ORIGINAL ARTICLE

Echocardiographic abnormalities in primary antibody deficiency

S L Johnston, S J Hill, R J Lock, J F Dwight, D J Unsworth, M M Gompels

Postgrad Med J 2004;**80**:214–218. doi: 10.1136/pgmj.2003.012443

See end of article for authors' affiliations

Correspondence to: Dr Sarah L Johnston, Department of Immunology and Immunogenetics, Southmead Hospital, Westbury-on-Trym, Bristol BS10 5NB, UK; sljoh@hotmail.com

Submitted 11 July 2003
Accepted
8 September 2003

Objective: To document cardiac abnormalities secondary to pulmonary disease in primary antibody deficiency.
Patients and methods: A cross sectional audit study of patients from a regional immunology centre. Subjects undergoing two dimensional and Doppler transthoracic echocardiography were reviewed. Ventricular dimensions and function, valvular competence, and estimated pulmonary artery pressure were recorded. Data were compared with clinical variables, pulmonary function tests, and thoracic computed tomography data.
Results: Nineteen patients with common variable immunodeficiency and one with IgG_2 subclass deficiency were included, mean age at diagnosis 37.5 years, mean estimated diagnostic delay 10.94 years. Left ventricular impairment was found in 15% and right heart dilatation in 20%. Pulmonary hypertension (mean pulmonary artery pressure >25 mm Hg) was found in 45% (9/20), graded as moderate (40–60 mm Hg) in 44% of cases. Pulmonary function was obstructive in 47% (9/19). Fifty five percent of the patients with computed tomography data within the last five years (10/18) had confirmed bronchiectasis. Patients with right heart dilatation and/or moderate pulmonary hypertension (n = 6) had a more prolonged diagnostic delay (p = 0.04) and more severe lung disease.
Conclusion: Echocardiographic abnormalities are common in primary antibody deficiency, associated with diagnostic delay and pulmonary complications. Pulmonary hypertension should be considered in those with severe lung disease and can be confirmed by echocardiography.

Primary antibody deficiency syndromes are uncommon and often poorly recognised.[1] Patients present with recurrent upper and lower respiratory tract infections with consequent chronic pulmonary damage and the development of bronchiectasis (fig 1). Primary antibody deficiency syndromes can be subdivided into several distinct disease categories of which common variable immunodeficiency (CVID) is the most frequent, with an estimated incidence of one in 10 000 to one in 50 000.[2] CVID is characterised by defective antibody formation accompanied by decreased serum IgG and IgA levels with or without IgM deficiency. Early recognition and adequate immunoglobulin replacement treatment aims to reduce the infection rate and thereby avoid pulmonary complications.

An audit of patients with antibody deficiency in the UK from 1993–96 (including 686 patients with CVID) found that the diagnostic delay for CVID was 7.3 years. Nearly 20% had bronchiectasis, which in most cases was established before the patient was first seen by an immunologist.[1] Cardiac complications secondary to underlying chronic pulmonary disease have not been previously documented in this patient population. Dyspnoea secondary to poor cardiac function may be ascribed to poor pulmonary function and therefore not addressed adequately. By analogy to patients with cystic fibrosis complicated by bronchiectasis where cardiac manifestations are well documented,[3–5] right sided heart disease was postulated to occur in antibody deficient patients with the most severe pulmonary disease.

