

PostScript

LETTERS TO THE EDITOR

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Airway obstruction and autoimmunity

Birring and colleagues have shown an interesting link between respiratory symptoms and autoimmunity in the form of both hypothyroidism and Crohn’s disease.¹ In addition, they have previously demonstrated a link between autoimmune disease and airway obstruction in non-smokers.² We have reported a similar association between airway obstruction and rheumatoid arthritis with a 2–3-fold increased prevalence of wheeze and physiological abnormalities in patients with rheumatoid arthritis compared with controls with osteoarthritis.³

Our group has also found correlations between the severity of airway obstruction and the extent of rheumatoid disease at both the systemic⁴ and articular⁵ levels. Our data would favour Birring’s first theory—namely, homing of activated inflammatory cells into the pulmonary compartment. We have also previously demonstrated the presence of excess lymphocytes in bronchial biopsy specimens in patients with rheumatoid arthritis, together with an increase in neutrophils in the bronchoalveolar lavage fluid (personal communication, W U Hassan). The neutrophil numbers correlated with physiological evidence of increased bronchial reactivity to methacholine and airflow obstruction, suggesting recruitment of neutrophils as the effector cell by the controlling lymphocytes. At the cytokine level, tumour necrosis factor (TNF α)—a key driver of inflammation in rheumatoid arthritis, Crohn’s disease, and hypothyroidism—has a significant role in the pathophysiology of asthma and chronic obstructive pulmonary disease (COPD).^{6,7}

Their second hypothesis—that airway obstruction might just be a hitherto unrecognised autoimmune bronchitis—merits further investigation. COPD due to smoking itself has been suggested to be an autoimmune disease.⁸ A key investigation would be to study the origin of proinflammatory cells and cytokines when airway obstruction occurs in the presence of organ specific autoimmune diseases to determine whether these are produced elsewhere before “homing” into the lung or are activated and produced de novo in the lung.

We would also like to explore a third possibility—namely, the role of the lung in the aetiopathogenesis of autoimmunity. The lung is an ideal interface between the environment and the immune system. Smoking is linked to both Crohn’s disease and rheumatoid arthritis. The increased prevalence of rheumatoid factor in smokers with airway obstruction compared with smokers with normal airways⁹ and the presence of bronchus associated lymphoid tissue in the lung mainly in smokers¹⁰ may not be mere coincidence. Is the lung (that is, the airway) a “culprit” rather than a “target” organ in autoimmune diseases?

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New technique for treating spontaneous pneumothorax

The BTS guidelines advocate aspiration as a first line procedure in patients with dyspnoea or complete collapse.¹ Despite being common practice, there is no specifically designed equipment widely used for this procedure. The BTS guidelines suggest assembling equipment from a cannula, three way tap, and 50 ml syringe. The assimilation and use of equipment not designed for chest aspiration often leads to a prolonged and cumbersome procedure with the following inherent problems:

- blind insertion of a sharp needle into the chest cavity risks damage to thoracic and upper abdominal viscera;
- intravenous cannulae are designed to facilitate the flow of fluid and are therefore relatively short; as a result, some fail to traverse the chest walls of larger patients;
- the thin plastic sheath is prone to damage as it passes through the chest wall;
- kinking of the plastic sheath outside of the patient during use;
- the equipment is cumbersome and time consuming to use;
- the BTS guidelines suggest the removal of a maximum of 2.5 l (that is, 50 \times 50 ml syringes).

We have used a Verres needle adapted with a one way valve designed to treat uncomplicated spontaneous pneumothorax and to overcome the shortfalls of the method of aspiration advocated by the BTS guidelines. We used pre-production equipment provided by Rocket Medical plc. A Verres needle, normally used to establish a pneumoperitoneum in laparoscopic surgery, is used to insert the cannula. It has a spring loaded blunt tip that retracts into the needle upon pressure while passing through the thoracic wall. On entering the pleural cavity the spring loaded tip rapidly protrudes, shielding the needle and preventing visceral damage. At this point there is a palpable and audible click which indicates that the needle has traversed the thoracic wall. The sheath is advanced over the Verres needle. It is thicker than those of intravenous cannulae and thus resists damage from the chest wall and external kinking. The Verres needle is then removed.

