Thorax

Editorials

Maintenance treatment of chronic *Pseudomonas aeruginosa* infection in cystic fibrosis

Niels Høiby, Christian Koch

Thirty years ago *Staphylococcus aureus* and not *Pseudomonas aeruginosa* was considered to be the most important lung pathogen in cystic fibrosis.[1] Those who believed that *P aeruginosa* was a pathogen in cystic fibrosis thought that various virulence factors such as exotoxin A, exoenzyme S, elastase, alkaline protease, phospholipase C, lipopolysaccharide and phenazine pigments were responsible for the lung tissue damage by drawing parallels with acute *P aeruginosa* infections in patients with burns or leukaemia.[2] Only acute exacerbations, frequently caused by a virus,[3] were therefore treated with antibiotics, although invasive disseminating *P aeruginosa* infection including bacteraemia was never found in cystic fibrosis.[4] However, a very pronounced antibody response to *P aeruginosa* antigens, including its virulence factors, was detected in patients with cystic fibrosis and the pathogenesis of the lung tissue damage was subsequently found to be caused by immune complex mediated inflammation dominated by polymorphonuclear leucocytes releasing proteolytic enzymes.[5–7] Since the annual mortality of cystic fibrosis patients with chronic *P aeruginosa* infection in the Danish Cystic Fibrosis Centre increased to nearly 20% in 1974, a comprehensive therapeutic approach was started to try to reduce the inflammation by (1) reducing the antigenic load by treating the patients with intravenous antibiotics regularly for two weeks every three months (maintenance therapy = chronic suppressive therapy), (2) reducing the antibody titres by plasmapheresis, and (3) the use of nebulised corticosteroids. The use of nebulised steroids was not successful at that time, probably because the dose of steroid used was too small[8]; a recent study with a larger dose was found to be effective in reducing inflammation.[9] Attempts to reduce the antibody titres by plasmapheresis were not successful as it was only possible to reduce the titre of anti-pseudomonas antibodies by 50–80% for a period of a few weeks (unpublished results). However, Szaff *et al*[10] found reduction of the antigenic load with intravenous antibiotics to be successful in 58 patients with cystic fibrosis (2.9 courses/year in 1976–80, approximately every three months) compared with 51 historical controls (one course/year in 1971–75 against acute exacerbations). This study included all patients with chronic *P aeruginosa* infection defined as an increase in the number of precipitating antibodies to these bacteria.[5] A follow up study in 1985[11] showed an increase from a five year survival of 54% to a 10 year survival of 90% from the onset of chronic *P aeruginosa* infection and a decrease in the annual mortality from 10–20% to 1–2%. The addition of nebulised colistin, prevention of cross infection in the clinic, and early aggressive treatment of the initial *P aeruginosa* infection further improved survival.[12]

In this issue of *Thorax* Elborn *et al*[13] report a prospective randomised multicentre study in which they compared elective and symptomatic treatment with intravenous antibiotics of cystic fibrosis patients infected with *P aeruginosa*. No benefit of the elective approach was found. This is hardly surprising since the difference in the amount of intravenous antibiotic used in the two groups of patients was only 45%, 24%, and 33% in the one, two, and three year periods of the study, whereas the difference in each year during the five year maintenance treatment period reported by Szaff *et al*[10] in 1983 was 190%. The bacteriological effect obtained by Szaff *et al*[10] was higher than that achieved in current studies, with 35–36% being free of *P aeruginosa* at the end of the treatment period, a few for up to three months.[10] This probably reflects the higher bacteriological efficacy of treating the chronic infection early[14] and the lower level of resistance 20–25 years ago.[15] Furthermore, whereas none of the patients in the study by Szaff *et al* received nebulised antibiotics, these were given to 40% of the symptomatic patients and 25% of the elective group in the study by Elborn *et al*, further decreasing the difference between the two arms of the study.[13] Another major difference between the two studies is the early treatment approach used by Szaff *et al*. All new chronically infected cystic fibrosis patients were treated regularly from the onset of the infection during the maintenance treatment period, since onset of infection before puberty was found to be associated with a poor prognosis,[10] and the major benefit on the survival of the patients was maintenance of lung function in the younger patients as confirmed by Elborn *et al*.[13]

Several reports have shown the benefit on lung function of the treatment of *P aeruginosa* infection in patients with cystic fibrosis[16 17] but, although the proteolytic activity in the lungs decreases during treatment, it is still significant between courses.[17] The addition of daily nebulised colistin[18] to the maintenance regime[12] or the use of four weekly cycles of on/off nebulised tobramycin[19] has further improved the maintenance of lung function in these patients, but a subsequent analysis of the placebo group in the study by Ramsey *et al*[19] showed that treatment of exacerbations only did not arrest the progressive decline in lung function in patients with cystic fibrosis.[20] An important conclusion of the study by Elborn *et al*[13] is the suggestion that many patients with advanced disease need 3–4 annual courses of antibiotics for respiratory exacerbations.

