

but must be openly discussed, communicated and documented. A predicted moderate to high risk of death from community-acquired pneumonia is a highly relevant piece of information required to mount an ethically valid treatment recommendation and decision, particularly in those patients with pneumonia regarded to be a terminal event. Nevertheless, we recalculated the predictions of the CRB-65 score excluding all those who died without having received any ventilator support during hospitalisation. The results are: overall death rate 8618, 2.5%, CRB-65 risk class 1: 0.5%, risk class 2: 1.7% and risk class 3: 12.2%. These numbers support the following conclusions: (1) the CRB-65 score remains useful in predicting deaths in a three class pattern; (2) obviously, virtually no previous study on community-acquired pneumonia truly excluded all patients with treatment limitations.

### S Ewig,<sup>1</sup> N Birkner<sup>2</sup>

<sup>1</sup>Thoraxzentrum Ruhrgebiet, Kliniken für Pneumologie und Infektiologie, Herne und Bochum, Germany; <sup>2</sup>BQS Institut für Qualität und Patientensicherheit, Düsseldorf, Germany

**Correspondence to** Dr N Birkner, BQS Institut für Qualität und Patientensicherheit, Kanzlerstr. 4, D-40472 Düsseldorf, Germany; n.birkner@bqs-institut.de

**Competing interests** None.

**Provenance and peer review** Not commissioned; not externally peer reviewed.

Accepted 24 August 2010  
Published Online First 23 November 2010

*Thorax* 2011;**66**:262–263.  
doi:10.1136/thx.2010.149716

### REFERENCE

1. Charles P. Predicting CAP-related mortality with CRB-65. *Thorax* 2011;**66**:262.

## Pulmonary rehabilitation in patients with MRC Dyspnoea Scale 2

The recent INTERCOM study emphasises the point that community-based rehabilitation is effective, even in patients with chronic obstructive pulmonary disease (COPD) with less advanced airflow obstruction.<sup>1</sup> However, COPD and pulmonary rehabilitation guidelines recommend offering pulmonary rehabilitation (PR) to patients who consider themselves functionally disabled (usually defined as MRC Dyspnoea Scale grades 3 or above).<sup>2–3</sup> We wished to test whether less breathless patients with COPD (ie, MRC Dyspnoea Scale grade 2) also benefit from PR.

### METHODS

All patients with MRC grade 2 dyspnoea referred to the Lambeth & Southwark Community Pulmonary Rehabilitation Team

**Table 1** Effects of pulmonary rehabilitation in patients with MRC 2 and MRC 3/4 dyspnoea

Outcomes	Change following PR		p Value
	MRC 2	MRC 3/4	
Mean (SD) ISW (m)	83 (7)	68 (5)	0.08
Median (25 <sup>th</sup> , 75 <sup>th</sup> centile) ISW% change	27 (12, 45)	33 (9, 68)	0.07
Mean (SD) CRQ-D	0.75 (0.11)	0.75 (0.07)	0.96
Median (25 <sup>th</sup> , 75 <sup>th</sup> centile) HAD-anxiety	−1 (−3, 1)	−1 (−3, 0)	0.74
Median (25 <sup>th</sup> , 75 <sup>th</sup> centile) HAD-depression	0 (−2.5, 1)	−1 (−3, 0)	0.46

HAD, Hospital Anxiety and Depression Scale; ISW, incremental shuttle walk; PR, pulmonary rehabilitation.

between the years 2004–7 were included in the study. Patients were offered PR at one of two hospital or five community sites. Each programme consisted of two supervised sessions per week for 8 weeks (with one unsupervised home session) delivered by the same team. Outcome measures were the incremental shuttle walk (ISW), the Chronic Respiratory Disease Questionnaire Dyspnoea score (CRQ-D) and the Hospital Anxiety and Depression Scale (HAD-Anxiety and HAD-Depression). Patients with COPD with MRC dyspnoea grades 3 or 4 undertaking PR over the same time period acted as controls. Changes in outcomes between patients with MRC grade 2 and those with MRC grades 3 or 4 dyspnoea before and after PR were compared using t tests or Mann-Whitney tests.

