CONTINUING MEDICAL EDUCATION

Aftercare for Patients With Transplanted Organs

Harald Schrem, Hannelore Barg-Hock, Christian P. Strassburg, Anke Schwarz, Jürgen Klemphauer

SUMMARY

Background: The postoperative management following solid organ transplantation requires close cooperation between family doctors, internists, the local hospital, and the transplant center.

Methods: Selective analysis of current national and international guidelines and relevant review articles.

Results/conclusion: In the early phase post transplantation, aftercare involves inpatient treatment and outpatient or inpatient rehabilitation with the aim of complete social and professional reintegration. Early diagnosis and treatment of typical general complications such as post-transplant diabetes, hyperlipidemia, arterial hypertension, osteoporosis, and kidney failure is essential. Early detection and treatment of malignant disease and opportunistic infections in patients with long-term immunosuppression is desirable. Moreover, organ-specific factors have to be taken into account. In the event of transplant dysfunction, recurrence of the underlying disease in the transplant, chronic or acute rejection, and organ-specific infections and drug toxicity have to be considered.

Dtsch Arztebl Int 2009; 106(9): 148–56
DOI: 10.3238/arztebl.2009.0148

Key words: organ transplantation, rehabilitation, quality of life, treatment outcome, cooperation

Klinik für Allgemein-, Viszeral- und Transplantationschirurgie, Medizinische Hochschule Hannover: Dr. med. Schrem, Dr. med. Barg-Hock, Prof. Dr. med. Klemphauer

Abteilung Gastroenterologie, Hepatologie und Endokrinologie, Medizinische Hochschule Hannover: Prof. Dr. med. Strassburg

Abteilung Nephrologie, Medizinische Hochschule Hannover: Prof. Dr. med. Schwarz

Physicians are increasingly having to deal with transplant patients in daily practice because of the generally growing number of transplants performed and the steadily improving prognosis (1). The aim of transplantation and subsequent rehabilitation is to achieve the fullest possible reintegration into normal life, including occupational and social rehabilitation. Long-term success of organ transplantation depends to a great extent on the ensuing interdisciplinary aftercare program (*figure*).

The learning goals of this article are to equip the reader

- to ensure that the transplant patient achieves a good quality of life
- to apply essential therapeutic principles to produce a good long-term result regardless of the organ transplanted in long-term aftercare of organ transplant patients.

This paper is based on the current national and international guidelines and review articles from the last six years.

Immunosuppression in patients with transplanted organs

In addition to basic immunosuppression, depending on the transplant center and the transplanted organ, a so called induction therapy is often performed intraoperatively and during the first few days after transplantation. This therapy involves the center-specific use of mono- or polyclonal antibodies (such as antithymocyte globulin or antilymphocyte globulin) (2). Basic immunosuppression is a lifelong requirement aimed at eliminating the risk of transplant loss resulting from immunological rejection (2). In the initial phase, basic immunosuppression frequently consists in the use of corticosteroids (methylprednisolone or prednisolone) in decreasing doses. In the long-term course, a prednisolone dose between 5 and

Basic immunosuppression

Basic immunosuppression is a lifelong requirement to prevent graft loss due to immunological rejection.

TABLE 1

Overview of estimated immunosuppressive potency and typical side effects of widely used immunosuppressives after organ transplantation*1

	Ciclosporin	Tacrolimus	Sirolimus	MMF	Prednisolone
Immunosuppressive potency	+++	+++(+)	++(+)	++	+
Nephrotoxicity	++	++	–	–	–
Neurotoxicity	+	++	–	–	–
Hirsutism/hypertrichosis	++	–	–	–	++
Diabetogenicity	+	++	–	–	++
Diarrhea	–	–	+	++	–
Hepatotoxicity	(+)	(+)	+	–	–
Bone marrow suppression	–	–	+	+	–

*1 modified from (2). The effects shown in this table are dose-dependent and reflect clinical assessments and experience. A direct comparison of the different active agents is therefore not without problems. MMF, mycophenolate mofetil

a maximum of 10 mg daily is often administered. In many cases, however, steroid-free immunosuppression is now a widely employed alternative (2).

