Asthma exacerbations
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Management of asthma exacerbations

W W Busse, R F Lemanske Jr

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A double dose is not enough

The management of asthma consists of the regular use of anti-inflammatory medications and an action plan for worsening of symptoms or an asthma exacerbation. Guidelines for the treatment of asthma have recommended doubling the dose of maintenance inhaled corticosteroids for deteriorations in asthma control that are not responding to β agonist rescue treatment in the usual manner.[1] [2] Although this approach has been advocated, evidence to support its effectiveness has been largely wanting.

In this issue of *Thorax* FitzGerald and colleagues[3] and members of the Canadian Asthma Exacerbation Study Group evaluated this approach. They identified 290 patients with well characterised asthma, all of whom had a history of at least one previous asthma exacerbation—defined as an increase in symptoms and the need for a change in medication not more than 12 months and not less than 1 month before the start of the run in period. During the run in period all subjects were maintained on their usual dose of inhaled corticosteroids. Subjects were then either assigned to maintenance treatment and received their usual dose of budesonide (100, 200, or 400 µg twice daily) plus a placebo inhaler to be used twice a day with an exacerbation, or were on the same doses of inhaled corticosteroid plus an inhaler containing active inhaled corticosteroid which therefore doubled their maintenance dose of inhaled corticosteroids during the exacerbation. An asthma exacerbation was defined as a combination of two of the following six criteria:

- fall in peak flow to less than 80% baseline value;
- bronchodilator use more than four times a day;
- night time waking;
- increase in asthma symptom scores;
- inability to go to school or work for two consecutive days;
- unscheduled visit to a physician during the study period.

The major outcome was the proportion of patients who failed to regain control after developing symptoms of an impending exacerbation of asthma, as judged by the need for treatment with oral corticosteroids or an unscheduled visit to a physician after 14 days of treatment.

Of the recruited subjects, 52 in the maintenance treatment group and 46 of those assigned to the double dose of inhaled corticosteroid had an asthma exacerbation. Treatment failure was equivalent in both study groups, and the major component of treatment failure was asthma instability: 23% were unstable on maintenance treatment after the appropriate observation period compared with 13% in the doubling dose group. The difference between the two treatment approaches did not achieve statistical significance. Other outcomes were also similar between the two groups. The authors therefore concluded that doubling the dose of inhaled corticosteroids was not effective in the management of impending asthma exacerbations.

Their findings are similar to and support those recently published by Harrison and colleagues[4] who monitored morning peak flows and asthma symptoms for up to 12 months in 390 patients with asthma. When peak flow values and symptoms began to deteriorate, an active inhaled corticosteroid or placebo was added to the maintenance treatment for 14 days. The primary outcome (number of individuals starting oral prednisolone) did not differ between the treatment groups. The reasons for starting prednisolone were a 40% fall in peak flow, advice from a general practitioner, or a subjective deterioration in asthma control.

These two studies thus provide evidence that early or impending exacerbations of asthma are not always effectively treated by doubling the dose of inhaled corticosteroids. What explanations do we have for these observations? As pointed out by FitzGerald *et al*,[3] there are a number of reasons why doubling the dose of inhaled corticosteroids may have been ineffective: (1) some studies have indicated that four times a day administration may be more effective than twice a day dosing as used in these two studies;[5] (2) the onset of action with inhaled corticosteroids may be slower than with systemic corticosteroids; (3) airflow limitation may impair drug delivery; and (4) the dosage increase may have been insufficient.

It is, however, more likely that other factors play a role in this failure to achieve a beneficial response to an increased amount of inhaled corticosteroids. Reddel and colleagues[6] compared differences between asthma exacerbations and poor asthma control and showed that unstable asthma could be controlled with the initiation of inhaled corticosteroids. With exacerbations maintenance inhaled corticosteroid therapy was not sufficient to regain and maintain control, and the reversal of airflow obstruction to β agonists was also diminished. They speculated that the loss of asthma control with exacerbations was caused by respiratory infections and that increased asthma under these circumstances may be very different from the physiological abnormalities seen with unstable asthma which could occur from chronic exposure to aeroallergens or other environmental stimuli.

As shown by Johnston and colleagues,[7] the major cause (80%) of asthma exacerbations is viral upper respiratory infections. With viral respiratory infections the inflammatory response is more likely to be neutrophilic than eosinophilic,[8] with the latter marker usually predicting a response to inhaled corticosteroids.[9] Previous attempts to treat acute asthma exacerbations caused by respiratory infection with inhaled corticosteroids have not always been successful.[10] [11] The use of inhaled corticosteroids, even in large doses, may not, therefore, be sufficient to control asthma exacerbations under these circumstances in some patients.