### RESULTS

The results were analysed for 126 patients with MRC grade 2 dyspnoea and 316 with MRC grades 3/4 dyspnoea who completed PR (attended >8 supervised sessions). The groups were well matched for age (mean 69 vs 68 years), gender (50% vs 43% male) and mean forced expiratory volume in 1 s (58% vs 54% predicted), although the MRC grade 2 group had increased ISW (304 vs 201 m;  $p<0.001$ ), less dyspnoea (median CRQ-D 3.2 vs 2.6) and reduced anxiety and depression scores (median HAD-Anxiety 6.0 vs 9.0; median HAD-Depression 5.0 vs 8.0). Following PR, the MRC grade 2 dyspnoea group showed similar improvements in ISW, CRQ-D, HAD-Anxiety and HAD-Depression to the MRC grades 3/4 dyspnoea group (table 1).

### DISCUSSION

Although patients with MRC dyspnoea grade 2 referred for PR have better exercise capacity and fewer symptoms of dyspnoea, anxiety or depression than patients with MRC dyspnoea grades 3/4, they show similar improvements with PR. Exercise-based interventions for COPD should not ignore less severe patients (either in terms of lung function or subjective dyspnoea).

**W D-C Man, A Grant, L Hogg, J Moore, R D Barker, J Moxham**

Department of Respiratory Medicine, King's College Hospital and Lambeth & Southwark Pulmonary Rehabilitation Team, Harefield, UK

**Correspondence to** W D-C Man, Harefield Hospital, Hill End Road, Harefield UB9 6JH, UK; research@williamman.co.uk

**Funding** WD-CM is supported by a National Institute for Health Research Clinician Scientist award. The views expressed in this publication are those of the authors and not necessarily those of the NHS, The National Institute for Health Research or the Department of Health.

**Competing interests** None.

**Provenance and peer review** Not commissioned; not externally peer reviewed.

Accepted 8 February 2010  
Published Online First 29 September 2010

*Thorax* 2011;**66**:263. doi:10.1136/thx.2010.136085

### REFERENCES

1. van Wetering CR, Hoogendoorn M, Mol SJ, *et al*. Short- and long-term efficacy of a community-based COPD management programme in less advanced COPD: a randomised controlled trial. *Thorax* 2010;**65**:7–13.
2. National Institute for Health and Clinical Excellence (NICE). Chronic obstructive pulmonary disease: national clinical guideline for management of chronic obstructive pulmonary disease in adults in primary and secondary care. *Thorax* 2004;**59**(Suppl 1):1–232.
3. BTS Standards of Care Subcommittee on Pulmonary Rehabilitation. Pulmonary rehabilitation. *Thorax* 2001;**56**:827–34.

## The potential danger of a solely interferon- $\gamma$ release assay-based approach to testing for latent *Mycobacterium tuberculosis* infection in children

The study reported by Lucas *et al*<sup>1</sup> is a valuable addition to recent publications that have compared the performance of commercial interferon- $\gamma$  release assays (IGRAs) with that of the tuberculin skin test (TST) for the diagnosis of latent tuberculosis infection (LTBI) in high-risk children.<sup>2–3</sup> However, we believe that the principal conclusions are not supported by the data provided and that a more guarded interpretation is warranted.

In agreement with previous studies in children,<sup>3–5</sup> Lucas *et al* found significant discordance between the results of IGRAs and TST. Specifically, of 420 T-SPOT.TB and 460

**Table 1** IGRA results without interpretable results

	T-SPOT.TB	QFT-GIT
Total number of patients	524	524
Insufficient blood volume obtained for test	47	64
Test failed	57	0
Indeterminate result	8	70
Total number (%) without an interpretable result	112 (21.4%)	134 (25.6%)

