*Internal Medicine Journal* **37** (2007) 432–435

EDITORIAL

# Respiratory infectious disease: complacency with empiricism in the age of molecular science. We can do better!

The recently launched document, 'Burden of Respiratory Infectious Disease in Australia' is a timely reminder of the full impact of respiratory infection on the health of Australians, both as multiple specific disease entities that are significant in their own right and as an important complicating factor that cuts across all areas of respiratory health.[1] The document outlines the dramatic mismatch between the enormity of total disease burden and the relative paucity of effective management strategies. In the first instance this mismatch may seem surprising, but on further reflection, this should not be the case.

## A few home truths

(i) Viral infections are an important cause of respiratory infection and yet a specific diagnosis is rarely made, (ii) few antiviral therapies exist and when they do – such as in the case of influenza – they are either underused or overused because of diagnostic inefficiencies, (iii) our approach to using antibacterial agents is guided by 'what should reasonably be covered' or 'what organisms are being missed' rather than a treatment regimen targeted for a particular organism, (iv) in association with diagnostic uncertainty, we do not make sufficient allowances for immunocompromised states or overexuberant immune responses to respiratory infectious disease (RID) and (v) current antibiotic guidelines encourage an approach of increasingly covering all potential organisms depending on the severity of illness. These issues lead to increased direct costs both to the individual (unnecessary exposure to side-effects) and the community (exposure to antibiotic selection pressure and future antibiotic resistance, financial cost) and indirect costs in that other potentially useful treatment approaches are not considered (e.g. anti-inflammatory and immune-modifying drugs).

Development of antibiotic guidelines for RID has progressively taken these home truths into consideration. Such guidelines recommend minimizing antibiotic use when the primary pathogen is likely to be a virus and maximizing antibiotic use when there is a high probability of significant bacterial infection.[2–5] Individual risk stratification, according to patient comorbidities and illness severity is used to varying degrees in all guidelines. Physicians managing patients with RID are encouraged to do the best for both the individual and society where antibiotic usage is concerned. It is suggested that continuing these approaches, while incorporating new value adding information, will ensure the development of future significant improvements in both our knowledge and management of all forms of RID. In addition, such a strategy may have the added benefit of prioritizing ongoing antimicrobial drug development and even streamlining regulatory drug approvals.

## Acute respiratory infection

Despite the many different syndromes and aetiological agents covered, the 'Burden of Respiratory Infectious Disease in Australia' document presents an overwhelming theme of diagnostic inefficiency in spite of advances in molecular technology.[1] As an example, numerous studies have shown that a specific microbial diagnosis is routinely made in very few cases of patients hospitalized with community-acquired pneumonia. Although this number approaches 50% with detailed microbiological and molecular testing in some studies, a microbial diagnosis eludes us in approximately half of all patients.[6] Whether this is because 'uncommon' organisms have not been tested for, or 'common' organisms have been missed because of an overexuberant host response is not known. Diagnostic inefficiency not only leads to a heavy reliance on empirical treatment strategies, but also contributes to lack of knowledge. Diagnostic inefficiency handicaps innovative thinking regarding the management of acute RID, particularly in those who are severely ill and not responding to empirical antimicrobial therapy.

Our current reliance on empirical antibiotic strategies to cover 'likely bacterial pathogens' as set out in numerous guidelines is unavoidable in the short term given the current diagnostic limitations for respiratory infection syndromes. In the long term, however, there is a need to move away from an almost absolute requirement for empirical antibiotics in RID and move towards targeted antibiotic strategies as is the case for most other organ-based infections.[5] To achieve this, there needs to be considerable improvement in the development of diagnostic

tools for RID. These tools need to be rapid, reliable and available at the point of care. This is not impossible as has >been shown by the development of rapid HIV/CD4 diagnostic tests to help stratify limited antiretroviral use in developing countries.[7,8] Improvements in the sensitivity and specificity of diagnostic assays for specific respiratory pathogens are also required. Improved sensitivity would enhance our ability to avoid using antibacterials in viral infections. Improved specificity would enhance our ability to use specific antibiotics and/or antivirals in the first instance and to use them to their maximum potential according to pharmacodynamic principles. Although the recent developments of multiplex polymerase chain reaction assays for viral and atypical bacterial organisms and enzyme-linked immunosorbent assays for some bacterial antigens (e.g. *Legionella, Streptococcus pneumoniae*) are promising, this area requires considerably more basic and applied research.