Questions remain as to how best to prevent asthma exacerbations. Studies indicate that the addition of maintenance treatment with a long acting inhaled β agonist to inhaled corticosteroids is more effective in reducing rates of asthma exacerbations than identical doses of inhaled corticosteroids alone.[12] [13] Whether the addition of long acting β agonists at the onset of symptoms that foreshadow asthma exacerbations would be more effective than larger doses of inhaled corticosteroids has yet to be ascertained. Moreover, Bisgaard[14] has recently indicated that the leukotriene receptor antagonist montelukast may be effective in hastening the recovery from airway changes associated with bronchiolitis induced by respiratory syncytial virus (RSV) in young children. Whether this approach is effective in attenuating the development of significant lower respiratory tract involvement at the onset of

symptoms with RSV or other viruses has yet to be established.

How do we translate the recent observations by FitzGerald *et al*[3] and Harrison *et al*[4] into current and future asthma care? Firstly, for most asthma exacerbations a doubling of the inhaled corticosteroid does not appear to be sufficient and perhaps a more rapid initiation of a prednisone burst is the most appropriate step. Secondly, the prevention of asthma exacerbations needs to be a primary target of treatment and inhaled corticosteroids[15] or the combination of inhaled corticosteroids and long acting β agonist maintenance treatment;[12][13] both approaches may be underused. Moreover, although combination therapy is effective in preventing asthma exacerbations, a significant proportion of these individuals still suffer worsening of asthma on this treatment regimen.[12][13] Finally, and perhaps most importantly, insights into the mechanisms by which respiratory infections provoke asthma will probably give us better direction for controlling this important and underserved outcome of asthma.

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Lung cancer staging

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Endoscopic (oesophageal) ultrasound guided fine needle aspiration (EUS-FNA)

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A new tool in lung cancer staging

The management of lung cancer depends to a great extent on its histological type and the stage of disease. Although most patients with non-small cell lung cancer (NSCLC) have advanced disease at presentation, approximately 30% have tumour confined to the lung and locoregional lymph nodes. For these patients surgery offers the best hope of a cure. Despite apparent complete resection, 5 year survival rates after surgery are approximately 40–50%.[1] This highlights the importance of accurately staging lung cancer to determine resectability and provide prognostic information.

In clinical practice a presumptive diagnosis and stage are based on presentation, risk factors, and radiological appearances—particularly CT scans. Obtaining a histological diagnosis and confirming the stage of the disease often take place at the same time. One of the most difficult tasks is accurate staging of nodal involvement in the mediastinum.

It is reported that mediastinal lymph nodes contain metastatic disease in 28–38% of patients with NSCLC at the time of diagnosis.[2] Traditionally, CT scanning has been used to assess mediastinal lymph node involvement. Lymph nodes greater than 1 cm in short axis diameter are considered abnormal and suggest involvement. However, CT detection of lymph node spread has sensitivity and specificity rates of 61% and 79%, respectively.[3] Positron emission tomography with 18-fluorodeoxyglucose (FDG-PET) is more accurate in identifying mediastinal lymph node involvement. FDG-PET in combination with CT scanning has been shown to further improve sensitivity and specificity rates in detecting lymph node involvement,[3] but in much of Europe—and particularly in the UK—it is not widely available for the routine staging of lung cancer.

The generally accepted practice has therefore been that enlarged lymph nodes seen on CT scans should be investigated further and, in most instances, this is performed by mediastinoscopy. Although currently considered the gold standard in mediastinal staging, mediastinoscopy has some drawbacks. Mortality in experienced centres is negligible but morbidity rates (mainly arrhythmias) are reported to be 0.5–1%.[4] Mediastinoscopy involves a general anaesthetic and in most UK centres requires an overnight stay in hospital. Not all lymph node stations are accessible via the standard cervical approach,

including those in the aortopulmonary window (stations 5 and 6) and the lower mediastinum (8 and 9).[4][5]

Other tools are available to stage the mediastinum including mediastinotomy, transbronchial needle aspiration (TNBA) or Wang needle biopsy, with or without ultrasound guidance, transthoracic needle aspiration (TTNA), and endoscopic ultrasound guidance for fine needle aspiration (EUS-FNA).

Anterior mediastinotomy, also known as the Chamberlain procedure, involves an incision in the second or third intercostal space just to the left of the sternum. This method is useful for visualising nodes in the aortopulmonary window. Left upper lobe tumours frequently metastasise to these nodes and, for this reason, they are the most important group of nodes not accessible by standard cervical mediastinoscopy. Video assisted thoracoscopy (VATS) has also been used to assess some lymph node stations not accessible by mediastinoscopy.[4][5] Both VATS and anterior mediastinotomy require a general anaesthetic and, in most cases, an overnight stay in hospital.

