Applied Cardiopulmonary Pathophysiology 15: 245-255, 2011

Early postoperative therapy after heart transplantation: Prophylaxis, diagnosis and antibiotic, antimycotic and antiviral therapy of infections

Manfred Hummel

Paulinenkrankenhaus, Berlin, Germany

Abstract

Aside from early graft failure, infections are the second leading cause of death after heart transplantation (HTx). Therefore, prophylaxis, diagnosis and adequate therapy of infections are fundamental for the short and long-term success of heart transplantation. Because immunosuppressive drug therapy is a prerequisite for transplantation, the range of infection is much larger than after other kinds of major thoracic operation. For prophylaxis, diagnosis and therapy, bacterial, viral, fungal and protozoal infections have to be taken into account, also as part of opportunistic infection. So far evidence-based recommendations for the prophylaxis and therapy of infections after HTx are rare. Therefore, it is necessary to use clinically proven strategies to prevent and treat infections.

Key words: heart transplantation, infection, immunosuppression

Introduction

Except for early graft failure, nowadays infections are the most serious threat in the early period after heart transplantation (HTx), whereas rejection associated mortality has decreased significantly during the last decade. The relative increase of infection associated death is related to better immunosuppressive therapy for the prevention of acute rejection, and increased perioperative risk factors attributed to the recipient (long lasting course of heart failure with incipient multiple organ failure, assist device support) and the donor organ (age, left ventricular hypertrophy, CAD).

Therefore, strategies to avoid perioperative infection have to be directed by general as well as by individual risk analysis.

Bacterial infections occur in about 25 – 40% of all patients early (days to weeks) after heart transplantation; the second most prevalent are fungal infections (8 – 13%). Later on (weeks to months), depending on the choice of immunosuppressive drug therapy and individual donor and recipient risk factors for herpes viruses (mismatch of CMV, EBV), CMV (cytomegaly virus) and EBV (Epstein-Barr virus) de novo infection or reactivation are important causes for morbidity. Furthermore, environmental factors such as exposure to fungal spores in plants or food or Legionella contaminated water supply or transmission of viruses (Influenza, norovirus) by visitors to the transplant patient may increase the probability of serious infections.

Because about 30% of all patients who receive heart transplantation nowadays are supported preoperatively by ventricular assist

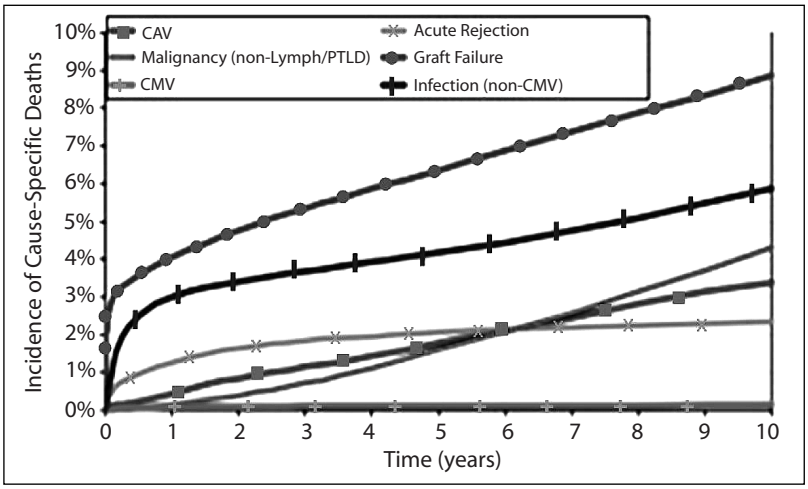

Figure 1: Cumulative incidence of the leading causes of death for adult heart transplants performed between January 1992 and June 2008. CAV, coronary allograft vasculopathy; CMV, cytomegalovirus; lymph/PTLD, lymphoma or post-transplant lymphoproliferative disease. Modified from the Journal of Heart and Lung Transplantation 2010; 29: 1089-1103