Most immunosuppressive protocols are based on a combination of a calcineurin inhibitor (ciclosporin or tacrolimus) with steroids. m-TOR (mammalian target of rapamycin) inhibitors like sirolimus or everolimus—alone or in combination with a calcineurin inhibitor and/or corticosteroids—are gaining in clinical importance in various basic immunosuppressive protocols used in patients who have had transplants because of malignant disease or progressive renal failure. The purine synthesis inhibitor mycophenolate mofetil (MMF) has proved successful in many cases in combination with steroids and/or a calcineurin inhibitor (2). In patients with post-transplant renal failure, the nephrotoxic calcineurin inhibitors can also be replaced completely or partially by MMF or everolimus or sirolimus (3).

It is imperative to be aware of known interactions between calcineurin inhibitors and other drugs, since they may lead to relevant increases or decreases in the blood levels of calcineurin inhibitors with associated toxicity or the risk of graft rejection (4).

Calcineurin inhibitors, like m-TOR inhibitors, have to be administered in blood level adapted doses (2). It has been shown for ciclosporin that the value measured two hours after intake, the 'C2 level', accurately reflects the pharmacokinetic area under the curve (AUC) and

allows optimized dose adjustment during drug monitoring (4). The optimal therapeutic trough and C2 levels depend on the organ transplanted, the time after transplantation, the inclusion of other immunosuppressive agents in the protocol (e.g. mycophenolate mofetil and/or corticosteroids), and the patient's medical history. The selection of an individualized immunosuppressive protocol should also be left to the transplant center during long-term aftercare. A comparative listing of the most commonly used immunosuppressive agents is provided in *table 1*.

In aftercare, the nephrotoxic, neurotoxic, and diabetogenic side effects are important factors in determining the long-term prognosis and quality of life, especially with the widely used calcineurin inhibitors ciclosporin and tacrolimus. Mycophenolate mofetil may be associated with diarrhea and/or clinically relevant bone marrow suppression that limit the use of this drug (2, 3).

Hyperlipidemia during immunosuppression

Almost all immunosuppressive agents cause hypercholesterolemia which often cannot be controlled by dietary management alone. In these cases statins should be used (5). In combination therapy with calcineurin inhibitors, pravastatin and fluvastatin are most suitable because these agents are so far the most thoroughly studied in combination with immunosuppressives and are not bio-transformed mainly by the cytochrome P450 3A4

Treatment regimen

Most long-term immunosuppressive therapies are based on a combination of a calcineurin inhibitor with steroids.

Adverse drug reactions

The nephrotoxic, neurotoxic, and diabetogenic side effects are an important factor for long-term prognosis and quality of life in aftercare, especially with the widely used calcineurin inhibitors ciclosporin and tacrolimus.

system like the calcineurin inhibitors (5). Dose increases should be based on the results of lipid electrophoretic monitoring and in conformity with the known target values for risk patients: LDL cholesterol below 2.6 mmol/L (6, 7, 8). Creatine kinase monitoring is important since statin and calcineurin inhibitor therapy has been associated with rhabdomyolysis which has occasionally been fatal when the symptoms were misinterpreted (5). Bezafibrate is contraindicated in kidney transplant patients with impaired renal function.

Post-transplant diabetes

Immunosuppression with steroids and/or a calcineurin inhibitor is associated with an increased incidence of diabetic metabolic derangements that can lead to insulin-dependent post-transplant diabetes (9). Diagnosing post-transplant diabetes requires the determination of fasting blood glucose, which is above 125 mg/dL. An oral glucose tolerance test (OGTT) is already required for transplant patients with a fasting blood glucose level between 110 mg/dL (6.1 mmol/L) and 125 mg/dL (6.9 mmol/L) to check for the presence of post-transplant diabetes or impaired glucose tolerance (7, 9). If post-transplant diabetes or impaired glucose tolerance is detected, it is essential to treat the condition because of the associated elevated cardiovascular risk (7, 9). During the further course, regular HbA1c monitoring every three to six months is advisable. If substantially reducing or tapering out steroids or replacing tacrolimus or ciclosporin in the immunosuppressive protocol as well as dietary measures fail to produce normoglycemia, oral antidiabetic therapy (e.g. with a sulfonylurea preparation) or insulin therapy should be initiated depending on the serum glucose level (7, 9).

Arterial hypertension in patients with transplanted organs

Many patients develop hypertension requiring treatment during immunosuppressive therapy. Corticosteroids and calcineurin inhibitors are known to have pressor effects. Arterial hypertension is a relevant risk factor for cardiovascular diseases with a significant influence on morbidity and mortality in transplant patients. Besides hyperlipidemia and post-transplant diabetes, arterial hypertension is one of the main prognostic factors for long-term survival in transplant patients (7, 10, 11).