Even if the logistic issues associated with obtaining a test sample and immediate test results mean that empirical antibiotics continue to be used at least initially in RID, improved diagnostic tests can possibly allow for treatment to be subsequently tailored. There would also be a longer-term benefit as epidemiological data on local respiratory infections could enhance decision-making regarding empirical antibiotic use. Another potential spin-off from enhanced data collection would be a better understanding of the pathogenetic mechanisms associated with specific virus or bacterial infections. This information may also positively influence the development of the antimicrobial pipeline of pharmaceutical companies.

## At-risk groups

All the issues related to acute respiratory infections in otherwise-healthy individuals apply to an even greater degree to 'at-risk' groups. These persons have either an underlying lung disease (e.g. asthma, chronic obstructive pulmonary disease (COPD) or immune impairment (e.g. being elderly and having immunodeficiency syndromes). Compared with the rest of the population, the 'at-risk' population is susceptible to a wider range of infections and more severe disease from any given infecting organism. There is often a greater imperative to make a specific diagnosis in these patients as the risk–benefit ratio of an ongoing reliance on empirical antibiotic strategies is usually not acceptable.

Improvements in the sensitivity and specificity of diagnostic assays for RID have been shown to offer dramatic benefits to the clinical management of 'at risk' patients. As an example, the management of HIV/AIDS and its associated opportunistic infections has been revolutionized over the last 15 years by an approach that combines quantitative viral load and CD4 testing and effective antiretroviral therapy.[9] Similarly, lung and other organ transplantation has now become commonplace in western countries and one of the commonest infections post-transplantation used to be cytomegalovirus (CMV) pneumonitis due to reactivation of this ubiquitous DNA virus. Twenty years ago, transplant physicians relied on poorly sensitive histopathological and non-specific viral culture diagnostics for CMV disease and relatively blunt treatment approaches using antiviral treatments. The whole field was transformed when sensitive molecular testing was routinely applied and combined with more focused antiviral strategies yielding both better results and a richness of information regarding pathobiological events.[10] First, subclinical CMV reactivation was identified as being very common in the lung allograft and hence, a period of universal prophylaxis was appropriate for all CMV 'at-risk recipients' (>90% lung transplant recipients). Second, an understanding of the dynamics of CMV reactivation following cessation of antivirals had immediate direct benefits to the patient (i.e. quantitative CMV detection to determine the need for specific antiviral use) and indirect benefits (subtle reactivation syndromes could now be related to specific immunological profiles and long-term lung allograft outcomes). Third, the efficacy of specific intervention strategies could now be easily monitored. This conceptual framework is now being extended to other reactivating DNA viruses post-transplantation and in the case of lung transplants is being increasingly used to delineate the overall influence of community respiratory RNA viruses on the lung allograft with a view to developing novel antiviral intervention strategies. In the setting of lung transplantation, the potentially direct and indirect (i.e. allograft rejection) life-threatening consequences of respiratory infection are an important drive for innovation in management.[11]

These concepts relating to the specific example of lung transplantation can be extended to more general respiratory conditions. In addition to diagnostic improvements, the management of at-risk patients could be enhanced by obtaining disease-susceptibility information in well-defined 'at-risk' populations (e.g. cystic fibrosis, allergic bronchopulmonary aspergillosis, bronchiectasis, tuberculosis and even immunosuppression treatment profiles). This information could aid decision-making in terms of whether to use prophylactic or pre-emptive antibiotics to avoid specific acute infection syndromes in certain 'at-risk' patient groups, a strategy already used in HIV/AIDS. This information could also provide insights into host–pathogen interactions in acute conditions, such as pneumonia as well as asthma and COPD, where acute exacerbations and chronic progression are an important burden of respiratory disease. This research could also provide a greater

understanding of the heterogeneity of host–pathogen interactions, thereby better explaining why patients vary in their susceptibility to RID and why the clinical expression of disease differs so much between patients.

## Public health and emerging viral infections

Interpandemic influenza is a yearly public health concern and continues to be associated with significant morbidity and mortality despite the benefits that have come from an active influenza surveillance network, national influenza vaccination strategies and the availability of antivirals against influenza. One can only imagine the potential nightmare scenarios that may result from a new influenza pandemic (e.g. H5N1 'Avian' influenza), particularly if the emergent virus achieves human-to-human transmission while retaining a high degree of pathogenicity. So there is a great deal of government investment in 'Pandemic Flu Preparation Plans' around the world. These protocols are invariably built around an appropriately staged plan of action concentrating on surveillance, containment and antiviral strategies in the early phases of any epidemic outbreak to buy as much time as possible for appropriate vaccines to be developed and distributed. More subtly, there is also a great deal of research and development aimed at developing novel antiviral interventions and optimizing vaccine efficacy and production.

