Recent advances in exacerbations of COPD

Terence Seemungal,1 Annemarie Sykes,2 and the ICEAD Contributors

The First International Conference on Exacerbations of Airways Disease (ICEAD) brought together experts from both sides of the Atlantic to discuss problems in the management of exacerbations of both asthma and chronic obstructive pulmonary disease (COPD). A brief overview of these discussions on COPD exacerbations follows.

DEFINITIONS AND EPIDEMIOLOGY

Symptom and treatment based definitions

Up to 18 definitions of a COPD exacerbation have been advanced, from less explicit1 to very explicit symptom based criteria.2 3 However, large therapeutic trials in COPD have all used treatment based definitions.4 5 The first consensus definition was treatment based but the current GOLD guidelines accept a symptom based definition.6 7 Biochemical or physiological markers applied in studies

Health burden

COPD patients have about 0.5–3.5 exacerbations/year, 0.09–2.4 hospitalisations/year and in hospital mortality varies between 10% and 60%, depending on the severity of COPD. Overall, the death rate varies from 5.4 per 1000 person years among normal subjects to 42.9 among subjects with GOLD stage 3 or 4.8 Thus COPD exacerbations are a significant cause of death, mainly in patients with more severe COPD. This leads to a high cost of COPD care which can be effectively reduced through decreasing hospitalisation.9

AETIOLOGY AND SUSCEPTIBILITY

Airway bacterial infection

Bacteria may be detected in up to 60% of exacerbations and viruses in 23–60%.13 14 A study of hospitalised patients found bacteria in 25%, bacteria and viruses alone in 25%, and no infectious agent in another 25%.14 The acquisition of new strains of bacteria is associated with an increased risk of COPD exacerbation, more inflammation and strain specific immunity.15 16 However, non-specific reduction of bacterial load during recovery from COPD exacerbation has been associated with resolution of inflammation.9

Viruses and coinfection

Respiratory viruses have been associated with higher exacerbation sputum interleukin (IL)-6 levels, with prolonged COPD exacerbations and significant health burden.13 17 18 Furthermore, bacteria–virus coinfection leads to greater lung impairment and longer inhospital stay.14

Susceptibility and inflammation

Frequent COPD exacerbators appear to be a distinct phenotype characterised by a faster decline in lung function, poorer quality of life scores, more viruses at exacerbation, higher mortality, greater airway inflammation and higher arterial blood lactate.3 9 10 13 33 Frequent exacerbators also have smaller reductions in systemic inflammation post-exacerbation further. Interestingly, a high serum C reactive protein concentration post-exacerbation is associated with recurrence.20

Susceptibility and other factors

Viruses detected in lower airway samples of patients with stable COPD affect systemic inflammatory processes as well as lower airway bacterial load.13 21 Thus it is likely that the susceptibility of the frequent exacerbator phenotype is associated with viral colonisation of the lower airway though this has yet to be proved.
Other factors that may affect susceptibility are upper airway inflammation and bacterial colonisation, previous infection with non-typeable Haemophilus influenzae, season and environmental temperature.22 23

PATHOGENESIS
Pathophysiology
The acute and variable increase in end expiratory lung volume above its stable baseline is termed dynamic hyperinflation and occurs during COPD exacerbations.24 This leads to falls in spirometric parameters and increased functional residual capacity and residual volume. The resulting increased loading and functional weakness of the respiratory muscles may prevent a response to increased neural drive and thus neuromechanical uncoupling of the respiratory system occurs. This dissociation in response to acute dynamic hyperinflation is thought to contribute to the sensation of dyspnoea during COPD exacerbations.25

Cell mediated mechanisms
Both eosinophils and neutrophils are recruited during COPD exacerbations.14 25 Bacterial infection has been related to neutrophil chemoattractant gene expression which is upregulated during COPD exacerbation.16 26

Amplification of inflammation at COPD exacerbation
The amplification of airway and mucosal inflammation at COPD exacerbation is thought to be due to activity along two pathways involving (a) nuclear factor κB (NFκB) translocation, which involves NFκB inducing kinase 2 ( IKK2) and (b) histone deacetylase activity via a novel mechanism and restores HDAC activity in alveolar macrophages from patients with COPD.29 39 Macrolides have anti-inflammatory activity and are effective in cystic fibrosis and diffuse panbronchiolitis.40 Both of these agents appear to potentiate the effects of steroids and different combinations of well known drugs may be more useful than current combinations.

New anti-inflammatory drugs
Phosphodiesterase inhibitors have been shown to inhibit the formation of reactive oxygen species and leukotriene B4 synthesis in vitro.41 Because of their systemic side effects, their use may require inhaled administration. Blockade of the NFκB pathway by an IKK2 inhibitor is associated with decreased granulocyte macrophage colony stimulating factor production and inhibition of p38-MAPK decreases luciferase activity in response to TNFα/interferon-γ.42 Leukotriene B4 and IL8 antagonists have also been shown to inhibit neutrophil chemotaxis,43 and combined blockade of the neutrophil chemokine receptors CXCR1 and CXCR2 slows LPS induced neutrophil migration. Most of these newer agents have yet to be tested in clinical trials.

Future directions
A definition based on prolonged deterioration in chronic symptoms is useful but subjective. A surrogate marker of a COPD exacerbation would be of interest but such a marker should have reproducibility,
sensitivity to change and the clinically minimally important change in the marker must be known. Reducing hospitalisation rates through strategies to prevent COPD exacerbations may reduce the high health burden in COPD.

Further work must be done on the interaction between viruses and bacteria: does viral infection trigger the shift in strain of colonising bacteria seen during COPD exacerbations or is the effect mainly on bacterial load? Viruses are related to increased dyspnoea at exacerbation and thus an infective agent may be related to dynamic hyperinflation and hence to exacerbation severity. Frequent exacerbations are a marker of host susceptibility to exacerbation. Both pro-oxidants and chemokines cause inflammation through pathways mediated by NFKB. Blockade of steps along this pathway may be useful in attenuating the inflammatory response to infection. In the future, we may have to treat COPD exacerbations using receptor specific inhibitors along the inflammatory pathway.


Competing interests: None.

A list of the International Congress on Exacerbations of Airway Disease (ICEAD) contributors is published online at: http://thorax.bmj.com/content/vol63/issue10


REFERENCES

Recent advances in exacerbations of COPD

Terence Seemungal, Annemarie Sykes and the ICEAD Contributors

Thorax 2008 63: 850-852
doi: 10.1136/thx.2008.099127

Updated information and services can be found at:
http://thorax.bmj.com/content/63/10/850

These include:

References
This article cites 39 articles, 13 of which you can access for free at:
http://thorax.bmj.com/content/63/10/850#BibL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections

Inflammation (1020)
Epidemiologic studies (1829)
Therapeutic trials (13)
Drugs: infectious diseases (968)
Asthma (1782)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/