PEF monitoring

Peak expiratory flow (PEF) monitoring

R Ruffin

The role of PEF monitoring in the diagnosis and monitoring of asthma

The Wright peak expiratory flow meter was introduced in 1959[1] and provided a portable piece of equipment for assessing some aspects of lung function in the ambulatory care setting. The original device has been supplanted by the mini Wright peak flow meter (and a range of other devices) which have become relatively cheap but are reasonably reliable for home monitoring.[2]

So, with an available device for measuring peak expiratory flow (PEF), what is its role in the 21st century? PEF reflects a range of physiological characteristics of the lungs, airways, and neuromuscular characteristics of individuals. These include lung elastic recoil, large airway calibre, lung volume, effort, and neuromuscular integrity.[3] The reflection of airway calibre makes the PEF meter suitable for measuring variation in PEF over time to provide support for:

- confirmation of the diagnosis of asthma;
- diagnosis of occupational asthma;
- monitoring variation in PEF over time;
- identification of asthma control;
- use in self-management of asthma by patients via written action plans based on changes in PEF.

We must note that the PEF is not the same as the forced expiratory volume in 1 second (FEV_1)—either in repeatability or in the interpretation of what it is measuring—and they cannot necessarily be interchanged.[4] An earlier trend to suggest regular PEF monitoring for many asthmatics has been modified as issues of balancing adherence versus need versus usefulness have been recognised. Regular PEF monitoring in asthma does remain relevant in particular situations such as monitoring of poor perceivers of symptoms.[5]

The report by Reddel *et al*[6] in this issue of *Thorax* highlights a further advance in the evidence for the use of PEF monitoring. The identification of best PEF provides a target for individual asthma patients and treating health professionals to enable the development of action plans and for the assessment of asthma control. The finding by Reddel *et al*[6] that, on average, the best PEF can be determined using high dose inhaled corticosteroids for 3 weeks from an unstable asthma state with twice daily PEF measurements therefore provides helpful information for the treating doctor. It is noteworthy that the time frame moves out to approximately 8 weeks if a single daily morning measurement of PEF is done—possibly a reflection of the number of measurements, but the time for drug effect cannot be dismissed.

Can we translate these data to our usual practice? The answer has to be a cautious yes because of (a) the use of electronic spirometers in the study and (b) the involvement of the patients in a clinical trial. Neither of these conditions is available to the usual asthma patients. However, the concept of an average of 3 weeks of inhaled budesonide (1600 μg) or its equivalent to achieve best PEF with twice daily readings provides a sound basis for the therapeutic trial which may become more important in the diagnosis as well as the management of asthma. Daily morning PEF monitoring in the study by Reddel *et al*[6] showed that an average of 8 weeks of high dose inhaled corticosteroid treatment study is needed to obtain the best PEF across a population of at least moderate and even severe asthma. We can therefore take away two messages from this study. The first is that, in reliable morning PEF data, a period of 8 weeks of high dose inhaled corticosteroids results in identification of the best PEF function for individuals on average. The second message is that, on average, 8 weeks of treatment with up to 1600 μg budesonide daily or its equivalent is a reasonable therapeutic trial for diagnosis or identifying best function in symptomatic patients. This is an important concept because the therapeutic trial over a period of time to confirm a diagnosis of asthma is likely to become more important, given the recognised reduced usefulness of a single bronchodilator response in either predicting future management or in diagnosis.[7]

Other data have supported an 8 week time frame for maximising the major airway effects of inhaled corticosteroids.[8 9] Providing we are not absolute in our application of average data, the study by Reddel *et al* can be usefully applied in day to day clinical practice and provides a guide to an appropriate level of inhaled corticosteroid for a treatment trial. The study has not necessarily identified the lowest dose, but the time frame of 8 weeks for daily morning PEF measurements and the dose equivalent of 1600 μg inhaled budesonide seems to provide a reasonable baseline for clinical practice. It is possible that a lower dose of inhaled corticosteroids may be effective in a therapeutic trial, and this needs to be tested despite a recent meta-analysis.[10] The combination of an inhaled corticosteroid with a long acting β agonist is likely to have a place in the future therapeutic trial.

A further question to be answered for treatment trials is whether the PEF (maximum) before and at the completion of a treatment trial is compared or whether it is the change in PEF variation. In children, questions have been raised about PEF monitoring missing important changes.[11] We therefore must remember that much of our evidence base relates to averages, and in the clinical setting we should individualise our assessments and management. The diagnosis of asthma remains a clinical diagnosis.