Rather than aspirating air, the patient is encouraged to expire against gentle resistance. This raises intrathoracic pressure, forcing air from the pneumothorax via the cannula. Due to the one way valve, air cannot return. Furthermore, the one way valve has been adapted to whistle when air passes through it, so once the pneumothorax has resolved there is no whistling. At this point a check x ray is indicated. Conversely, an air leak will be indicated by continuous whistling.

We have used this equipment several times with no complication and describe a typical example of its use. A 23 year old man with a primary spontaneous pneumothorax fulfilled the BTS criteria for simple aspiration. With patient consent the Verres needle was introduced under local anaesthesia into the fifth intercostal space in the anterior axillary line. The click as the blunt tip of the Verres needle sprung forward indicated that the drain was in the pleural cavity. The patient was encouraged to expire against gentle resistance. On expiration the drain whistled. After 5 minutes the whistling stopped. A check x ray was taken which showed complete resolution of the pneumothorax. The patient was discharged and a review with x ray 3 and 10 days following the procedure revealed no complication or recurrence of the pneumothorax.

Other devices are available which detect placement of cannulae in the pleural space.

The Tru-Close Thoracic Vent (Davis and Geck, USA) is an aspiration device comprising, in part, an external diaphragm that indicates pressure change upon entering the pleural cavity. This device does not have a mechanism to shield the needle tip and, despite the advantage of the diaphragm indicating intrapleural placement, there has been a case report of bronchopleural fistula following its use in a patient with chest wall adhesions.² While no device can ensure that damage to lung tissue does not occur during this blind procedure, the Verres needle affords more protection than other established techniques. Despite limited experience with this device, we found it was simple to prepare and use and intrapleural placement was easy to recognise. Furthermore, it overcame the disadvantages that are associated with the widely used method advocated by the BTS.

The product becomes commercially available in March 2004 at an approximate price of £30 per unit.

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Estimation of size of pneumothorax under the new BTS guidelines

I read with interest the new BTS guidelines for the management of spontaneous pneumothorax.¹ Henry and colleagues acknowledged that the plain radiograph was a poor method of quantifying the size of a pneumothorax, yet then went on to use one radiographic method of assessment to estimate the degree of lung collapse.

Under the new guidelines, the size of a pneumothorax is divided into “small” or “large” depending on the presence of a visible rim of <2 cm or ≥2 cm between the lung margin and the chest wall. The authors then explained in detail how these distances could be used to estimate the percentage of lung collapse. A schematic figure was even used to illustrate the calculations. However, the method used by the authors (the method of Axel)² like most other methods, has been found to be unsatisfactory for determining pneumothorax size under clinical conditions.³

I do not see any evidence that the new classification is in any way better than the old one. The calculations based on the distance of the rim correlated poorly with the actual size of the pneumothorax.³ The “2 cm” used is an arbitrary figure. It is even more confusing to have the American guidelines use another arbitrary system of classification.⁴ In spontaneous pneumothorax, practitioners

should at least agree on the same classification system of size before they continue to debate about what is the best option of treatment.

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Authors' reply

We thank Dr Chan for his comments relating to the recently published guidelines for the diagnosis and management of spontaneous pneumothoraces.¹ Dr Chan raises the contentious issue of estimation of the size of a pneumothorax from a plain chest radiograph. We have attempted to use a variation of the method of Axel based on the largest distance from the chest wall to the pleural line and using the assumption that, because the volume of the lung and the hemithorax are roughly proportional to the cube of their diameters, the volume of pneumothorax can be estimated by measuring an average diameter of the lung and the hemithorax, cubing these diameters, and finding the ratios.²

As Dr Chan rightly points out, this is not an exact science as the lungs have a propensity not to maintain a constant shape when they collapse. A CT scan of the thorax gives a more accurate estimate of the volume of the pneumothorax than a plain radiograph. However, while CT scanning may be the only way to obtain an exact estimate of pneumothorax volume and pattern of lung collapse, it is not often feasible in the emergency room. The correlation coefficient between CT scanning and plain radiography is 0.71 ($p < 0.01$).³ Thus, while chest radiography is not as effective as CT scanning, it does still provide a useful and reasonably accurate estimate of pneumothorax size in most cases using the method outlined in the current guidelines. We suggest that the guideline is an improvement on the 1993 pneumothorax guidelines which tended to underestimate the size—and thus potentially the importance—of a pneumothorax. Choosing a distance of 2 cm above which the volume of pneumothorax is usually above 50% gives the emergency room physician a guideline which is easy to use and fairly reliable. It has been shown that secondary pneumothoraces above this volume are unlikely to respond to simple aspiration and this hopefully will provide useful guidance as to which patients to treat with intercostal tube drainage.⁴ This is supported by evidence and is now a clear and unambiguous guideline. We also hope that, by suggesting that pneumothoraces <2 cm in depth should not usually be aspirated, we may reduce the number of aspiration needle injuries to the lung parenchyma which would have a much greater

approximation to the chest wall in primary spontaneous pneumothoraces of <2 cm depth.

