The expanding role of common respiratory viruses in human disease

In 1982, Meyers and colleagues published a retrospective review of the causes of non-bacterial and non-fungal pneumonia among 525 recipients of allogeneic bone marrow transplantation (BMT) (Meyers et al., 1982). Cytomegalovirus (CMV) accounted for 47 % of cases. A few cases were due to other herpesviruses or adenoviruses, but as many as 35 % had no identifiable pathogens. Growing evidence suggests that a large proportion of those idiopathic pneumonias were due to common or community-acquired respiratory viruses such as respiratory syncytial virus (RSV), influenza and parainfluenza viruses (PIV). There is good epidemiological evidence implicating these viruses as a cause of potentially fatal pneumonia after BMT. Pneumonia-complicating RSV infection is almost exclusively viral in origin, whereas influenza virus may cause both a primary viral and a secondary bacterial or fungal pneumonia. More limited data indicate that rhinoviruses, enteroviruses and possibly coronaviruses can also cause fatal pneumonia in BMT recipients. The list is likely to grow. In 2001, human metapneumovirus, a new member of the family Paramyxoviridae, was identified in young children with an infection resembling RSV and ranging from mild upper respiratory tract (URT) disease to severe bronchiolitis and pneumonia (van den Hoogen et al., 2001). It is feared that human metapneumovirus will soon emerge as an important pathogen in immunocompromised patients.

Surveillance studies have demonstrated that infections with respiratory viruses occur commonly in immunocompromised hosts. The infections are acquired in the community, but also in hospital, where respiratory viruses are spread by other patients, as well as visitors and healthcare workers, who often have only modest symptoms. Nosocomial infections tend to mirror the temporal occurrence of respiratory viruses in the community. Winter and spring, when RSV and influenza virus circulate, are recognized as high-risk seasons. However, infections occur in summer and autumn with viruses such as PIV, enteroviruses and rhinoviruses, and nosocomial RSV outbreaks are not uncommon outside the usual season. Current evidence indicates that, among immunocompromised patients, BMT recipients carry the highest risk of pneumonia and mortality following infection with a respiratory virus. Now that CMV disease has a relatively low prevalence due to prophylaxis and pre-emptive therapy, the potentially severe impact of these infections after BMT has become obvious. Leukaemic patients who receive heavily myelosuppressive chemotherapy may also be at risk of severe disease (Couch et al., 1997). There exist limited data on the impact of respiratory viruses after solid organ transplantation. A few case reports and retrospective studies suggest that disease may be severe after lung transplantation and a significant association has been detected between viral respiratory infections and obliterative bronchiolitis (Billings et al., 2001). Intriguing data also suggest an association with graft rejection after renal transplantation (Miller & Chavers, 1996). The significance of viral respiratory infections in human immunodeficiency virus-seropositive persons remains unclear.

In a surveillance study of BMT recipients conducted at the Fred Hutchinson Cancer Research Center in Seattle, WA, USA, between 1990 and 1996, infections with RSV, PIV, influenza virus or rhinoviruses occurred at a rate of 4.5 % per year (Bowden, 1997). Between 1992 and 1995, a surveillance programme of hospitalized adult BMT and leukaemia patients at the M.D. Anderson Cancer Center in Houston, TX, USA, found a respiratory virus in 27 % of 668 episodes of URT disease (Couch et al., 1997). European BMT centres with active surveillance programmes have detected similarly high rates of infection. In a surveillance study of patients undergoing BMT or chemotherapy for leukaemia or lymphoma at the Royal Free Hospital in London, UK, 44 % of 41 patients acquired a respiratory virus between October and April 1999 (A. M. Geretti, unpublished observation).

Risk factors for progression to pneumonia and mortality among BMT recipients infected with respiratory viruses are being identified. The highest impact is observed with RSV. In the study from the M. D. Anderson Cancer Center, pneumonia occurred in 20 of 33 (61 %) patients with RSV with a pneumonia-associated mortality of 60 %. In the same study, pneumonia occurred in 14 of 20 (70 %) patients with influenza virus and 26 of 45 (58 %) patients with PIV. The pneumonia-associated mortality rates were respectively 36 and 38 % (Couch et al., 1997). High mortality rates have also been observed with rhinoviruses. In one series of 22 patients with rhinovirus infection, 7 (32 %) developed pneumonia and all died (Ghosh et al., 1999).

Allogeneic BMT recipients have a greater risk of developing pneumonia than autologous recipients. Nonetheless, caution is required because, once pneumonia occurs, mortality rates may be high in both groups and well-defined criteria to predict those patients who will be severely affected are not available at present. In the case of RSV, a high risk of pneumonia and death has been observed during the pre-engraftment phase after BMT. However, patients who develop pneumonia in the post-engraftment phase may remain at risk of mortality. Additional risk factors include HLA-mismatch (Lujan-Zilbermann et al., 2001), graft versus host disease, immunosuppressive therapy and T-cell depletion.