QuantiFERON-TB Gold I Tube (QFT-GIT) assays that were successfully completed, results were positive in 38 (9%) and 45 (10%) children, respectively. In contrast, of 304 children in whom the TST was read, the result was positive in 54 (18%). The authors contend that the overall low level of agreement between TST and IGRAs ( $\kappa = 0.45-0.46$ ) in their study 'reflects the likely superior specificity of the IGRAs resulting from the use of antigens not found in either BCG or NTM'. However, the authors' own data suggest that previous BCG immunisation did not significantly impact on the results of either TST or IGRAs. Specifically, table 3 shows that the odds ratio of a positive TST result in children with a history of BCG immunisation (compared with those without) was 1.7 (95% CI 0.8 to 3.5), almost identical to those for the T-SPOT.TB (OR 1.8; 95% CI 0.8 to 4.0) and the QFT-GIT (OR 1.7; 95% CI 0.8 to 3.6). Therefore, prior BCG vaccination had no greater influence on the TST result than on the result of either IGRA. In addition, contrary to the authors' statement, orthologues of early secretory antigenic target and culture filtrate protein, which form the basis of both IGRAs, are also present in some non-tuberculous mycobacteria.<sup>6,7</sup> The clinical relevance of this is shown by a recent publication, which reported positive QFT assays in more than half of patients with *M. kansasii* or *M. marinum* infection.<sup>8</sup> This illustrates that commercial IGRAs are not entirely species-specific for *M. tuberculosis* infection.

On the basis of the observation that nine refugee children had a positive IGRA result (either T-SPOT.TB or QFT-GIT) while being TST negative (ie, IGRA+/TST- discordant), the authors conclude that the 'TST has inferior sensitivity for demonstrating LTBI'. However, this ignores the data in table 3 and figure 3 that suggest that TST may have had superior sensitivity to either of the two IGRAs in household TB contacts (ie, those at highest risk of LTBI). Notably, children in this subgroup were considerably more likely to have a positive TST than a positive IGRA (TST, OR 4, 95% CI 1.7 to 9.5; T-SPOT.TB, 2.4 95% CI 0.9 to 6.5; QFT-GIT, 2.4 95% CI 1.0 to 5.8). Therefore, this raises the possibility that the IGRA results in these children represented false negatives. However, in the absence of a gold standard for LTBI, the superiority of one test over another cannot be conclusively established.

The authors highlight that a considerable proportion (11%) of the 'TSTs could not be

completed, reflecting the logistical difficulties frequently encountered in reading this test'. However, the authors did not mention that the proportion of IGRA results without interpretable results in their study was even higher (21.4% for T-SPOT.TB and 25.6% for QFT-GIT) (table 1). The 'real-life' difficulties in obtaining sufficient blood for an IGRA in the paediatric setting is further highlighted by a previous study that reported a failure rate of 15% related to phlebotomy.<sup>9</sup> Notably, all patients with failed phlebotomy in that study had an interpretable TST. Obtaining sufficient blood volume for both IGRAs to increase sensitivity, as suggested by Lucas *et al*, is therefore likely to be a rather unrealistic goal in routine clinical paediatric practice. The relatively high proportion of indeterminate IGRA results reported in the study by Lucas *et al* and other studies in children further limit the usefulness of these tests in the paediatric age group.<sup>5,10,11</sup>

Important strengths of the study by Lucas *et al* include the size of the cohort and the novel information provided on the potential influence of helminth infection on the performance of IGRAs. Nevertheless, the data provided do not support the statement that 'IGRAs are the preferred screening tool for LTBI in refugee children' nor the conclusion that a primarily TST-based screening approach is 'inferior to a solely IGRA-based approach'. The TST retains an important place in the evaluation of children with suspected LTBI, particularly as there remains a paucity of data on the sensitivity and predictive value of IGRAs in children. Published data by our group and others suggest that the performance of IGRAs is compromised in young children, particularly those under the age of 5 years.<sup>2,10,11</sup> This suggests that the 'decreased positivity' (ie, sensitivity) of IGRAs in young children probably reflects intrinsic limitations of the assays, rather than 'less time for potential exposure to *M. tuberculosis*'. Until more convincing evidence becomes available, we, and others in this field, maintain that children at high risk of LTBI with an IGRA-/TST+ discordant result should be given preventive treatment, precluding a solely IGRA-based approach.<sup>12</sup> We agree with the authors that 'both IGRAs have methodological and performance characteristics that limit their usefulness in refugee children' and eagerly await the development of improved immunodiagnostic tools for the diagnosis of TB in children.

