Respiratory Syncytial Virus in Hematopoietic Cell Transplant Recipients: Factors Determining Progression to Lower Respiratory Tract Disease

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(See the major article by Kim et al on pages 1195–204.)

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Respiratory syncytial virus (RSV) is an important pathogen in infants and young children but is also important in the elderly and in individuals with chronic obstructive pulmonary disease (COPD). It was recognized 25 years ago that RSV can cause severe disease in immunocompromised patients, especially those having undergone allogeneic hematopoietic stem cell transplantation (HSCT) [1–3]. The early publications on this subject reported a very high mortality during lower respiratory tract disease. It has also been shown that RSV is an important nosocomial pathogen; therefore, infection control measures are very important in HSCT units. Over the last 2 decades, several studies on risk factors and outcome of HSCT have been published, and the article by Kim et al [4] in this issue of the Journal of Infectious Diseases adds important new information on the topic.

Kim et al [4] included both allogeneic and autologous HSCT recipients, and there was no difference in the risk of progression to lower respiratory tract disease. Other articles have suggested that autologous HSCT recipients have lower risk for poor outcome [5–7]. However, a recent publication shows no difference in the risk for lower respiratory tract disease or mortality [8]. These different results might have to do with different treatments given before autologous HSCT, such as the use of monoclonal antibodies, or the increasing age of patients undergoing autologous transplants in recent years, although in the study by Kim et al, age was not a risk factor for lower respiratory tract disease.

Other risk factors for lower respiratory tract disease found in the study by Kim et al [4] were being a smoker, having received total body irradiation, and severe lymphocytopenia, $<0.1 \times 10^9/L$ at the time of RSV infection. Lymphocytopenia has also been identified as a risk factor for outcome of RSV infection in previous studies [6, 9], as has contracting an RSV infection before stem cell engraftment. An important finding by Kim et al is that there was a gradual risk increase for lower respiratory tract disease as the lymphocyte count at diagnosis of RSV infection decreased. Furthermore, an absolute lymphocyte count of $>1.0 \times 10^9/L$ was completely protective against progression to lower respiratory tract disease. This finding allows risk stratification and thereby helps in patient management and in recruiting patients for future studies.

The negative effect of smoking is interesting, because it has not previously been documented in immunocompromised individuals. This finding fits, however, with knowledge obtained in other contexts. It is well known that RSV disease severity is increased in infants exposed to smoking in the household. It has also been shown in vitro that the inhibitory antiviral effect of interferon-γ against RSV messenger RNA (mRNA), and protein expression is decreased by cigarette smoke [10].

The major controversy in management of RSV infection remains the effects of therapy with ribavirin or immune globulin. There has been no controlled clinical study of sufficient size to allow conclusions regarding efficacy. There have been several reports, mostly retrospective, on ribavirin therapy for RSV infection [6–8, 12–16]. The only existing controlled trial of aerosolized ribavirin in HSCT recipients was only able to recruit 14 patients [11]. In this study, there was a trend for lower viral loads in the ribavirin treated patients but no differences in outcome. Assessment of the impact of ribavirin
becomes even more difficult because the treatment modalities differ, with aerosolized ribavirin used more commonly in the United States, whereas systemic ribavirin has been more commonly used in Europe. However, a recent large study of 280 patients with upper respiratory tract infections showed that use of aerosolized ribavirin was the most important factor for reducing the risk for RSV lower respiratory tract disease, RSV associated mortality, and all-cause mortality [16]. The use of ribavirin in HSCT recipients is also supported by a systematic review showing a reduction in the risk for lower respiratory tract disease when treatment is given at the upper respiratory virus stage and an improvement in outcome of RSV pneumonia by ribavirin therapy [17].

Another interesting question addressed by Kim et al [4] is the effect of specific humoral immunity on RSV outcomes; the authors were unable to find a protective effect by analyzing the levels of neutralizing antibodies or by weekly immune globulin therapy. The usefulness of immune globulin or pavilizumab added to ribavirin, either in the prevention or as therapy for lower respiratory tract disease in HSCT recipients, is also controversial. Controlled studies are also lacking on this topic. A systematic review suggested, however, an effect of immune globulin administration, especially when treating established lower respiratory tract disease [16].

Despite 2 decades of studies, we still need to better define optimal strategies of RSV infection management in severely immunocompromised patients. New antiviral agents are also needed because ribavirin, regardless of the route of administration, has several important limitations regarding efficacy and toxicity.

**References**