Table 1 CFTR mutations/sweat tests in 100 adults with bronchiectasis

Age	Sex	Allele 1	Allele 2	5T variant	Sweat test (chloride levels)
54	F	ΔF 508	−ve	+ve	38 mmol/l
70	F	ΔF 508	−ve	−ve	34 mmol/l
72	F	ΔF 508	−ve	−ve	36 mmol/l
69	M	G551D	−ve	−ve	Not done

number of carriers was the same as would be predicted in a normal population (95% confidence intervals (CI) 1.1 to 9.9). Similarly, the incidence of the 5T mutation was 7% which is similar to the incidence in a normal population[8] (95% CI 2.9 to 13.9).

These findings suggest that CFTR mutations do not have a major role in the pathogenesis of adult bronchiectasis and further investigation is needed to establish the predisposing factors involved in the development of this condition.

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BTS guidelines for investigation of unilateral pleural effusion in adults

We are pleased to see that formal guidelines for the investigation of the previously neglected and sometimes difficult area of pleural effusions have been published.[1] There have been many publications concentrating on the distinction of exudative from transudative pleural effusions as a means of aiding the diagnostic process, but not necessarily focusing on the underlying clinical aetiology.

We were, however, disappointed to find that the Pleural Disease Guidelines Group did not appear to have taken specialist advice about the clinical biochemistry investigations. This means that some of the important methodological aspects have not been commented on. For example, it is important to appreciate that most of the assays currently used in NHS laboratories in the UK have not been optimised and validated for use in fluid other than serum/plasma and may give inaccurate results. A review of the biochemical aspects of pleural fluid analysis was recently published in the *Annals of Clinical Biochemistry*.[2] Although pleural fluid testing accounts for a very small percentage of laboratory work, this area requires close collaboration between the clinician and the laboratory to ensure that the most appropriate tests for answering the clinical question are selected, rather than adopting a blanket approach.

The advice that there is no requirement to test bilateral effusions which, in the clinical setting, are strongly suggestive of a transudative process unless there are atypical features or a failure to respond to treatment is welcomed. We agree that the appearance of the fluid provides useful information and would suggest that this is included in the formal laboratory report.

We endorse the view that total protein is central to the investigation of an undiagnosed pleural effusion and that this is usually sufficient unless the pleural fluid protein lies in the range of 25–35 g/l. This recommendation is not made clear in the algorithm, which suggests that lactate dehydrogenase (LDH) and pH should be requested together with protein. Because of the problems of concurrent sampling, we were pleased to see that the use of a pleural fluid to serum ratio is not recommended. With respect to LDH, the use of modified Light's criteria as described by Heffner *et al* did not significantly improve the discrimination from that achieved using total protein alone.[3]

The recommendation that gives us most concern is that of measuring pleural fluid pH in all non-purulent pleural effusions. Although the pH of pleural fluid may vary depending on the cause of the effusion, there is no evidence that routine measurement adds value to the diagnostic process. The only situation for which clinical studies may support pH measurement is in aiding the decision about drainage of non-purulent parapneumonic effusions.[4] Aside from its clinical utility, the value of pH measurement is further compromised by analytical considerations. The samples must be collected anaerobically and analysed immediately under anaerobic conditions. This effectively means using a blood gas analyser. The suitability of pleural fluid samples for analysis by this method is unproven and, furthermore, brings concerns about whether such samples may cause blockage and instrument failure, especially since many blood gas analysers are now situated outside the laboratory and samples are run by non-laboratory personnel. This increases the concerns about compliance with Health and Safety regulations, especially since samples are often of high risk and the diagnosis of tuberculosis is specifically being queried. Additionally, such measurement would be outside the licensed indications for the analyser.

There are a few points to make about those tests used in specific clinical circumstances. We are pleased to see that the use of cholesterol and triglyceride is restricted to the investigation of suspected chylothorax, where high concentrations are likely, especially since cut-offs used in studies recommending cholesterol to separate exudates and transudates lie below the usual measuring range of routine assays. We are also pleased that the use of pleural fluid glucose is restricted to situations where the effusion is thought to be rheumatoid in origin and amylase where pancreatitis is the clinical query. We agree that creatinine is useful where a urinothorax is queried, that adenosine deaminase may be useful in TB pleurisy, and that ANA is not considered useful. Caution is advised, however, in using complement measurements on the basis of one positive reference, especially since the cut-off value quoted is 10 times less than the usual serum value and lies below the functional sensitivity of most assays.

