Selected abstracts from Respiratory Medicine Symposium 2010: Dark Clouds or Blue Skies?

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MULTI-DRUG RESISTANT AND EXTENSIVELY DRUG-RESISTANT TUBERCULOSIS

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The rates of active tuberculosis (TB) are increasing in the UK. In 2008, there were approximately 8,600 new cases (about 450 of these were in Scotland). Just over 1% of these had multi-drug resistance (MDR) on susceptibility testing (defined as resistance to at least isoniazid and rifampicin, two of the most effective anti-tuberculosis drugs currently available). Only a handful of cases of extremely drug-resistant (XDR) TB (where the bug has MDR and is also resistant to a quinolone such as levofloxacin and a second-line injectable drug, for example amikacin) have been treated in the UK. So why is TB drug resistance so important?

Globally, the World Health Organization estimates that there are around 500,000 new cases of MDR TB each year. The rates vary from country to country, and are highest in parts of the former Soviet Union (up to 35% of all TB isolates). More than 50 countries have reported XDR TB cases; overall it is thought that approximately 7% of all MDR is actually XDR TB. These forms of TB are much more expensive to treat, a lot less responsive to the second-line drugs required and hence have a far greater associated morbidity and mortality for the affected individual. For example, at least 85% of all drug-sensitive TB is cured. This falls to around 60% in most MDR TB treatment programmes and at best 30% for XDR TB. Throughout this time, the patient may remain infectious to others – leading to an isolated, desperate existence with little chance for optimism in the long term.

Drug resistance arises frequently from poor treatment regimens or patient adherence. In countries where there is a high rate of isoniazid-resistant TB – the most common type of mono-resistance and in the UK found in about 7% of all isolates – initial therapy for all TB cases should be sufficient to cure most mono-resistant disease with minimal risk of treatment failure (which could lead on to MDR TB).

Educating healthcare providers, patients and their carers of the importance of continuing medication for a complete treatment course, as well as methods to promote good adherence, are important. Bacillus Calmette-Guérin (BCG) provides a degree of limited protection; and there are new drugs that will also help to treat MDR and, probably, XDR TB.

However, if the UK is to avoid an inevitable increase in such cases, a rigorous, systematic approach to management needs to be adopted. The creation of a national MDR TB treatment advice service, in 2008, is the first step towards this. It is hoped that early, focused, expert advice will halt any increase in MDR cases that would otherwise be most likely associated with the increasing overall UK rates of active TB disease.

Declaration of interests None declared.

HOSPITAL-ACQUIRED PNEUMONIA

Professor Dilip Nathwani, Consultant Physician and Honorary Professor of Infection, Ninewells Hospital, Dundee

In a national hospital-acquired infection (HAI) prevalence survey of acute hospitals in Scotland (2005–06), the prevalence of pneumonia was 8.8%. The overall prevalence of all HAI was 9.5%. Hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP) and the relatively new entity of healthcare-associated pneumonia (HCAP) represent a considerable disease burden. In the UK data on prevalence and impact for HAP and HCAP are of relatively poor quality compared with VAP.

This presentation aims to provide primarily general and respiratory physicians in the UK with a pragmatic approach to the following key points:

- Definitions, epidemiology and disease burden of HAP, VAP and HCAP;
- Microbiology of the pneumonias and risk assessment of resistant pathogens;
- Clinical algorithm approach to diagnosis and assessment of HAP;
- Antibiotic treatment: choice, specific recommendations for methicillin-resistant *Staphylococcus aureus* treatment, duration of treatment, combination therapy, topical antibiotic therapy.

Recommendations are based on the author's opinion but include a synthesis of personal experience and practice, UK and international guidelines and views of key experts in the area.

Further reading

- Rotstein C, Evans G, Born A et al. Clinical practice guidelines for hospital-acquired pneumonia and ventilator-associated pneumonia in adults. *Can J Infect Dis Med Microbiol* 2008; 19:19–53.
- Masterton RG, Galloway A, French G et al. Guidelines for the management of hospital-acquired pneumonia in the UK: report of

the working party on hospital-acquired pneumonia of the British Society for Antimicrobial Chemotherapy. *J Antimicrob Chemother* 2008; 62:5–34.
- Muscedere J, Dodek P, Keenan S et al. Comprehensive evidence-based clinical practice guidelines for ventilator-associated pneumonia: diagnosis and treatment. *J Crit Care* 2008; 23:138–47.
- Lujan M, Gallego M, Rello J. Healthcare-associated infections. A useful concept? *Curr Opin Crit Care* 2009; 15:419–24.