As Dr Chan points out, the American College of Chest Physicians has proposed a different arbitrary system for estimating pneumothorax size. They suggest that “small” pneumothoraces should be defined by distances of <3 cm from the apex to cupula of the lung and “large” pneumothoraces by distances of >3 cm.⁵ This seems to have been arbitrarily defined and we are not provided with evidence to support these measurements. Several authors have suggested different distances ranging from 1 cm to 4 cm on the plain radiograph, or more complex equations depending on three separate distances between the pleural line and chest wall, or the routine use of CT scanning incorporating even more complex mathematics.^{6,7} Dr Chan comments on the lack of evidence regarding the classification of the chest radiograph; we have completed an analysis of the chest radiographic appearances in spontaneous pneumothorax, relating them to the various guidelines, and have presented it as an abstract at the winter meeting of the British Thoracic Society.⁷ Bearing in mind that the guidelines are primarily prepared for use by relatively inexperienced and non-specialist junior medical staff who often have to make management decisions in the middle of the night, we would suggest that the BTS guidelines have combined a fairly robust and accurate scientific approach with a guideline which is easy to interpret and implement to estimate and treat spontaneous pneumothoraces.

Finally, we would again take the opportunity to stress that, no matter what the size of a pneumothorax, the decision as to what constitutes appropriate treatment depends not just on the size of the pneumothorax on the chest radiograph but, more importantly, on the clinical status of the patient.

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Paradigm shift in surgical approaches to spontaneous pneumothorax: VATS

The recently published BTS guidelines on the management of spontaneous pneumothorax by Henry *et al*¹ have stimulated some discussion among our respiratory physicians and thoracic surgeons. We found it interesting that the authors quoted a pneumothorax recurrence rate of 5–10% after video assisted thoracoscopic surgery (VATS). Numerous large series from around the world have recently reported recurrence rates of primary spontaneous pneumothorax following VATS bullectomy combined with surgical pleurodesis to be in the range of 1.7–5.7%.^{2–3} Although the recurrence rates following VATS may be marginally higher than the open procedure, the benefit to the patient of a shorter postoperative hospital stay, less postoperative pain, and better pulmonary gas exchange in the postoperative period should be balanced against this. Furthermore, we found that patients who undergo VATS have significantly less shoulder dysfunction and pain medication requirements in the early postoperative period than after posterolateral thoracotomy.⁴ Whether VATS can be “established as being superior to thoracotomy” will in part be decided by our patients and become clearer with future trials.

With the lowered morbidity and proven safety of VATS, even for elderly and paediatric patients,² the old surgical algorithms based on the morbidity of thoracotomy should be re-evaluated.⁵ We feel there are two additional conditions that warrant inclusion in the list for “accepted indication for operative intervention”. Firstly, patients presenting with the life threatening condition of tension pneumothorax, even for the first time, should be considered for VATS because of the potential grave consequences of its recurrence. Secondly, the presence of radiologically demonstrated huge bullae associated with spontaneous pneumothorax should be an indication for VATS because of the increased risk of recurrence. In addition, the huge bullae may continue to expand and impair lung function by causing compression of adjacent healthy lung tissue, and can be a manifestation of lung carcinoma or a focus for recurrent infection.^{2–6}

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Authors' reply

We thank Dr Ng and colleagues for their comments on the recently published guidelines on the management of spontaneous pneumothorax.¹ Dr Ng points out that recurrence rates for pneumothorax after VATS preventative procedures were lower than those quoted in the guidelines. It should be pointed out that, in the multiple drafts of this document, it was recognised that recurrence rates after VATS were falling and that further improvements in these figures were likely as operator experience improved. This was recognised within the guidelines. It is fully expected that, as experience and provision of services improve, VATS will replace open thoracotomy for treatment of recurrent pneumothoraces.