Blood pressure management is essential in arterial hypertension to prevent long-term complications including renal insufficiency and cardiovascular events.

Schematic diagram of the three mainstays of successful aftercare in patients with transplanted organs

The current guidelines of the German Hypertension League are based on the guidelines of the European Society of Hypertension and the European Society of Cardiology (www.hochdruckliga.info) (12).

This evidence-based guideline and the Guideline of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC-7 Guideline) (13) recommend target blood pressure values below 140/90 mm Hg and for diabetics below 130/80 mm Hg. The JNC-7 Guideline also proposes target blood pressure values below 130/80 mm Hg for renal insufficiency patients. For post renal transplant patients, the European guidelines recommend a target blood pressure below 130/80 mm Hg in patients without proteinuria and below 125/75 mm Hg in patients with proteinuria (10).

24-hour blood pressure monitoring is favored as a means of ruling out unrepresentative elevated values. Antihypertensive therapy can then be initiated and adjusted as required on this basis. The cardio- and nephro-protective ACE inhibitors and AT-1 blockers are usually preferred for transplant patients (8, 11).

Renal insufficiency in patients with transplanted organs

Monitoring of renal function during long-term therapy with calcineurin inhibitors should be based on determinations of serum creatinine and urea values, as well as glomerular filtration rate (GFR) or creatinine clearance. Protein excretion should be regularly determined in 24-hour pooled urine samples. Important renoprotective factors are an adequate daily fluid intake of at least two

Hypercholesterolemia

Almost all immunosuppressive agents cause hypercholesterolemia which is often not amenable to dietary management alone. Statins should be employed in these cases.

Post-transplant arterial hypertension

Many patients develop treatment-related hypertension during immunosuppression.

liters, optimal management of arterial blood pressure, avoidance of potentially nephrotoxic medications, especially non-steroidal anti-inflammatory drugs (NSAIDs), and elimination of an infectious focus if present (14). Supportive nephrological care is recommended for all patients after kidney transplant and for organ transplant patients with consecutive renal insufficiency. A change of immunosuppression to not primarily nephrotoxic drugs such as MMF, sirolimus or everolimus lies within the discretion of the transplant center (2, 3).

Malignant diseases in patients with transplanted organs

The risk of malignant diseases of all kinds is significantly increased by the long-term immunosuppression necessary after organ transplant (*table 2*). Put simply: the higher the total dose of immunosuppression, the more likely malignancy becomes. All malignant diseases show more aggressive biological behavior during long-term immunosuppression (15–17). Regular cancer screening is therefore vitally important during aftercare (*table 3*).

Table 4 shows how much higher the estimated incidence of various malignant skin tumors is in patients after organ transplantation compared to the general population.

The risk of malignant skin tumors is further increased in transplant patients (15, 17) by

- advanced age
- increased exposure to ultraviolet light
- stronger immunosuppression
- infections with human papillomavirus (HPV)
- a history of malignant skin tumors
- Fitzpatrick I, II and III skin types.

Immunosuppressed patients should undergo a dermatological assessment once a year. Sunbathing and solarium use should be avoided during immunosuppressive therapy. Skin exposed to the sun should be protected with a lotion with a very high sun protection factor (at least SPF 30, the higher the better) (15, 17). Relevant patient education is essential.

Besides malignant skin tumors, post-transplant lymphoproliferative disorder (PTLD), which is usually induced by the Epstein-Barr virus (EBV), also plays a leading role in post transplant malignancies. Post-transplant lymphomas usually develop in patients with serological evidence of EBV infection during childhood or adolescence or when there is the constellation of an EBV seropositive organ donor with an EBV seronegative

TABLE 2

Estimated incidence of different malignancies in patients with transplanted organs compared to the general population*¹

Malignancies	Incidence
Lymphomas (PTLD)	30 to 50-fold higher incidence
Anogenital cancers (cervical, penile, and vulvar carcinoma)	30 to 100-fold higher incidence
Renal cell cancer	up to 100-fold higher incidence
Urothelial cancers	elevated in risk groups (e.g. analgesic abuse, cyclophosphamide treatment)
Hepatocellular carcinoma (HCC)	elevated in liver cirrhosis and/or chronic hepatitis B and/or hepatitis C

*¹ modified from (8);

PTLD, post transplant lymphoproliferative disorder

organ recipient. Monitoring for the lifelong latent infection of the B cells with EBV is based on cytotoxic T-cells whose function is specifically impaired, depending on the immunosuppressive protocol, by polyclonal (e.g. antithymocyte globulin) or monoclonal antibodies (e.g. muromonab-CD3; also known as OKT3) during induction therapy in organ transplant patients. As a result, the risk of monoclonal B-cell non-Hodgkin lymphoma increases after transplantation. The cumulative incidence is also linked to the nature and intensity of the immunosuppression (16).

