Infections after Heart Transplantation

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A main goal in the follow-up of patients after heart-transplantation (HTX) is the prevention and effective treatment of infections, one of the most common life threatening complications of long-term immunosuppressive therapy [1] (Figure 1). After solid organ transplantation a certain pattern of infections can be observed [1] (Figure 2). This helps developing a differential diagnosis in transplant recipients who present with infectious diseases and establishing effective preventive strategies. However, infections after heart transplantation should not only be recognized as an isolated problem. Especially regarding the impact on long term outcome negative effects of infections on the immune status of the recipient and the development of malignancies or cardiac transplant vasculopathy (TVP) have to be considered as well.

Key words: heart transplantation, infections

Epstein-Barr Virus

Although a mononucleosis-like syndrome similar to that produced by cytomegalovirus (CMV) has been identified in some patients, the critical effect of Epstein-Barr virus (EBV) on long term outcome after transplantation is its role in the pathogenesis of post-transplantation lymphoproliferative disease (PTLD). Especially patients after heart and lung, lung, and heart transplantation are at risk [2]. Immunosuppression causes the pathogenesis of post-transplantation lymphoproliferative disease by reactivation of latent EBV infection and, most likely, the loss of immune surveillance against EBV-immortalized B cells [1]. Elevated EBV-DNA levels have been shown to correlate with the degree of immunosuppression and are linked to the development of PTLD in children after HTX [3,4]. In adult patients, an association of EBV-DNA load with qualitative and quantitative immunosuppression was demonstrated as well [5]. In stable adult heart transplant recipients, the incidence of a positive EBV-DNA PCR was significantly higher in patients on Azathioprin or a calcineurin inhibitor and not on MMF medication [5].

Cytomegalovirus

One of the most important pathogens affecting the long-term outcome of transplant recipients is CMV. Serologic tests aid in defining the clinical risk from CMV at the time of transplantation, as seronegative recipients with seropositive donor organs are at greatest risk [6]. Depending on the extent of infection latent infection, active infection, CMV syndrome, and CMV disease can be distinguished. Once infected the patient harbors the virus for life. Activation from latency is induced by many
of the factors present in transplant recipients: therapy with antilymphocyte antibodies and cytotoxic drugs, allogeneic reactions, and systemic infection and inflammation [1]. After activation, a variety of symptoms can be observed ranging from viral syndromes with flu-like and mononucleosis like symptoms and organ manifestations, to allograft injury and allograft rejection, involvement in development of transplant vasculopathy (TVP) [7], reactivation of other viruses (e.g. EBV) and facilitation of opportunistic infections.

Two approaches regarding the prevention of CMV infection can be distinguished: preemptive therapy, with therapy being initiated after diagnosis of infection and prophylaxis which includes a mandatory application of virostatics early after transplantation for all patients. Currently published meta-analyses demonstrate that prophylaxis and preemptive therapy with ganciclovir are comparable [8,9], latest data in patients after renal transplantation favour CMV prophylaxis regarding the improved graft survival [10]. Due to the proven comparable bioavailability of intravenous ganciclovir and orally administered valganciclovir the prophylactic therapy with oral valganciclovir after HTX in a time dependent prophylactic regimen appears warranted [11], with adaptations in case of renal insufficiency or development of leukopenia. Further proof for the efficacy of CMV prophylaxis comes with the RAD001A2411 study where in R+/D+ patients without CMV-prophylaxis the rate of CMV infections was significantly higher in patients on Mycophenolate mofetil (13/21 patients 61.9%) compared to patients on Everolimus (1/19 patients, 5.3%). In patients on CMV prophylaxis this statistically significant difference was lost. Current own studies (submitted) regarding the
duration of CMV prophylaxis indicate that prophylaxis with oral Valganciclovir for 6 months is sufficient. After routine discontinuation of CMV-prophylaxis no significant rate of breakthrough infections was observed. However, when Valganciclovir has to be paused prematurely, e.g. due to leukopenia, close monitoring of CMV viral load appears warranted.

Toxoplasma gondii

Also other pathogens, less commonly associated with an adverse prognosis limit long term outcome after transplantation. For patients with a positive pretransplant toxoplasma serostatus an increased cardiac and all-cause mortality post HTX has been described [12]. Yet data regarding implications of toxoplasma serostatus are not unambiguous as a multivariate analysis including cardiac diagnosis, diabetes, recipient/donor age and gender identified a positive pre-operative toxoplasma serostatus as an independent predictor for a superior survival post HTX [13]. Infections after heart transplantation should not only be recognised as an isolated problem. Especially regarding the impact on long term outcome negative effects of infections on the immune status of the recipient and the development of malignancies or TVP have to be considered as well.

References