

EDITORIAL

Thorax – 1500 words, 20 references.

Exacerbation of COPD: transforming outcomes through research

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"Would you tell me, please, which way I ought to go from here?"

"That depends a good deal on where you want to get to."

[A]

The time has come for a revolution in the prevention and mitigation of exacerbations in chronic obstructive pulmonary disease (COPD). Here in the UK, recent data from the national COPD secondary care audit demands urgent attention. Admissions to hospital for COPD exacerbations have risen by 13% since 2008, to 115,000 /year [B]. In-patient mortality is 4%, and a further 3% will die and 24% will be re-admitted within 30 days of discharge [B]. There are unexplained variations in care-quality metrics across the country that exaggerate the health inequalities already associated with COPD. And these concerning statistics on secondary care admissions represent just a small proportion of the overall burden of exacerbations given that the majority of events are (quite appropriately) treated in the community.

At the most basic level we still have a problem with terminology and definitions. It is impossible to have an exacerbation of COPD if a person does not have COPD in the first place, yet the lack of access to - or willingness to access –confirmatory quality-assured diagnostic spirometry when a patient presents with symptoms that might represent exacerbation is of considerable concern [B]. The definition and diagnostic criteria for COPD exacerbation remain imperfect. The GOLD strategy document defines exacerbation as a change in symptoms requiring additional therapy [O]. In everyday practice exacerbation is a clinical diagnosis of exclusion, suggested by changes in symptoms, but only made when the clinician has considered and where appropriate excluded, other causes of symptom changes in a patient with known COPD (such as heart failure, or pulmonary embolus [C] for example). Despite considerable effort, there remains no diagnostic test for exacerbation that is sufficiently sensitive or specific to rule-in and rule-out exacerbation from other causes of symptoms changes, or to differentiate exacerbation of COPD from COPD in the stable state

[R]. This is analogous to the diagnosis of MI being made on the presence of chest pain alone. The search in COPD for a physiological (ECG equivalent) or blood biomarker (cardiac enzymes, then troponins) has thus far been futile. In addition to mimicking exacerbation, clinicians need to be aware that symptom changes at exacerbation may also be complicated by co-existent pathologies.

Current interventions to treat COPD are inadequate. Remarkably, there have been no new interventions to treat COPD exacerbations in our entire professional lifetime of over 20 years. The evidence for oral steroids is weak and based on outcomes that do not focus on the patient – typically speed of improvement in lung function [D]. Avoidable morbidity from over-use of steroids is considerable and, as commonly employed in ‘rescue packs’, it is known that not all patients are able to self-manage appropriately [E]. Over-use of antibiotics risks development of anti-microbial resistance in the individual, and in our societies. We have no reliable methods to differentiate bacterial, viral or environmental exacerbations at the point of care and, in any case, we have no effective anti-viral interventions to treat rhinovirus – the commonest single cause of COPD exacerbations [S]. Our fundamental understanding of the biology of a COPD exacerbation is incomplete, limiting therapeutic developments. Although it is now accepted that exacerbations are not all the same and can be ‘phenotyped’ [F], initial evidence to support a stratified medicine approach - better targeting of steroids (using blood eosinophils [G]) and/ or antibiotics (using biomarkers such as CRP, procalcitonin [H] or indeed sputum colour) have not been translated into routine clinical practice. Anecdotally, patients have long-acting bronchodilators stopped in preference to nebulised short-acting drugs and current national and international guidelines do not provide clear guidance to direct bronchodilator therapy at this time [O]. Patients still experience iatrogenic oxygen toxicity [B]. Attention to co-morbidities is poor despite the increasing prevalence of an ageing, multi-morbid patient population with poly-pharmacy and despite exacerbations being a time for increased risk of adverse events from inactivity, inflammation, hypoxia and therapies. We welcome the move to a rolling national COPD audit programme as a tool for quality improvement – specialist review at the front door and an evidence-based bundle of interventions prior to discharge – but also needed is a revolution in the evidence base for exacerbation treatment: both better use of existing interventions and the rapid development and testing of new interventions (anti-inflammatories, for example) based upon a deeper understanding of fundamental disease mechanisms.