Malignant gastrointestinal diseases such as colon cancer, especially in patients with chronic inflammatory bowel disease or a positive family history, must be ruled out or detected by regular colonoscopy and treated in a timely manner (18). If malignancy is detected during long-term immunosuppression, a modification of the immunosuppressive protocol should be discussed. It should then also be considered, as appropriate, whether the intensity of the immunosuppression should be reduced and/or whether to use everolimus or sirolimus for immunosuppression, since these m-TOR inhibitors have been observed to exert antiproliferative effects against tumor cells in vitro.

Osteoprotection in patients with transplanted organs

The risk of steroid-induced osteoporosis is increased in transplant patients by the administration of prednisolone for immunosuppression. To exclude or detect osteoporosis during glucocorticoid therapy of more than

Monitoring of renal function

Determinations of creatinine and urea in serum and of glomerular filtration rate (GFR) or creatinine clearance are important for monitoring renal function during long-term therapy with calcineurin inhibitors.

Malignant diseases

The higher the total dose of immunosuppression, the more likely malignant disease becomes.

TABLE 3

Recommendations for tumor screening in aftercare of patients with transplanted organs*¹

Tumor	Screening
Lymphomas	Medical history and clinical monitoring every three months in the first year, then once annually
Skin cancers	Dermatological evaluation including enoral and anogenital once annually, in high-risk patients every six months
Cervical cancer	Gynecological evaluation once annually including PAP smear in all women > 18 years and sexually active women < 18 years
Anogenital cancers	Clinical examination once annually
Colorectal cancers	> 50 years: once annual search for occult blood, colonoscopy every five to ten years, more often in high-risk patients (e.g. positive family history)
Prostate cancer	> 50 years: digital palpation and PSA assay once annually with a life expectancy > 10 years
Pulmonary malignoma	No screening currently recommended
Breast cancer	Women 50 to 69 years; mammography once every 1 to 2 years, women ≥ 70 years annual screening with life expectancy > 8 years
Renal cell cancer	Screening not generally recommended, possible: sonography of own kidneys once every 1 to 3 years, urine cytology
Hepatocellular cancer	For liver cirrhosis and/or chronic hepatitis B and/or chronic hepatitis C; sonography every 6 to 12 months, AFP determination every 6 to 12 months

*¹ modified from (8)

three months' duration or in the event of a typically osteoporotic fracture, bone density measurement by dual x-ray absorptiometry (DXA) of the lumbar spine and total hip is recommended during the course (19). With clinically apparent osteoporosis it is essential to consider changing the basic immunosuppression to a steroid-free protocol or at least reducing the prednisolone dose as far as possible (2).

A markedly increased fracture risk is already apparent from a daily dose of less than 2.5 mg prednisolone equivalent (21). Several studies have shown that bone density loss is particularly pronounced in the first 3 to 12 months of glucocorticoid therapy, then passing into a phase characterized by a much slower demineralization process (21). In patients receiving prednisolone therapy over a period exceeding three months, the current Guideline of the DVD (Dachverband Osteologie), which is the joint organization of the scientific German-language societies for osteology, recommends osteoporosis prophylaxis with vitamin D3 (400 to 1200 IU/d) and calcium (1000 to 1500 mg/d) from the outset (www.lutherhaus-essen.de/osteo/leitlinien-dvo). This guideline proposes drug therapy with bisphosphonates

during steroid therapy exceeding three months in the presence of a DXA-T value of less than -1.5 or in the event of osteoporotic fracture. Patients with esophageal varices or a history of ulceration, however, should only receive bisphosphonates intravenously (e.g. pamidronate or ibandronate intravenously every three months). As with the oral administration of alendronate, adequate pharmacological gastroprotection with a proton pump inhibitor should also be provided to counteract the increased risk of developing bisphosphonate-associated peptic and duodenal ulcers (22).

Corticosteroids are also a risk factor for avascular bone necrosis. In 90% of cases the femoral head is affected. The total incidence after organ transplantation is estimated as about 5%. In these cases, the implantation of a total hip replacement is unavoidable during the further course (23).