METHODS

Twenty adult patients with primary antibody deficiency under the care of a regional immunology centre underwent two dimensional and Doppler transthoracic echocardiography as part of their routine follow up. Inclusion criteria for the study were a confirmed diagnosis of primary antibody deficiency and ongoing immunoglobulin replacement therapy. Patients were excluded if they had a history of pre-existing cardiac disease. All echocardiograms were performed using an ATL (Hdi) ultrasound machine with the Harmonic Imaging option and 3.5 MHz probe, between May and December 2001. The cardiology technician (SJH) was blinded to the patient's clinical status. Standard views were used to assess function and size of the cardiac chambers as well as valve competence and patency. The extracardiac space was assessed using the subcostal view. Normal values were taken from Walsh and Wilde[6]; these are used in most cardiac centres in the UK. Estimated pulmonary artery pressure was derived from the amount of tricuspid regurgitation using the modified Bernoulli equation, in addition to the estimated right atrial pressure. Pulmonary artery pressure was considered normal up to 25 mm Hg and pulmonary hypertension was defined as mild (25–40 mm Hg), moderate (40–60 mm Hg), or severe (>60 mm Hg).

Information relating to age, diagnostic delay, time on replacement therapy before echocardiography, pulmonary function, and thoracic imaging was collected and analysed retrospectively.

Formal pulmonary function tests were performed through the respiratory medicine department at the regional centre. The Morgan Benchmark TT501 system was used after October 1999 for flow volume loops and spirometry, before this the Micro-Medical system was in use, with spirometry on a standard vitallograph spirometer. Oxygen saturations were recorded using an Omeda 3700e pulse oximeter and blood gas analysis was performed on a Rapid lab 248 (Chiron Diagnostics). Standard European pulmonary function

Abbreviations: CVID, common variable immunodeficiency; FEV_1/FVC, forced expiratory volume in one second/forced vital capacity

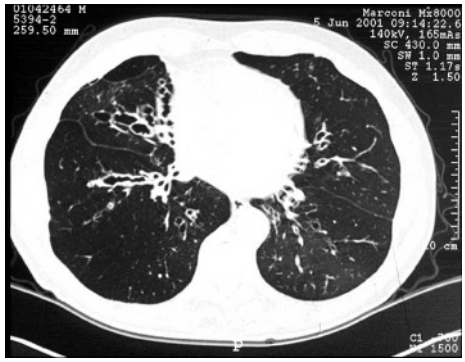

Figure 1 Thoracic computed tomogram demonstrating extensive bronchiectasis throughout both lungs. The airways are markedly dilated with both cylindrical and saccular changes.

reference ranges according to age, height, and gender were employed.[7]

High resolution thoracic computed tomography was performed on an El Scint twin spiral scanner before 2000, with subsequent scans on a Marconi Multispiral system via the radiology department at the regional centre (n = 17). Two had high resolution scans at outreach hospitals and one had a conventional scan at the regional centre. Films were reviewed by a single radiologist in 17 of 18 cases and previous scans were compared where available.

It is our routine practice to perform baseline thoracic computed tomography at diagnosis and, at the time of the study, at five yearly intervals thereafter. We aim to perform pulmonary function tests at two yearly intervals and maintain trough IgG levels (IgG just before the next infusion) at 8 g/l or above (see discussion).

As all investigations were part of the patients' routine follow up (an audit of care) ethics committee approval was not required.

Statistical analysis was performed using Fisher's exact test, Mann-Whitney U test or χ^2 test as appropriate, comparing those with right heart dilatation and/or moderate pulmonary hypertension to those without.

RESULTS

Twenty patients were included in the study, 19 with CVID and one with IgG_2 subclass deficiency. Demographic data are set out in table 1. The mean age of the patient cohort was 48.9 years, range 20.5–77.25 years. Mean age at diagnosis was 37.5 years, range 15.3–68.8 years, data not shown. The mean delay in diagnosis, defined as the delay between the onset of recurrent infection and recognition of antibody deficiency, as based on the patients' history, could be estimated in 17/20, and was 10.94 years, range 3–35 years. This delay was most marked in those patients with right heart dilatation and/or at least moderate pulmonary hypertension at 16.3 years, compared with eight years in those without such abnormalities. The correlation between diagnostic delay and right heart abnormalities was significant, p = 0.04. There was a trend towards a positive correlation between time from symptom onset and echo abnormalities, however this did not reach significance; echo abnormalities therefore were not simply a function of disease duration.