Exacerbation research is not easy to do. The best studies prospectively follow people with COPD, enabling comparison of pre-exacerbation baseline results with those obtained at exacerbation, ideally before the introduction of additional therapy. There is no valid animal model of COPD exacerbation. Research in primary care databases demands an understanding of how such events are coded [T].

Better communication and closer working across hospital clinicians, community-based COPD teams, and primary care may be one way to mitigate the risks of repeat admission (and to facilitate access to diagnostic spirometry results). An exacerbation event should be used as an opportunity to review the patient’s preventative strategies. There are data to support the idea that the timing of exacerbation events is not random, with a higher-risk for repeat exacerbation in the recovery period from a first [I]. The tempo of subsequent hospitalisations then accelerates [J]. Reducing the risk, and consequences arising from a first hospitalised exacerbation therefore appears particularly important and thus how best to reduce the risk of readmission is a major unanswered problem. Patients susceptible to frequent exacerbations, a relatively stable phenotype [K, L], experience an excess burden of disease including accelerated lung function decline, poorer quality of life and excess mortality [M].

We do, at least, have interventions that can to some degree reduce the risk of exacerbations. Current strategies achieve a 25% reduction at most, suggesting that 75% of events remain unmitigated. This assumes appropriate targeting, however it is clear that exacerbation reduction interventions remain poorly focused with considerable under- and over-treatment and therefore avoidable morbidity and excess health-care cost. Additional challenges include translating the benefit from interventions seen in high-quality randomised trials to the real life multi-morbid patients that dominate clinical practice. High value interventions include vaccinations and pulmonary rehabilitation [N], supplemented by judicious use of pharmacotherapy, which for many people should now be based on one or more long-acting bronchodilators [O]. Evidence to support robust identification of groups most likely to benefit (or not) from inhaled corticosteroids remain in evolution, and careful targeting of novel therapies is of increasing importance with the emergence of evidence to support the use of (higher cost) biologicals including anti-eosinophil strategies [P].

At a global scale the challenges managing COPD and COPD exacerbations are even greater. 90% of COPD deaths occur in low- and middle-income countries (LMIC), where much COPD is associated with household air pollution from biomass and solid fuels, in addition to that associated with tobacco smoke exposure [Q]. There is very little known about the biology of exacerbations in biomass COPD, or about the most appropriate strategies for exacerbation prevention and treatment in LMIC. Clearly, in all settings, exposure reduction initiatives – tobacco control and clean cook-stoves – provide the best opportunity to reduce the burden of COPD in future generations.

We argue that with an ageing and multi-morbid population, a revolution in the care and prevention of COPD exacerbations is urgently required – across all health-care settings. Clinicians should not accept exacerbations as inevitable. We need new, high-quality evidence to better target existing interventions, incompletely effective as they are, and the ability to rapidly test and implement new exacerbation prevention and treatment strategies - in real-world settings. Research funding must be directed to better understand the fundamental biology of exacerbations if we are to develop new therapies. The UK COPD national audit programme, appropriately resourced in individual units, can assess implementation and help assess impact on outcomes. There are learning opportunities for other health-systems. Only by acting urgently, with renewed enthusiasm, can we hope to reduce the current inadequate and unequal care for people living with COPD, and improve exacerbation experience and outcomes. We know where we are going. We know how to get there. It is now time for all of us to act.

References:

- A. From Liz
- B. National COPD Audit Report
- C. What is and isn't a COPD exacerbation editorial
- D. Lancet 1999 Lisa Davies steroids
- E. GUST self management – Charlotte
- F. Mona exacerbation phenotyping
- G. Eosinophil guide exacerbations
- H. Stolz procalcitonin exacerbations
- I. Clustering
- J. Suissa timing paper

- K. NEJM Eclipse
- L. LRM frequent exacerbator
- M. A frequent exacerbator review
- N. PR
- O. GOLD Strategy
- P. Anti-eos
- Q. WHO LMIC data
- R. Biomarker of exacerbation
- S. RV as primary cause
- T. Jenni coding