TBNA is used in many centres to obtain tissue from subcarinal and hilar lymph nodes. While it is possible to obtain a diagnosis from paratracheal lymph nodes, it is technically more difficult because of the inability to angle the bronchoscope and the needle sufficiently. Conventional TBNA is a "blind" procedure with placement of the needle guided by landmarks from the radiographic appearance alone. Diagnostic yield varies widely among inexperienced and experienced operators.

Endobronchial ultrasonography (EBUS) is a fairly new technique. It has previously been used to determine the depth of tracheobronchial invasion.[6] Recent studies have examined the value of EBUS in determining metastatic involvement of mediastinal and hilar lymph nodes.[7][8] These studies were small and were not controlled. It is therefore not yet possible to say whether EBUS-TBNA provides a higher yield than TBNA alone.

The paper published by Kramer et al in this issue of Thorax describes in detail their experience of EUS-FNA in mediastinal staging and proposes that the wider uptake of this method of staging could reduce the number of surgical procedures required.[9] They enrolled 81 patients with suspected or pathologically confirmed lung cancer in whom PET scans had shown activity in the mediastinum, but who were otherwise deemed to be surgically resectable. All patients were then investigated by EUS with or without FNA. No complications were reported. A positive diagnosis of malignancy was achieved in 50 of 81 patients (62%) using EUS-FNA alone. The remaining patients underwent an additional surgical staging procedure. A negative or inconclusive EUS-FNA result did not reliably exclude malignancy as 68% (19/31) of these patients were found to have lymph node involvement when staged by additional methods. The authors argue that, if EUS-FNA was routinely used to stage patients with enlarged mediastinal lymph nodes, 62% of these cases could be spared the need for mediastinoscopy or explorative thoracotomy. They have estimated that use of a staging algorithm with EUS-FNA could reduce the average staging cost from $3514 to $2101 per patient.

While these results are encouraging, it is important to understand the limitations of EUS-FNA. As with mediastinoscopy, not all lymph node stations can be viewed. EUS-FNA is particularly helpful for inferior pulmonary ligament, subcarinal and aortopulmonary window lymph nodes. The pretracheal and paratracheal lymph nodes are harder to visualise because of air in the trachea. This makes EUS-FNA of limited value for these lymph node stations. This study confirms that the lymph nodes most commonly involved in lung cancer are the paratracheal nodes (stations 2 and 4), the subaortic nodes (station 5), and the subcarinal nodes (station 7). It shows that, even with an experienced operator, abnormalities in the paratracheal areas were only identified in a very small proportion of cases compared with those seen in the subaortic and subcarinal areas.

Kramer et al also examined the difference between experienced and inexperienced operators. The trainees performed 25 and 29 procedures each. The numbers of abnormal mediastinal lymph nodes detected failed to reach the numbers detected by the more experienced operator. It seems reasonable to assume that the high diagnostic rate described in this paper would be lower in centres which lack the same degree of experience.

Furthermore, all patients enrolled in the study were initially staged by FDG-PET scanning. Unfortunately, this facility is still not widely available in Europe. It is unclear what the accuracy of EUS-FNA would be if CT scanning was the only radiological tool used in the staging work up. Currently, this practice is only available at a small number of institutions, but as this study and others have shown the value of this procedure in the staging of lung cancer, we hope that it will become more commonplace in the future. It is envisaged that EUS-FNA and other techniques such as EBUS will not replace but will complement surgical techniques like mediastinoscopy. The caveat to this is that both EUS-FNA and EBUS have poor negative predictive value and, as such, further staging investigations are required for lymph nodes that have been identified as suspicious on radiological grounds but in which EUS-FNA has been negative or inconclusive for malignancy.

In conclusion, Kramer et al have shown that EUS-FNA is a well tolerated and safe procedure that obviates the need for general anaesthesia or hospital admission. It can be used to diagnose lymph node involvement and, as such, can reduce the number of surgical staging procedures required and reduce costs. Perhaps most importantly, it may alleviate some of the burden on that scarce resource—the thoracic surgeon!

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Smoking cessation

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Smoking cessation services: use them or lose them

J Britton

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Medical professionals in the UK need to engage more in smoking cessation services

Of the 120 000 people who die from smoking each year in the UK, more than half die from a respiratory disease. In 1997 deaths from lung cancer, chronic obstructive pulmonary disease (COPD), and pneumonia caused by smoking totalled over 63 000,[1] all of which were potentially avoidable. These figures show that preventing smoking is more relevant to respiratory medicine than any other speciality. In this issue of *Thorax* Abdullah and Husten[2] review the priorities for tobacco control in the developing world and summarise the difficulties of developing smoking cessation in countries already severely challenged by generally low levels of health service funding and infrastructure, by competing public health priorities such as HIV, by low levels of public awareness of smoking as a dangerous behaviour, and other issues. However, one of the problems they identify that is especially relevant in the UK is the need to engage medical professionals in smoking cessation.

