

Most transplant programs monitor cyclosporine A and tacrolimus trough concentrations on a regular basis. For the most part, these blood levels are useful but are imprecise indicators of immunosuppression or drug toxicity. While whole-blood trough concentrations are often higher in patients suffering from toxicity than in patients suffering from rejection, they may not differ significantly from those of patients with stable function. Indeed, there is considerable overlap between groups. In addition, much toxicity remains unrecognized, and there is considerable intra- and interpatient variability in the area under the time-concentration curve (a measure of drug exposure), and the peak and trough blood concentrations generated by any given dosage of either agent.

Urinary tract infections

Urinary tract infections are common after transplantation [14]. Fever, enlargement of the transplanted kidney and tenderness of the surrounding tissues may result from pyelonephritis. Elevations in plasma creatinine as a result of a urinary tract infection are usually modest and oliguria should not ensue.

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III.6 Evaluation of patients with delayed graft function

Guidelines

A. Hypovolaemia, urinary catheter obstruction or other urological complications, vascular complications, acute pyelonephritis, immunosuppressive drug toxicity and acute rejection should be excluded as the cause of delayed graft function. If present, these conditions should be treated promptly.

(Evidence level C)

B. Conditions that result in an increased risk of delayed graft function due to acute tubular necrosis should be avoided both in donor and recipient.

(Evidence level C)

C. Graft function should be monitored closely in patients with delayed graft function, and surveillance biopsies should be considered.

(Evidence level C)

Commentary on Guideline III.6: Evaluation of patients with delayed graft function [1]

After hypovolaemia and urinary catheter obstruction, *acute tubular necrosis* is the most common cause of diminished urine output in the immediate post-transplant period. Acute tubular necrosis results from donor injury and instability prior to organ procurement, leading in turn to donor hypovolaemia and hypotension, particularly in the presence of nephrotoxic or vasopressive drugs, from insults during harvesting, preservation and surgical implantation, and from prolonged cold and warm ischaemia times. Acute tubular necrosis is more commonly encountered when kidneys are harvested from oliguric or elderly patients or from individuals with pre-existing hypertension or peripheral vascular occlusive disease.

Following donor nephrectomy, harvested kidneys are usually flushed with and suspended in a cold solution closely resembling intracellular fluid. The period during which a kidney is maintained in this hypothermic state is the cold ischaemia time. The incidence of acute tubular necrosis increases steadily with cold ischaemia times >24 h. Warm ischaemia occurs when the kidney is devoid of blood supply and

not maintained in a hypothermic state. This may occur during the nephrectomy and at the time of implantation prior to vascular anastomosis. After 40 min of total warm ischaemia, the transplanted kidney will exhibit vascular spasm, platelet aggregation and thrombosis, causing impairment of the microcirculation.

Post-transplant acute tubular necrosis is usually defined by the need for dialysis in the first week following transplantation or as a failure to achieve a target decrease in creatinine level in the first days after transplantation. Depending on how it is defined, acute tubular necrosis affects 10–30% of cadaveric renal transplants.

As long as the kidney remains viable and shows no signs of rejection, no specific treatment is necessary other than continued administration of immunosuppressive medication, dialysis, optimal hydration and curtailed use of nephrotoxins. Patients seldom require more than a week or two of post-transplant dialysis but more prolonged recovery has been observed. Because kidneys with delayed graft function or acute tubular necrosis are more likely to develop acute rejection [2], it is important to follow these kidneys very carefully. It is furthermore important to recognize that cyclosporine A or tacrolimus nephrotoxicity, acute tubular necrosis and acute rejection may co-exist. Consequently, despite careful clinical observation, the precise diagnosis of the cause or causes of oliguria in this clinical setting may be difficult and a transplant biopsy may be necessary.

A recent multivariate analysis of acute post-transplant tubular necrosis identified the following risk factors: a recipient mean arterial blood pressure of <100 mm Hg, female donor to male recipient, donor age >50 years, cold ischaemia period >28 h and a peak panel reactive antibody of >50% [2]. It was also shown that delayed graft function on the basis of acute tubular necrosis is an independent risk factor for acute rejection and suboptimal graft function at 1 year [2].

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III.7 Evaluation of the patient with fever

Guidelines

A. Fever in a renal transplant patient should be evaluated promptly and treatment should be instituted as soon as possible.

(Evidence level C)

B. The minimal evaluation prior to treatment should include blood count, blood and urine cultures. The

optimal work-up should be designed to detect bacterial, viral, parasitic and fungal infections.

(Evidence level C)

Commentary on Guideline III.7: Evaluation of the patient with fever

Guideline A. Fever must be thoroughly evaluated in patients in the immediate and later post-operative period. Fever could be due to typical post-operative complications such as atelectasis, wound infection, urinary tract infection, line sepsis or drug-induced fever. Other sources of infection include possible transmission of infectious organisms with the allograft or the preservation fluid, or a previously undetected infection in the recipient. In the Efficacy Endpoints Database study, 32% of patients with confirmed acute rejection had fever [1].

A thorough history and careful evaluation should be performed for rashes, oral or pharyngeal lesions, crackles or wheezes, cardiac murmurs, perirectal or axillary abscesses, erythema or drainage from bladder or peritoneal dialysis catheter sites or dialysis fistula, otitis media or sinusitis, and the urine sediment and graft function should be examined [2].

More than 90% of the infections that occur in the first post-transplant month are due to technical problems related to the surgery and the management of devices such as the endotracheal tube, drains and catheters, and the vascular access. Although the daily dose of immunosuppressive agents is highest during this period, opportunistic infections do not emerge unless an unusual exposure occurs [3].

Guideline B. Urinary tract infections remain an important cause of post-transplant morbidity. From 1 to 6 months post-transplant there are two other causes of infection: clinical infection due to the effects of the modulating viruses CMV and EBV, and opportunistic infections due to *Pneumocystis carinii*, *Listeria monocytogenes* and *Aspergillus fumigatus*. Although relatively rare, these opportunistic infections are made possible because of the combination of sustained immunosuppressive therapy and the immunomodulating effect of certain viruses.

After 6 months, >80% of patients have good renal function and are on low-maintenance immunosuppression. These patients are at risk of the same infections as the general population: viral respiratory infections, pneumococcal pneumonia and urinary tract infections. Five to 10% of patients have less than optimal graft function, usually those who have received a lot of immunosuppression, and they often have chronic viral infection. These patients are at risk for opportunistic infections with *P. carinii*, *L. monocytogenes*, *A. fumigatus* and *Cryptococcus neoformans*. Finally, there is a small group of patients with chronic viral infections such as HBV, herpes virus (HV) or CMV who need effective antiviral therapy to prevent organ destruction [3].

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III.8. Infectious complications

III.8.1 Cytomegalovirus (CMV) infection

Guidelines

A. CMV antibody status (seronegative vs seropositive) must be systematically evaluated in both the donor and the recipient before or at the time of renal transplantation. It should be determined using a sensitive ELISA technique for specific IgG antibody. This distinction allows the recipient a better evaluation of the risk of CMV infection/disease and more adequate use of prophylactic treatment if appropriate.

(Evidence level A)

B. Because of the high prevalence of CMV infection early after renal transplantation, systematic surveillance for CMV infection is justified in all recipients during the first 3 months. This survey must be repeated if any febrile episode or evocative sign of CMV disease, for example thrombocytopenia or elevated liver enzymes, occurs during the first 6 months or later.