Table 1

	Everolimus 1.5 mg	**Everolimus 3.0 mg**	**Azathioprin**
Viral (%)	16.3*	17.1*	32.2
CMV (%)	8.6*	8.1*	22.2
Herpes simplex (%)	8.1	5.7	10.7
Herpes zoster (%)	3.8	6.6	5.6
Bacterial (%)	37.3*	40.3*	25.7
Fungal (%)	8.6	12.8	8.9
Aspergillus (%)	1.9	2.4	0.5
Candida (%)	5.7	9.0	7.4

devices and others are treated for a long time in intensive care units before surgery, possible assist device associated infections as well as nosocomial infections often caused by indwelling catheters or CAD (Clostridium associated diarrhea) or other factors have to be taken into account for the individual risk analysis.

One of the cornerstones of infection prevention and therapy is the availability of rapid and valid diagnostic tools for the treatment of bacterial, viral and fungal agents. These include cultural (bacteria, Aspergillus spp.) methods, PCR technology (MRSA, CMV, EBV, hepatitis, other viruses, toxoplasmosis) and serology (Legionella antigen in urine; CMV and EBV, toxoplasmosis, syphilis, hepatitis, preoperative status). The microbiologist is an important part of the postoperative team to ensure appropriate and rapid communication of the patient's current situation and precise choice of diagnostic methods.

Environmental factors such as the personal hygiene of the hospital staff to avoid bacterial transmission, Legionella free water, and freedom from aspergillus spores in the air can be greatly influenced by the availability

of and strict adherence to SOPs (standard operating procedures).

Preoperatively the following examinations of the recipient and donor should be performed:

Donor:
Serology: VDRL, CMV-Ab, EBV-Ab, HBV, HCV (if in doubt: HCV-PCR), HIV, toxoplasmosis
Culture of organ perfusate and transport media.
If the donor may have suffered from infection, results of microbiologic examination or blood culture for further evaluation.

Recipient:
Serology: CMV-Ab, EBV-Ab, toxoplasmosis, HBV, HCV, lues, HIV
Cultural: Smears for diagnosis of MRSA; facultative: stool specimens for diagnosis of Clostridium difficile or examination for the presence of Clostridium difficile toxins; blood cultures if assist devices or long-term indwelling catheters are present, urine
PCR: MRSA screening, if available
Other diagnosis : x-ray, CT, other clinically indicated procedures.

Surgical complications with increased risk of infection after heart transplantation

Aside from the immunosuppressive drug therapy, heart transplantation is a major surgical procedure, associated with the risk of wound infection, intrathoracic infection and catheter associated infection like other major and long lasting thoracic operations. Therefore, it is recommended to give calculated perioperative antibiotic prophylaxis with a second generation cephalosporine e.g. Cefuroxim (3 x 2 g) for 48 hours, starting already preoperatively, with a second shot intraoperatively.

If further risk factors such as evidence of assist device or catheter-induced infections are present, vancomycin or alternative drugs such as linezolid or daptomycin should be added.

All other antibacterial drugs should be added, if indicated after clinical examination, especially for calculated therapy of respiratory infections in the case of prolonged ventilator therapy, if possible, guided by results of microbial diagnosis.

The principal of rapidly started and high dose antibiotic therapy in case of infection is strictly recommended. In addition, more than in other patients, after heart transplantation the risk of renal failure is increased because of the necessary application of potentially nephrotoxic immunosuppressive drugs such as cyclosporine A or tacrolimus. Therefore, careful monitoring of the renal function with calculation of the eGFR (estimated glomerular filtration rate) for selection and dosing of antibiotics, antifungal agents and antiviral drugs is essential.

Increased risk of infection after heart transplantation caused by immunosuppression

Immunosuppressive drug therapy increases not only the risk for and the severity of surgery associated and nosocomial infections but also the risk of opportunistic infections such as CMV, EBV, Pneumocystis jirovecii, nocardiosis and aspergillosis.