In patients with pneumonia, available treatment strategies appear to have virtually no impact on the risk of mortality after the onset of respiratory failure. However, with the exception of adenoviruses, pneumonia due to the respiratory viruses is preceded by the development of URT disease in over 85 % of patients (Whimbey et al., 1997). This opens a window of opportunity for active clinical and virological surveillance.
to identify infected patients in the early stages of the infection and offer them pre-emptive therapy to prevent pneumonia, in a strategy similar to that adopted in CMV surveillance. Treatment options include the use of amantadine against influenza virus A, the neuraminidase inhibitors (zanamivir and oseltamivir) against influenza viruses A and B and ribavirin against RSV and PIV. Co-administration of immunoglobulins, either as normal human immunoglobulin or preparations containing high titres of RSV-specific antibodies, is commonly recommended. Experimental options include the monoclonal antibody Palivizumab against RSV and pleconaril against the rhinoviruses and enteroviruses. Palivizumab or antivirals such as zanamivir and oseltamivir may also be used for the prophylaxis of RSV or influenza virus infection in high-risk patients.

Unlike CMV, however, prophylactic and pre-emptive treatment protocols have not been clearly defined for the respiratory viruses and no randomized, placebo-controlled studies have been conducted in BMT recipients or can be anticipated. In a recent retrospective review from the Memorial Sloan-Kettering Cancer Center in New York, a 5 % mortality rate was observed among 55 BMT recipients infected with RSV who were treated aggressively with aerosol ribavirin and/or intravenous RSV-specific antibodies (Small et al., 2002). This mortality rate compares favourably with historical controls and provides at least circumstantial evidence in favour of an active diagnostic and treatment approach to RSV infections in BMT recipients. In contrast, less encouraging data on the benefit of antiviral therapy with or without intravenous normal human immunoglobulin have emerged from a retrospective review of 222 BMT recipients infected with PIV-3 (Nicholls et al., 2001). While data that have emerged over the last decade have highlighted the severe impact of respiratory viruses in BMT recipients, prospective studies are clearly now needed to optimize pre-emptive and, where appropriate, prophylactic treatment strategies.

It is not surprising that the impact of common respiratory viruses is being redefined in immunocompromised patients, as their significance is also beginning to be understood in immunocompetent hosts. Traditionally, viruses such as RSV or influenza virus have been associated with significant disease at the opposite ends of life, with RSV causing bronchiolitis and pneumonia in young children and influenza virus causing peaks of excess mortality in the elderly. More recently, it has been recognized that influenza virus is a significant pathogen in young children and, conversely, that RSV causes peaks of mortality in the elderly that may be equal to or even greater than those associated with influenza virus (Fleming & Cross, 1993). A clear association has also emerged between infection with respiratory viruses and exacerbations of underlying disease including asthma and chronic obstructive pulmonary disease.

Even healthy young adults appear to be more vulnerable to the respiratory viruses than previously recognized. In a recent study by Zambon et al. (2001), PCR testing of over 2000 nasopharyngeal swabs from adults presenting to primary-care physicians with influenza-like illness demonstrated that 30 % were infected with influenza virus and 20 % with RSV. This is consistent with a previous study of nearly 1200 adults hospitalized with community-acquired pneumonia, which identified Streptococcus pneumoniae in 62 %, influenza virus in 5-4 % and RSV in 4-4 %. Among 57 patients with RSV pneumonia, 32 % were aged <65 years and 14 % were otherwise healthy adults below 40 years of age (Dowell et al., 1996). In the study by Zambon et al. (2001), as many as 50 % of adults with influenza-like illness remained undiagnosed. Recent data suggest that a proportion was infected with the human metapneumovirus, which, like influenza virus and RSV, appears to circulate predominantly during winter and spring. In a study of 71 patients with respiratory disease in Canada, 11 (15 %) were infected with the newly discovered virus and flu-like illness occurred in approximately 50 % of cases (Chan et al., 2002). Growing evidence also implicates rhinoviruses as a cause of flu-like illness in otherwise healthy adults.

Yet, respiratory viruses remain an under-recognized cause of disease in adults. Lack of an appropriate diagnostic approach is one major obstacle to a full appreciation of their role. Current diagnostic methods rely on the collection of nasopharyngeal secretions that, if received, in skilled hands, are diagnostic in immunocompetent hosts. However, serological assays such as complement-fixation tests continue to be used in many settings. These tests yield little useful information and, at best, only provide a retrospective diagnosis, which seems hardly satisfactory in the era of rapid virological assays that help guide patients’ management. In addition, serological assays can be seriously misleading in immunocompromised hosts. Provided a good nasopharyngeal specimen is received, in skilled hands, immunofluorescence tests can detect RSV, influenza virus, PIV and adenoviruses within a few hours with high sensitivity and specificity. Detection of rhinoviruses and enteroviruses, however, relies on culture-based methods that display suboptimal sensitivity, whereas coronaviruses and human metapneumovirus escape detection by routine methods. This emphasizes important limitations of current diagnostic methods. There is a clear need for molecular assays to increase the sensitivity of detection of viral respiratory infections. Although molecular diagnostic of respiratory viruses is being implemented in surveillance and research settings (Zambon et al., 2001), its introduction in routine diagnostic laboratories is occurring at a very slow pace. A perception that respiratory viruses other than influenza virus do not play an important role in adult respiratory disease and the reluctance of physicians to collect respiratory specimens from adults remain important obstacles to the widespread adoption of improved diagnostic methods for these common infections.

Anna Maria Geretti
Department of Infection and South London Public Health Laboratory, King's College Hospital, Guy's, King's and St Thomas' School of Medicine, East Dulwich Grove, London SE22 8QF, UK

Correspondence: Anna Maria Geretti (AnnaMaria.Geretti@kingsch.nhs.uk)


Couch, R. B., Englund, J. A. & Whimbley, E. (1997). Respiratory viral infections in...


