

IMMUNOLOGICAL TESTING IN NON-CYSTIC FIBROSIS BRONCHIECTASIS

The review of non-cystic fibrosis bronchiectasis by Smith¹ elegantly highlights the lack of evidence available in some areas. In particular, approach to immunological testing is varied. Table 2 on page 134 in this review describes the diagnostic features required for immunodeficiency (including immunoglobulin G [IgG] subclass 2 deficiency amongst other IgG subclass deficiencies). However, IgG subclass testing has not been favoured by recent national guidelines², because IgG subclass deficiency can occur in well, asymptomatic individuals with normal functional antibody responses (due to heavy-chain deletions), and this therefore gives no information on functional antibody response to particular antigens.³ Rather, the British Thoracic Society² advocates functional testing to peptide and polysaccharide antigens, as well as measurement of serum IgG, immunoglobulin A (IgA) and immunoglobulin M (IgM) in the routine assessment of possible antibody deficiency before more detailed second line tests are considered.

On the basis that this is the current recommendation from expert authorities in this area, it might be helpful for readers and practising clinicians seeing such patients daily, if this approach could be incorporated into review articles in this area, until such time as there is a change in consensus.

ARL Medford

Consultant Chest Physician and Honorary Senior Clinical Lecturer, North Bristol Lung Centre, Southmead Hospital, North Bristol Hospitals NHS Trust, Westbury-on-Trym, Bristol UK.

e mail andrew.medford@nbt.nhs.uk

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- 3 Buckley RH. Immunoglobulin G subclass deficiency: fact or fancy? *Curr Allergy Asthma Rep* 2002; 2:356–60. <http://dx.doi.org/10.1007/s11882-002-0067-1>

In reviewing non-cystic fibrosis bronchiectasis¹, Dr Smith appropriately indicates the importance of considering immunodeficiency as a possible underlying causative factor. This is particularly the case for primary antibody deficiency disorders where structural tissue damage in the respiratory tract secondary to recurrent or persistent infection is a common and significant burden for patients. The entity of primary antibody deficiency encompasses a heterogeneous range of defined conditions.² Bronchiectasis occurs (with varying degrees of frequency) as a complication in all forms of the condition from severe panhypogammaglobulinaemia to subtle defects of specific antibody production. The three most commonly encountered disease variants are

common variable immune deficiency (CVID), x-linked agammaglobulinaemia (XLA) and immunoglobulin A (IgA) deficiency. In CVID and XLA, bronchiectasis is a commonly established finding at diagnosis, frequently resulting from delayed diagnosis. Bronchiectasis appears to complicate isolated selective IgA deficiency relatively rarely, but may occur at greater frequency when IgA deficiency is part of, or evolves into, a more clinically significant and complex antibody deficiency disorder.

In the context of the Review's Table 2 it should be noted, however, that there is considerable doubt about whether a low serum IgG 2 subclass level has any intrinsic significance, whether IgG subclass deficiency even constitutes a robustly definable clinical entity and whether measurement of IgG subclass levels has any useful role in the diagnosis of significant antibody deficiency.³ These doubts are based on the poor correlation of measured subclass levels with susceptibility to infection and with the functional ability of the immune system to make specific antibodies to, for instance, the capsular polysaccharides of *Streptococcus pneumoniae* or *Haemophilus influenzae*.

Patients with bronchiectasis and suspected (or proven) immune deficiency should be discussed with local specialist immunology service providers. Close clinical liaison is necessary to confirm or exclude a significant immunodeficiency, to arrange necessary specialist investigations in order to refine a precise diagnosis and to institute appropriate management measures.⁴ The United Kingdom Primary Immunodeficiency Network (<http://www.ukpin.org.uk>) has developed an online diagnostic tool for non-specialists faced with the scenario of possible immunodeficiency. Although basic initial screening investigation (e.g. measurement of serum IgG/A/M) is entirely appropriate in the non-specialist setting, interaction between specialist service teams is the key to early detection/diagnosis of underlying immune deficiency and institution of optimised treatment within a shared care arrangement.