The consequences for antibiotic, antifungal and antiviral therapy are to start therapy very rapidly as soon as minimal signs of infection (laboratory data, hypotension and tachycardia, hypo- or hyperthermia and changes in awareness probably not associated with other causes) are present. Samples must be taken for microbial cultures from wound secretion, blood, urine, catheters and bronchial secretion (BAL) using puncture when necessary, and the drug doses used should be as high as possible, with the duration of therapy adapted to the course of the disease.

Careful and at least daily examination of patients for signs and symptoms of infection early after heart transplantation is obligatory

because typical signs of infection may be mitigated by the reduced immune response (fever, chills) and the course of infections can develop rapidly into serious life threatening symptoms with sepsis associated with hypotension, renal failure and impairment of consciousness within a very short time (hours).

Nosocomial infections are mainly of pulmonary origin. Knowledge of the spectrum of infective agents in the transplant unit and their resistance to antibiotics is very important for the choice of antibiotics for calculated initial therapy.

Risk for nosocomial and opportunistic infection is increased by suppression, specifically of the T-cell response, by cytolytic agents (ATG), cyclosporine A, tacrolimus, azathioprine, mycophenolic mofetil and everolimus and also by steroids, which in addition decrease the response of macrophages and non-T-cell-dependent immune mechanisms.

The most powerful drug to suppress T-cell and also B-cell function is ATG, which conversely is one of the main risk factors for viral infections, predominantly CMV de novo infection in the case of CMV mismatch (donor CMV positive, recipient: CMV negative) or CMV reactivation if CMV is already present in the recipient. EBV-negative patients, especially children, are susceptible for EBV infections and diseases during and after strong T-cell suppression, with the risk of EBV disease and also the development of lymphoproliferative disease (PLD). Therefore, to prevent EBV disease and PLD, it is wise to withhold ATG, if at all possible, in EBV-negative individuals (mostly children) with EBV-positive donor organs. Furthermore, cytolytic therapy with ATG is also associated with increased morbidity and mortality due to infections in older transplant recipients.

For risk analysis of CMV disease it is important to know whether MMF or everolimus is part of the drug regimen, because compared to everolimus the use of MMF substantially increases the risk of CMV reactivation in CMV-positive recipients.

Dose and duration of steroids markedly influence the risk of nosocomial infection as well as of opportunistic infection and especially of dangerous fungal infection (Aspergillus spp.).

While giving antibiotic, antiviral, antifungal and antiprotozoal drugs it is not only necessary to carefully monitor renal function, because of their additive or potential nephrotoxicity in combination with the immunosuppressive drugs cyclosporine A, tacrolimus

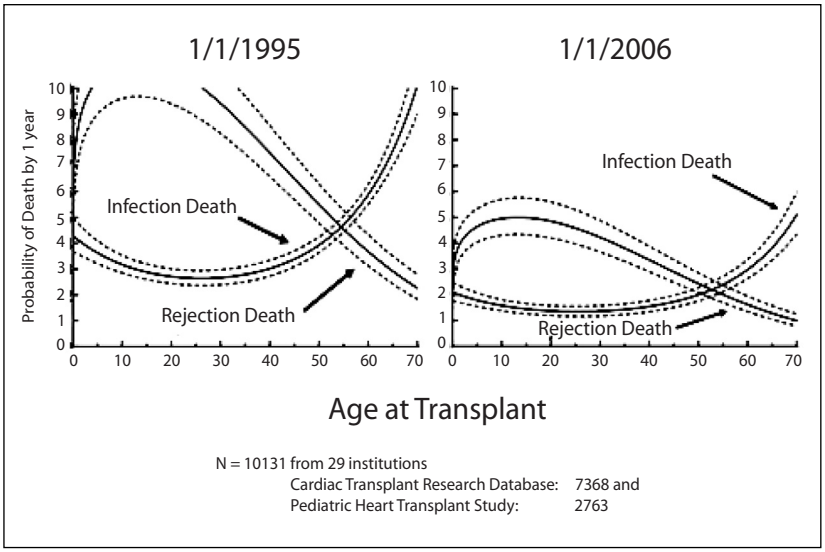

Figure 2: Probability of Death by 1 Year by infection or rejection (%) depending on age (y). From the Journal of Heart and Lung Transplantation 2011;30:151-157