The echocardiographic findings are summarised in table 2. Left ventricular impairment was identified in 15% (patients 1, 6, and 16), all of whom had bronchiectasis and evidence of arterial hypoxaemia. Left ventricular hypertrophy was identified in 20% (4/20), 1/4 with known systemic hypertension. Aortic root dilatation was seen in 15% (patients 1, 6, and 12). Mitral regurgitation of any degree was found in 65% (13/20) but was thought to be trivial and insignificant in all but two patients. Tricuspid regurgitation of any degree was found in 90% (18/20) but again thought to be trivial and insignificant in all but three patients. No significant pulmonary regurgitation was identified and the aortic valve was competent in all cases. Right heart dilatation was found in 20% (patients 2, 3, 4, and 6). Pulmonary hypertension, estimated pulmonary artery pressure >25 mm Hg was found in 45% (9/20). This was mild in 5/9, only one of these five having a pressure above 30 mm Hg (patient 16). Moderate pulmonary hypertension occurred in 4 (patients 1, 3, 5, and 6), with a maximum estimated pressure of 48 mm Hg.

Table 3 documents pulmonary function results and findings on thoracic computed tomography. Spirometry was obstructive (forced expiratory volume in one second/forced vital capacity (FEV_1/FVC) <70%) in 47% (9/19), patient 16 was unable to perform the test because of dyspnoea. However formal pulmonary function data within the last two years was only available for 31.5% (6/19). Spirometry was previously normal in 9/13 where data were more than two years old. Hypoxia was recorded by oximetry (oxygen saturation <93% on room air) in two cases and arterial hypoxaemia (arterial oxygen pressure <10.5 kPa) was confirmed by blood gas analysis in five. These two groups were not overlapping. Fifty five percent of patients with a thoracic computed tomogram within the last five years (10/18) had documented bronchiectasis. This was stable, single lobe in 10%, progressive single lobe in 10%, mild multilobar in 50%, and severe multilobar in 30% (patients 1, 2, and 6). Patient 7 had had a lobectomy for bronchiectasis before a diagnosis of antibody deficiency, bringing the total with documented bronchiectasis to 60%.

For statistical analysis, oxygen status was defined as abnormal if oxygen saturations were less than 93% or arterial oxygen pressure <10.5 kPa on room air. Thoracic computed tomography results were divided into three categories: normal/no significant bronchiectasis (patients 5, 10, 17, 18, 19); mild/moderate abnormality (patients 7, 8, 9, 11, 12, 14, 15); and severe with or without emphysema (patients 1, 2, 3, 4, 6, 13, 16, 20). The correlation between computed tomography and echo abnormalities was significant, p = 0.03.

The 30% (6/20) with evidence of right heart dilatation and/or moderate pulmonary hypertension (defined as having right heart abnormalities) were those with the most severe lung disease on computed tomography, obstructive pulmonary function (83%), and hypoxia/arterial hypoxaemia (67%). The correlation between computed tomography and right heart abnormalities was significant (χ^2 analysis), p = 0.03, table 3. The correlation between spirometry and right heart abnormalities was highly significant p = 0.007, fig 2. However the correlation between oxygen status and echo findings was not significant. Five of the six were male but this did not reach significance when compared with those without right heart abnormalities.

DISCUSSION

Primary antibody deficiency syndromes are uncommon but are associated with significant morbidity. Of these CVID is the most frequent, with an estimated incidence of one in 10 000 to one in 50 000.[2] Patients tend to present with recurrent respiratory tract infections so that chronic pulmonary complications are common, especially when there has been diagnostic delay. However CVID is a heterogeneous disorder which in some patients also includes cellular immune deficiency, so that disease phenotypes vary. Immunoglobulin replacement therapy can reduce the frequency of acute infections and improve lung function when trough IgG levels are maintained above 5 g/l.[8] The optimal trough IgG level is not well established in CVID. A recent