(Evidence level B)

C. The screening procedure for CMV infection should include virus detection in blood leukocytes using the PP65 antigenaemia technique or a more sensitive technique. For urine, the use of the rapid culture technique is an option.

Serial CMV serology tests should be performed to detect seroconversion from negative to positive and from IgM to IgG production.

(Evidence level B)

D. To decrease the risk of CMV infection in CMV seronegative recipients, they may receive CMV-secured blood products when appropriate. This can be achieved either by selection of blood products from CMV seronegative blood donors or after adequate filtration of CMV non-typed leukodepleted or leukofiltered blood.

(Evidence level C)

E. All CMV seronegative recipients receiving a kidney from a CMV seropositive donor (D+/R-) or from a CMV non-typed donor, should receive a prophylactic treatment for CMV infection initiated at the time of surgery.

(Evidence level A)

F. During the first year post-transplant, all CMV seropositive recipients, treated with polyclonal (ALG, ATG) or monoclonal (OKT3) antibodies either as induction

therapy or for an acute steroid-resistant rejection, should receive CMV prophylaxis.

(Evidence level B)

G. Prophylaxis must be selected from the following five different validated modalities of preventive treatment for CMV infection/disease:

(i) Weekly intravenous infusions of hyperimmune globulins for 6 weeks (with high dose) or for 16 weeks (with a lower dose).

(ii) Oral acyclovir administered for 12 weeks at a daily dose of 3200 mg (800 mg × 4) adjusted regularly to GFR.

(iii) Oral valacyclovir given for 90 days at a daily dose of 8000 mg (2000 mg × 4) adjusted regularly to GFR.

(iv) Ganciclovir administered for at least 14 days at a daily dose of 10 mg/kg (5 mg/kg × 2) adjusted regularly to GFR.

(v) Oral ganciclovir given for a longer period (2–12 weeks) at a daily dose of 3000 mg (1000 mg × 3) adjusted regularly to GFR.

(Evidence level A)

H. All recipients with documented CMV disease (symptomatic CMV infection) must receive a curative treatment. Currently, the only validated treatment is IV ganciclovir at a daily dose of 10 mg/kg (5 mg/kg × 2) adjusted to GFR for at least 14 days.

(Evidence level A)

Alternatively, they may receive IV ganciclovir for at least 5 days followed by oral ganciclovir at a daily dose of 3000 mg (1000 mg × 3) for a longer period (2–12 weeks).

(Evidence level B)

I. All recipients with asymptomatic CMV infection early after renal transplantation, documented by routine screening should receive a pre-emptive treatment in order to limit spread of the virus and avoid CMV disease. This can be achieved by early use of the validated curative treatment described above.

(Evidence level B)

J. Acute rejection episodes are clearly associated with CMV infection or disease. In this situation, CMV infection or disease should be treated first using IV ganciclovir as recommended and, only when necessary, acute rejection may be treated by methylprednisolone pulses. ALG/ATG/OKT3 should be avoided whenever possible.

(Evidence level C)

Commentary on Guideline III.8.1: Cytomegalovirus (CMV) infection

Background information on CMV [1]

Human CMV is a double-stranded DNA virus belonging to the family of beta herpes viridae. It is also named human herpes virus 5 (HHV5) and has a slow replication with intact and defective virions. It can replicate in many types of susceptible cells includ-

ing polymorphonuclear cells, monocytes, macrophages, lymphocytes, epithelial and endothelial cells. The virus has a DNA polymerase enzyme and no thymidine kinase, but does possess a protein kinase enzyme (encoded by UL 97). It has a linear genome with a unique long (UL) sequence of 200 kb and a unique short (US) sequence of 40 kb, separated by internal repeats (IR) and terminal repeats (TR) at each end. Replication involves expression of three classes of genes. These are immediate early (IE) genes encoding IE proteins or antigens (IEA), early (E) genes encoding for E antigens (EA) and late (L) genes encoding L antigens (LA). The pp 65 matrix protein is a late antigen.

Guidelines A and B [1,2]

The overall frequency of CMV infection after renal transplantation varies from 50 to 80% of patients, whereas CMV disease is observed in 30 to 60% of recipients. Primary CMV infection occurs in seronegative recipients (IgG specific antibody titre less than 1:64 dilution) who receive a kidney from a CMV positive donor. It is an early post-transplant infection and has a usual median time of detection of 5 weeks after renal transplantation. Secondary CMV infection occurs in seropositive recipients and corresponds to either a re-activation of latent virus favoured by immunosuppression or re-infection by a new strain of CMV. It usually occurs after transplantation with a median time of 3–4 months.

CMV disease is a CMV infection accompanied by sign(s) and/or symptoms of the disease. The most common of these is fever ($>38^{\circ}\text{C}$). Leucopaenia, thrombocytopenia and elevated ALT are also frequent manifestations. The most severe form is CMV pneumonia which carries a high risk of mortality. CMV retinitis is mainly observed in AIDS patients and has a poor visual prognosis.

CMV disease has been the major cause of early post-transplant mortality, and still remains the first cause of morbidity in renal transplantation. For this reason, it is mandatory to screen systematically for CMV infection.

A CMV seropositive donor carries a risk of CMV transmission to the recipient. CMV seronegative recipients are at high risk of developing CMV primary infection. The highest risk combination of donor and recipient is D+ to R-, which produces a 60–80% chance of CMV infection and 60–80% of CMV disease in the recipient.

Guideline C: Diagnosis of CMV infection

CMV infection can be directly detected by isolation of the virus itself, by detection of specific CMV antigens, or by detection of specific CMV genomic sequences. The virus can be detected in different biological fluids, but blood leukocytes and urine are commonly used.

Virus isolation/identification [3,4]: Classical culture takes at least 7 days with fibroblasts, and CMV is responsible for a specific cytopathic effect. Rapid culture needs only 2 days, is performed on fibroblasts, and the virus can be identified by detection of IE antigens with specific monoclonal antibodies.

CMV antigenaemia (PP65) assay [3,4]: This is currently the most useful test for detection of CMV in the blood. Blood leukocytes are isolated and fixed on glass slides. A monoclonal antibody specific for late antigen, called PP65, is used in an immunoperoxidase technique to detect and count infected cells (positive nuclei). The technique is very fast (<24 h) with a sensitivity of 89% and a specificity of 100%. Some groups fix a cut-off value for the number of infected cells. In primary CMV infection, this test is positive 7 days before CMV disease.

Detection of CMV nucleic acids: These tests involve application of molecular biology techniques:

(i) Leukocyte CMV DNA [3–5]. A simple polymerase chain reaction (PCR) with specific primers allows the detection of CMV genomic sequences. The sensitivity is high (95–100%), but the specificity is low (33%). The predictive positive value (PPV) is 54%, and the predictive negative value (PNV) is 100%. It allows a diagnosis in primary CMV infection 11 days before CMV disease. A semi-quantitative assay with a cut off value of 7000 copies/sample improved the specificity to 89% and PNV to 82% [5]. The test could be run on plasma, but with lower sensitivity.

(ii) Leukocyte CMV-mRNA [6]. This is also called nucleic acid sequence-based amplification (NASBA). Blood leukocytes are isolated and RNA extracted. The first step is reversed transcription to transform RNA in cDNA, followed by PCR with specific primers for IE, or E and L genes. This technique allows the earliest detection at 16 days before primary CMV disease.