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However, therapeutic findings from other studies indicate that the decline in lung function continues to take place between courses but can be diminished by the intensive use of nebulised antibiotics and steroids.[9 18 20] The major side effects of the intensive use of antibiotics in cystic fibrosis are the development of resistance, allergy to β-lactam antibiotics, possible ototoxicity and renal toxicity caused by aminoglycosides (although this has not yet been a significant problem), cost, and compliance of patients, as also reported by Elborn *et al*.[13] New efficient anti-pseudomonas antibiotics and new treatment strategies are therefore needed for patients with cystic fibrosis.[21–24]

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Diagnosis of lung cancer: FOB before CT or CT before FOB?

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Any patient presenting to a respiratory physician with a possible diagnosis of lung cancer requires a rapid and accurate histological diagnosis, together with enough staging information to enable a correct management plan to be arranged. Standards for these processes have been suggested.[1] In practice it is incumbent upon physicians to assess each case and to determine the optimum combination of sampling and imaging tests that will be likely to achieve a firm diagnosis and staging at the minimum inconvenience to his or her patients, and with a minimum of delay which is known to be very distressing to them.[2]

Since the advent of fibreoptic bronchoscopy (FOB) in 1974, and with its current very wide availability, most physicians would consider this as their first investigation after a clinical assessment and plain radiology. Selection would be influenced by the latter, so that lesions clearly falling into the category of small solitary pulmonary nodules would be far more likely to be investigated by computed tomographic (CT) scanning and fine needle aspiration biopsy (FNA). For lesions of less than 2 cm in diameter FNA is superior to bronchoscopy even if imaging is used to guide the transbronchial biopsy or transbronchial needle aspiration.[3 4]

The probability that a lesion, thought by a physician to be accessible to bronchoscopy, can actually be diagnosed in this way is not easy to ascertain. However, a recent UK multicentre prospective study of 1660 consecutive cases investigated by FOB because of a prior likelihood of lung cancer showed that a definite tumour was seen in 57%.[5] In a further 20% the appearances were very suggestive of a tumour. Thus, overall, one in five of these tests was negative. The proportion with a positive histological examination at bronchoscopy is likely to have been between 75% (diagnosis within seven days of bronchoscopy) and 85% (diagnosis up to 14 days). Only one in eight patients (15%) had had a prior CT scan, and whether or not this guided the bronchoscopist at all is not known.

This large study with a sensitivity for bronchoscopy of about 77% and a definite histological diagnosis rate of

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about 75% or better seems to suggest that the traditional way of assessing lung cancer should continue to be by bronchoscopy first, followed by a CT scan when indicated. However, a paper in this issue of *Thorax* by Laroche *et al*[6] from the Oncology Unit at Papworth suggests strongly that, where the facilities and organisation exist, there may be advantages in reversing this sequence at no greater cost and with a reduction in the number of invasive tests needed to make a firm histological diagnosis. This possibility has been suggested in several retrospective series[7–9] but theirs is the first prospective study.

The authors studied a consecutive series of 171 patients thought on the basis of their basic examination and/or plain radiographs to have a high probability of tumour accessible to bronchoscopy. They showed that a prior spiral CT scan in the randomly allocated "test" population prevented any further tests in six of 90 patients (7%), increased the diagnostic yield of subsequent bronchoscopy to 75% (compared with 54% in the control group in whom bronchoscopy was performed before the result of the spiral CT scan was known), and increased the percentage of patients diagnosed after a single invasive test from 55% to 76%. If the diagnosis was eventually confirmed as lung cancer, 89% of patients were correctly sampled and diagnosed when bronchoscopy was done in the knowledge of the scan result compared with 71% when bronchoscopy was performed before the CT scan. The additional cost of performing spiral CT scans on each patient (given as £121 or US$195) was offset by the need for fewer other invasive tests as a result of the information available from the CT scan, even though they were more expensive—for example, the cost of an FOB was given as £387 (US$620) per case.