Table 1 Demographic data of 20 patients with primary antibody deficiency undergoing echocardiography

Patient No	Age in years	Sex	Diagnosis date	Estimated diagnostic delay (years)	Time on IgG pre-echo (years)
1†	70.4	M	May 79	15	22.0
2†	49.4	M	April 89	10	12.0
3†	53.75	M	October 97	11	3.5
4†	49.1	M	May 81	20	20.25
5†	48.5	F	March 81	7	20.4
6*†	55.3	M	May 93	35	8.0
7	61.6	F	March 82	20	13.8
8	37.4	M	March 98	5	3.5
9	69.0	F	1961	N/A	35.0
10	51.25	M	1974	6	27.0
11	57.9	M	1972	10	29.0
12	51.6	M	September 97	3	4.25
13	35.5	M	October 99	3	1.8
14	31.8	F	September 97	5	4.0
15	49.0	M	April 81	4	20.0
16	77.25	F	January 94	14	7.5
17	20.5	F	August 99	10	2.0
18	36.6	F	1986	N/A	15.0
19	23.1	F	October 94	8	7.0
20	49.8	M	1981	N/A	20.0

N/A, data not available.
*Patient with IgG_2 subclass deficiency.
†Patients with right heart dilatation and/or moderate pulmonary hypertension.

study of pulmonary abnormalities in patients with primary hypogammaglobulinaemia (including 18 with CVID) has shown that pulmonary abnormalities develop in most patients and that silent progression can occur despite ''adequate'' replacement therapy with trough levels of 5 g/l or more.[9] Studies in patients with an X-linked primary antibody deficiency syndrome, X-linked agammaglobulinaemia, suggest that trough IgG levels >8 g/l can prevent the onset of bronchiectasis, chronic sinusitis, and non-bacterial infections if treatment is instituted early.[10] On the basis of the latter study we aim for a trough IgG level above 8 g/l in all of our antibody deficient patients, acknowledging that breakthrough infections can still occur and require early antibiotic therapy.[11]

Table 2 Positive echocardiographic findings in 20 patients with primary antibody deficiency

Patient No	Positive echocardiographic findings
1	Mild left ventricular dilatation and hypertrophy with moderate contraction, dilated aortic root and left atrium, mild mitral regurgitation + tricuspid regurgitation, PAP 41 mm Hg
2	Mild LVH, mild right heart dilatation
3	Right heart dilatation, right atrial pressure 18 mm Hg, dilated hepatic veins, presumed moderate pulmonary hypertension, unable to measure PAP
4	Mild right heart dilatation
5	PAP 48 mm Hg
6	Dilated aortic root, moderate left ventricular contraction, right atrial dilatation, PAP 44 mm Hg
7	Mild tricuspid regurgitation
8	Mild tricuspid regurgitation, PAP 28 mm Hg
9	Mild LVH, mildly dilated left atrium
10	Normal
11	Mild LVH
12	Mildly dilated aortic root
13	Normal
14	PAP 28 mm Hg
15	Normal
16	Anterior pericardial effusion <1 cm, moderate left ventricular contraction, PAP 33 mm Hg
17	Normal
18	Mild mitral regurgitation, PAP 29 mm Hg
19	PAP 26 mm Hg
20	Normal

LVH, left ventricular hypertrophy; PAP, mean pulmonary artery pressure.