Serological titration [3,4]: This is done using classical ELISA techniques. Antibody specificities are directed against capsid, matrix and/or nuclear proteins. Specific antibody of the IgM type usually indicates a primary CMV infection or re-infection with a new strain. Specific IgG antibodies give a negative result (<64 titre) in seronegative recipients/donors and a positive result (>64) in seropositive recipients/donors. Any significant increase in IgG titre (>4 -fold) indicates CMV infection, but is a rather late indicator.

Guideline D [7]

There is a risk of transmission of CMV by blood products from CMV seropositive blood donors, because of the latent infection common to all herpesviridae viruses. The virus is present in the peripheral blood mononuclear cells (PBMC) and does not replicate or replicates at a very low level. Any replication would be targeted by immunosuppressive drugs.

Blood products could be selected only from CMV

seronegative donors (secured gift) as in bone-marrow transplantation. Alternatively, adequate pre-filtration of blood or red blood cells would lead to the exclusion of the great majority of PBMC. This is an important point of consideration during the perioperative period.

Guidelines E and F [2,8]

All CMV seronegative recipients are at a higher risk of CMV disease with a potential risk of death from CMV pneumonia. With the availability of efficient preventive treatment, it has become mandatory to initiate prophylactic treatment in these recipients. Protection could be avoided in rare donor recipient combinations of D-/R-, but both should be tested with the same technique and all blood products given to the recipient should be secured against CMV infection.

It was also clearly shown that in CMV seropositive recipients, the risk was greater if patients were treated with biological agents such as ALG/ATG or OKT3 [9] either as induction therapy or as anti-rejection treatment. This observation leads to the recommendation made in guideline F. However this guideline does not apply with the use of anti IL2 receptor mAbs like basiliximab or daclizumab, which do not increase the risk of viral infections including CMV infection.

Guideline G

There are five possibilities for prevention:

(i) Selection of an organ from a *CMV seronegative donor* [10]. This could be justified for a CMV seronegative recipient. In the general population, the proportion of CMV seronegative individuals ranges from 40% in well developed countries to only a few percent in less well developed countries. In either case, additional selection criteria will limit the possibility of renal transplantation and therefore this protocol is impractical.

(ii) *CMV hyperimmune globulin* [11,12]. Most experience in this area has been obtained in bone marrow transplantation where the recommended dose is 400 mg/kg once a week for 6 weeks. Snyderman *et al.* [11] reported a randomized trial of CMV hyperimmune globulins in the treatment of renal transplantation recipients with the combination (D+/R-). Fifty-nine patients were administered a relatively low dose of 150 mg/kg at time of surgery, followed by 100 mg/kg at weeks 2 and 4, and then 50 mg/kg at weeks 6, 8, 12 and 16. With this protocol, CMV infection is not modified, but CMV disease is significantly decreased (21% in the study group vs 71% in the control group; $P=0.01$). The recommendation is either 400 mg/kg hyperimmune globulin once a week for 6 weeks or a lower dose for a longer time (16 weeks, 150 mg \times 1, 100 mg/kg \times 2, 50 mg/kg \times 4).

(iii) *Oral acyclovir* [13,14]. The trial was performed in 104 renal transplantation patients from day 0 to week 12. The dose administered was 800 mg every 6 h adjusted to GFR. The maximum dose was

3200 mg/day. CMV infection was reduced to 36% compared with 61% ($P=0.01$) with an even greater efficacy on CMV disease, reducing it to 7.5% from 29.0% ($P=0.002$). In the combination D+/R-, the reduction was very significant (17 vs 100%; $P=0.005$). Thus the recommendation is acyclovir 3200 mg/d for a normal GFR over 12 weeks.

(iv) *IV infusion or oral ganciclovir* [15–18]. Prophylaxis with IV ganciclovir was first established in heart transplantation [15]. Treatment for 14 days has also been validated in renal transplantation. Ganciclovir treatment of 113 seropositive recipients with ALG/ATG treatment showed a significant reduction in CMV disease with a relative risk (RR) of 0.21 (0.12–0.64) compared with controls who did not receive ganciclovir. A meta-analysis [17] confirmed the efficiency of such treatment with a significant reduction in CMV infection (RR=0.74, 0.62–0.88; $P<0.001$) and in CMV disease (RR=0.50, 0.40–0.62; $P<0.001$). Therefore the recommendation is IV treatment for at least 14 days at a dose of ganciclovir 5 mg/kg twice daily adjusted to GFR.

Oral ganciclovir [18] is now available with good bioavailability. The recommended dose is 1 g three times per day adjusted to GFR for a longer period (weeks 2–12). The use of ganciclovir for prophylaxis carries in theory a risk of future resistant strains, but nothing has, as yet, been concluded.*

(v) *Oral valacyclovir* [19]. Valacyclovir is a prodrug transformed in acyclovir, but its bioavailability has been increased 3–5 times. In a randomized, placebo controlled trial, the effect was most pronounced in the D+/R- combination with a reduction of CMV disease at 3 months from 45 to 3% and at 6 months from 45 to 16% ($P=0.001$). In seropositive recipients, the reduction was from 6 to 0% at 3 months and from 6 to 1% at 6 months ($P=0.03$). In addition, a significant reduction from 52 to 26% ($P=0.001$) was shown in acute rejection frequency. The dose administered was 2 g four times a day over 90 days adjusted to GFR.

In general, with most of these preventive procedures, there is a significant reduction in CMV disease but not always in CMV infection.

Guideline H [20,21]

Because untreated CMV disease still carries a high risk of morbidity and mortality in transplant recipients, it is mandatory to use curative treatment in all recipients with documented CMV disease.

IV ganciclovir has been demonstrated to be a specific antiviral agent and is the recommended treatment. It should be used for at least 14 days or for a longer time in cases of persistent CMV disease or CMV infection. Oral ganciclovir is more convenient and may be used to complete the treatment. There is a case for longer treatment (1–3 months) in organ transplantation.

* Since submission the following paper has been published: Limaye AP, Corey L, Koelle DM, Davies CL, Broeckh M. Emergence of ganciclovir-resistant cytomegalovirus disease among recipients of solid-organ transplants *Lancet* 2000; 356: 645–649

It is recommended to adapt immunosuppression in case of severe CMV disease by stopping any ATG, ALG or OKT3 treatment and decreasing or stopping immunosuppressive medications. In the case of viral or clinical resistance to IV ganciclovir, the compound foscarnet can be used, but it is nephrotoxic. The protocol is IV infusion of 60 mg/kg three times daily adjusted to GFR for 2 weeks.

Guideline I [22]

In the early post-transplantation period (0–6 months), the replication of CMV in blood and/or urine carries a risk of further spread of the virus and the development of CMV disease, including CMV pneumonia. There is also a risk of acute rejection triggered by CMV infection. Acute rejection episode requires additional immunosuppression (methyl prednisolone IV boluses or ALG/ATG) which could further worsen CMV spread and disease. Therefore it is wise to administer pre-emptive treatment to these patients before the occurrence of CMV disease [22].

Six months after transplantation, the detection of CMV infection could represent a persistent or chronic infection, which carries the risk of chronic rejection in transplantation of some organs (heart transplantation). However, this is not well documented for renal transplantation. In cases of persistent or chronic infection, patients may also receive pre-emptive treatment with oral ganciclovir for >2 weeks (1–3 months).