The treatment of persistent renal osteopathy following renal transplantation with or without hypercalcemia should remain the exclusive preserve of the nephrologist in cooperation with the transplant center. Especially parathyroidectomy, which may become necessary after renal transplant and which in 50% of cases results in a

Osteoporotic risk

The risk of steroid-induced osteoporosis is increased in transplant patients due to the administration of prednisolone for immunosuppression.

Clinically apparent osteoporosis

With clinically apparent osteoporosis, it is vital to consider changing the basic immunosuppression to a steroid-free protocol or at least reducing the prednisolone dose as far as possible.

deterioration of renal function, should under all circumstances be decided in consultation with the transplant center. We refer readers particularly interested in this topic to the Guideline of the National Kidney Foundation for the diagnosis and treatment of renal osteopathy (20).

Infections in patients with transplanted organs

Organ transplant patients with infections represent a major challenge for the managing physician. While the presence of fever may prompt differential diagnostic consideration of possible graft rejection, the symptoms of an infection may be less pronounced in transplant patients than in non-immunosuppressed patients.

An early-stage microbiological diagnostic program including microbial identification and an antibiogram is essential for the successful treatment of bacterial infections. After obtaining material for microbiological diagnosis, however, calculated antibiotic therapy should be initiated as rigorously and rapidly as possible. Viral infections should be included in the differential diagnostic evaluations and should be diagnosed or excluded accordingly. The risk of certain infections depends on the intensity of immunosuppression and the further post-transplant course. Urinary tract infections and upper airway infections predominate in the long-term course (*box*) (8, 24).

Transplantation may be followed by infections transmitted by the organ donor via the graft, nosocomial infections, or community-acquired infections. Immunosuppressed transplant patients may also be expected to exhibit reactivation of latent, clinically inapparent infections such as tuberculosis or latent cytomegalovirus (CMV) infections. Most infections transmitted by organ donors are caused by CMV, tuberculosis, and *Trypanosoma cruzi* (24). Donors may also transmit Epstein-Barr virus (EBV) and other viruses. As regards donor-derived infections it should also be considered that these persons may also be infected or colonized with multi-resistant nosocomial microorganisms. Microbiological and virological screening of organ donors is limited by the short time elapsing between the onset of brain death and organ harvest (24).

When initiating immunosuppression, prophylactic antibiotic, antiviral and antimycotic pharmacological interventions are necessary, in some cases restricted to a period of three to six months. These include *Pneumocystis carinii* prophylaxis with cotrimoxazole and, for CMV-IgG-positive organ donors and non-immunized

TABLE 4

Estimated increased incidence of different malignant skin tumors in patients with transplanted organs compared to the general population*¹

Skin tumors	Incidence
Kaposi sarcoma	84-fold higher incidence
Squamous epithelial cancer of the skin	65 to 250-fold higher incidence
Squamous epithelial cancer of the lip	20-fold higher incidence
Malignant basaliomas	10-fold higher incidence
Melanomas	3.4-fold higher incidence

*¹ modified from (15, 17)

patients, the administration of valganciclovir in creatinine clearance based dosage. Amphotericin B suspension is given to prevent stomatitis or esophagitis caused by candidiasis (8, 24). The combined use of valganciclovir and mycophenolate mofetil may be expected to cause leukocytopenia. Regular blood count monitoring is therefore strongly advised (24). An increased incidence of infections with herpes zoster and herpes simplex viruses is quite often seen with mycophenolate mofetil (MMF) because of the pronounced B-cell inhibition. Oral therapy with aciclovir or valaciclovir and a temporary reduction of the MMF dosage are usually sufficient. In severe cases, the immunosuppression should be changed to an MMF-free regimen and initiated with intravenous aciclovir therapy (24).

In immunosuppressed transplant patients, perioperative antibiotic prophylaxis is recommended for all surgical interventions. The current guidelines for heart transplant patients, however, no longer recommend the general use of antibiotic prophylaxis unless a defect is present (25). If the heart valves are sclerotic, which is frequently the case in kidney transplant patients after prolonged periods of dialysis, the need for peri-interventional endocarditis prophylaxis should be decided on the basis of echocardiographic evidence.

Conflict of interest statement

The authors declare that no conflict of interest exists according to the guidelines of the International Committee of Medical Journal Editors.

Manuscript received on 5 November 2007; revised version accepted on 30 October 2008.