Pulmonary hypertension is the major cardiovascular complication of obstructive lung disease. Hypoxaemia is associated with pathological changes that predominantly affect the peripheral blood vessels. Small arteries accumulate vascular smooth muscle cells in the intima and medial hypertrophy occurs in muscular pulmonary arteries. Structural change therefore, not simply hypoxic vasoconstriction, is the major factor in development of sustained pulmonary hypertension.[12] Other contributory mechanisms may include hypercapnia, acidaemia, airway resistance, and endothelial derived vasoactive factors.[12] Development of pulmonary hypertension is thought to adversely affect prognosis in obstructive lung disease, but whether this is a primary effect or simply a reflection of the severity of the underlying pulmonary disease is unclear. Treatment options for secondary pulmonary hypertension are limited, but include long term oxygen therapy, treatment of right heart failure and in some cases, anticoagulation.[13] More recently, inhaled iloprost and oral bosentan (a dual endothelin receptor antagonist) have undergone clinical trials in severe pulmonary hypertension, both primary and secondary to connective tissue disease.[14 15] Their place in the management of pulmonary hypertension secondary to obstructive lung disease, however, remains to be established.

Pulmonary hypertension and cor pulmonale are well documented complications of cystic fibrosis. This was used as a model disease for our current study as recurrent pulmonary infection and bronchiectasis are common to both cystic fibrosis and antibody deficiency syndromes. In 1980, Lester *et al* suggested a scoring system of echocardiographic abnormalities in patients with cystic fibrosis that correlated with clinical, chest imaging and pulmonary function scores.[3] It has subsequently been shown that subclinical right ventricular dysfunction correlates with the severity of lung disease in cystic fibrosis.[4] In addition, right ventricular overload can distort left ventricular diastolic function and left ventricular diastolic impairment closely correlates with pulmonary hypertension levels in chronic cor pulmonale.[16 17] Aortic root dilatation has also been described as in our cohort,[3] but the clinical significance of this is not well established.

Table 3 Spirometry, oxygen status, and thoracic computed tomography findings in 20 patients with primary antibody deficiency

Patient No	Spirometry FEV_1/FVC (%)	Oxygen status*	Thoracic computed tomography
1†	0.5/2.7 (19)	8.3	Stable multilobar bronchiectasis
2†	1.0/2.4 (42)‡	90%	Stable multilobar bronchiectasis
3†	0.6/2.9 (21)	10.5	Severe emphysema
4†	3.1/5.7 (54)	10.0	Stable single lobe bronchiectasis + emphysema
5†	2.7/3.5 (77)	13.4	Normal
6†	0.9/1.55 (58)‡	84%	Multilobar severe bronchiectasis
7	1.66/2.5 (66)‡	96%	No residual bronchiectasis§
8	4.5/6.0 (75)	10.8	Mild progressive bronchiectasis in left base
9	1.2/2.3 (52)	9.0	Mild multilobar bronchiectasis
10	3.64/5.75 (63)‡	95%	No significant bronchiectasis
11	3.4/4.9 (69)	12.0	Reduced volume in left lower lobe
12	3.8/5.0 (76)	N/A	Right basal scarring: not HRCT
13	2.7/4.0 (68)‡	98%	Multilobar bronchiectasis
14	0.93/1.08 (86)‡	95%	? Alveolitis
15	3.8/4.9 (78)	10.3	Mild multilobar bronchiectasis
16	N/A	9.14	Stable multilobar bronchiectasis
17	2.76/2.95 (94)	96%	Normal
18	4.7/5.8 (81)	12.6	Normal
19	1.95/1.95 (100)	N/A	Normal
20	3.0/3.7 (81)	N/A	Stable multilobar bronchiectasis

HRCT, high resolution computed tomography
*Figures with % value measured by oximetry, figures without % represent arterial oxygen pressure in kPa.
†Patients with right heart dilatation and/or moderate pulmonary hypertension.
‡Patient with formal pulmonary function tests within the last two years.
§Lobectomy for bronchiectasis before antibody deficiency diagnosis.

Bronchiectasis was identified in 50% of the patients in this study, multilobar in 80% of these cases. We were interested to document the effect of such chronic lung disease on cardiac function in primary antibody deficiency.