Clearly, when there is an ever-present threat to the nation's future health, every effort is made to eliminate as much diagnostic and management uncertainty as possible. The risks posed by the outbreak of severe acute respiratory syndrome (SARS) in 2003 were responsible for marshalling all the newly available technologies at the time to successfully isolate, identify and sequence the new strain of *Coronavirus* that was responsible in record time.[12] All this was achieved with a view to fast track the development of effective antiviral and other treatments for SARS. Finally, the potential threat of bioterrorism has also led to government-sponsored dramatic alignment of molecular science and new technologies to provide rapid diagnostic testing for 'suspicious' samples.[13]

In conclusion, in our day-to-day management of RID problems, we can learn much from our approach to infectious disease complications in 'at-risk' individuals and to emerging viral threats. In the former case, we seem to have become complacent with an empirical treatment approach that is compounded by lack of knowledge and a relatively blunt approach to matching specific conditions to specific treatments. The latter cases, however, indicate that we currently can obtain and use value-adding information so that we can begin to do better; all that is required is a sense of vision and a prioritization to do so.

Identification of RID as an important health priority will simultaneously raise the awareness of the unmet clinical need posed by respiratory infection across many areas of medicine and offer a clear path forward to focus efficiently and coordinate future clinical science research and health policy initiatives directed at reducing the current and future burden of RID. Investing today in reducing this burden will pay future dividends many times over for us all – irrespective of whether we become ill or not.

Received 16 April 2007; accepted 17 April 2007.

doi:10.1111/j.1445-5994.2007.01424.x

T. Kotsimbos[1]
J. McCormack[2]
[1]Department of Allergy, Immunology and Respiratory Medicine Alfred Hospital and Monash University, Melbourne, Victoria and [2]Infectious Diseases Service, Mater Hospital and University of Queensland, Brisbane, Queensland, Australia

## References

1 Respiratory Infectious Disease Consultative Group. *Respiratory Infectious Disease Burden in Australia 1st edn*. 2007 Mar. Available from URL: www.lungnet.com.au
2 Niederman MS, Mandell LA, Anzueto A, Bass JB, Broughton WA, Campbell GD *et al*. Guidelines for the management of adults with community acquired pneumonia:diagnosis, assessment of severity, antimicrobial therapy, and prevention. *Am J Respir Crit Care Med* 2001; **163**: 1730–54.
3 Bartlett JG, Dowell SF, Mandell LA, File Jr TM, Musher DM, Fine MJ. Practice guidelines for the management of community acquired pneumonia in adults. Infectious Disease Society of America. *Clin Inf Dis* 2000; **31**: 347–82.
4 Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC *et al*. ATS/IDSA CAP guidelines for adults. *Clin Inf Dis* 2007; **44** Suppl. 2: S27–S72.
5 *Therapeutic Guidelines: Antibiotic*. Version 12. Melbourne: Therapeutic Guidelines Ltd; 2003. www.tg.com.au
6 Diaz A, Barria P, Niederman M, Restrepo MI, Dreyse J, Fuentes G *et al*. Etiology of community-acquired pneumonia in hospitalized patients in Chile: the increasing prevalence of respiratory viruses among classic pathogens. *Chest* 2007; **131**: 779–87.
7 Fiscus SA, Cheng B, Crowe SM, Demeter L, Jennings C, Miller V *et al*. HIV-1 viral load assays for resource limited settings. *PLoS Med* 2006; **3**: e417.
8 Balakrishnan P, Solomon S, Mohanakrishnan J, Cecelia AJ, Kumarasamy N, Murugavel KG *et al*. A reliable and inexpensive EasyCD4 assay for monitoring HIV-infected individuals in resource-limited settings. *J Acquir Immune Defic Syndr* 2006; **43**: 23–6.
9 Nelson R. AIDS treatment enters its 25th year. *Lancet Infect Dis* 2006; **6**: 466–7.

10 Westall G, Michaelides A, Williams T, Snell G, Kotsimbos T. HCMV DNA load in plasma and bronchoalveolar lavage fluid: a longitidinal study of lung transplant recipients. *J Infect Dis* 2004; **190**: 1076–83.
11 Westall G, Kotsimbos T. Cytomegaloviral infection & other infections related to lung allograft survival. *Curr Opin Organ Transpl* 2004; **9**: 342–9.
12 Peiris JS, Guan Y, Yuen KY. Severe acute respiratory syndrome. *Nat Med* 2004; **10**(12 Suppl.): S88–S97.
13 Lim DV, Simpson JM, Kearns EA, Kramer MF. Current and developing technologies for monitoring agents of bioterrorism and biowarfare. *Clin Microbiol Rev* 2005; **18**: 583–607.