Translated from the original German by mt-g.

Femoral head necrosis

Corticosteroids are a risk factor for avascular bone necrosis. In 90% of cases the femoral head is affected. Implantation of a total hip replacement during the further course is often unavoidable in such cases.

Fever—a warning sign

If fever develops, differential diagnostic evaluation should also consider the possibility of underlying rejection.

REFERENCES

- Schrem H, Till N, Becker T et al.: Langzeit-Outcome nach Lebertransplantation. *Chirurg* 2008; 79(2): 121–9.
- Taylor AL, Watson CJ, Bradley JA: Immunosuppressive agents in solid organ transplantation: Mechanisms of action and therapeutic efficacy. *Crit Rev Oncol Hematol* 2005; 56(1): 23–46.
- Schlitt HJ, Barkmann A, Böker KH: Replacement of calcineurin inhibitors with mycophenolate mofetil in liver-transplant patients with renal dysfunction: a randomised controlled study. *Lancet*. 2001; 357: 587–91.
- Schrem H, Lück R, Becker T, Nashan B, Klempnauer J: Update on liver transplantation using cyclosporine. *Transplant Proc* 2004; 36: 2525–31.
- Kobashigawa JA: Statins in solid organ transplantation: Is there an immunosuppressive effect? *Am J Transplant* 2004; 4: 1013–8.
- National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III): Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002; 106: 3143–421.
- Wilkinson A, Davidson J, Dotta F et al.: Guidelines for the treatment and management of new-onset diabetes after transplantation. *Clin Transplant* 2005; 19: 291–8.
- Mayr M: Management nach Transplantation. *Ther Umschau* 2005; 62: 487–501.
- Pham PT, Pham PC, Lipshutz GS, Wilkinson AH: New onset diabetes mellitus after solid organ transplantation. *Endocrinol Metab Clin North Am* 2007; 36: 873–90.
- EBPG Expert Group on Renal Transplantation: European best practice guidelines for renal transplantation. Section IV: Long-term management of the transplant recipient. IV.5.2. Cardiovascular risks. Arterial hypertension. *Nephrol Dial Transplant* 2002; 4: 25–6.
- Mells G, Neuberger J: Reducing the risks of cardiovascular disease in liver allograft recipients. *Transplantation* 2007; 83:1141–50.
- European Society of Hypertension—European Society of Cardiology Guidelines Committee: 2003 European Society of Hypertension—European Society of Cardiology guidelines for the management of arterial hypertension. *J Hypertens* 2003; 21:1011–53.
- Chobanian AV, Bakris GL, Black HR, et al.: National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003; 289: 2560–72.
- Ojo AO: Renal disease in recipients of nonrenal solid organ transplantation. *Semin Nephrol* 2007; 27: 498–507.
- Euvrard S, Kanitakis J, Claudy A: Skin cancers after organ transplantation. *N Engl J Med* 2003; 348: 1681–91.
- Birkeland SA, Hamilton-Dutoit S: Is posttransplant lymphoproliferative disorder (PTLD) caused by any specific immunosuppressive drug or by the transplantation per se? *Transplantation* 2003; 76: 984–8.

BOX

Change in most likely anticipated infections post transplantation depending on time course^{*1}

< 1 month post-transplant

- Infections with resistant microorganisms:
 - MRSA, VRE, Candida species
- Further complications of infectiological relevance:
 - Aspiration
 - Catheter infection
 - Wound infection
 - Anastomotic insufficiency
 - Clostridium difficile colitis
 - Aspergillus infection
 - Pseudomonas infection
- Infections acquired from organ donor (rare):
 - HSV, LCMC, rabies, West Nile virus, HIV, Trypanosoma cruzi

1 to 6 months post-transplant

- With antiviral and PCP prophylaxis (cotrimoxazole + valganciclovir)
 - BK virus infection with nephropathy, Clostridium difficile colitis
 - HCV infection, adenovirus infection, influenza
 - Cryptococcus neoformans, Mycobacterium tuberculosis
 - Anastomotic complications
- Without antiviral and PCP prophylaxis (cotrimoxazole + valganciclovir)
 - Pneumocystitis carinii
 - Herpes virus infections (HSV, VZV, EBV), HBV infection
 - Infections with Listeria, Nocardia, Toxoplasma gondii, Strongyloides, Leishmania, Trypanosoma cruzi