Overall cardiac abnormalities, including secondary pulmonary hypertension, were common. There was no correlation between current age nor age at presentation with echo abnormalities; age itself therefore does not appear to be a significant determining factor. Left ventricular function was generally good in the absence of severe pulmonary hypertension but impaired function was observed in three patients, all of whom had evidence of hypoxaemia. When concentrating on right heart dilatation and/or at least moderate pulmonary hypertension, 30% of the patients were affected. Those with the most significant cardiac abnormalities had greater diagnostic delay ($p = 0.04$), the most severe structural lung disease ($p = 0.03$), the worst pulmonary function ($p = 0.007$), and hypoxaemia, as postulated. However hypoxaemia was not significantly correlated with the presence of pulmonary hypertension, consistent with previous findings that hypoxia is not the single driving force.[12] Neither were echo abnormalities simply a function of disease duration in our cohort. The delay in recognition of antibody deficiency, the adequacy of replacement immunoglobulin, and the access to antibiotics for intercurrent infection are all likely factors contributing to the degree of lung damage.

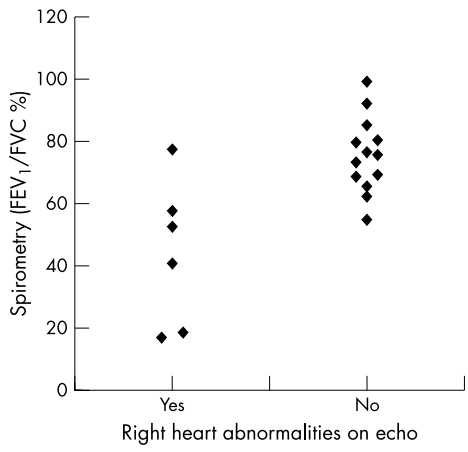

Figure 2 Correlation between spirometry and right heart abnormalities. The correlation between the spirometric values and right heart abnormalities is clearly demonstrated. Those patients with right heart abnormalities (defined as right heart dilatation and/or the presence of moderate pulmonary hypertension) have the most severely reduced lung function as measured by FEV_1/FVC.

One patient (patient 5) had a normal thoracic computed tomogram within the previous five years and at the time of testing was not hypoxic. She had the highest recorded pulmonary artery pressure, which may therefore represent primary rather than secondary pulmonary hypertension. This is currently under further investigation.

Two of the six patients defined as having right heart abnormalities had peripheral oedema, treated with diuretics, but no other signs of right heart failure. No other patients had apparent clinical signs, supporting the concept of subclinical heart disease as seen in cystic fibrosis. Dyspnoea is a common symptom of pulmonary hypertension, bronchiectasis, and impaired left ventricular function so it is difficult to ascertain whether our patients had truly asymptomatic right heart abnormalities. Electrocardiographic data were available only for two of six patients with right heart abnormalities, one being normal and one showing partial right bundle branch block. We therefore have insufficient data to correlate electrocardiographic and echo findings. Smoking histories were not taken into account in this study. We advise all of our antibody deficient patients not to smoke. In view of this and the prolonged diagnostic delay in many cases, any such retrospective information is likely to be inaccurate and therefore of doubtful utility.

Despite the small patient numbers, our findings support the hypothesis that those with the most severe lung disease have the most significant cardiac abnormalities. This has not been previously documented in CVID. There is no reason to suspect that patients with primary antibody deficiency should behave any differently in terms of cardiac complications than patients with other chronic obstructive pulmonary

disorders. We wish to emphasise that antibody deficiency is treatable and if recognised early does not have to lead to inexorable pulmonary damage that otherwise results in secondary pulmonary hypertension. Early recognition and adequate replacement therapy, probably aiming for trough IgG levels of 8 g/l or above, may prevent progressive lung disease and hence cardiac manifestations. The optimal trough IgG level requires further prospective study, as our interpretation of ''adequate'' therapy is different from that of Kainulainen *et al*.[9] This is likely to impact not only on lung disease but also on the availability of a scarce therapeutic resource.