Dr Richard Herriot

Aberdeen Royal Infirmary

e mail richard.herriot@nhs.net

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I read with great interest the paper by MP Smith (Non-cystic fibrosis bronchiectasis. *J R Coll Physicians Edinb* 2011; 41:132–39).

Bronchiectasis is a chronic disorder punctuated with frequent exacerbations. A district general hospital in the UK has 100–200/250,000 patients with bronchiectasis. We have reported our hospital experience of macrolides in patients with non-cystic fibrosis bronchiectasis.

In Harrogate District Hospital, the clinical practice of using low dose azithromycin as long-term prophylaxis was started in 2008.

A retrospective analysis done in 2010 has shown that 27 (12 males, 15 females) patients (mean age 58.4 years, range 30–83) with persistent symptoms and/or recurrent infective exacerbations (three or more episodes) requiring oral or parenteral antibiotics were started on azithromycin. The dosing regimen was 500 mg once daily for six days, 250 mg once daily for six days, and 250 mg thrice weekly. The aetiology in 15 patients was idiopathic, seven were post-infective (tuberculosis and recurrent bacterial infections), one post-radiotherapy, two congenital (Young's and Kartagener's syndrome) and two autoimmune/inflammatory disorders (rheumatoid arthritis and sarcoidosis) respectively. The clinical response, cough frequency, sputum colour, sputum volume, sputum cultures, and infective exacerbations pre- and post-six week antibiotic period were noted.

In 18 (66.7%) cases, there was an improved response clinically as assessed by both physicians and patients with reduction in sputum volume, sputum colour and cough frequency. Ten patients had reduced infective exacerbations requiring fewer antibiotics. Azithromycin altered the microbiological flora except in patients who had chronic pseudomonas colonisation (n=4). One patient was intolerant and 17 patients were on thrice weekly prophylaxis.

Macrolides have a role in patients with persistent symptoms and/or recurrent infective exacerbations who are not chronically colonised with pseudomonas. A multicentred double blind randomised controlled trial will be the ideal way forward.

Dr A Dwarakanath
Spr-Respiratory Medicine, West Yorkshire Training Programme

e mail akshay.dwarakanath@leedsth.nhs.uk

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RAE GILCHRIST

Might I be allowed to add a few anecdotes to Derek Doyle's excellent profile of Dr Rae Gilchrist (Doyle D. Andrew Rae Gilchrist. *J R Coll Physicians Edinb* 2011; 41:185)?

In 1944 in the summer term of our second year, all 184 students were invited into the Royal Infirmary in order to hear each of the medical 'chiefs' give an introductory lecture to clinical medicine. We entered that sacrosanct ground with the ear pieces of our newly bought stethoscopes sticking out of our jacket pockets to hear 'the giants'. ARG, as he was always called, chose a title of 'Red, White and Blue'. Red for polycythaemia, white for anaemia and blue for cyanosis demonstrating each with patients so afflicted. His theme was observation. I was fascinated and went immediately to the Dean's office to enrol in his clinic during my third year.

I did the same in my final year and became his houseman after qualifying in 1947. His teaching was always thought out and exact. When a fellow student was asked to describe what she thought of a patient's very severely distorted rheumatoid arthritic hands and said 'They are a little stiff, sir', ARG blew up and said 'And so are you'. Looking out of the window, he said 'Is it raining (it was of course) or not? Be precise. It is not a little raining'.

He was a large, formidable man with a high complexion and a demeanour that commanded respect. Apparently with little humour and moody – we never knew if it was to be a good or glum day. Later, I found that he did in fact laugh a lot. We did not know that his home life was sometimes trying.

After two years general practice in Leith, I returned to his ward rounds and finally asked if I might work with him. He appointed me through a Kirk Duncanson Fellowship of the RCPE with a starting salary of £600 a year (£900 in the second year) saying 'I don't want to see you for two months. Go and learn how to use a medical library and learn all you can about coronary heart disease. This is the future for cardiology. Come back and give us all a lecture on it'. My first ever lecture and I was terrified – far worse than the finals, since it was his test of my competence.