Guideline J. Acute rejection episode and CMV infection/disease [23]

Acute rejection results in an increased use of immunosuppressive medication, including polyclonal or monoclonal antibodies, which in turn increase the risk of CMV infection and disease. On the other hand CMV infection can trigger an acute rejection episode. When an acute rejection episode is diagnosed in a patient with CMV infection or disease, the CMV infection should be treated first with IV ganciclovir (for efficient and fast control of infection) for 2 weeks, followed by oral ganciclovir. If rejection is not resolved after a few days of ganciclovir treatment given for at least 3 days, treatment should be with IV steroid pulses alone. Polyclonal and monoclonal antibodies must be avoided unless graft function is seriously jeopardized.

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III.8.2 Hepatitis B virus infection

Guidelines

A. Transplant recipients positive for hepatitis B surface antigen (HBsAg) should be carefully followed after transplantation with monitoring of liver function and viral replication (HBV-DNA). This follow-up should also detect early infectious complications.

(Evidence level C)

B. Tailored immunosuppression and possibly specific antiviral therapy may be recommended in these patients.

(Evidence level C)

Commentary on Guideline III.8.2: Hepatitis B virus infection (see also section I.5.2: Infectious risk)

Guideline A. As commented before, the most important clinical effects of HBV infection are seen in the late post-transplant period [1–4]. In the first year after transplantation, clinical manifestations of liver disease are usually not evident but hepatitis B contributes to the overall state of immunosuppression [2]. The combination of chronic immunosuppression and HBV infection actually favours the risk of opportunistic infections (*P. carinii*, *Aspergillus*, *L. monocytogenes*) between 1 and 6 months after transplantation [2]. The majority of HBV-positive transplant patients have good renal function and quality of life during the first post-transplant year. This clinical course seems to be similar in HBsAg-positive patients who receive kidneys from HBV-positive donors compared with those transplanted with kidneys from HBV-negative donors [6]. Recipients of kidneys from HBsAg and Ab-negative but HBe antibody-positive donors have a small risk of hepatitis B seroconversion, but have no additional risk of graft failure or short-term morbidity and mortality [7].

Guideline B. [8–11] As discussed previously, hepatitis B contributes to the overall state of immunosuppression. Also, immunosuppression induces viral replication. Both favour the presence of opportunistic infections. Therefore, immunosuppression should be administered cautiously, avoiding routine OKT3, ATG or ALG for induction. Maintenance immunosuppression should be modulated depending on histological lesions [10]. Antiviral therapy has been administered with encouraging results [8]. Thus, lamivudine or adenosine arabinoside and gamma globulin may be administered early in the course of HBV infection.

Recommendations

For HBsAg-positive renal transplant patients several measures should be recommended during the first post-transplant year:

(i) *Immunosuppression.* These patients should receive the local standard immunosuppressive therapy for

induction but, if possible, avoid the use of OKT3, ATG or ALG [9]. In the maintenance period, reduction of immunosuppression early in the course of HBV infection may be useful in preventing long-term complications [3].

(ii) *Clinical follow-up.* Patients should be followed monthly in the first year. Clinical symptoms, renal function and particularly liver function and serology for HBV infection should be monitored. Also, febrile episodes should be diagnosed early and treated. Modification of immunosuppression is important as discussed above.

(iii) *Liver function.* Serum transaminases, particularly ALT, bilirubin, gamma-glutamyl-transpeptidase and alkaline phosphatase should be tested at each assessment. Abdominal echography should be performed at transplantation.

(iv) *When is a liver biopsy necessary?* In patients with evidence of acute hepatitis evidenced by acute elevation of ALT—3-fold or more over the upper limit of normal laboratory values on two consecutive determinations on at least 3 different days.

In patients that will be treated with antiviral drugs. Especially in patients who develop a cholestatic pattern of liver disease evidenced by jaundice, hyperbilirubinaemia and mild to moderate elevations of ALT with deterioration of liver function. In these cases early liver biopsy is mandatory [6].

(v) *HBV serology monitoring.* In the first post-transplant year, HBV serology should be tested at least once. HBV-DNA by PCR is the gold standard to assess viral replication [2,3]. In patients with acute hepatitis, complete HBV serology including hepatitis delta should be tested.

(vi) *What patients should be treated?* Patients with viral replication after transplantation who are HBeAg-positive and DNA-HBV-positive should be treated.

Despite promising results with lamivudine, there is currently insufficient evidence to recommend the early treatment of all HBV-infected patients after transplantation.

(vii) *Treatment of HBV infection* after renal transplantation. Lamivudine therapy may be used, but to date a practical guide to treatment in these patients remains unclear, except in those with fibrosing cholestatic hepatitis (FCH) [9].

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III.8.3 Hepatitis C virus infection

Guidelines

A. HCV antibody positive patients should be carefully followed after transplantation with monitoring of liver disease, viral replication (HCV-RNA) and renal disease. (Evidence level B)

B. Tailored immunosuppression is recommended in these HCV antibody-positive patients to reduce the risk of death from infectious diseases. (Evidence level C)

C. Interferon therapy should not be used during transplantation in HCV antibody positive patients with chronic active hepatitis. Currently no effective therapy is available. (Evidence level B)

Commentary on Guideline III.8.3: Hepatitis C virus infection (see also section 1.5.2: Infectious risk)

Guideline A. Renal transplant patients with HCV infection may develop progressive liver disease in the long term [1–6]. Progression occurs at a slower rate than liver disease induced by hepatitis B virus. Chronic hepatitis is the most frequent histopathological diagnosis [4–10], leading to cirrhosis in the long term. Repeated biopsies demonstrate that liver disease is progressive [7]. Strong immunosuppression, pre-transplant liver disease dependent on severity and time of evolution, and time after transplantation are risk factors associated with the development of severe liver disease [5]. HCV RNA titres and genotype do not appear to influence the course of liver disease [7,9].

Over the short term, particularly during first year, liver disease in patients due to HCV infection is not usually complicated, showing an excellent quality of life similar to HCV-negative patients [3]. The exception

is represented by the presence of fibrosing cholestatic hepatitis (FCH) [11]. This picture has been described in HCV-positive patients like HBV-positive patients, with identical clinical, pathological characteristics and similar course [11,12]. FCH can appear early after transplantation, even during the first 6 months. If a severe cholestatic pattern is observed, early diagnosis by biopsy should be made and immediate therapy with interferon started as this has been reported to modify the ominous course [13].

HCV infection has been associated with membrano-proliferative glomerulonephritis (GN) with or without cryoglobulinemia and membranous GN [14]. Recently, renal thrombotic microangiopathy associated with anticardiolipin antibodies in HCV-positive patients has been observed [15]. A possible association between HCV infection and transplant glomerulopathy has also been suggested [16]. Therefore, renal function and proteinuria should be monitored in these patients to rule-out associated glomerular lesions. In fact, MPGN and MGN can appear early in the first post-transplant year. Also, immunological assessment by cryoglobulins, complement and rheumatoid factor should be performed.

Guideline B. La Quaglia *et al.* [17] reported in 1981 that patients with non-A non-B hepatitis had ‘a marked increase of life-threatening extrahepatic infections’. Rao and Ma [18] described sites of infection and the type of organism identified in 86 patients with hepatitis B or C. These patients had more infections in the post-operative period, more infections per patient and an increased incidence of potentially fatal infections involving the central nervous system, lungs and bloodstream compared with patients without hepatitis. We have also found a significantly higher frequency of severe infections (cytomegalovirus, tuberculosis, sepsis and *P. carinii* infections) [14]. Therefore, infection is an important complication and in patients with severe chronic liver disease and cirrhosis, sepsis is a frequent cause of death.