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Microbiology of CF

Difficult bacteria, antibiotic resistance and transmissibility in cystic fibrosis

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Three papers published in this issue of *Thorax* add some further twists to our understanding of the microbiology of CF

The link between dysfunction of the CFTR protein and the pathophysiology of lung disease in cystic fibrosis (CF) has recently become clearer. Abnormal sodium and chloride ion transport in respiratory epithelial cells results in depletion of airways surface liquid volume, delayed mucus transport, and impaired bacterial clearance.[1 2] This initiates airways inflammatory responses leading, ultimately, to lung injury in CF. The most important predictors of poor outcome are chronic infection with *Pseudomonas aeruginosa* and *Burkholderia cepacia* complex and reduced forced expiratory volume in 1 second (FEV_1).[3–5]

Pseudomonas aeruginosa

Pulmonary infection in CF is characterised by a narrow spectrum of microorganisms and is dominated in older patients by *P aeruginosa*. This organism and other related Gram-negative bacteria adapt to the conditions found in airways mucus and establish biofilms which allow chronic infection to be established.[6] Recent studies suggest that this microenvironment is relatively hypoxic and this creates a hospitable environment for *P aeruginosa* which, when exposed to low oxygen concentrations, increases alginate formation which assists in the development of micro-colonies within a biofilm.[7] The biofilm protects *P aeruginosa* from host defence, bacterial clearance mechanisms, and antibiotics. In addition, bacterial adherence to mucus is increased in CF which may also contribute to difficulties in clearing it from the airways.[7]

The source of early *P aeruginosa* infection is either the environment or other patients with CF. Aggressive treatment of early infection with this organism can frequently eliminate it for some years but, by the end of the second decade, over 80% of patients with CF have chronic *Pseudomonas aeruginosa* infection.[8 9]

Recent studies have shown that, in some CF centres, clonal spread of *P aeruginosa* can occur.[10 11] This is sometimes associated with a multiply resistant antibiotic profile, although not necessarily so. In general, antibiotic resistance is increasing in the CF population, particularly against the most commonly used antibiotic, ceftazidime. This probably represents antibiotic pressure and the ability of *P aeruginosa* to mutate because of its rather large genome. Antibiotics may select hypermutable strains which can maintain and possibly pass on resistance.[12] A close link between transmissibility, antibiotic resistance, and patient survival has not been unequivocally demonstrated. Transmissibility of resistant strains of *Pseudomonas* is intuitively something that should be avoided. However, further studies are awaited to determine if this has an important clinical outcome for patients with CF.

In addition to *P aeruginosa*, a number of other Gram-negative bacteria have emerged as important potential pathogens in CF lung disease. *Burkholderia cepacia* complex, *Stenotrophomonas maltophilia*, and *Achromobacter (Alkaligines) xyloxidans* are the most important and, although probably environmental in origin, cause chronic airways infection in patients with CF. These organisms, although phylogenetically unrelated, are usually all multiply resistant to antibiotics.

Burkholderia species

Burkholderia cepacia complex was the first of these organisms to be recognised and is the most pathogenic. A number of epidemics in CF centres have been described. Infection with this group of organisms is associated with an acceleration in the decline in FEV_1 and increased morbidity and reduced survival.[4 13–15] The taxonomy of this genus has recently been fully elucidated and nine groups have been speciated.[16] All these species of *Burkholderia* have been described in patients with CF but the predominant are *B multivorans* and *B cenocepacia*. *B multivorans* is a less common cause of infection than *B cenocepacia*.[17] A number of studies have suggested that *B multivorans* is generally less virulent that *B cenocepacia*. However, *B multivorans* has been associated with ''*cepacia* syndrome'' and epidemic spread.

In a study reported in this issue of *Thorax* from a single centre, patients with *B multivorans* and *B cenocepacia* and *P aeruginosa* were compared.[18] Patients with *B multivorans* had a lower mortality than those infected with *B cenocepacia*. *B multivorans* had a similar clinical impact to chronic infection with *P aeruginosa*. This finding supports studies from other centres. No significant differences in morbidity were found, although others have shown an accelerated decline in FEV_1.[4 19] This study also confirms previous studies which reported mostly unique strains in patients with *B multivorans* infection, suggesting that this organism is usually acquired from the environment rather than by patient to patient transmission. Patients with *B multivorans* should therefore not be exposed to those with *B cenocepacia*, which is strongly associated with patient to patient transmission and is more virulent. This study emphasises the much greater virulence of *B cenocepacia* than *P aeruginosa* and supports the need for careful infection control measures to minimise the risk of cross infection.