In response to Dr Ng's second point regarding surgical treatment of tension pneumothoraces and hugh bullae, the guidelines obviously could not take into account every possible clinical scenario. As far as we are aware, there is no evidence to suggest that tension pneumothoraces are more likely to recur than “non-tension” spontaneous pneumothoraces. This does not mean, of course, that an individual physician should not decide that the clinical risk in an individual patient—either from rupture of a huge bulla or recurrence of a tension pneumothorax—should not warrant surgical intervention.

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Role of CFTR mutations in adult bronchiectasis

Over 1000 different mutations of the cystic fibrosis transmembrane conduction regulator (CFTR) gene have so far been identified. These mutations have been associated with a spectrum of clinical phenotypes ranging from classic cystic fibrosis (CF) presenting in early childhood to CFTR related conditions that may present in adulthood such as congenital bilateral absence of the vas deferens, chronic pancreatitis, and rhinosinusitis. In addition, the 5T variant in the polythymidine tract is felt to be important in atypical CF as it significantly reduces the amount of normal CFTR transcript because intron 8 is inefficiently spliced.¹

Bronchiectasis in adults is most commonly idiopathic² and is a significant cause of chronic morbidity. The chief manifestation of CF is bronchiectasis, and the role of CFTR

mutations in adult bronchiectasis is still not well defined. Several small studies have suggested that there is an increased prevalence of CFTR mutations in diffuse adult bronchiectasis,^{3–5} and one large study found that there was a marginally higher prevalence of mutations in adult bronchiectasis.⁶ Most of these studies have had little information on the patients' clinical status and family history of disease and have not assessed the 5T mutation.

A joint project was undertaken between Monash Medical Centre (MMC) and the Murdoch Children's Research Institute to assess the role of CFTR mutations in adult bronchiectasis. A sequential series of 100 adults with bronchiectasis confirmed on high resolution computed tomographic (CT) scanning was studied. The patients were screened for the 10 most common mutations in the local population ($\Delta F508$, $\Delta 1507$, $V520F$, $G542X$, $G551D$, $R553X$, $R117H$, $G21+1G \rightarrow T$, $A455E$ and $N1303K$) responsible for 82% of cases of CF and the 5T mutation by previously published methods.^{7,8} Ethical approval for the project was obtained from the ethics committee at MMC.

The group comprised 36 men and 64 women of mean (SD) age 61 (13) years. Most of the patients were white ($n=95$), predominantly from a northern European background ($n=84$). The main symptom was chronic mucopurulent sputum production which was present in 98 of the 100 subjects and, in most cases ($n=78$), this had started in childhood. Chronic rhinosinusitis was also common ($n=75$). Lung function tests showed moderate airway obstruction in the cohort. Most patients ($n=86$) had multilobar disease on CT scanning, predominantly in the lower zone. The mean (SD) number of lobes with bronchiectatic changes on the CT scan was 2.5 (0.98). Nine of the patients had *Pseudomonas aeruginosa* isolated from their sputum and one of these isolates was a mucoid strain. The most common pathogen was *Haemophilus influenzae* (37%) followed by *Streptococcus pneumoniae* (10%). Screening for underlying causes of bronchiectasis showed that most patients ($n=84$) had idiopathic disease. All subjects were asked about the presence of chronic respiratory illness in first degree relatives. There was not a high incidence of familial chest disease. No relative had a diagnosis of CF and only one had a history of bronchiectasis.

The patients did not have a high prevalence of features in addition to bronchiectasis and rhinosinusitis which are known to be associated with CF (none had pancreatitis, one had unexplained infertility, and three had predominantly upper zone bronchiectasis).

Screening of the cohort showed that none of the subjects was homozygous and four were heterozygous for CFTR mutations (table 1). Three of the subjects had mutations of the most common CFTR mutation ($\Delta F508$) which is responsible for 67.5% of CFTR mutations in the local population and the other subject had the second most common mutation ($G551D$, 4.7%). Sweat tests on the heterozygote subjects showed normal chloride levels.

The prevalence of CFTR mutations in normal predominantly white populations based on several studies is approximately 1/25.^{9–10} The expected level of heterozygotes in this group which had been screened for 82% of mutations was 3–4 subjects. Thus, in this group of subjects with bronchiectasis the

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 population⁸ (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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