Infections are clearly also favoured by heavy immunosuppression. Therefore, in HCV-positive patients, given the frequency of life-threatening infection, immunosuppression should be prescribed cautiously in each patient. Also, in these patients, close outpatient monitoring to detect infective episodes as early as possible is mandatory.

Guideline C. Alpha interferon can induce acute rejection in allograft recipients [19]. Therefore, the use of interferon is not recommended after renal transplantation, except in cases of FCH. At present, there is no effective therapy and decreased immunosuppression is the only therapeutic approach currently available. Ribavirin therapy may represent a promising alternative.

Recommendations

For renal transplant patients with pre-transplant HCV infection, several measures should be recommended in the early period post-transplant:

(i) *Immunosuppression.* Patients should receive the standard local initial immunosuppressive treatment, avoiding if possible the use of OKT3, ATG and ALG. In the maintenance period, early reduction of immunosuppression may be useful in preventing long-term complications.

(ii) *Clinical follow-up.* Patients should be reviewed monthly during the first year. Renal function, proteinuria, liver enzymes and serology (every 6 months ELISA2 and HCV RNA once a year) should be monitored. Febrile episodes should be diagnosed and treated early.

(iii) *Liver function.* Serum transaminases, especially ALT, bilirubin, gamma-glutamyl-transpeptidase and alkaline phosphatase should be tested at each assessment. Abdominal echography should be performed at the time of transplantation.

(iv) *HCV infection serology.* Anti-HCV antibodies (ELISA2 or ELISA3) and serum HCV RNA (by PCR) should be tested once a year. Serum HCV RNA is the gold standard to diagnose ongoing infection [2]. Genotype should be known at transplantation.

(v) *When should a liver biopsy be performed?* In patients fulfilling the criteria for chronic liver disease. In patients treated with antiviral drugs. In patients who develop a severe cholestatic pattern of liver disease (jaundice, hyperbilirubinaemia and mild to moderate elevation of ALT) with deterioration of liver function. In these cases early liver biopsy is mandatory.

(vi) *Treatment for HCV infection* after renal transplantation. Alpha interferon is not recommended after transplantation. The only indication where it is recommended is FCH.

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III.9 Rejection: Diagnosis and treatment

III.9.1 Clinical and pathological diagnosis of acute rejection

Guidelines

A. Acute rejection should be suspected in patients with established graft function who experience a rapid increase within 1–2 days in their plasma creatinine concentration of >10–25% over baseline with or without decreased urine output, graft tenderness or fever in the absence of other obvious causes of acute graft dysfunction. The baseline plasma creatinine is the most recent creatinine concentration prior to the diagnosis of rejection.

(Evidence level C)

B. It is recommended to exclude other causes of graft dysfunction and to take a biopsy to confirm the clinical diagnosis of acute rejection. The biopsy result can be used to guide the intensity of anti-rejection therapy or to assess the long-term prognosis.

(Evidence level B)

C. Reporting of biopsies should be standardized according to an internationally agreed scheme to reflect the histopathological pattern and severity of the rejection episode.

(Evidence level B)

D. In patients with prolonged delayed graft function, surveillance biopsies should be considered to detect or exclude acute rejection episodes.

(Evidence level B)

Commentary on Guideline III.9.1: Clinical and pathological diagnosis of acute rejection

Guideline A: In the Efficacy Endpoints Database study [1] all presumed rejection episodes occurred in patients

whose plasma creatinine concentration increased by at least 19% or 0.2 mg/dl (18 μ mol/l) above the most recent reading. The increase in the creatinine level was as great as 1515% or 19.7 mg/dl (1734 μ mol/l), with a mean of $77 \pm 124\%$ or 1.4 ± 1.9 mg/dl (123 ± 167 μ mol/l) and a median of 46% or 1.0 mg/dl (88 μ mol/l), whereas the time frame over which this increase developed was not specified. Plasma creatinine concentrations expressed as absolute value, absolute increase, or relative percent increase above the most recent plasma creatinine concentration were also studied in relation to the final diagnosis. Although the absolute increase in plasma creatinine concentration gave the best correlation with confirmed acute rejection [1], the percent change is more reliable in patients with a low muscle mass, such as children and older recipients, as well as in patients with impaired function. We therefore recommend assessing changes of function as a percentage change from baseline over a period of 1–2 days.

In the pre-cyclosporine era most acute rejection episodes were accompanied by one or more clinical signs such as fever, graft tenderness or decreased urine output [2]. In contrast, most acute rejection episodes today occur without clinical signs. In the Efficacy Endpoints Database study, 54% of patients with confirmed acute rejection had no clinical signs while 32% had fever, 28% had decreased urine volume and 25% had one other sign. Such clinical signs have a low specificity and can also be observed in renal dysfunction of other aetiologies.

Risk factors for acute rejection: Retransplantation, donor age > 50 years, an organ from a female donor, mismatches for broadly cross-reactive class I MHC antigens, HLA-DR mismatches and delayed graft function are independent risk factors for biopsy proven acute rejection episodes [Sijpkens YWJ, Paul LC *et al.*, manuscript in preparation].

Guidelines B, C and D.

Diagnostic work-up for acute rejection: While an acute rejection episode is an immune-mediated process, there are no routine tests to prove the immunological nature of the suspected rejection episode. Many tests have been proposed but none is specific or sensitive enough to diagnose acute rejection reliably. Therefore, other acute events that alter graft function such as drug toxicity, cytomegalovirus nephritis, dehydration or obstruction of the urinary tract must be excluded. The most important considerations in the differential diagnosis are acute rejection vs toxicity of calcineurin inhibitors.

The renal biopsy is still considered the gold standard for the diagnosis of rejection as demonstrated by the 85% biopsy rate in the Efficacy Endpoints Database [1]. A biopsy is advisable after exclusion of vascular and urological complications, including a lymphocèle. Many clinical studies require biopsy proof [3,4] of suspected acute rejection episodes. The risks and bene-

fits of a renal transplant biopsy, the merits and drawbacks of empirical therapy, and the overall effect of intensifying immunosuppression must be considered for patients not involved in clinical trials [5].

A recent preliminary study illustrated that the clinical prediction is generally poor as a correct biopsy diagnosis was predicted in only 43% of cases, a partially correct diagnosis was predicted in 28%, and incorrect diagnosis was predicted in 26% of cases [6]. In another study, renal transplant biopsy findings altered patient management in ~40% of cases where a presumptive diagnosis had been made on the basis of clinical and laboratory findings [7]. Importantly, in 19% of cases unnecessary immunosuppression was avoided. Patients who had a change in management because of the biopsy findings displayed a response to therapy and graft survival rate similar to that of patients with no post-biopsy management change, suggesting that the changes made after the biopsy were appropriate [7].

Renal transplant biopsies are currently taken using a needle mounted in an automatic spring-loaded device under ultrasonographic guidance (gun-biopsy). The gun-biopsy technique has a higher diagnostic yield and fewer complications than the conventional manual 'Tru-Cut' technique [8]. The needle size used is 14, 16 or 18 gauge. The 14 gauge needle is preferred for histopathological evaluation but has theoretically a higher risk of bleeding complications.

The rate of serious complications of the procedure is low. In a study of >650 transplant biopsies, there were no deaths or graft losses due to biopsy complications [9]. Bleeding was the primary complication of biopsy; 1.1% of biopsies were complicated by a bleed that required blood transfusion and in 0.4% of cases embolisation of a bleeding kidney was performed. The mean decrease in haemoglobin after all biopsies was 0.2 mmol/l (Standard Deviation 0.5). In 3% of biopsies blood clots were formed in the bladder and a urinary catheter had to be inserted. Macroscopic and microscopic haematuria was found after 9 and 64% of biopsies, respectively [9].

