.[3,4] At risks below 7.5%, preventive therapies are not considered net beneficial, whereas at predicted risks above 20% they are considered highly beneficial. Within the 7.5–20% range (i.e. the "grey zone"), the benefit–harm balance hinges on how the patient values reduction in CVD risk versus the risk of adverse events. For some patients, postponing preventative treatment may be the preferred approach; while in those who are more willing to accept the risk of adverse events, aggressive preventive pharmacotherapeutics may be warranted. Thus, a shared decision-making approach is recommended when the risk falls in the grey zone. There are many examples of explicit treatment thresholds on predicted risks in other subspecialties such as fracture prevention in post-menopausal women,[5] or screening for breast cancer.[6]

The implicit treatment threshold in history-based COPD management

Contemporary AECOPD prevention strategies are based on patients' AECOPD history over the previous year premised on the idea that *previous exacerbation history is the best predictor of future risk*.[7] As a case in point, both the Canadian Thoracic Society (CTS) and the Global initiative for chronic Obstructive Lung Disease (GOLD) recommend dichotomisation of patients into high- or low-AECOPD risk groups based on ≥2 moderate AECOPDs or ≥1 severe AECOPDs over the past year.[8] This approach does not explicitly attach a quantifiable risk value to high- and low-risk patients, but that does not a mean a risk treatment threshold is not applied.

To elucidate this implicit risk threshold, we analyzed data from ECLIPSE (Evaluation of COPD Longitudinally to identify Predictive Surrogate Endpoints), a prospective three-year observational cohort study to document the natural history of AECOPDs.[7] We used the AECOPD patterns during the first year to classify patients into risk groups. We then used the second-year data to determine the observed risk of experiencing a moderate/severe AECOPD. For this analysis, there were 1821 individuals who had complete AECOPD data for both years 1 and 2. Ethics approval was obtained from The University of British Columbia/Providence Health Care Human Ethics Board (H11-00786). The results are provided in Table 1.

Each row reports the calculated risk of patients experiencing at least one moderate or severe AECOPD in year 2 according to their year 1 AECOPD history. There are two groups that are considered non-frequent exacerbators according to the CTS/GOLD definition: those with no AECOPDs, and those with one moderate AECOPD (the

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Table 1
Year 1 frequent exacerbator status and year 2 AECOPD risk based on ECLIPSE.

AECOPD pattern in year 1	Year 1 status	AECOPD risk (95% CI) in year 2
Severe: 0/Moderate: 0	Non-frequent exacerbator	33% (30%–36%)
Severe: 0/Moderate: 1	Non-frequent exacerbator	62% (57%–67%)
Severe: 0/Moderate: 2+	Frequent exacerbator	83% (79%–87%)
Severe: 1+/Moderate: 0	Frequent exacerbator	71% (62%–80%)
Severe: 1+/Moderate: 1	Frequent exacerbator	74% (64%–84%)
Severe: 1+/Moderate: 2+	Frequent exacerbator	97% (94%–100%)

first two rows). The second-year risk of AECOPD in these groups was, respectively, 33% and 62%. All other groups are considered frequent exacerbators. The second-year risk among frequent exacerbators ranged from 71% to 97%.

Imagine we are considering treatment in a patient who currently uses inhaled long-acting beta-2 agonists (LABA) and long-acting muscarinic antagonists (LAMA). GOLD/CTS guidelines recommend inhaled corticosteroid (ICS) therapy only for frequent exacerbators (highlighted rows in Table 1). If we apply guideline treatment recommendations to ECLIPSE data, we would prescribe ICS for those with 71% risk for future AECOPDs (fourth row), but not those with a 62% chance (second row). One conclusion is thus inescapable: the current definition of a frequent exacerbator phenotype implicitly assigns a treatment threshold of somewhere between 62% and 71% on the 12-month AECOPD risk.

Is this an evidence-based threshold for ICS therapy? Are there any empirical data on patient or physician-based values and preferences of ICS therapy that support this range of treatment threshold? To the best of our knowledge, no formal assessment was conducted to choose a particular range of treatment thresholds for stepping up therapy. Further, because this range of thresholds is opaque, the idea of risk cannot be properly conveyed to patients and thus their voice cannot be incorporated into their management plans. We also note that this range of thresholds is affected by the case-mix observed in ECLIPSE, and might be different in different patient population. This threshold may also be affected by biomarkers of efficacy such as blood eosinophil count. For example, a recent modelling study showed that in patients with a blood eosinophil count of less than 150 cells/μL, ICS was not net beneficial regardless of the baseline risk of AECOPD.[9]

Towards a risk-based approach for prevention of AECOPDs

If the principles of rational decision-making are to be applied, the treatment threshold should be determined based on a careful consideration of the benefit–harm profile of individual treatments as well as the preferences and values of patients who ultimately bear the consequence of our decisions. To move the COPD community towards true personalized medicine and precision health, we advocate several important next steps. The first is to embrace the idea of multivariable risk prediction for quantitative risk generation. While AECOPD history carries some information on the risk of AECOPD, other patient and disease characteristics in aggregate can significantly improve the predictability of AECOPD risk,[10] with a recent analysis demonstrating that validated risk prediction algorithms provide higher clinical utility compared to AECOPD history alone across a wide range of treatment thresholds.[11]

Another step is to decide on treatment thresholds. This can be based on quantitative benefit–harm analysis that considers the totality of evidence on the effectiveness and adverse events profile of a given medication, combined with eliciting the preferences of patients on how they trade off the benefits and harms of a treatment.[12] Importantly, treatment thresholds might be different for different subgroups and across different treatment modalities. For example, it is unlikely that the decision to add a relatively safe drug like LAMA would correspond to the same threshold as a more controversial treatment such as maintenance oral azithromycin. Finally, we will need empirical evidence in terms of real world 'impact' studies that compare the outcomes of using such risk-based approach towards disease management versus the *status quo*. The path in front of us might be long, but the shortcomings of a history-based approach are apparent, and so are the promises and potentials of an objective and transparent risk-based approach for COPD management.

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