**T G Connell, M Tebruegge, N Ritz, P Bryant, N Curtis**

<sup>1</sup>Department of Paediatrics, The University of Melbourne, Royal Children's Hospital Melbourne, Australia; <sup>2</sup>Infectious Diseases Unit, Department of General Medicine, Royal Children's Hospital Melbourne, Australia; <sup>3</sup>Murdoch Children's Research Institute, Royal Children's Hospital Melbourne, Australia.

**Correspondence to** Professor Nigel Curtis, Department of Paediatrics, The University of Melbourne, Royal Children's Hospital Melbourne, Parkville, VIC 3052, Australia; nigel.curtis@rch.org.au

**Competing interests** None.

**Provenance and peer review** Not commissioned; externally peer reviewed.

Accepted 29 June 2010

Published Online First 27 September 2010

*Thorax* 2011;**66**:263–264.

doi:10.1136/thx.2010.143396

## REFERENCES

- Lucas M, Nicol P, McKinnon E, *et al*. A prospective large-scale study of methods for the detection of latent *Mycobacterium tuberculosis* infection in refugee children. *Thorax* 2010;**65**:442–8.
- Bergamini BM, Losi M, Vienti F, *et al*. Performance of commercial blood tests for the diagnosis of latent tuberculosis infection in children and adolescents. *Pediatrics* 2009;**123**:e419–24.
- Connell TG, Ritz N, Paxton GA, *et al*. A three-way comparison of tuberculin skin testing, QuantiFERON-TB gold and T-SPOT.TB in children. *PLoS One* 2008;**3**:e2624.
- Chun JK, Kim CK, Kim HS, *et al*. The role of a whole blood interferon-gamma assay for the detection of latent tuberculosis infection in Bacille Calmette-Guerin vaccinated children. *Diagn Microbiol Infect Dis* 2008;**62**:389–94.
- Connell TG, Curtis N, Ranganathan SC, *et al*. Performance of a whole blood interferon gamma assay for detecting latent infection with *Mycobacterium tuberculosis* in children. *Thorax* 2006;**61**:616–20.
- Gey van Pittius NC, Warren RM, van Helden PD. ESAT-6 and CFP-10: what is the diagnosis? *Infect Immun* 2002;**70**:6509–10.
- Tebruegge M, Connell T, Ritz N, *et al*. Discordance between TSTs and IFN-gamma release assays: the role of NTM and the relevance of mycobacterial sensitins. *Eur Respir J* 2010;**36**:214–15.
- Kobashi Y, Mouri K, Yagi S, *et al*. Clinical evaluation of the QuantiFERON-TB Gold test in patients with non-tuberculous mycobacterial disease. *Int J Tuberc Lung Dis* 2009;**13**:1422–6.
- Tsiouris SJ, Austin J, Toro P, *et al*. Results of a tuberculosis-specific IFN-gamma assay in children at high risk for tuberculosis infection. *Int J Tuberc Lung Dis* 2006;**10**:939–41.
- Connell TG, Tebruegge M, Ritz N, *et al*. Indeterminate interferon-gamma release assay results in children. *Pediatr Infect Dis J* 2010;**29**:285–6.
- Haustein T, Ridout DA, Hartley JC, *et al*. The likelihood of an indeterminate test result from a whole-blood interferon-gamma release assay for the diagnosis of *Mycobacterium tuberculosis* infection in children correlates with age and immune status. *Pediatr Infect Dis J* 2009;**28**:669–73.
- Powell DA. Interferon gamma release assays in the evaluation of children with possible *Mycobacterium tuberculosis* infection: a view to caution. *Pediatr Infect Dis J* 2009;**28**:676–7.