A bleeding diathesis and severe hypertension that cannot be controlled by appropriate medication are contra-indications for a percutaneous biopsy.

Histopathological diagnosis of acute rejection: Acute rejection is a T-cell mediated process in which donor-directed cytotoxic T-lymphocytes and delayed-type hypersensitivity reactions cause graft damage. Consequently, acute rejection is characterized by tissue infiltration with T lymphocytes, monocytes and macrophages. The pattern of tissue damage is categorized as interstitial or predominantly vascular. Acute interstitial rejection is typified by varying degrees of interstitial tissue infiltration by mononuclear cells. In more severe stages, these cells invade the tubules and destroy tubular epithelial cells causing tubulitis. Approximately 70–85% of acute rejection episodes are predominantly interstitial. Acute vascular rejection is characterized by endovascular inflammation with or without transmural extension of the inflammatory reaction. These changes

are often accompanied by variable degrees of interstitial inflammation. Vascular rejections occur in 15–30% of acute rejection episodes.

Some acute rejection episodes are characterized by the presence of circulating antibodies against donor HLA or non-HLA antigens [10–12]. Such antibodies may contribute to graft injury, albeit that not all donor-specific antibodies formed following transplantation are associated with acute rejection [13]. Although the histopathology of such rejections is not specific, certain morphological features are helpful in indicating antibody-mediated rejection, such as the presence of neutrophils in peritubular capillaries, fibrinoid necrosis of the vessels and glomerular thrombosis [10,14]. Immunofluorescent staining for IgG, IgM, C3 or fibrin are not helpful [14], but C4d deposits in the peritubular capillary walls distinguish acute humoral rejection from acute cellular rejection [15].

The Banff scheme of allograft pathology: The use of the Banff scheme [3] to classify allograft pathology provides for a more rational allocation of immunosuppressive therapy than does descriptive terminology and may decrease the incidence of therapeutic complications [16].

The latest Banff scheme on allograft pathology defines three types of acute or active rejection [4]. Type I rejection is tubulointerstitial rejection without arteritis. Grade IA rejection represents cases with significant interstitial infiltration (>25% of parenchyma affected) and foci of moderate tubulitis (>4 mononuclear cells per tubular cross section or group of 10 tubular cells) whereas grade IB rejections show significant interstitial infiltration (>25% of parenchyma affected) and foci of severe tubulitis (>10 mononuclear cells per tubular cross section or group of 10 tubular cells). Type II rejections are vascular rejections where type IIA represents cases with mild to moderate intimal arteritis and type IIB rejections are those with severe intimal arteritis comprising >25% of the luminal area. Type III rejections show transmural arteritis and/or arterial fibrinoid change and necrosis of medial smooth muscle cells.

Biopsies with only mild inflammation are graded 'borderline or suspicious for rejection' [4].

Rejections due to anti-donor antibodies are categorized as a separate group in the Banff scheme. The biopsy may also reveal changes considered not due to rejection.

Prognostic value of the diagnostic biopsy:

Short-term prognosis. The Efficacy Endpoint Conference reported that the Banff grading correlates with measured loss of renal function, steroid responsiveness and 1-year graft survival [17]. However, with the current immunosuppressive drug regimens, graft loss due to acute rejection is rare and biopsies are not likely to indicate the short-term prognosis.

Intermediate-term prognosis. Several studies have shown that the histopathological pattern of acute

rejection correlates with later graft loss. Interstitial acute rejection episodes have a better prognosis up to 5 years than predominantly vascular rejections [18,19]. Other histological features associated with an impaired intermediate-term outcome are the amount of macrophages [20] or plasma cells [21] in graft biopsies at the time of rejection.

Prognostic value of surveillance biopsies:

Delayed graft function. In patients with delayed graft function secondary to preservation and ischaemic damage, plasma creatinine concentrations are not useful for reliably assessing graft function. As delayed graft function is associated with an increased acute rejection risk but most acute rejection episodes lack constitutional symptoms, many centres often perform weekly surveillance biopsies to monitor for acute rejection episodes until the graft has recovered.

Short- and intermediate-term prognosis. Some centres perform surveillance or protocol biopsies frequently in the first 6 months after transplantation, irrespective of graft function or other clinical parameters. In about a third of such biopsies, cellular infiltrations are observed and are considered 'subclinical rejection episodes'. The cellular infiltrate in subclinical rejection is intermediate between that found in grafts with no rejection and grafts with manifest acute rejection [22]. Expression of macrophage activation markers also helps to distinguish subclinical from clinical rejection episodes [22].

The importance of borderline or modest cellular infiltration in grafts with apparently unimpaired function is unknown. In 72% of cases, 'borderline lesions' in biopsies taken because of an acute or persistently elevated serum creatinine level, do not evolve into acute rejection episodes within 40 days if left untreated [23]. Anti-rejection therapy prompted by cellular infiltrations in surveillance biopsies results in an improvement in renal function in only a small fraction of patients, whereas increasing baseline maintenance immunosuppression fails to suppress these subclinical rejections [24]. However, treatment of subclinical rejection episodes with corticosteroids results in a significant decrease in early and late acute rejection episodes, a reduced chronic tubulointerstitial score at 6 months and a lower serum creatinine level at 24 months compared with control patients [25].

It seems prudent to perform surveillance biopsies in patients with delayed graft function in whom the diagnosis of acute rejection cannot be made on clinical grounds. The data justifying routine biopsies to detect subclinical rejections is, as yet, only suggestive and requires confirmation.

The 'late' protocol biopsy. Interest has recently emerged in defining parameters in the early post-transplant months that reliably predict the intermediate-term prognosis [26]. Several groups have examined the prognostic value of 6 or 12 month biopsies on the 5-year outcome and found that chronic changes such as interstitial fibrosis, tubular atrophy, glomerulopathy and vasculopathy all correlate with long-term out-

comes [27–31]. At this stage, it is unclear whether interventions prompted by biopsy findings will improve the intermediate- or long-term outcome.

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III.9.2 Treatment of acute rejection episodes

Guidelines

A. For the treatment of the first acute cellular rejection episode, high doses of intravenous methylprednisolone are recommended. This treatment is expected to reverse most acute rejection episodes. Although the use of polyclonal (ATG/ALG) or monoclonal (OKT3) antibodies as first-line therapy is effective, their adverse event profile and cost mean that the use of corticosteroids as first-line therapy is preferred.

(Evidence level C)

B. ATG/ALG or OKT3 are recommended for the treatment of severe acute rejection episodes (Banff grade III), recurrent acute rejection episodes, corticosteroid-resistant rejection episodes or in patients with contraindications to corticosteroids.

(Evidence level C)

C. In patients with recurrent rejection after anti-T lymphocyte antibody treatment, it is recommended to modify baseline immunosuppression.

(Evidence level B)

D. ALG/ATG is preferable to OKT3 for the treatment of acute rejection episodes. Although both preparations are effective in reversing such episodes, OKT3 has a slightly poorer adverse event profile because of the first-dose effect.

(Evidence level B)

E. Rabbit anti-T lymphocyte antisera are preferable to horse anti-T lymphocyte antisera.

(Evidence level A)

Commentary on Guideline III.9.2: Treatment of acute rejection episodes

Guidelines A, B and C

Treatment of a first acute rejection episode.