He was one of the enthusiasts for and pioneers of the British Heart Foundation and I still have a letter dated March 1959 outlining an exploratory meeting in London. This year is its 50th anniversary. But he did not like going abroad and was more satisfied with fly fishing in Loch Morar.

One morning in 1965, when seeing outpatients with Bobby Marquis and me, he left rather suddenly with several more patients yet to see. He telephoned me saying that he was not feeling well and would I please bring an electrocardiogram. It turned out that he had

had angina for about three days and, like many cardiologists, he tried to prove to himself that he did not have angina by walking fast uphill the day before.

I decided immediately that he should be admitted to our new Coronary Care Unit (opened in 1964). He resisted, of course. So, I plucked up courage and said 'Dr Gilchrist, you are my patient now and you are to do what I say!' The ambulance did not have a defibrillator but, fortunately, we got there without any crisis ('The most uncomfortable journey I have ever had', he said). All went well after morphine and lignocaine. He was a pioneer of anticoagulants and, taking them, he lived without angina, but with exercise claudication, for 30 years. We became firm friends and he was particularly pleased when I was elected PRCPE in 1986, since he had also been President from 1957–60.

Professor Michael Oliver
Professor Emeritus of Cardiology, University of Edinburgh
 e mail michaeloliver@mac.com

I was delighted to read in the latest issue of *The Journal* the tribute to Dr Rae Gilchrist and was honoured to be mentioned among his students who had continued to teach. I first encountered – rather than met – Dr Gilchrist as a student when I went on the ward for the first time. The other 6–8 students in the group and I were invited to follow him into the middle of Ward 25. After we had gathered around him, he swept his arm around, indicating the twelve beds on each side, and said dramatically, 'Gentlemen, you are in the middle of an art gallery. Over here is a man with yellow eyes. Here there is a man sitting high in bed, breathing with difficulty. In a few years you will recognise these appearances as well as you would recognise a Van Gogh or a Rembrandt in an art gallery.'

The 'Big Red Man', as Gilchrist was affectionately known, was a master clinician, relying on a good history, his powers of observation and accurate examination. As the late Hamish Watson said, 'If you were examined by Rae Gilchrist you knew you had been examined.'

In the early 1950s the young men around Gilchrist were a close-knit group. John Tulloch had been my medical officer when I served in 45 RM Commando and John Richmond and I were fellow house officers and became lifelong friends. Bobby Marquis had dropped on D-day as a doctor with the Airborne Division. Michael Oliver was embarking on his distinguished career into the aetiology of coronary disease.

In these days of interventional cardiology and remarkable advances in cardiac surgery it is amazing to realise that every open heart operation in the world has been done since I first started as Dr Gilchrist's house officer and that the stethoscope, the ECG and the X-ray were then, essentially, the only diagnostic tools for adult patients.

But the emphasis on observation, physical examination and good history-taking are still as valuable as when Rae Gilchrist first led that small group of students into the middle of Ward 25.

Professor Bruce Paton
Emeritus Clinical Professor of Surgery, University of Colorado
 e mail cardsurg@comcast.net

A PILOT AUDIT OF A PROTOCOL FOR AMBULATORY INVESTIGATION OF PREDICTED LOW-RISK PATIENTS WITH POSSIBLE PULMONARY EMBOLISM

Congratulations to Drs McDonald and Murphy for their thought-provoking and revealing audit of a protocol for ambulatory investigation of predicted low-risk patients with possible pulmonary embolism (PE) (McDonald AH, Murphy R. A pilot audit of a protocol for ambulatory investigation of predicted low-risk patients with possible pulmonary embolism. *J R Coll Physicians Edinb* 2011; 41:196–201).