In another paper published in this issue of *Thorax*, Coenye and colleagues describe a clonal strain of *B cenocepacia* not previously identified in Europe.[20] Over the past few years it has become clear that *B cenocepacia* is made up of clonal subspecies and there may be differences in virulence and transmissibility between clones. The most common subspecies in the UK is the ET12 group (Electrophoresis Type 12), first described in Edinburgh and associated with most of the severe epidemics in the

UK and Canada. This strain is very virulent and is associated with ''*cepacia* syndrome''. A new strain, PHDC, has now been described and has affected patients in a number of centres around Europe. No clinical data are yet available with regard to its virulence in patients from whom this organism has been isolated, but it is of considerable concern that there is evidence of clonal spread between continents. The majority of samples were from patients with CF but one was from a urine sample from 1964. This is an unusual finding which is unexplained. Further studies will be required to determine the clinical relevance of this and possibly other clonal strains of *B cepacia* complex organisms. It is possible that a number of other clonal variants of *B cenocepacia* and other species are present in CF clinics and that there may be differences in the clinical impact of these clones.

This new finding emphasises the need for careful microbiological surveillance of patients with CF. Phenotypic identification of *B cepacia* is difficult. It is almost always pan-resistant to commonly used antipseudomonal antibiotics and this cannot be used for typing purposes. There are now specific phenotypic tests for identifying *B cepacia* complex species, but these are not helpful in identifying clonal subgroups such as ET12 or PHDC which require diagnosis at a molecular level using various DNA typing methods. It is very important that all CF centres should have access to such surveillance. This is available from two laboratories in the UK and reference laboratories in the US and in Europe.

Stenotrophomonas maltophilia

In a third paper published in this issue of *Thorax*, Goss *et al* provide further data on the virulence of *Stenotrophomonas maltophilia*.[21] This organism is multiply resistant but, in contrast to *B cepacia* complex, it appears to have a comparatively benign effect on the CF lung. This is the second study of *S maltophilia* published by this group from the North American database and reports morbidity on a large cohort of people infected with the organism. The previous study showed that *S maltophilia* infection is not associated with an increase in short term mortality.[22] Their data do not tell us whether this organism is transmissible, although this seems in general to be unlikely. However, one centre is reported to have a case rate of 38% which raises the possibility of cross infection in some situations. Their data suggest that the organism, although multiply resistant to antibiotics, is not associated with an acceleration in the decline in FEV_1. Those with *S maltophilia* infection had a lower starting FEV_1 before infection, suggesting that poorer lung function predisposes to acquisition of this organism. The majority (66%) were co-infected with *P aeruginosa*, but it is not clear if this was of any clinical significance.

Significance of these findings

The microbiology of CF can be very confusing. The nomenclature is complex and organisms change their names, and there are few generalisations that can be made across the different species. The studies published in this issue of *Thorax* add some further twists. A hierarchy of virulence of Gram-negative organisms is emerging. *S maltophilia* seems to be the most benign followed by *P aeruginosa*. *B multivorans* is similar to *P aeruginosa* but *B cenocepacia* is the most virulent by a significant degree. There may be important differences in the virulence of subspecies of *B cenocepacia* but this requires further epidemiological study. It is not yet clear how other organisms which cause chronic infection in CF such as *A xyloxidans* or *Pandorea* species fit into this hierarchy.

These organisms are generally multiply antibiotic resistant, but this by itself does not imply transmissibility or virulence. There must be other virulence factors associated with specific organisms or possibly host-bacteria interactions which ultimately result in lung injury. These studies further emphasise the importance of surveillance of patients with CF to determine their airway microbiology. Careful infection control policies are required to prevent acquisition of the more problematic organisms such as *B cenocepacia*. These should be tailored to the epidemiology of the individual centre and based on accurate identification and typing of the bacteria. There is a need for further understanding of how infection and inflammation result in airway damage, hopefully to find ways of circumventing the lung damage which ultimately leads to early death in individuals with CF.

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Salt transport in CF

Unravelling salt transport in cystic fibrosis

P G Noone, K W Southern

Sodium hyperabsorption may be a key therapeutic target in CF

Cystic fibrosis (CF) lung disease is characterised by thick viscid airway secretions, the development of progressive airways obstruction and bronchiectasis, and colonisation with specific bacteria, notably *Pseudomonas aeruginosa*.[1] Although the precise pathogenic pathways in CF are still debated (see below), airway epithelial ion transport has been known to be defective in CF for two decades. This can be assessed in the airway in vivo by measuring potential difference (PD)—that is, the voltage generated across an electrically tight epithelium by the active transport of charged sodium and chloride ions.[2] In patients with CF the magnitude of sodium absorption across airway epithelia and the response to the sodium channel blocker amiloride are substantially increased compared with normal subjects, coupled with an inability to secrete chloride ions.[3] In the 1990s the putative gene (the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene) was cloned[4] and the affected protein was identified as a gated chloride channel,[5] supporting the hypothesis that CF is linked to abnormal transepithelial ion transport.

Despite this clear link between abnormal ion transport and CF, the pathogenesis of lung disease in CF is complex, and much effort has been expended trying to elucidate the pathways involved in the development of airways disease. One hypothesis suggests that lung disease in CF develops in large part because of the deranged ion transport, resulting in a reduction in airway surface liquid volume and compromised mucociliary clearance.[6] These abnormal mechanisms set up a cycle of retained airway secretions, accumulation of mucus with infection and inflammation in the airways, ultimately leading to airway destruction, respiratory failure, and death from lung disease.

