



**Karolinska  
Institutet**

**Institutionen för Laboratoriemedicin**

# Pulmonary complications after allogeneic hematopoietic stem cell transplantation

**AKADEMISK AVHANDLING**

som för avläggande av medicine doktorsexamen vid Karolinska  
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## ABSTRACT

The respiratory tract is one of the most common and serious sites for complications in HSCT patients. In this project the incidence, outcome, and risk factors for patients with infectious or non-infectious pulmonary complications were studied. Bronchoscopy and pulmonary function tests (PFTs) were evaluated as diagnostic tools.

Between 1975 and 2003, pneumonia was found to be the most common cause of early death (within 100 days) after HSCT. The cumulative incidence was 5.6% compared to 10% for all other causes. However, this three-decade study exhibited a striking change over time: the cumulative incidence of early death due to pneumonia decreased from 8.9% in the first decade studied to 2.8% in the third decade. In the fourth study (2000-2009) this incidence was 3.2%. However, death from overall pneumonia (early and late pneumonia) was 10.5%, indicating that pneumonia is still a common cause of death. Bronchoalveolar lavage (BAL) was shown to be a safe and useful diagnostic tool to establish the causative pathogens of pneumonia: this procedure contributed to the diagnosis in 43 of 68 (63%) episodes of pneumonia in the second study (1998-2004). BAL was especially important for establishing pneumonia due to Aspergillus and Cytomegalovirus. Comparing the results of other culture specimens, these pathogens would not have been found pre-mortem without this procedure. In 42 (62%) cases of pneumonia, the treatment was either changed or continued according to the BAL results. PFTs are also important diagnostic tools. We considered FEV1 as the most important parameter for detection and monitoring the development of BO, a progressive and persistent non-infectious complication characterized by airflow obstruction. Furthermore FEF75 was reduced in 28% patients with BO and thus may serve as an early warning. Patients who developed BO late (> 1 year after HSCT) had a better five-year survival than those with an early onset BO.

Statistical analyses revealed that risk factors for early pneumonia death also changed over time. Receiving a T-cell depleted (TcD) graft was identified as a risk factor in the first study ( $p<0.001$ ). However, this immunosuppressive strategy was abandoned in the early 1990s, due to reports of increased risk of relapse, graft rejection, and infections. During the last decade, other strategies have been increasingly used, to either facilitate engraftment, suppress the recipient's own immune system, prevent relapse, graft failure or Graft-versus-host disease (GVHD) while maintaining, if possible, the graft-versus-leukemia (GVL) effect. Such strategies include reduced intensity conditioning (RIC), treatment with donor lymphocyte infusion (DLI), and treatment with mesenchymal stem cells (MSCs). RIC was shown to reduce significantly the cumulative incidence of early death from pneumonia compared to myeloablative conditioning (MAC) (2.1% and 4.2%, respectively) and DLI treatment to have a potentially protective role for BO. However, MSC treatment was associated with overall pneumonia death.

In conclusion, early death due to pneumonia has decreased in the past decades. We believe that new diagnostic and prophylactic strategies and treatments as well as supportive care have been of utmost importance for this improved outcome. For BO patients, DLI seemed to have a protective role. However, because some of the new strategies, such as MSCs may also increase the risk of pneumonia, they should be used with caution. Diagnostic tools such as bronchoscopy and PFTs help determine the etiology of pneumonia (BAL) and detect and monitor BO (PFT) at an early stage. Therefore, these tools should be used as early and correctly as possible.