The National Health Service (NHS) approach to smoking cessation in the UK has changed radically in the past 5 years. Although the effectiveness of behavioural support and nicotine replacement therapy (NRT) for smoking cessation had been recognised for many years, it is only since the publication of the government White Paper *"Smoking Kills"* in 1998[3] that these treatments, and subsequently bupropion therapy, have been made routinely available to smokers through the NHS. Before 1998, smoking cessation services were available to a tiny minority of smokers through sporadic local initiatives and the private sector, but this is no longer the case. All smokers should now be able to access effective cessation services providing evidence based and cost effective[4] interventions, and many have already done so: in the year to April 2003 in England over 230 000 smokers attended NHS cessation services and set a quit date, and over 120 000 reported cessation for at least 4 weeks.[5] This

number was nearly double that of the previous year, and further ambitious targets have been set for throughput in the next 3 years.[5] Therefore, while many countries lack the infrastructure, funding and political will to provide smoking cessation services, the UK does not. So, are these services actually being used to their full potential?

> "... if we don't use smoking cessation services we will lose them"

Surveys of attitudes to smoking by smokers in the UK have shown consistently that most smokers—typically about 70%—intend to give up smoking.[6] The figures also show that in many cases this is not an expression of a vague and distant aspiration, since consistently about 50% state that they intend to give up within the next year, 30% within 6 months, and 10% in the next month (fig 1).[6] In absolute terms, these percentages translate into around 6 million smokers wanting to give up within the next year and 1.2 million in the next month. Against these totals, the 230 000 or so who set a quit date through NHS cessation services in the 12 months to April 2003 represent a very small proportion and, indeed, reflect a failure to capitalise on a major preventive opportunity. At least some of the responsibility for this lies with the medical profession.

It has been argued for some time now that smoking status should be considered a vital sign—as routine a component of any medical consultation as measuring the pulse or blood pressure.[7] This has been emphasised repeatedly in clinical practice guidelines for smoking cessation in the UK[8 9] and USA,[10–12] which stress the importance of asking about smoking status at all consultations, advising all smokers to stop smoking, and arranging appropriate smoking cessation support for all smokers who are motivated to try. In practice, however, it is clear that, at least until very recently, this has not occurred. Recent clinical audit data from

primary care[13] and from my own[14] and at least one other hospital[15] in the UK show that inquiring about smoking status and advising cessation are still far from routine activities. At a national level, even in 2002, less than half of all smokers recall receiving advice to quit from a health professional at any time in the last 5 years,[6] while the proportion of smokers who have used specialist services and/or pharmacotherapy in the past year has remained below 20% for the last 4 years.[6 16] Undergraduate medical training in the UK still does not typically deliver adequate clinical training in smoking cessation methods, leaving most junior doctors feeling unprepared to deal with smoking in their patients.[17] Hospital managers have also been slow to respond to the opportunities available to fund cessation support, since half the hospitals in the UK still do not provide a cessation counselling service for inpatients.[18] Data from the USA are similar and indicate that medical schools are not delivering appropriate training,[19] that many practising physicians feel underprepared to deal with smoking in their clinical work,[20] that cessation advice is provided during consultations only to a minority of smokers[21] and that, as in the UK,[22] this advice tends to be limited to those with a smoking related disease.[21]

In the developing world many of the obstacles to implementing effective smoking cessation services arise from political and economic influences that are beyond the immediate control of individual clinicians. In the UK the situation is now very different—the services are or should be available but are not being used. As a result we are not only missing a major opportunity to improve the individual health of our patients and the collective public health, but also running the risk that the political will to continue to provide the services will stall. The danger is that, if
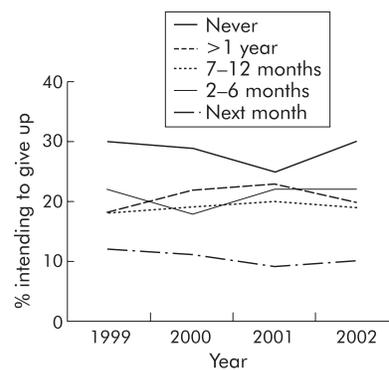
Figure 1 Intention to give up smoking, and when, in smokers aged 16 and over in Great Britain. Data from Lader and Meltzer.[6]

we don't use smoking cessation services, we will lose them.

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