While we acknowledge that the desire to minimise the number of invasive procedures leads to development of an all-inclusive algorithm, provided there is good liaison between the laboratory and clinician, a stepwise approach may be more cost effective without compromising patient management. In addition, good liaison and discussion will lead to a better appreciation of any test limitations and an individualised investigation strategy.

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Authors' reply

We would like thank Drs Tarn and Lapworth for their letter, largely supporting the approach of the BTS guidelines in the investigation of undiagnosed unilateral effusions.[1] In answer to their specific queries, we did seek advice from local biochemists when compiling the guidelines. We also appreciate that laboratory testing on pleural fluid has not been formally validated on many machines used in UK laboratories. However, these tests have been validated against clinical outcome which indirectly provides some reassurance about laboratory reproducibility in pleural fluid. If the laboratory results were completely inaccurate because of major problems in pleural fluid analysis, the tests would have no clinical predictive power.[2]

The primary purpose of the guideline is best patient care and not the reduction of laboratory costs. The algorithm is intended to represent a summary of a logical approach when investigating these patients which will hopefully result in a prompt diagnosis with a minimal number of pleural interventions. Repeated pleural aspirations are clearly disadvantageous to patients (especially those who end up with mesothelioma who require expensive radiotherapy to every aspiration site). Prompt diagnosis is in the patients' interest in resolving uncertainty, and a sequential approach is likely to be expensive through repeated use of the healthcare services during the prolonged investigation. It is important that healthcare cost analysis should take a ''societal'' perspective and cannot be quantified from laboratory test costs alone.

With regard to pH, there are few settings in which it is substantially depressed and, of these, infection is much the most prevalent. Other causes can usually be quickly identified clinically—for example, clinical rheumatoid arthritis, history of oesophageal rupture, obvious advanced malignancy. Since clinical management is totally changed by a diagnosis of infection (antibiotics and tube drainage rather than pleural biopsies) and there are sometimes no triggers to clearly identify this possibility, before measuring the pH, we feel it should be included in the general test battery.

Finally, with regard to the measurement of pleural pH in blood gas analysers, this has been standard practice in the US for over 15 years. In our unit we have been doing this for 6 years and have not encountered any of the potential problems mentioned (as long as measurements are avoided in grossly purulent and frank pus samples where the pH is not required anyway).

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LUNG ALERT

Human metapneumovirus: a new cause of respiratory tract infections in children?

▲ Williams JV, Harris PA, Tollefson SJ, *et al*. Human metapneumovirus and lower respiratory tract disease in otherwise healthy infants and children. *N Engl J Med* 2004;**350**:443–50

Human metapneumovirus was first isolated from humans with respiratory tract infections in 2001 and is closely related to respiratory syncytial virus (RSV). This paper examines its prevalence in a large cohort of otherwise healthy children followed from birth to 5 years of age. Children attending a primary care clinic in Tennessee between 1976 and 2001 with acute respiratory tract infections had nasal washings collected and cultured for common respiratory viruses.

There were 1127 episodes of acute lower respiratory tract infection in the 2009 children attending the clinic. In 687 cases nasal washings were obtained and 408 (59%) were culture negative for viruses. 248 of these culture negative specimens remained available for subsequent polymerase chain reaction and 49 (20%) were positive for human metapneumovirus. Extrapolation of these data suggests that human metapneumovirus can be isolated in 12% of all acute lower respiratory tract infections in this cohort. The spectrum of clinical diagnoses was comparable to that caused by RSV: 59% had bronchiolitis, 18% croup, 8% pneumonia, and 14% exacerbations of asthma. The virus was also detected in 15% of samples from children with upper respiratory tract infection, but in only one of 86 asymptomatic children.

Causality cannot be assumed from this study. The use of different viral detection methods makes frequency comparisons problematic, and there is potential for selection bias as 39% of respiratory tract infection episodes did not provide samples for analysis. However, it is likely that human metapneumovirus is a new pathogenic virus in children. This paper should lead to further work to examine its prevalence outside the US and in other age groups.

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