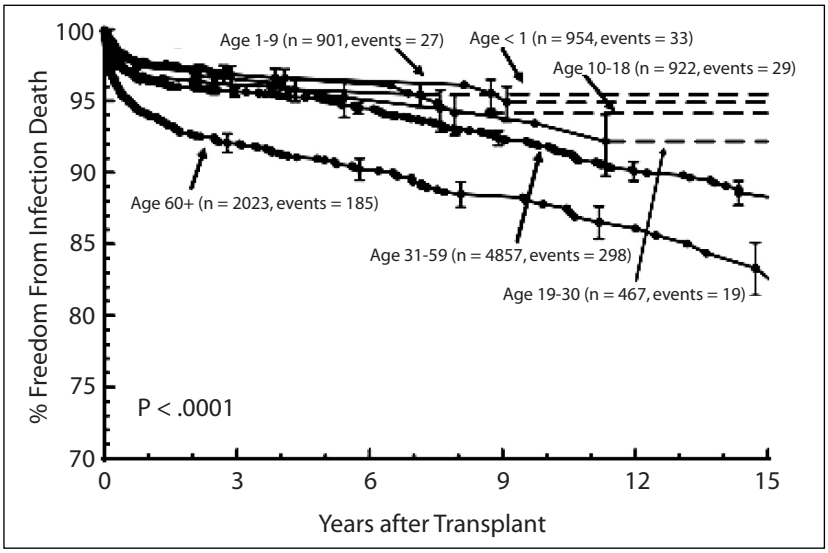

Figure 3: Freedom from infection death and age at transplantation. From the Journal of Heart and Lung Transplantation 2011; 30: 151-157

and everolimus. But also to note drug – drug interactions, which may cause toxicity of the immunosuppressants, or a decrease of drug levels, with risk of acute rejection episodes. Particular caution is necessary with the use of erythromycin and azoles (fluconazol, itraconazol, voriconazol), which may increase drug levels of CyA, tacrolimus and everolimus and the use of rifampicin (rapid and substantial decrease of drug levels).

Prevention and therapy of bacterial infection after heart transplantation

Prevention of bacterial infections after heart transplantation is based on the same principles as in patients after other major surgery. This includes care according to SOPs with hand disinfection and the wearing of gloves when procedures with intravasal and urine catheters and drains are performed. The use of water, which may be contaminated by bacteria (Legionella spp. especially serogroup 1) E. coli and Pseudomonas spp. must be avoided. It is mandatory to regularly draw samples of water in the transplant ward for bacterial control. Prophylactic use of antibiotics is not recommended, because this may induce the growth of multiply resistant pathogens.

If the patient is discharged home, he or she should be advised how to reduce the risk of Legionella infection.

Prevention and therapy of protozoal infection after heart transplantation

Although rarely occurring, protozoal infections mainly with Pneumocystis jirovecii and Toxoplasma gondii may cause severe damage to the patient.

Up until now, Pneumocystis jirovecii cannot be cultured; therefore it is unclear how it is transmitted. Clearly its main manifestation is in the lung, leading to interstitial pneumonia with severe hypoxemia. Diagnosis is primarily based on BAL with special staining or PCR. Incidence of this infection in the heart transplant population is lower than after kidney transplantation (less than 1%).