Recent in vitro studies on airway cell cultures grown to confluence with an air/liquid interface have yielded further insights into the impact of the CF ion transport defect on airway defence mechanisms.[7] In the absence of CFTR, sodium absorption (through the epithelial sodium channel (ENaC)) is upregulated. Subsequent dehydration of the airway surface liquid results in abolition of normal ciliary function. Thus, sodium (and fluid) absorption appears to dominate the normal "steady state" in the airway; however, recent data have shown that, under certain circumstances, airway epithelium can shift its phenotype and chloride (and fluid) secretion becomes predominant.[8] In CF airway cultures this ability to shift to a secretory phenotype is compromised.

Which ion transport abnormality is most important in CF lung disease?

So which of these abnormalities—upregulation of basal fluid absorption or an inability to switch efficiently to a secretory phenotype—is most important for the development of CF lung disease? Both mechanisms could theoretically result in similar reductions in airway surface liquid volume with the resulting impact on mucociliary transport. This question is important, since potential therapeutic strategies currently target both loops of the cascade, for example, with sodium channel blockers and chloride secretagogues.[9 10] It may be that both the sodium and chloride ion transport defects have a role (a double hit) in the pathogenesis of CF; however, murine models suggest that sodium hyperabsorption may be more important.

In the 1990s a number of *cftr* knockout mice were generated.[11–13] These mice have a form of gastrointestinal disease but no overt lung disease. This has been explained by chloride secretion through alternative channels in the airway.[14] Nasal PD in these "CF mice" is raised, as in humans with CF and consistent with sodium hyperabsorption; however, surprisingly, there is no increased PD in the lower airway.[15]

A major development has been the recent generation of a transgenic mouse with overexpression of the β subunit of the *ENaC* gene in the airways (driven by a lung specific promoter), but with normal *cftr* expression and function.[16] These mice have an increased magnitude of PD throughout the airway, consistent with sodium hyperabsorption, and develop early respiratory distress with a significant number dying in the first month of life. Investigations reveal depletion of airway surface liquid and mucus accumulation with reduced airway and bacterial clearance. The striking similarity to human CF disease provides convincing evidence that sodium hyperabsorption may be a primary determinant of CF lung disease.

Does the extent of ion transport abnormality in the airway determine the severity of CF lung disease?

Many groups have looked for a link between the degree of abnormality of airway ion transport (as determined by the nasal PD) and disease severity. Some have suggested relationships between the respiratory condition and sodium hyperabsorption (as determined by basal PD/response to amiloride),[17] and others with chloride secretion (as determined by the change in PD under specific conditions—that is, following perfusion of a solution with chloride ions replaced by gluconate with a β agonist such as isoprenaline).[18] These different results probably reflect small numbers and differing techniques. A European study reduced the confounding variables of environment and genotype by examining twins and siblings homozygous for ΔF508.[19] A weak relationship between respiratory disease and chloride secretion was demonstrated (concordant sibling pairs with mild disease had a small but significantly increased level of chloride secretion compared with pairs with severe disease). Subsequent groups have not been able to identify a link between respiratory phenotype and chloride secretion.[20 21]

In this issue of *Thorax* Fajac and colleagues provide data which add to this debate.[22] Using nasal PD, they measured ion transport in 79 adult patients with CF of varying severity and related PD outcomes to pancreatic status (pancreatic sufficient (n = 17) or pancreatic insufficient (n = 62)) and lung function (forced expiratory volume in 1 second (FEV_1) >50% predicted (n = 49) or <50% predicted (n = 30)). All patients with CF had diagnostic sweat chloride levels except for four patients with mild genetic mutations (73/79 had two recognised *CFTR* mutations). At baseline, patients with CF either had a raised basal PD with increased sensitivity to amiloride (typical of CF) and/or a lack of response to perfusion with a low chloride solution with isoprenaline. They found a weak relationship between the severity of lung disease (as determined by FEV_1)

and increased sodium transport (as determined by basal PD and response of that PD to amiloride). With a univariate analysis, basal PD was slightly higher in subjects with severe lung disease (mean −54 mV) than in those with milder lung disease (mean −45 mV). The reduction with amiloride was also greater in the severe group although, in a multivariate analysis including chronic infection with *P aeruginosa*, the relationship between lung function and basal PD disappeared but remained for lung function and amiloride sensitivity (odds ratio 3.7). There was no relationship between FEV_1 and chloride secretion (+2 mV in severe lung disease, +1 mV in mild lung disease).

Where does this leave us in our understanding of the impact of ion transport on CF lung disease?