The important question then for all cancer units is whether this evidence is good enough to justify a change in routine practice and also whether it is generally practicable to do so.

The technical advances in fibreoptic bronchoscopes since 1974 have been essentially to reduce their diameter, increase their flexibility, and improve their angle of vision and optics. It is unlikely, however, that further changes will alter the performance of these instruments significantly. The application of fluorescence bronchoscopy is still a research tool for early diagnosis. Additional techniques such as perbronchoscopic needle biopsy have been studied intensively but are still not in widespread use because they are technically difficult and have not been shown conclusively to increase the sensitivity of the test, as surgeons still rightly prefer to stage patients preoperatively by mediastinal sampling.[10 11]

By contrast, there have been definite and continuing advances in imaging technology. The time taken to scan patients has reduced, and reconstruction technology has changed in a number of ways. Although conventional scanners are being replaced by spiral/helical scanners, not all of these machines have the same reconstruction ability. This has led to the use of various scanning protocols, although all the recommended techniques involve thinner sections through the main airways. Most units use 5 mm collimation rather than the 3 mm collimation used in the study by Laroche *et al*. The thinner section protocols allow the bronchial anatomy to be visualised very well and this is most vividly demonstrated when the reconstructions allow "virtual bronchoscopy".

The practical issues for most units will inevitably be whether the putative cancer workload could be reorganised to allow same day CT scans and bronchoscopic examinations with no loss of CT or bronchoscopy "slots". There is some preliminary evidence that this can be organised with benefit, even when the referral rate is fairly low—for example, 54 patients in 31 weeks in the study by Williams *et al*.[12] Many units in the UK, and possibly in other countries, do have very busy scanning departments where 2–3 week delays in staging CT scans are not uncommon.[13] The introduction of helical scanners could change this picture because of their greater throughput, but new techniques such as scanning for pulmonary emboli add more cases to the overall CT workload. Yet most patients with lung cancer do have a CT scan, so the challenge of providing early CT scanning is one of organisation.

A second general point, not specifically considered in the paper by Laroche *et al*, is whether CT scanning is better than bronchoscopy in the further investigation of a patient with significant unexplained haemoptysis and a normal examination and radiograph. The evidence here is more clear cut; several series, admittedly retrospective,[14 15] have suggested that CT scanning is more sensitive than routine bronchoscopy for these patients, although at present many patients are referred from primary care specifically for bronchoscopy. Prior CT scanning should aid the bronchoscopist, particularly in the less straightforward case, but it will not completely obviate the need for bronchoscopy as studies have shown that endobronchial disease is missed by spiral CT scanning. This concerns not only in situ disease but includes endobronchial lesions, particularly in subsegmental airways.

The study by Laroche *et al* is important because it shows once again the advantage of assessing and managing patients with cancer in a multidisciplinary way. Although confirmation of these results is necessary, it is highly likely that patients referred to a chest physician with a clinical suspicion of cancer and a compatible radiograph will, in due course, proceed with an initial spiral CT scan before routine bronchoscopic examination. As the paper by Laroche *et al* has shown, a number of these patients will be fully diagnosed by the imaging investigation and the success rate of bronchoscopy may be improved in the others.

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Role of bronchial responsiveness testing in asthma prevalence surveys

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Standardised comparisons of the prevalence of asthma are important for generating and testing hypotheses about the causes of asthma and, in particular, the causes of the global increases in its prevalence. Such surveys may involve international comparisons[1 2] or comparisons between "subpopulations"—for example, age, sex, socioeconomic, or regional subgroups—within a single geographical population or country. It is important that such population surveys should use the most practical and valid methods for measuring the prevalence of asthma in populations and differences between populations. This is inherently problematic because of the difficulties in defining asthma and the practical considerations that must be taken into account in achieving high response rates in large random population surveys.