Corticosteroid therapy is still the most commonly used primary treatment for acute rejection episodes. In the Efficacy Endpoints Conference Database, 88% of the rejection episodes were treated with corticosteroids [1]. For treatment of an acute cellular rejection episode, 250, 500 or 1000 mg bolus doses of methylprednisolone should be administered intravenously for 2–4 days. Successful responses are more common in recipients without fever (72 vs 61%; $P < 0.004$) and in recipients experiencing less than a Banff grade III rejection (92 vs 75%; $P = 0.009$). Success of steroid treatment is identifiable by day 2 or 3 of therapy. In the Efficacy Endpoints Conference Database, the serum creatinine concentration on days 2 and 3 of therapy as a ratio of the rejection creatinine were 104% and 105% respectively in patients with a successful response vs 122% and 125% in case of treatment failure ($P < 0.0001$). The most important advantages of corticosteroids are the ease of administration and their low cost.

The use of anti-lymphocyte or OKT3 monoclonal antibody therapy as first-line therapy for acute rejection results in rejection reversal from 67 to 98% of cases [2,3]. In the Efficacy Endpoints Conference database, the serum creatinine concentration decreased significantly below the rejection creatinine level on day 5 of treatment in patients with a successful course but remained at or above the rejection creatinine concentration in those who failed the treatment (90 vs 135%; $P < 0.01$) [1]. Because of the adverse event profile and cost considerations, many centres reserve the use of anti-T lymphocyte antibody therapy for severe acute rejections (Banff IIB or -III), second rejection episodes or steroid-resistant rejections. For rescue treatment with anti-lymphocyte antibody therapy, a response is also usually evident after 5 days of therapy (days 9–10 of rejection) when the creatinine concentration will begin to decrease and continues to lower throughout the 10-day course of therapy [1].

Assessment of therapy outcome. It has been proposed to define a successful response to therapy as a relative serum creatinine concentration value that is $< 110\%$ of the day 0 (or rejection) creatinine level, and returns

to the day 0 creatinine level or lower during the first 5 days of therapy [4]. Therapy success is best reflected by relative changes in the serum creatinine concentration rather than by absolute levels, probably because the latter depend more on the severity of the rejection and the time of diagnosis than on the efficacy of therapy.

The Efficacy Endpoints Database group has suggested defining steroid-resistant rejection as an acute rejection episode that has been treated only with 250–1000 mg of methylprednisolone and where the serum creatinine concentration increases as early as the third day of therapy, and continues to rise unless treated with a different anti-rejection therapy [4]. It is important to emphasize that the qualification of steroid resistance is a clinical one. Renal biopsies taken after initial steroid treatment overestimate the incidence of steroid resistance, as shown in a recent study in which patients with a steroid-responsive acute rejection episode displayed histopathological signs of acute rejection in 60% of biopsies taken 5 days after therapy and in 27% of biopsies taken 10 days after therapy [5]. Similarly, protocol biopsies taken 1–2 weeks following the end of a 7–14 day course of anti-lymphocyte antisera for primary rejection, showed an improvement of at least one Banff grade in 58% of patients, but two-thirds of the biopsies showed residual inflammation, despite clinical success in 86% of cases [6].

Treatment of acute rejection episodes refractory to standard therapy. The initial approach in the treatment of steroid-resistant rejection episodes is to switch to anti-T-lymphocyte preparations. However, in a minority of patients repeat therapy with anti-T-cell antibody preparations does not provide an optimal solution while these patients continue to experience rejection refractory to standard therapy with corticosteroids. In such cases, a change in baseline immunosuppression may be considered.

In one study of patients with refractory rejection while on CsA maintenance treatment, CsA was discontinued and replaced by tacrolimus. Graft function improved in 78% of patients, stabilized in 11% and showed progressive deterioration in 11% after the treatment change [7]. The risk of progressive deterioration was related to the pre-conversion serum creatinine concentration. A concentration of 3.0 mg/dl (264 $\mu\text{mol/l}$) was associated with only a 3% risk of deterioration compared with 23% if the serum creatinine was > 5 mg/dl (440 $\mu\text{mol/l}$). In this study, renal biopsies were obtained at the time of inclusion in the tacrolimus treatment protocol, 1 week after initiation of therapy, and weekly thereafter if a lack of clinical response was observed. One week after tacrolimus therapy, protocol biopsies showed no rejection in 60% of cases, histological improvement in 13%, no change in 20% and worsening rejection in 7%, and there was no correlation between histological resolution and clinical improvement in the majority of patients [8]. The most commonly observed adverse events following the

treatment change were neurological, consisting of tremor, headache and insomnia, diarrhoea, nausea and abdominal pain, hyperkalaemia and nephrotoxicity [7]. Adverse events were treated primarily by reduction of tacrolimus dose, which provided resolution in most patients as cessation of the drug was not required in 92% of patients.

Patients showing persistent rejection within 28 days of receiving at least 7 days of anti-T lymphocyte antibodies or antisera were studied in a randomized, open-label, multicentre trial. Patients were assigned to receive either mycophenolate mofetil (MMF) at a dose of 3 g/day in combination with CsA and corticosteroids, or high doses of methylprednisolone intravenously for 5 days, together with triple therapy of azathioprine, CsA and corticosteroids [9]. Treatment with MMF resulted in 45% reduction in graft loss and death by 6 months post-enrollment. MMF treatment also significantly reduced the risk of subsequently experiencing a biopsy-proven rejection episode or treatment failure by almost 50%. The number of patients receiving one or more full courses of anti-lymphocyte therapy for a rejection episode subsequent to enrollment was >2-fold greater in the intravenous steroid group compared with the MMF group. However, more adverse events were reported for patients in the MMF group [9].

Comparison of MMF and tacrolimus databases showed that both drugs are equally effective in patients with refractory rejection in terms of patient- and graft-survival and function, albeit that tacrolimus produced a lower recurrent rejection rate, was associated with less use of anti-lymphocyte antibodies to treat recurrent rejections, and produced less serious adverse events and cytomegalovirus disease [10]. One explanation for the high rate of serious adverse events in the MMF group may be related to the relatively high dosing regimen used.

Antibody-mediated acute rejection. The immediate outcome of antibody-mediated acute rejection episodes are uniformly worse than those of acute cellular rejection episodes, and often appear to be steroid and anti-lymphocyte antibody therapy-resistant [11]. Graft loss in antibody-mediated rejection is frequent, ranging from 29 to 75%, compared with 4% for acute cellular rejection [11–14]. The treatment of antibody-mediated rejection has not been well defined. Plasma exchange has been used to remove antibodies in various renal diseases [15] but in most transplant studies it does not seem to confer any additional benefit when used with standard immunosuppressive drugs to treat acute rejection episodes. However, in an uncontrolled open study involving only five patients, plasma exchange was used in conjunction with switching from CsA and azathioprine to tacrolimus and MMF [16]. This approach rescued all grafts, decreased donor-specific antibodies and improved graft function.

Guidelines D and E

Various anti-T lymphocyte antibody preparations have been used, including horse anti-lymphocyte globulin (ALG) (Pharmacia & Upjohn), rabbit anti-thymocyte globulin (ATG) (SangStat Medical Corporation, Institute Merieux), rabbit ATG (Fresenius) and OKT3 monoclonal antibodies (Ortho Biotech).