> 6 months post-transplant

- Community acquired pneumonia
- Urinary tract infections
- Infections with aspergillus, atypical mould fungi, Mucor species
- Infections with Nocardia, Rhodococcus species
- Late viral infections
 - CMV infections, hepatitis (HBV, HCV), HSV encephalitis, SARS, West Nile virus, JC-polyomavirus, skin cancer, PTLD lymphoma

^{*1} The onset and course of possible infections are influenced by, among other factors, prophylactic measures (e.g. with cotrimoxazole and valganciclovir), the intensity of immunosuppression, leukopenia as a possible adverse reaction to drug therapy, and immunomodulatory infections with, e.g. CMV, HCV, or EBV. ^{*1} Modified from (24)
 MRSA, methicillin-resistant Staphylococcus aureus; VRE, vancomycin-resistant Enterococcus faecalis; HSV, Herpes simplex virus; LCMV, lymphocyte choriomeningitis virus; HIV, human immunodeficiency virus; PCP, pneumocystitis carinii; HBV, hepatitis B virus; HCV, hepatitis C virus; VZV, Varicella zoster virus; CMV, cytomegalovirus; EBV, Epstein-Barr virus; SARS, severe acute respiratory syndrome; PTLD, post-transplant lymphoproliferative disorder

Surgical interventions in already transplanted patients

Antibiotic prophylaxis is strongly recommended before surgical interventions in transplant patients.

17. Traywick C, O'Reilly FM: Management of skin cancer in solid organ transplant recipients. *Dermatol Ther* 2005; 18: 12–8.
18. Morath C, Mueller M, Goldschmidt H, Schwenger V, Opelz G, Zeier M: Malignancy in renal transplantation. *J Am Soc Nephrol* 2004; 15: 1582–8.
19. Torres A, Lorenzo V, Salido E: Calcium metabolism and skeletal problems after transplantation. *J Am Soc Nephrol* 2002; 13: 551–8.
20. National Kidney Foundation: K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis* 2003; 42: S1–201.
21. Kanis JA, Johansson H, Oden A, et al.: A meta-analysis of prior corticosteroid use and fracture risk. *J Bone Miner Res* 2004; 19: 893–9.
22. Cruz DN, Brickel HM, Wysolmerski JJ, et al.: Treatment of osteoporosis and osteopenia in long-term renal transplant patients with alendronate. *Am J Transplant* 2002; 2: 62–7.
23. Abbott KC, Oglesby RJ, Agodoa LY: Hospitalized avascular necrosis after renal transplantation in the United States. *Kidney Int.* 2002; 62: 2250–6.
24. Fishman JA: Infection in solid-organ transplant recipients. *N Engl J Med* 2007; 357: 2601–14.
25. Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Circulation* 2007; 116: 1736–54.

Corresponding author

Dr. med. Harald Schrem
Klinik für Allgemein-, Viszeral- und Transplantationschirurgie
Medizinische Hochschule Hannover,
Carl-Neuberg-Str. 1
30625 Hannover, Germany
schrem.harald@mh-hannover.de

Further Information on CME

This article has been certified by the North Rhine Academy for Postgraduate and Continuing Medical Education.

Deutsches Ärzteblatt provides certified continuing medical education (CME) in accordance with the requirements of the Chambers of Physicians of the German federal states (Länder). CME points of the Chambers of Physicians can be acquired only through the Internet by the use of the German version of the CME questionnaire within 6 weeks of publication of the article, i.e., by 13 March 2009. See the following website: cme.aerzteblatt.de

Participants in the CME program can manage their CME points with their 15-digit "uniform CME number" (einheitliche Fortbildungsnummer, EFN). The EFN must be entered in the appropriate field in the cme.aerzteblatt.de website under "meine Daten" ("my data"), or upon registration. The EFN appears on each participant's CME certificate.

The solutions to the following questions will be published in volume 17/2009. The CME unit "Lyme Disease—Current State of Knowledge" (volume 5/2009) can be accessed until 13 March 2009.

For volume 13/2009 we plan to offer the topic "Heart Valve Surgery Today—Indications, Operative Technique, and Selected Aspects of Postoperative Care in Acquired Valvular Heart Disease"

Solutions to the CME questionnaire in volume 1–2/2009:

Mrowietz U, Reich K.: "Psoriasis—New Insights Into Pathogenesis and Treatment": 1c, 2a, 3a, 4d, 5d, 6e, 7a, 8c, 9c, 10c

Please answer the following questions to participate in our certified Continuing Medical Education program. Only one answer is possible per question. Please select the answer that is most appropriate.