Furthermore, there is no single test or pathognomonic feature which defines the presence or absence of asthma. The variability of the condition also means that evidence of it may or may not be present on the day or at the time of assessment. Thus, a diagnosis of asthma in clinical practice is made on the basis of combined information from history, physical examination, and respiratory function tests, often over a period of time. However, comparisons of the prevalence of diagnosed asthma between populations are fraught with difficulty, as the differences in diagnostic practice may be as great in magnitude as the real differences in asthma morbidity. It may be possible to address some of these issues by adopting common criteria for asthma diagnosis and applying these uniformly in prevalence studies. However, for large scale prevalence studies this is not practical because of the need for repeated contacts between study participants and doctors. Thus, surveys comparing the prevalence of asthma between populations usually focus on self-reported (or parental reported) "asthma symptoms" rather than diagnosed asthma.[1 2]

An alternative approach to symptom questionnaires has been to use more "objective" measures such as bronchial responsiveness testing, either alone or in combination with questionnaires. Thus, it is commonplace for asthma epidemiologists to note that "bronchial hyperresponsiveness (BHR) is not the same thing as asthma", but nevertheless to use it routinely in population surveys since it is assumed to be "more objective" than symptom questionnaires. In particular, it is assumed that BHR testing avoids the problems of subjective symptom recall that may occur with symptom questionnaires. It has therefore been suggested that asthma in epidemiological surveys should be defined as symptomatic BHR—that is, BHR together with symptoms in the previous 12 months.[3 4]

However, "objectivity" is not the same as validity. Thus, a test may be "objective" (in that it is not dependent on subjective judgements such as recognition or recall of symptoms) but may not be more valid in terms of the "gold standard" for which the test is a surrogate.[5] This editorial will examine the role of BHR testing in surveys of the prevalence of asthma. We first consider issues of validity in comparisons in which there are no significant differences in language or symptom recognition or reporting in the populations (or subpopulations) being compared. We then consider comparisons between countries or between different cultural or language groups, since these comparisons involve additional issues of comparability of survey information.

Validity

The value of a population survey depends on maximising both precision (lack of random error) and validity (lack of systematic error).[5] Systematic error includes selection bias (for example, through poor response rates), information bias (for example, through misclassification of "exposure" or disease), and confounding.[6] We initially focus on issues of information bias (particularly misclassification of disease), but we also briefly consider issues of random error and selection bias. We do not consider confounding since this is likely to be of similar relevance for all of the survey instruments under consideration.

The validity of a survey instrument, with regard to the classification of disease, depends on its intended use and the measure of effect (either relative risk or risk difference) that is being used.[7] In comparisons of differences in asthma prevalence within and between populations, Youden's index (sensitivity + specificity − 1) is the best single measure of validity.[5] In contrast, in case-control studies of prevalence or other "aetiological" investigations in which the relative risk is the main effect measure of interest, the positive predictive value of a test is most relevant,[7] but we do not consider this situation here.

It is important to emphasise that, when assessing which measure is most valid for population comparisons, this assessment must itself be based on random population surveys rather than on studies of selected clinical populations. Although BHR has validated well against asthma in clinical studies,[8] this is partly a result of the case mix in such studies in which patients with reasonably severe asthma are compared with non-asthmatic subjects who have been screened for possible asthma risk factors such as atopy or a family history of asthma.[9] BHR does not fare so well in general population surveys since these include many mild or borderline asthmatic subjects, as well as non-asthmatics who may have various "risk factors" for asthma.[5]

A recent review by Pekkanen and Pearce[7] found that there have only been two general population surveys[10 11] that have independently compared BHR testing and standard symptom questionnaires with a standardised approach to physician diagnosed asthma. In both studies, although BHR had a greater specificity for asthma, it had a low sensitivity and questions on "wheeze" had a higher Youden's index value than BHR alone or in combination with symptoms. For example, Jenkins *et al*[10] studied population samples of 91 adults aged 28–44 years and 168 children aged 13–14 years, and compared the results from a symptom questionnaire and from a hypertonic saline challenge with the diagnoses of current asthma based on a blinded history taken by a trained physician. Self-reported symptoms had a higher Youden's index than BHR in both children (0.66 versus 0.43) and adults (0.76 versus 0.29), mainly because of the better sensitivity of symptom questionnaires (0.85 versus 0.54 in children, 0.80 versus 0.37 in adults). Combining symptoms with BHR increased the specificity, especially in children, but caused a strong decline in sensitivity, thereby decreasing Youden's index (to 0.41 in children and 0.36 in adults) to a lower level than the use of symptoms or BHR alone.

In addition to avoiding information bias in population surveys, it is also important to avoid selection bias and to

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maximise precision. Thus, the value of a population survey depends not only on using the most valid survey instrument, but also on the size of the survey and its response rate. Small surveys are more prone to random error, and surveys with poor response rates may be subject to selection bias—for example, whether asthmatic subjects are more likely to participate than non-asthmatic subjects. Symptom questionnaires have considerable practical advantages over BHR testing as they can be administered to larger numbers of participants with higher response rates.