Toxoplasmosis is also a rare disease. It occurs only in exceptional cases, when the recipient is toxoplasmosis (antibody) negative and the donor is toxoplasmosis positive, indicating previous infection with Toxoplasma gondii or there is intake of food with Toxo-

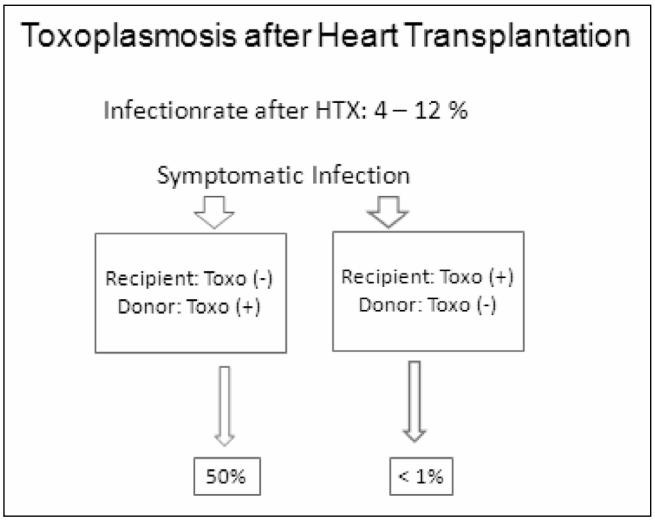

Figure 4: Toxoplasmosis after heart transplantation. From the Journal of Heart and Lung Transplantation 2011; 30: 151-157

plasma gondii (mainly raw meat); see figure 4.

Diagnosis is difficult, because seroconversion (occurrence of Toxoplasma antibodies) or the development of IgM antibodies is mitigated by immunosuppressive drugs. Alternatively, PCR technology can be used.

Because prevention of both infections is very safe and easy with a low complication rate, by antibiotic drugs, it is generally recommended that prophylactic antibiotic therapy be performed with TMP/SMZ 960mg/tablet twice a week (e.g. on Tuesdays and Fridays) after the patient's general condition, kidney function and hemodynamics become stable postoperatively with a duration of 6 months after transplantation. Thereafter, further administration can be recommended if intensive immunosuppressive drug therapy is necessary or T-cell depletion has to be performed after recurrent acute rejection episodes.

If Pneumocystis jirovecii (PC) or Toxoplasma gondii infections occur, treatment is based on the general recommendations also applied in patients with HIV disease.

Prevention and therapy of fungal infection after heart transplantation

The incidence of invasive fungal infections is low compared to that of bacterial infections. However, they are always life-threatening. The most dangerous germs found in Europe are Aspergillus spp. (Aspergillus fumigatus, Aspergillus flavus, Aspergillus niger, Aspergillus terreus). In America blastomyces infections are also reported.

Compared to Candida infections, which originate from the gastro-intestinal tract, Aspergillus infections are air-borne. If spores of Aspergillus spp. with a diameter of about 2 µm are inhaled, they can enter the bronchial system. If the phagocytic system (macrophages) is impaired, mostly by granulocytopenia often occurring after bone marrow transplantation or by therapy with steroids, hyphae develop and infiltrate bronchial and pulmonary tissue. If the fungus gets access to blood vessels in the lung it is transmitted by the blood stream throughout the body (brain, heart muscle, thyroid tissue, cartilage, liver, kidney). Depending on the activity of cellular defense mechanisms, the fungus can destroy organs and lead to deaths.