The bottom line is that, if a true relationship between ion transport (as measured by nasal PD) and the severity of respiratory disease exists, it is likely to be weak. These data are consistent with the notion of a "point of no return"—that is, the ion transport abnormality provides the setting for CF lung disease early in life but, once established, other factors such as non-*CFTR* gene modifiers, the response of the innate immune system, mucus secretory control mechanisms, or environmental factors are more important in determining disease severity.[23]

Is this concept important? Certainly; nasal PD has frequently been employed as a surrogate outcome measure for "proof of principle" trials of new treatments.[24] If fundamental treatments are to work, these data suggest that early intervention is necessary as other factors may have a more profound influence on the eventual severity of lung disease. If ion transport is to be used as a surrogate outcome for fundamental treatments, then the data from murine studies suggest that correction of sodium hyperabsorption is the least required to halt the development of CF lung disease rather than correction of the chloride secretory defect alone.[25]

Although Fajac and colleagues did not find a strong relationship between ion transport and respiratory disease, they did find that pancreatic sufficient patients are significantly more likely to have evidence of chloride secretion in their nasal airway.[22] If nasal PD reflects ion transport elsewhere, such as in the pancreatic ducts, then this is an important observation in terms of the pathogenesis of CF pancreatic disease.

From a practical point of view, this finding has a bearing on the interpretation of nasal PD measurement when used to determine a diagnosis in people with atypical clinical features and equivocal sweat test results. The combination of a raised magnitude of basal PD and a lack of cftr-mediated chloride response is strong supportive evidence of a CF diagnosis, with the latter having been advocated as the most reliable component of the nasal PD tracing for making a diagnosis of CF.[26 27] However, groups have presented data demonstrating significant chloride secretion in some patients with "classic" CF.[17 21] Therefore, in the presence of a high magnitude of basal PD (>40 mV), the finding of chloride secretion does not negate a diagnosis of CF; indeed, the data of Fajac *et al* suggest that, in patients who are pancreatic sufficient, this may regularly be the case.

From a treatment standpoint, it seems logical to focus efforts on modulating the sodium channel to restore volume to the airway surface liquid, improve mucociliary clearance, and prevent the first step towards CF lung disease early in life. A balance may be required between agents that stimulate chloride secretion and agents that block sodium absorption, in order to restore airway surface liquid volume and achieve adequate airway clearance mechanisms in CF. However, at present, the weight of evidence suggests that sodium hyperabsorption may be a key therapeutic target.

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Failure of empirical treatment for CAP

Identifying failure of empirical treatment for pneumonia: vigilance and common sense

W-S Lim

Some progress in identifying the risk factors associated with treatment failure in CAP

In patients with community acquired pneumonia (CAP), clinical and radiological features at the time of presentation do not predict the microbiological aetiology with any certainty.[1] Initial treatment is therefore usually empirical and directed by the severity of the illness at the time of presentation. A large number of studies have been conducted over the last 10 years to determine prognostic factors in CAP. In turn, clinical prediction rules based on a number of key prognostic factors have been developed, such as the pneumonia severity index (PSI) and the CURB-65 score, and incorporated into CAP management guidelines.[2–6] Most of these CAP severity studies, and the resulting prediction rules, use mortality as the main outcome measure. However, mortality is not the only clinically important outcome. In this issue of *Thorax*, Menéndez and colleagues report on a large observational study of the risk factors related to failure of initial empirical treatment for CAP.[7]

The definition of treatment failure adopted was complex and based on (a) the time from admission (less than or more than 72 hours corresponding to ''early'' and ''late'' treatment failure) and (b) the occurrence of clinical features such as ''haemodynamic instability'', ''the appearance or impairment of respiratory failure'', and ''radiographic progression''. While pragmatic, these features were not rigorously defined, thus making it difficult to compare the results of this study with other research. Also, the ordering of repeat chest radiographs, a key element in the definition, was left to the discretion of the attending physician, so introducing a potential bias into the detection of treatment failure. Accepting these limitations, 15% of a cohort of 1424 hospitalised patients experienced treatment failure. These patients had a longer mean length of hospital stay (18.5 days *v* 9.4 days) and increased mortality (25% *v* 2%). Most of the treatment failures occurred in the first 72 hours.