Question 1:

What is the main goal of patient rehabilitation after organ transplantation?

- a) Rapid discontinuation of the patient's occupational life to safeguard the social situation
- b) Determination and assessment of the patient's occupational or professional incapacity
- c) Fullest possible occupational and social reintegration
- d) Removal from family ties to promote self-responsibility and independence
- e) Provision of psychotherapy to cope with the transplant

Question 2:

What is usually the foundation of basic immunosuppressive therapy after organ transplant?

- a) Long-term treatment with the corticosteroid betamethasone
- b) Prior induction therapy with OKT-3
- c) An initial phase with escalating dosage of methylprednisolone
- d) Combination of calcineurin inhibitors with steroids
- e) Monotherapy with mycophenolate mofetil

Question 3:

A renal transplant patient develops hypercholesterolemia during long-term ciclosporin therapy. Which statins and/or lipid reducers are most suitable for combination therapy with calcineurin inhibitors, being the most thoroughly researched to date in this combination?

- a) Atorvastatin and bezafibrate
- b) Cerivastatin and pitavastatin
- c) Simvastatin and lovastatin
- d) Pravastatin and fluvastatin
- e) Rosuvastatin and mevastatin

Question 4:

Which of these measures should be taken for prevention in renal insufficiency patients (without symptoms of cardiac insufficiency) after organ transplantation?

- a) Oral fluid intake at least two liters daily, optimal management of arterial blood pressure
- b) Oral administration of phosphate preparations, reduction of oral fluid intake to 1 liter
- c) Maintenance of a diet consisting of high protein foods with polysaturated fatty acids
- d) Administration of ACE inhibitors to improve insulin sensitivity in patients with diabetes
- e) Increased intake of potassium and silicon preparations by means of dietary supplements

Question 5:

Post-transplant lymphomas are predominant among malignant diseases after organ transplantations and are induced by viruses. Which virus is usually responsible?

- a) Human papillomavirus
- b) Epstein-Barr virus
- c) Hepatitis B virus
- d) Herpes simplex virus
- e) Human herpes virus

Question 6:

The risk of osteoporosis is increased in transplant patients during immunosuppression. What preventive approach is recommended by the current guideline of the joint organization of the scientific German-language societies for osteology (DVD, Dachverband Osteologie)?

- a) Vitamin D (1200 IU/d) supplementation is to be avoided because of the drug interaction with the immunosuppressive agents.
- b) Post-transplant osteoporosis can be counteracted by including prednisolone (2.5 mg/d) in the basic immunosuppression.
- c) Six-months' post-transplant bisphosphonate therapy should be given orally—even with an endoscopically confirmed history of ulceration.
- d) With a DXA value below -1.5 during 3-month steroid therapy, medical therapy with bisphosphonates is indicated.
- e) Development of osteoporosis in patients with transplanted organs can be ruled out by including m-TOR inhibitors in basic immunosuppression.

Question 7:

According to the European Guideline recommendations, which target blood pressure values should not be exceeded during antihypertensive therapy in a renal transplant patient with proteinuria?

- a) 160/90 mm Hg
- b) 150/85 mm Hg
- c) 110/70 mm Hg
- d) 140/90 mm Hg
- e) 125/75 mm Hg

Question 8:

Which complication is most likely to occur six months after transplantation?

- a) Urinary tract infection
- b) Wound infection
- c) Catheter infection
- d) Anastomotic insufficiency
- e) Aspiration

Question 9:

Your 65-year-old patient received a donor kidney one year ago. He would now like to vacation in the Canary Islands and enjoy the sun and sea. What recommendations would you give him?

- a) Sunbathing is to be encouraged for immunosuppressed patients because of the increased osteoporotic risk.
- b) Sunbathing is to be avoided and skin exposed to the sun should be protected with a sunscreen agent with the highest possible sun block factor.
- c) He should substitute trace elements because of the intense insolation and high temperatures.
- d) To allow the skin to become accustomed to sun exposure, advise him to visit a solarium before vacationing.
- e) Reduce the immunosuppressive regimen so that vitamin D can be synthesized under UV exposure.

Question 10:

How much higher is the probability of patients with transplanted organs developing renal cell carcinoma compared to the general population?

- a) about 20-fold
- b) about 40-fold
- c) about 60-fold
- d) about 80-fold
- e) about 100-fold