Aftercare for Patients With Transplanted Organs

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

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.

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

Basic immunosuppression

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

### TABLE 1

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

<table>
<thead>
<tr>
<th></th>
<th>Ciclosporin</th>
<th>Tacrolimus</th>
<th>Sirolimus</th>
<th>MMF</th>
<th>Prednisolone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunosuppressive potency</td>
<td>+++</td>
<td>+++(+), +</td>
<td>++ (+), +</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Nephrotoxicity</td>
<td>++</td>
<td>++</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Neurotoxicity</td>
<td>+</td>
<td>++</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Hirsutism/hypertrichosis</td>
<td>++</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>++</td>
</tr>
<tr>
<td>Diabetogenicity</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>++</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>(+, +)</td>
<td>(+, +)</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Bone marrow suppression</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>–</td>
</tr>
</tbody>
</table>

*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.
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.

**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.

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 nephroprotective 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
livers, 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 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

<table>
<thead>
<tr>
<th>TABLE 2</th>
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<tbody>
<tr>
<td><strong>Estimated incidence of different malignancies in patients with transplanted organs compared to the general population</strong>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Malignancies</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphomas (PTLD)</td>
<td>30 to 50-fold higher incidence</td>
</tr>
<tr>
<td>Anogenital cancers</td>
<td>30 to 100-fold higher incidence</td>
</tr>
<tr>
<td>Renal cell cancer</td>
<td>elevated in risk groups (e.g. analgesic abuse, cyclophosphamide treatment)</td>
</tr>
<tr>
<td>Urothelial cancers</td>
<td>elevated in liver cirrhosis and/or chronic hepatitis B and/or hepatitis C</td>
</tr>
<tr>
<td>Hepatocellular carcinoma (HCC)</td>
<td></td>
</tr>
</tbody>
</table>

* modified from (8);

PTLD, post transplant lymphoproliferative disorder

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.
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.

**TABLE 3**

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Screening</th>
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<tbody>
<tr>
<td>Lymphomas</td>
<td>Medical history and clinical monitoring every three months in the first year, then once annually</td>
</tr>
<tr>
<td>Skin cancers</td>
<td>Dermatological evaluation including enoral and anogenital once annually, in high-risk patients every six months</td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>Gynecological evaluation once annually including PAP smear in all women &gt; 18 years and sexually active women &lt; 18 years</td>
</tr>
<tr>
<td>Anogenital cancers</td>
<td>Clinical examination once annually</td>
</tr>
<tr>
<td>Colorectal cancers</td>
<td>&gt; 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)</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>&gt; 50 years: digital palpitation and PSA assay once annually with a life expectancy &gt; 10 years</td>
</tr>
<tr>
<td>Pulmonary malignoma</td>
<td>No screening currently recommended</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>Women 50 to 69 years; mammography once every 1 to 2 years, women ≥ 70 years annual screening with life expectancy &gt; 8 years</td>
</tr>
<tr>
<td>Renal cell cancer</td>
<td>Screening not generally recommended, possible: sonography of own kidneys once every 1 to 3 years, urine cytology</td>
</tr>
<tr>
<td>Hepatocellular cancer</td>
<td>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</td>
</tr>
</tbody>
</table>

*modified from (8)*

**Osteoporotic risk**

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

**Clinically apparent osteoporosis**

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
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 (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 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.

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Translated from the original German by mt-g.

### Table 4

<table>
<thead>
<tr>
<th>Skin tumors</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaposi sarcoma</td>
<td>84-fold higher incidence</td>
</tr>
<tr>
<td>Squamous epithelial cancer of the skin</td>
<td>65 to 250-fold higher incidence</td>
</tr>
<tr>
<td>Squamous epithelial cancer of the lip</td>
<td>20-fold higher incidence</td>
</tr>
<tr>
<td>Malignant basaliomas</td>
<td>10-fold higher incidence</td>
</tr>
<tr>
<td>Melanomas</td>
<td>3.4-fold higher incidence</td>
</tr>
</tbody>
</table>

*1 modified from (15, 17)

**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.
Surgical interventions in already transplanted patients

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

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

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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