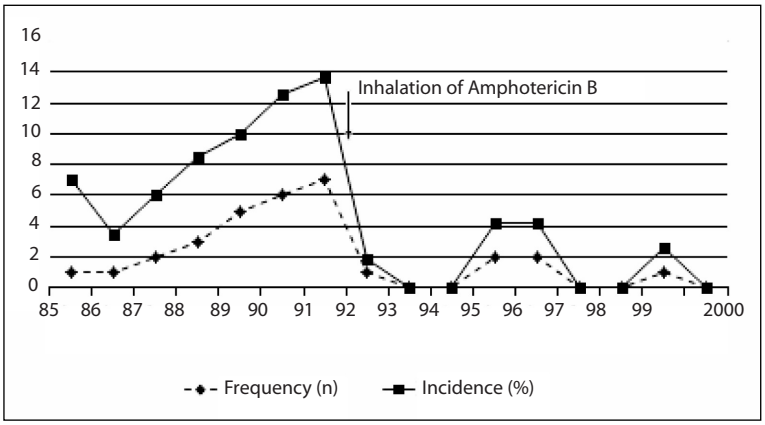

Figure 5: Invasive aspergillosis after heart transplantation at the Deutsches Herzzentrum Berlin, 1985-2000.

Candida infections (C. albicans, C. krusei, C. glabrata) are more frequent than Aspergillus infections after transplantation. However, they mostly affect mucous membranes and the skin. Rarely, they became invasive and the possibility of effective treatment is much better than in Aspergillus infections.

The cornerstone to prevent Aspergillus infections, which can already occur within the first week after transplantation, is prevention of exposure to spores of Aspergillus. Therefore, if possible, patients should be cared for in rooms with special air filtration systems. In such units, the windows must be kept closed. Furthermore, in all transplant units flowers, which may carry Aspergillus, raw nuts, pepper and old food are not allowed.

In high-risk patients with high immunosuppression, long term antibiotic therapy and leucopenia it has been shown in a few studies, that inhalation of amphotericin B (10 mg three times a day) can reduce the rate of invasive aspergillosis. However, those studies do not reach that kind of scientific power, that this therapy can be in general recommended, although frequently performed after bone marrow and thoracic organ transplantation. If the patient can tolerate inhalation of amphotericin B after inhalation of a ß-adrenergic bronchodilating drug, this kind of prophylaxis should be performed until the patient can leave the transplant unit.

Early diagnosis of pulmonary aspergillus infection is important, so that therapy can be started early to avoid organ damage not only in the lung but also in other organs. To achieve this aim, frequent microbiologic examination of bronchial secretion not only for bacteria but always also for aspergillus spp. should be performed. It is important that the microbiologist is able to find hyphae of aspergillus even in low concentrations. In high-risk patients, effective therapy of aspergillus infection should be stared if aspergillus is documented in bronchial secretion, because tissue invasion happens rapidly in highly immunocompromised patients and mortality of this infection is high.

Therapy of aspergillosis can be performed with voriconacol, amphotericin B and ecchinocandines (caspofungin, anidulafungin). Often the use of amphoterin B is limited by its nephrotoxicity and also bone marrow toxicity, even if sodium chloride is supplied by infusion before administration of AmB.

In severe infections combination of an ecchinocandine with voriconacol is recommended. Duration of therapy of aspergillosis should be at least one week longer than clinical signs or tissue infiltration documented by X-ray is present.

Prevention and therapy of viral infections after heart transplantation

Herpes virus infections are frequently occurring after transplantation, caused by the diminished T-cell response after high dose immunosuppression.

Early after transplantation often mucocutaneous herpes simplex infection develops with a painful aphtous disease in the mouth, lips and tongue, which can impair intake of food and swallowing considerably. This complication can be treated effectively with acyclovir i.v. followed by oral application. If only some local aphtae are present, local application of acyclovir in an ointment may be used. In contrast to infection and disease with herpes simplex, the herpes virus 6 called CMV is replicating much slower and its clinical manifestation is about (2) 3 – 4 weeks later.

The occurrence of CMV-infection and disease mainly depends on 4 factors: The presence or absence of CMV antibodies in the recipient, the presence or absence of CMV-antibodies in the donor, the CMV match of donor and recipient, cytolytic therapy with ATG and the use of MMF or everolimus in combination with cyclosporine A or tacrolimus.