Initial treatment with fluoroquinolones was found to be associated with a lower risk of treatment failure but not with in-hospital mortality. The researchers offer a good discussion on the possible explanations for this finding. The high prevalence of penicillin resistant *Streptococcus pneumoniae* (~30% of isolates) in the study country (Spain)[8 9] compared with the prevalence of fluoroquinolone resistant strains (<1%) may indeed be relevant.[10] The excellent coverage of atypical pathogens by the fluoroquinolones may also be important. Patients in the study were treated according to prevailing Spanish guidelines. This means that hospitalised non-ICU patients could be treated with either a third generation cephalosporin or co-amoxiclav with *or without* a macrolide, or monotherapy with a fluoroquinolone. Certainly those patients treated with only a third generation cephalosporin or co-amoxiclav (29% of cases) would not have had coverage for infection by an atypical pathogen compared with those treated with a fluoroquinolone

Retrospective studies have suggested that treatment with β-lactam drugs in combination with a macrolide or a quinolone is associated with lower mortality in CAP compared with other antibiotic regimens.[11] Unfortunately, the difficulty with these observational studies is the inability to correct adequately for confounding factors that might have influenced the initial choice of antibiotic. Conversely, the emergence of fluoroquinolone resistant pathogens in areas with a high consumption of fluoroquinolones is a very real problem and cautions against their overenthusiastic use.[12] More work is needed to clarify the advantages of the fluoroquinolones in comparison with other antibiotic regimens in the empirical treatment of CAP.

The following risk factors were found by Menéndez and colleagues to be independently associated with treatment failure: the PSI prediction rule for risk of mortality (the PSI categorises patients into risk classes I–V corresponding to ascending risk of mortality), leucopenia (<4000 cell/mm^3), liver failure, and the presence of adverse chest radiographic features on admission (specifically, the presence of pleural effusions (OR 2.6), multilobar involvement (OR 2.2), or cavitation (OR 5.2)). Each of these risk factors (except lung cavitation) has previously been reported to be independently associated with mortality in CAP.[13 14] Indeed, the presence of liver disease and a pleural effusion are two of the 20 variables included in the PSI prediction rule. This is not altogether surprising since treatment failure was itself associated with mortality, and no clinical prediction rule can be expected to fully account for all the recognised features of disease severity.

Impact on clinical management

How then might these findings enhance our current management of CAP, if at all? Their main contribution is going to be in the management of patients at low risk of mortality. With regard to the decision to admit to hospital, current recommendations are based on an assessment of mortality risk, social circumstances, and the stability of comorbid illnesses. In recognition of the limitations of assessing disease severity solely according to risk of mortality, all guidelines underline the importance of clinical judgement.[4 15] The study by Menéndez and colleagues is helpful in highlighting the additional risk factors associated with failure of empirical treatment (such as adverse chest radiographic features) that should be taken into account in patients identified as being at low risk of mortality according to the PSI. However, how these patients should best be managed is not known. Patients at risk of treatment failure may still be suitable for ambulatory care provided adequate early outpatient follow up is arranged. Alternatively, they may require hospital admission.[16]

Awareness of the expected time course of clinical resolution allows timely detection of treatment failure. Halm and colleagues have shown that the median time to clinical stability is 2 days for heart rate (⩽100/min) and systolic blood pressure (⩾90 mm Hg) and 3 days for respiratory rate (⩽24/min), oxygen saturation (⩾90%), and temperature (⩽37.2℃).[17] Measurement of the C-reactive protein (CRP) level is also helpful because a CRP level that does not fall by 50% within 4 days of admission is suggestive of treatment failure.[18 19]

What to do once treatment failure is recognised is not well studied. Repeat and supplementary microbiological investigations are generally recommended in order to detect new,

resistant, or nosocomial infections. Bronchoscopy yields a diagnosis in up to 41% of patients.[20] One study found it to be beneficial mainly in non-smoking patients aged less than 55 years with multilobar infiltrates.[21]

Where do we go from here? Further work using robust and reproducible definitions for treatment failure is required to confirm the findings of Menéndez and colleagues. The use of a different prediction rule to adjust for risk of mortality—for example, CURB-65 instead of PSI—may result in the identification of different risk factors for treatment failure. Most importantly, the optimal management of patients at risk of treatment failure and how it might differ from usual management needs to be determined, ideally through intervention studies with clinically relevant end points.

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Flying with respiratory disease

What happens to patients with respiratory disease when they fly?

R K Coker, M R Partridge

Updated guidelines now available but more research is needed into the safety of air travel for those with respiratory disease

Despite current concerns about terrorism, commercial air travel remains a common mode of travel for millions. It has been estimated that a single major UK airline carries over 30 million passengers each year. There are no data available to indicate how many passengers flying on commercial aircraft have respiratory disease, but as far back as 1974 it was estimated that around 5% of passengers were ambulatory patients. As the average age of western populations continues to rise, so does the propensity for passengers to have some form of medical condition. In addition, flights are getting longer and aircraft bigger. The new Airbus 380, for example, will carry around 600 passengers for up to and in some cases exceeding 20 hours.