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MOLECULAR IMAGING IN THE LUNG

Professor Chris Haslett, Professor of Respiratory Medicine, University of Edinburgh

Incisive molecular diagnosis in lung disease and the design and rapid assessment of mechanism-based drugs require the application of new imaging technologies. High-resolution computed tomography and magnetic resonance imaging scans now provide detailed structural information but give little insight into cellular and molecular disease mechanisms. However, positron-emission tomography and the advent of in-vivo confocal microscopy, together with novel probes targeted at specific disease mechanisms, provide exciting new opportunities for the non-invasive diagnosis, monitoring and assessment of therapeutic efficacy in inflammatory/scarring conditions of the lung. The utility of these molecular imaging tools combined with mechanism-targeted, positron-emitting and fluorescent probes will be discussed.

Declaration of interests None declared.

NOVEL MEASUREMENTS OF AIRWAY PHYSIOLOGY

Dr Per Gustafsson, Associate Professor of Paediatrics, Central Hospital, Skövde, and Sahlgrenska Academy at the University of Gothenburg, Sweden

The prominence of the peripheral airways in the pathogenesis of important conditions such as asthma and cystic fibrosis is increasingly recognised. Peripheral airway involvement has been documented not only on pathological specimens but with non-invasive tests such as advanced imaging techniques, inert gas washout and forced oscillation. These findings have improved our understanding of the underlying disease processes. While major advances in the treatment of these conditions have been achieved in recent decades, targeting of treatment to peripheral airway involvement may represent the next major step in improving the morbidity and mortality of these important diseases in both adults and children. The presentation focuses on experiences with inert gas washout in asthma and cystic fibrosis.

Declaration of interests None declared.

STEM CELL RESEARCH: IMPLICATIONS FOR NEW STRATEGIES FOR THE TREATMENT OF ASTHMA

Professor Stephen Holgate, Professor of Immuno-pharmacology, University of Southampton

Asthma is an inflammatory disorder of the conducting airways that has a strong association with allergic sensitisation. The disease is characterised by a polarised T-helper 2 (Th2)-type T-cell response, but in general targeting this component of the disease with selective therapies has been disappointing and most therapy still relies on bronchodilators and corticosteroids rather than treating underlying disease mechanisms. With the disappointing outcomes of targeting individual Th2 cytokines or manipulating T-cells, the time has come to re-evaluate the direction of research in this disease.

A case is made that asthma has its origins in the airways themselves, involving defective structural and functional behaviour of the epithelium in relation to environmental insults. Specifically, a defect in barrier function and an impaired innate immune response to viral infection may provide the substrate upon which allergic sensitisation takes place. Once sensitised, the repeated allergen exposure will lead to disease persistence. These mechanisms could also be used to explain airway wall remodelling and the susceptibility of the asthmatic lung to exacercerbations provoked by respiratory viruses, air pollution episodes and exposure to biologically active allergens. Variable activation of this epithelial-mesenchymal trophic unit could also lead to the emergence of different asthma phenotypes and a more targeted approach to the treatment of these. It also raises the possibility of developing treatments that increase the lung's resistance to the inhaled environment rather than concentrating all efforts on trying to suppress inflammation once it has become established.

Declaration of interests None declared.

NEW STRATEGIES FOR THE TREATMENT OF BRONCHIECTASIS

Dr Diana Bilton, Consultant Physician and Honorary Senior Lecturer, Royal Brompton Hospital, London

Bronchiectasis is a pathological description of thick-walled dilated airways, representing the result of persistent damaging inflammation in response to persistent microbial infection. This disease was thought to be in decline following the introduction of successful antibiotic treatment for tuberculosis and childhood respiratory infections. Recent data, however, suggest that bronchiecta-sis represents a significant cause of respiratory morbidity. As a result, the British Thoracic Society have commissioned new guidelines to improve

the diagnosis and management of this disorder. These will be published during 2010.

The clinical diagnosis is suspected when a patient complains of a persistent cough productive of purulent sputum associated with general malaise. The diagnosis is confirmed by a high resolution computed tomography scan. Once the diagnosis of bronchiectasis is secured, a careful search for underlying causes that may necessitate specific therapy (e.g. immunoglobulins for immune deficiency) is performed.

Following that, a treatment plan is formulated with the aim of improving quality of life, reducing exacerbations and maintaining lung function.

The development of a therapeutic approach is aided by considering the vicious circle hypothesis of disease. The key components are mucociliary clearance, infection and inflammation.

Therapies that target each of these components are being evaluated in bronchiectasis.

Inhaled dry powder mannitol, a hyperosmolar agent, represents a new approach to enhancing mucociliary clearance that may have benefit in improving quality of life and reducing exacerbations.

Antibiotics represent the current mainstay of treatment for bronchiectasis, but evidence for their best use is lacking. The role of inhaled antibiotics, which produce high levels of active drug to the airway and avoid side effects related to systemic absorption, is well established in cystic fibrosis but less so in non-cystic fibrosis bronchiectasis. Recent trials in bronchiectasis, however, have produced promising results in terms of microbial efficacy.

The use of anti-inflammatory medication requires careful evaluation but holds theoretical benefit.

The latest evidence on these new treatment strategies will be presented.

Declaration of interests None declared.