Thus, current evidence suggests that BHR testing has no greater (and may even have lesser) validity than symptom questionnaires for measuring the difference in asthma prevalence between populations (or subpopulations) with the same language and similar symptom recognition and reporting.[7] Furthermore, its use may reduce study sizes (thereby reducing precision) and response rates (thereby increasing selection bias).

Comparability

An alternative argument for using BHR testing in prevalence surveys is that it gives a more valid comparison between populations since it is "objective", whereas responses to questions on symptoms can depend on a wide variety of psychological, social, and cultural characteristics including health care practices, as well as on the translation of the questionnaire. Thus, BHR may not be more valid when comparing populations or subpopulations which share the same language, culture, health care system, and perceptions and labelling of asthma symptoms, but it may provide more comparable (and hence more valid) information when comparing populations which do not share these characteristics. However, standardising the performance of BHR testing is a major problem, especially in international comparisons.[12] Comparisons among children are especially difficult, and it has been concluded that BHR tests cannot be compared between children of different ages and sizes.[13] The problem of low response rates in studies involving BHR testing is also of concern for international comparisons. For example, in the ECRHS study the response rates for the phase II testing (including BHR testing) were relatively low[14] and differences between populations could, in part, have been the result of differences in response rates. An alternative approach to standardising comparisons between populations is the use of video questionnaires such as the ISAAC asthma video questionnaire.[15] This appears to have similar or greater validity than written questionnaires, and is likely to avoid the problems of comparability of information from written questionnaires across populations.

What is the role of BHR testing?

What then is the role of BHR testing in asthma prevalence surveys? Is there any reason to use BHR testing at all? It might be argued that BHR is of interest and worthy of study in itself. However, it is clinical asthma that is the fundamental clinical and public health problem, and this should be the principal focus of population surveys. Nevertheless, we consider that there is an important role for BHR testing as a supplementary component of prevalence studies, but that it should be used sparingly and the findings must be interpreted carefully. BHR testing cannot provide validation of the existence of differences in the prevalence of asthma between populations. However, BHR is one possible mechanism by which asthma can occur, and BHR testing can therefore be used to assess whether the observed differences in prevalence are occurring through this mechanism. BHR testing is therefore most useful in terms of interpreting, rather than validating, the findings of symptom prevalence questionnaires and/or clinical examinations. Thus, when performing a prevalence survey, a good way to combine the best qualities of the symptom questionnaires and BHR testing is to perform a large phase I questionnaire survey (written or video) first and then to perform more intensive phase II examinations on a subsample to ascertain whether or not the observed differences in prevalence are caused by mechanisms involving BHR.

Conclusions

It is commonplace for epidemiologists to note that "BHR is not the same thing as asthma", but nevertheless to use it routinely in population surveys since it is assumed to have greater "objectivity" than symptom questionnaires. In particular, it is assumed that BHR testing reduces information bias by avoiding the problems of subjective symptom recall that may occur with symptom questionnaires. However, when the focus is on estimating differences in the prevalence of asthma between populations who share the same language, symptom perception, and labelling and diagnostic practice, current evidence suggests that BHR has no greater (and may even have lesser) validity than symptom questionnaires. Furthermore, the increased response rates and larger sample sizes obtainable with symptom questionnaires indicate that they will, in general, have greater validity and precision than BHR testing. In comparisons across populations and/or language groups there is currently little evidence on the relative validity of BHR testing and symptoms, although it is evident that, once again, response rates are generally better, and possible study sizes larger, with symptom questionnaires. Furthermore, the video questionnaire approach provides an alternative method of collecting standardised data on the prevalence of asthma symptoms across populations.[15]

To explore the reasons for differences in the prevalence of asthma within and between populations, questionnaires can be supplemented with BHR and other testing in subsamples of symptomatic and non-symptomatic subjects. However, the main reason for doing this is to ascertain the mechanism by which population prevalence differences have occurred, and not because BHR provides a more valid measure of asthma prevalence. Furthermore, if we define asthma by combining symptoms with BHR, we not only lose validity, but we also lose the possibility of studying the separate contributions of these factors to differences in asthma prevalence. Asthma symptoms and BHR should therefore be analysed separately rather than combined in a single definition. The method of choice for population prevalence comparisons is standardised written or video symptom questionnaires, and BHR testing should be regarded as a supplement to, rather than a replacement for, such questionnaires.

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