The fact that PE was confirmed in 25% of ventilation/perfusion (VQ) scans or computed tomography pulmonary angiograms (CTPAs) in patients despite low predicted risk scores was extremely important. Sadly, PE remains a major cause of death and not just as the 'old man's friend'; it occurs too amongst many otherwise healthy individuals in their prime.¹ In cases of fatal PE, experience with medical negligence claims leads to certain sobering conclusions about the recurring causes of death, including failures of care and lessons which do not seem to have been learned from clinical research. Most of these failures have stemmed from a lack of basic understanding of the pathology of deep vein thrombosis (DVT) and PE, and thus, the avoidable fatalities persist. Common clinical errors include:

- Failure to take a thorough history of thromboembolism risk factors.
- Failure to appreciate that superficial phlebitis is not necessarily a trivial condition. It is accompanied by DVT in around 25% of cases and, especially when there have been recurrent episodes, can be a sign of sinister underlying prothrombotic disorders.^{2–4}
- Failure to appreciate that the protean manifestations of both DVT and PE are such that the absence of 'classical' signs in no way excludes the diagnosis.
- Failure to appreciate that DVT, especially in its early and most dangerous phase, commonly gives rise to no symptoms at all. Research shows that around 80% of individuals dying of PE have no prior symptoms in their legs.^{5–7}
- Failure to appreciate that predictive scoring systems (e.g. Wells) are not infallible and should not be allowed to override clinical judgement.

- Failure to appreciate that duplex ultrasound scanning (as performed in many hospitals) cannot be relied upon to exclude DVT especially when that DVT is in the calf, the pelvic veins or the inferior vena cava.
- Failure to repeat duplex scanning when it is at variance with clinical suspicions.
- Failure to appreciate that around 80% of small PEs do not cause infarction and therefore cause no clinical symptoms, especially in previously healthy lungs.⁵⁻⁷ They can however be detected on CTPA.
- Failure to appreciate that a small PE, if untreated, may herald a big one.⁵⁻⁸
- Failure to commence heparin early, on clinical suspicion, while awaiting investigation (McDonald and Murphy remind us of this vital BTS guideline point⁹).
- Failure to appreciate that guidelines are designed to be advisory, not mandatory, and are not intended to supplant clinical judgement.

Key studies come from the last century when the high post-mortem rates allowed the critical clinic-pathological correlations to be made. Could it be that we have become a little too preoccupied with creating guidelines, protocols and scoring systems without inculcating proper understanding of the underlying disease and without applying clinical judgement to the individual case? The performance of CTPA on the basis of careful history taking, clinical judgement plus D-dimer could save many lives. As there are significant cost implications, it is an important topic, as the authors say, for further research.

Professor Vaughan Ruckley CBE FRCSE FRCPE

e mail vaughan.ruckley@btinternet.com

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Authors' response

We are grateful to Professor Ruckley for his kind comments on our paper. We echo the concerns he expresses regarding failure to identify thromboembolic disease. In our experience this seems to be because doctors do not consider it, in its many guises, when they should. If they do consider it, they do not seem to be aware of the limitations of the investigations they undertake, particularly when these are negative. Professor Ruckley has described many of these limitations very well in his letter. Our guideline was developed to support what is a new way of investigating and managing patients with possible PE in our hospital and mirrors similar pathways in other hospitals. We think it is reasonable to put this in a protocol to help guide staff, maximise patient safety and incorporate best available evidence into what we do. Indeed we have recently updated the risk stratification section with the simplified revised Geneva score and introduced an arm whereby patients with confirmed PE can, under certain conditions, continue to be managed as ambulatory care patients.

We feel that guidelines like this do have a role in helping to get a patient from symptoms to diagnosis but concur with Professor Ruckley that it is vital that they are used in conjunction with sound clinical knowledge and clinical assessment. With the huge growth in the number of guidelines that now exist there is a real risk that patient management could become too didactic with little room for clinical acumen. We vigorously agree that protocols and guidelines should support clinical practice and not dictate it. They should build on the lessons and knowledge from the past rather than replace them.

¹Dr Alex McDonald, ²Dr Ross Murphy

¹ACCS (Acute Medicine) Trainee in Department of Emergency Medicine, Royal Infirmary of Edinburgh, Edinburgh, UK;

²Consultant in Department of Emergency Medicine and Acute Medicine, Royal Infirmary of Edinburgh, Edinburgh, UK