If there is a CMV mismatch (Donor CMV positive, Recipient negative), cytolytic induction therapy with ATG is performed and MMF is used for maintenance immunosuppression, in more than 80% of the patients CMV will replicate and spread into several organs, leading to bone marrow suppression, gastroenteritis, fever, and impairment of kidney function.

In contrast if there is no CMV mismatch (Donor CMV negative, recipient: CMP positive) or CMV is absent in donor and recipient, no cytolytic therapy is performed and MMF is not used for maintenance immunosuppression, risk of CMV infection and disease is low.

Therefore, prevention of CMV infection and disease should be adapted to the individual risk.

Actually and worldwide, two general strategies to prevent CMV disease are used. One is based on pre-emptive therapy if CMV-replication is documented, either by measurement of the concentration of pp65 (the early CMV antigen) in PMNC (Peripheral mononuclear cells), usually calculated on the basis of 200 000 counted PMNC.

Because PMNC are present in peripheral blood for about 3 days, increase or decrease of the number of pp65 positive PMNC is an

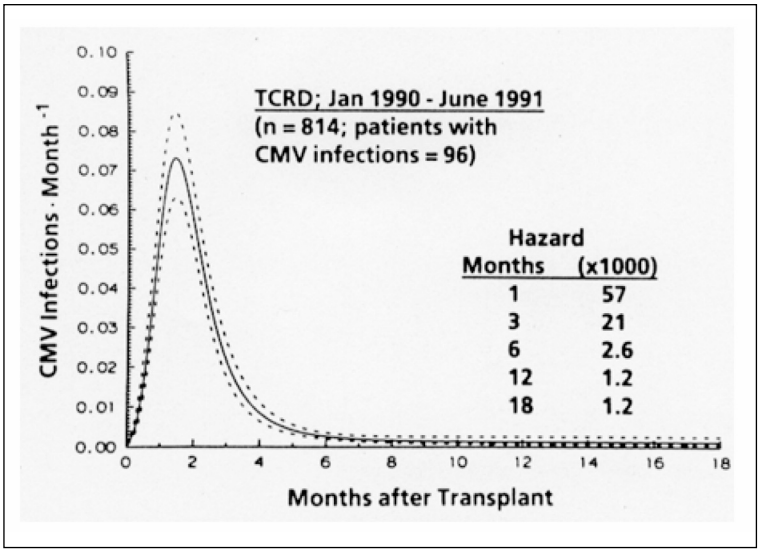

Figure 6: Incidence of CMV infection after HTx

Table 2: Summary of opportunistic infections – MMF versus Azathioprin

	1 Year		3 Years	
	AZA N = 289	**MMF N = 289**	**AZA N = 289**	**MMF N = 289**
Any opportunistic infection	43.6%	53.3%	47.4%	57.4%
Candida	17.6%	18.7%	20.4%	21.1%
Herpes simplex	14.5%	20.8%	15.9%	22.8%
CMV viremia/syndrome	10.0%	12.1%	10.7%	12.8%
CMV tissue invasion	8.7%	11.4%	8.7%	13.1%
Herpes Zoster	5.9%	10.7%	9.7%	14.5%
CMV infection	2.8%	2.8%	3.1%	3.1%

Table 3: Infections: Everolimus vs. Azathioprin

	Everolimus 1.5 mg	**Everolimus 3.0 mg**	**Azathioprin**
Viral (%)	16.3*	17.1*	32.2
CMV (%)	8.6*	8.1*	22.2
Herpes simplex (%)	8.1	5.7	10.7
Herpes zoster (%)	3.8	6.6	5.6
Bacterial (%)	37.3*	40.3*	25.7
Fungal (%)	8.6	12.8	8.9
Aspergillus (%)	1.9	2.4	0.5
Candida (%)	5.7	9.0	7.4

*$p < 0.05$ vs. AZA

indicator for increase or decrease of the rate of CMV replication and can be used as a tool for surveillance of success or failure of antiviral therapy and also to estimate the risk for the development of CMV-disease.