Air travel is in general safe, even for those with medical conditions, and there are no established methods for determining morbidity associated with air travel. Nevertheless, available airline data consistently record around 10% of in-flight medical emergencies as being respiratory in nature, with approximately one third attributed to asthma. Medaire, a North American company offering radio link emergency medical assistance to commercial aircraft, has published figures for 2002 which show that respiratory problems are the third most common cause of in-flight medical emergency (A Hawkins, Medaire, personal communication). Respiratory problems are also the third most common cause of medical diversion after cardiac and neurological events (including syncope), accounting for 9% of diversions. In 2002 Medaire recorded 414 diversions, 206 advised by Medaire and 208 initiated by the pilot. In 2004 British Airways estimate the cost of a diversion at around £100 000 (€150 000, US$185 000) (M Popplestone, British Airways, personal communication). This includes hotel accommodation for passengers and staff, maintenance costs and landing fees. In addition, there is

knock-on disruption to the airline's schedule and there are safety concerns about an enforced landing at an unfamiliar airport.

Commercial aircraft routinely fly at around 38 000 ft and are pressurised to a relatively modest intermediate cabin altitude not exceeding 8000 ft (2438 m). The reduced partial pressure of oxygen at this altitude is equivalent to breathing 15% oxygen and will cause the arterial oxygen tension (Pao_2) of a healthy passenger to fall to between 7.0 and 8.5 kPa. The effects usually go unnoticed. However, exposure to this altitude may worsen hypoxaemia in patients with lung disease, especially if the subject is already hypoxaemic at sea level. Other factors to be taken into consideration include immobility predisposing to venous thromboembolism, an increase in gas volumes, reduced humidity, and increased potential for transmission of infection through promixity of seating arrangements.

In 2002 the British Thoracic Society (BTS) published recommendations for assessing passengers with respiratory disease planning air travel.[1] These were the first UK recommendations on air travel in the context of lung disease and, in contrast to existing disease-specific North American and European guidelines, considered a wide range of respiratory disorders. A patient information leaflet and summary for primary care physicians were published alongside the recommendations on the BTS and British Lung Foundation websites (www.brit-thoracic.org.uk and www.britishlungfoundation.org). It was recognised at the time that the BTS recommendations represented a consensus statement based on expert advice, with little solid evidence on which to base formal guidelines.

Two years on, the BTS flight recommendations have been updated with available evidence and published on the BTS website in September 2004. The data remain relatively sparse, but updated sections include reference to the demise of Concorde and the introduction of the Airbus 380, and a detailed explanation of the effect of Boyle's law on gas expansion in relation to humidified gas. Changes have also been made to the recommendations for pre-flight assessment in children based on new data from the Royal Brompton Hospital in London. There is some new advice for those travelling with oxygen. Some airlines now issue a Frequent Traveller's Medical Card to frequent flyers with special medical needs, and this may be of value to passengers in reducing the paperwork required before each trip.

With regard to patients with asthma and chronic obstructive pulmonary disease (COPD), from April 2004 a new law requires all aircraft on flights to and from the United States to carry bronchodilator inhalers as part of their medical kit. A new study of children with Down's syndrome has drawn attention to the fact that these patients probably merit careful evaluation before air travel, and there is reference to two studies of patients with diffuse parenchymal lung disease. An entire new section has been added on severe acute respiratory syndrome (SARS) with a hyperlink to the World Health Organisation site. Importantly, review of the available evidence has meant that the arbitrary ''six week rule'' has been discarded for patients with pneumothorax. A delay of just 1 week is recommended after the chest radiograph shows complete resolution, except in the case of a traumatic pneumothorax (or thoracic surgery) when a delay of 2 weeks is advised. There is further evidence strengthening the previous recommendations that low molecular weight heparin may be of benefit to travellers at high risk of venous thromboembolism.

Taken together, however, with the exception of the paediatric data there is little new evidence to suggest a need for radical change to the previous recommendations. Most previous investigations into the effects of air travel on lung disease have examined patients with COPD, and the available controlled studies involve relatively small numbers with stable disease and no co-morbidity. Simulated altitude did not generally exceed 1 hour and these studies have largely excluded additional stressors such as exercise, dehydration, and sleep. In 2002 the BTS Air Travel Working Party highlighted the need for further research and drew attention to those areas where data are particularly lacking. These included the predictive value (or otherwise) of spirometry, regression equations, hypoxic challenge, and walk tests in different disease groups, and the risk of air travel for patients with diffuse parenchymal lung disease.

In this setting, the paper by Seccombe *et al*[2] published in this issue of *Thorax* is especially welcome. The authors examined the effect of simulated cabin altitude—both at rest and during a 50 metre walk test—on 15 subjects with interstitial lung disease (ILD) and 10 subjects with COPD. All subjects were clinically stable, able to walk 100 metres, and had resting Pao_2 equal to or above 9.3 kPa—well above the level at which most physicians would have concerns about potential complications from air travel. In both groups Pao_2 fell significantly from that at rest on room air to that breathing 15% oxygen at rest, and again to completion of the walk test. Mean Pao_2 fell to 5.5 kPa after exercise in the ILD group and to 5.3 kPa after exercise in the patients with COPD. Interestingly, 80% of subjects had flown in the previous 5 years and 64% were unaware that their oxygen levels might be lower when flying.