We conclude that echocardiography does have a role in the evaluation of patients with primary antibody deficiency syndromes who present late with established bronchiectasis. Clinical signs of right ventricular dysfunction are often lacking. Dyspnoea may reflect secondary pulmonary hypertension in addition to the structural lung damage. Confirmation of pulmonary hypertension allows additional therapeutic options to be explored such as long term oxygen therapy.

Authors' affiliations

S L Johnston, R J Lock, D J Unsworth, M M Gompels, Department of Immunology and Immunogenetics, Southmead Hospital, Bristol, UK
S J Hill, Department of Cardiology, Southmead Hospital, Bristol, UK
J F Dwight, Department of Cardiology, John Radcliffe Hospital, Oxford, UK

REFERENCES

1 **Spickett GP**, Chapel HM. *Report on the audit of patients with primary antibody deficiency in the United Kingdom 1993–1996*. Newcastle upon Tyne: Newcastle upon Tyne Hospitals NHS Trust, 1998.
2 **Report of an IUIS Scientific Committee**. Primary immunodeficiency diseases. *Clin Exp Immunol* 1999;**118**(suppl 1):1–28.
3 **Lester LA**, Egge AC, Hubbard VS, *et al*. Echocardiography in cystic fibrosis: a proposed scoring system. *J Pediatr* 1980;**97**:742–8.
4 **Ionescu AA**, Ionescu A-A, Payne N, *et al*. Subclinical right ventricular dysfunction in cystic fibrosis. A study using tissue Doppler echocardiography. *Am J Respir Crit Care Med* 2001;**163**:1212–18.
5 **Vizza CD**, Lynch JP, Ochoa LL, *et al*. Right and left ventricular dysfunction in patients with severe pulmonary disease. *Chest* 1998;**113**:576–83.
6 **Walsh C**, Wilde P. *Practical echocardiography*. 1st Ed. London: Greenwich Medical Media Limited, 1999 (distributed worldwide by Oxford University Press).
7 **Official Statement of the European Respiratory Society**. Standardized lung function testing. *Eur Respir J Suppl* 1993;**16**:1–100.
8 **Roifman CM**, Levison H, Gelfand EW. High-dose versus low-dose intravenous immunoglobulin in hypogammaglobulinaemia and chronic lung disease. *Lancet* 1987;**i**:1075–7.
9 **Kainulainen L**, Varpula M, Liippo K, *et al*. Pulmonary abnormalities in patients with primary hypogammaglobulinemia. *J Allergy Clin Immunol* 1999;**104**:1031–6.
10 **Quartier P**, Debré M, De Blic J, *et al*. Early and prolonged intravenous immunoglobulin replacement therapy in childhood agammaglobulinemia: a retrospective survey of 31 patients. *J Pediatr* 1999;**134**:589–96.
11 **Pettit SJ**, Bourne H, Spickett GP. Survey of infection in patients receiving antibody replacement treatment for immune deficiency. *J Clin Pathol* 2002;**55**:577–80.
12 **MacNee W**. Pathophysiology of cor pulmonale in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1994;**150**:833–52.
13 **Ricciardi MJ**, Rubenfire M. How to manage secondary pulmonary hypertension. Recognising and treating cor pulmonale and chronic thromboembolism. *Postgrad Med* 1999;**105**:183–90.
14 **Olschewski H**, Simonneau G, Galiè N, *et al*. Inhaled iloprost for severe pulmonary hypertension. *N Engl J Med* 2002;**347**:322–9.
15 **Rubin LJ**, Badesch DB, Barst RJ, *et al*. Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med* 2002;**346**:896–903.
16 **Tutar E**, Kaya A, Güleç S, *et al*. Echocardiographic evaluation of left ventricular diastolic function in chronic cor pulmonale. *Am J Cardiol* 1999;**83**:1414–17.
17 **Schena M**, Clini E, Errera D, *et al*. Echo-Doppler evaluation of left ventricular impairment in chronic cor pulmonale. *Chest* 1996;**109**:1446–51.