Alternatively PCR with calculation of the number of copies of CMV-DNA can be used to diagnose CMV replication. However because of lack of standardization there are no recommendations for treatment of CMV-infection, dependent from the number of DNA-copies detected. Like measurement of the number of pp65 positive PMNC/200 000 cells, increase and decrease of the concentration of CMV-DNA copies can be used for control of therapy.

For patients at a high risk of developing CMV infection and disease antiviral prophylaxis is recommended early postoperatively by administration of valganciclovir (Valcyte®) (p.o.) 900 mg once or twice daily for about 6 months after transplantation, until immunosuppressive drug therapy can be lowered. Medication should be started if the patient is clinically stable, kidney function is good and oral intake of food and drugs is possible. The dose of valganciclovir has to be adjusted according to kidney function.

Surveillance of CMV replication by determination of the CMV-early antigen pp65 in PMNC or CMV-DNA by PCR is also recommended, as clinically indicated (once a week

Bacteriae	
– Perioperative prophylaxis	IA (Cephalosporine)
– Legionella	IIB (Filter systems)
Virus	
– Herpes simplex	IIB (Aciclovir)
– CMV	IB (Pre-emptive therapy IgG)
– EBV	None
Fungus	
– Candida	IIB (Nystatin, Ampho B oral)
– Aspergillus	III (Ampho B inhalation)
Protocoae	
– PC	III (TMP/SMZ oral)
– Toxoplasmosis	None

Table 4

to twice a month) for the first 6 postoperative months.

In low-risk patients, depending on the access to regular diagnosis of CMV replication, pre-emptive therapy by administration of valganciclovir should be started only if CMV replication is detected. If regular monitoring of CMV replication is not possible, acyclovir (Zovirax®) 800 mg t.i.d. for prophylaxis of herpes viruses should be given, taking into account the patient's immunosuppressive drugs, age, kidney function and bone marrow function.

CMV disease with fever, gastrointestinal symptoms, bone marrow depression, kidney impairment and malaise must be treated by intravenous ganciclovir (Cymeven®) 5 mg/kg/day b.i.d. with adaptation of doses to kidney function. The effect of therapy should be monitored by surveillance of CMV replication and clinically. If CMV infection occurs frequently, immunosuppressive drug therapy should be tailored.

In general, CMV recurrence is an indicator for inadequate depression of the function of T-cells, sometimes of lack of CMV-restricted T-cells. Therefore, lowering of immunosuppression is recommended and if MMF is part of the immunosuppressive protocol, it should be switched to everolimus.

Summary

Nowadays, infections are the second most important cause of death after heart transplantation. Diagnosis, prophylaxis and surveillance of infections are essential in the early postoperative period. After heart transplantation not only are community acquired and nosocomial infections are present, but also opportunistic infections. Aside from prevention of acute rejection episodes by immunosuppression, diagnosis, surveillance and therapy of bacterial, viral and protozoal infections are imperative shortly after heart transplantation. Prophylaxis and therapy of infections are the precondition of long-term success after transplantation. Specific recommendations for diagnosis and therapy of infections after heart transplantations are rare and typically of low grade of evidence and strength.

This situation makes it necessary to use clinically proven strategies to prevent and treat infections after heart transplantation. Because immunosuppressive drug therapy has changed substantially during the last two decades, with significant reduction of acute rejection episodes und rejection associated death, prophylaxis, surveillance and therapy of infection have now become the most challenging tasks for the future, to improve outcome after heart transplantation. Shortly after heart transplantation, diagnosis and therapy of infections should be guided by the risk fac-

tors of the patients, including transplant function, age, data from donor and recipient (preoperative), kind of immunosuppression and adverse drug actions. The individual risk profile is the most important guide for infection control.

Correspondence address
Manfred Hummel, MD, PhD
Paulinenkrankenhaus Berlin
Dickensweg 25-39
14055 Berlin
hummel@paulinenkrankenhaus.de