These results suggest that resting Pao_2 is a poor predictor of hypoxaemia under simulated cabin altitude conditions. They also highlight the need for further research into predictors of hypoxaemia, better patient education, and improved methods for collecting data on passengers who do experience health problems while flying. The authors of this study suggest that prospective evaluation of a large number of patients with lung disease who plan to fly may be of value. The ongoing UK Flight Outcomes Study, funded by the BTS and British Lung Foundation, sets out to do this, and we hope it will help to answer some of the questions raised by this and other studies. Meanwhile, further high calibre laboratory research remains very welcome, together with more in-flight studies of those potentially at risk.

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TB and anti-TNF-α treatment

Tuberculosis and anti-TNF-α treatment

L P Ormerod

New evidence-based guidance on anti-TNF-α treatment is being developed by the Joint Tuberculosis Committee of the BTS in conjunction with the British Societies of Rheumatology and Gastroenterology

Anti-tumour necrosis factor (TNF) treatment for rheumatoid arthritis and Crohn's disease has been introduced over the last few years. Infliximab (Remicade; Schering-Plough), a humanised monoclonal antibody, is licensed for the treatment of both rheumatoid arthritis[1] and Crohn's disease,[2] while etanercept (Enbrel; Wyeth Laboratories), a fusion protein binding free TNF-α using the soluble portion of the TNFR-2 receptor,[3] and adalimumab (Humira; Abbott Laboratories), a fully humanised monoclonal antibody,[4] are licensed for treating rheumatoid arthritis. Post-marketing surveillance in the USA[5] has identified cases of tuberculosis (TB) associated with infliximab use and a smaller number with etanercept. TB cases have also been reported in association with adalimumab (Humira prescribing information, Abbott Laboratories, 2002). The cases associated with infliximab occurred within three cycles of treatment, with a median of 12 weeks from commencing treatment,[5] and most were in extrapulmonary sites.[6] Calculations have suggested that TB rates in patients in the USA treated with infliximab or etanercept are six times that of untreated patients.[7]

The increase in active TB in association with anti-TNF-α treatment has led to a requirement for patient screening for active and latent TB before anti-TNF treatment is given. However, the screening—which the manufacturers suggest should include tuberculin testing—introduces further complications. Firstly, in the study of infliximab, Keane *et al*[5] found that up to 79% of patients were receiving immunosuppressive therapy before anti-TNF treatment which would have precluded effective skin testing for TB. Secondly, in Europe, where the population may have received prior BCG vaccination, the interpretation of tuberculin tests is further complicated. Thirdly, chemoprophylaxis or preventive treatment for TB itself carries a risk—principally of drug induced hepatitis—which increases with age, varies with the chemoprophylaxis regimen, and can occasionally be fatal.

Clearly, persons found to have active TB or with evidence of previous TB disease which has not been adequately treated will need at least some anti-tuberculosis treatment before anti-TNF treatment can commence. However, since the majority of patients will not be assessable for prior TB infection by skin testing, a judgement of the individual risk of TB disease will have to be made. Within the UK, and probably in other developed countries, the individual risk of TB can vary markedly. In the UK the major determinants of risk are age, ethnicity and—for those born outside the UK—the length of time since first entry.[8] For example, the annual risk of disease can vary from 2/100 000 in a white person aged 15–34 years to 593/100 000 in a South Asian aged over 35 years who has been in the UK for less than 5 years. The ''individual risk'' would then need to be multiplied by five to allow for the additional effect of anti-TNF treatment and this derived figure would then have to be compared with the risk of significant hepatitis (level 3 or 4) from the proposed TB chemoprophylaxis regimen, with at least one regimen used in the USA (rifampicin and pyrazinamide for 2 months) being too toxic for use.[9] The risk of chemoprophylaxis compared with the chance of contracting TB will therefore favour observation in some individuals and TB chemoprophylaxis in others. In future, gamma-interferon production from whole blood and/or stimulated lymphocytes[10] may be able to determine whether patients receiving immunosuppressive treatment which interferes with tuberculin skin testing have been previously infected with TB, but an individual assessment of the risk/benefit ratio in such patients with respect to chemoprophylaxis will still be needed.

All these factors have led to many requests for guidance in this area. The Joint Tuberculosis Committee of the British Thoracic Society, a subcommittee of the Standards of Care Committee, is developing practical evidence-based guidance in conjunction with the British Societies of Rheumatology and Gastroenterology. In order to meet the AGREE criteria,[11] however, this will take some time. Initial draft proposals have been posted on the members' website for comment. There are, however, some concerns that this will be an additional workload for already stretched respiratory medicine specialists.

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