Efficacy of monoclonal OKT3 vs polyclonal anti-T lymphocyte preparations in the reversal of acute rejection episodes. Both polyclonal and monoclonal anti-T lymphocyte preparations are usually successful in reversing acute uncomplicated as well as corticosteroid-resistant acute rejection episodes. Retrospective comparisons of OKT3 with polyclonal rabbit ATG have suggested either that both preparations are equally effective [17], that polyclonal antisera are more effective [18], or that OKT3 monoclonal is more effective especially in treating episodes of acute vascular rejection [19]. In a randomized study comparing low-dose OKT3 with low-dose rabbit ATG in the treatment of steroid-resistant rejection episodes, the reversal of rejection was similar in the two treatment arms although there was a trend in favour of ATG with a graft failure rate of 13% compared with 23% in the OKT3 group. Moreover, ATG was better tolerated because of the first-dose effect in the OKT3 group [20]. There is consensus that the use of OKT3 is associated with more side effects, especially those related to the cytokine release syndrome.

Rabbit vs horse anti-T lymphocyte antisera. To compare the efficacy of rabbit with horse ATG preparations, a multicentre, double-blind, randomized trial was undertaken in North America with an enrollment stratification based on the Banff grading of the biopsies [21]. Patients with a proven acute rejection episode received 7–14 days of treatment with either a rabbit anti-human thymocyte globulin at a dose of 1.5 mg/kg/day, or a horse anti-human thymocyte globulin at a dose of 15 mg/kg/day. Using an intent-to-treat analysis, rabbit ATG had a better rejection reversal rate than horse ATG (88 vs 76%; $P=0.027$) but there were no differences in the day 30 graft survival rate, the day 30 serum creatinine concentrations as a percentage of baseline, or improvements in post-treatment biopsy results. Recurrent rejection at 90 days after therapy occurred less frequently with rabbit ATG (17%) than with horse ATG (36%) ($P=0.011$), but graft survival rates were similar as was the incidence of adverse events and post-therapy infections. Protocol biopsies 1–2 weeks following the end of therapy indicated that residual inflammation was less in rabbit ATG-treated patients than in those receiving horse ATG ($P<0.05$) and correlated with the incidence of recurrent rejection [22]. Therefore, rabbit ATG is superior to horse ATG in reversing acute rejection episodes and in preventing recurrent rejection.

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III.10 Standards of graft and patient survival

Guidelines

A. A centre's actuarial probability of graft survival at 1 year in unselected primary renal transplants should exceed 80%.

(Evidence level B)

B. A centre's actuarial patient survival at 1 year in an unselected renal transplant population should exceed 90%.

(Evidence level B)

Commentary on Guideline III.10: Standards of graft and patient survival

Guideline A

In most registries, death with a functioning transplant is recorded as graft failure, whereas in single-centre studies these patients are often censored, explaining some of the numerical discrepancies between registry data and single-centre studies. According to registry reports, the 1-year graft survival rate following live donor transplantation is between 83 and 92% compared with 81 and 84% for recipients of a cadaveric graft. The 5-year graft survival is between 70 and 79% and 59 and 68%, respectively [1,2]. In the Collaborative Transplant Study registry, graft survival in Europe following transplantation with a kidney from a related donor was 92% at 1 year, 89% at 2 years, 85% at 3 years and 79% at 5 years. Following transplantation with a kidney from a spousal donor, graft survival was 88, 84, 82 and 78%, and following transplantation of a kidney from a cadaveric donor 84, 80, 76 and 68% at the same time points (Figure III.1).

Guideline B

Transplantation vs dialysis. It has been difficult to compare death rates after transplantation with those on dialysis because of the selection bias in favour of transplantation. Therefore, the comparison of survival outcomes needs to be done using patients eligible for transplantation. Studies performed in the pre-cyclosporin era were unable to demonstrate a survival advantage of transplant recipients over dialysis patients on the waiting list [3], but recent data from national registries and single-centre studies suggest that kidney transplantation reduces mortality [4,5]. Using a Cox

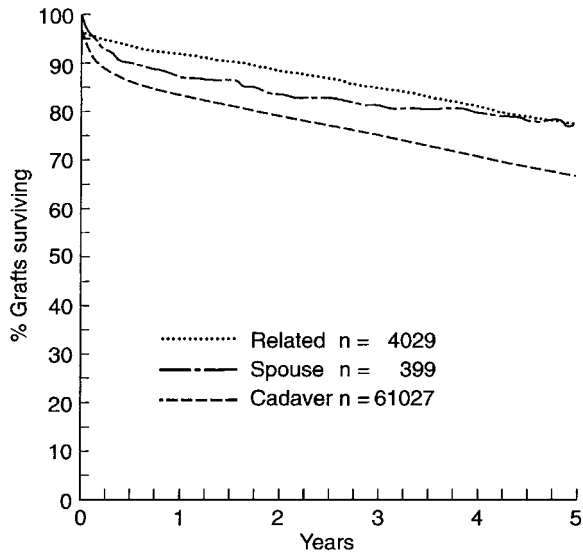


Fig. III.1. Graft survival in Europe of patients transplanted between 1987 and 1997 with a kidney graft from a related donor, a spousal donor or a cadaveric donor (courtesy of Dr Gerard Opelz, Heidelberg).

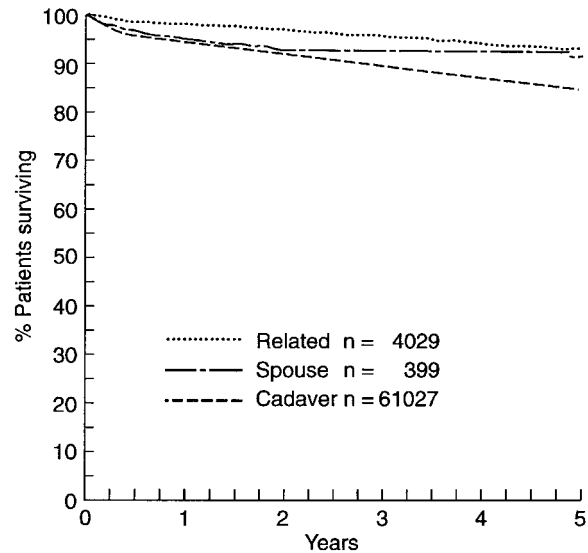


Fig. III.2. Patient survival in Europe of patients transplanted between 1987 and 1997 with a kidney graft from a related donor, a spousal donor or a cadaveric donor (courtesy of Dr Gerard Opelz, Heidelberg).

regression model with a time-dependent covariate, it was recently shown that intermediate-term survival is superior in transplant recipients than in waiting-list transplant candidates [6]. Similarly, HCV-positive renal transplant recipients show better survival after 2 years than HCV-positive patients who are awaiting transplantation [7].

Port *et al.* emphasized that transplant related mortality is increased in the perioperative phase but this is counterbalanced by the beneficial effect of transplantation after the first year. Crude mortality of the waiting list population was 10.7% per year, while the relative risk of mortality increased to 2.43 by 30 days after transplantation [8]. Thus, the additional mortality risk attributable to the transplant surgery is estimated at 15%.

Transplantation in the elderly. With increasing recipient age, patient survival after transplantation declines. However, various studies assessing the suitability of elderly patients for transplantation conclude that transplants can be done safely and successfully in patients over the age of 60 [9]. This viewpoint was confirmed in a population-based study comparing the impact of transplantation vs dialysis on mortality in this age group. Using a Cox regression analysis, the time-dependent hazard ratio of death was estimated at 0.47 [10]. However, because renal transplant candidates exhibit fewer co-morbid conditions than the average dialysis population, these studies tend to overestimate the benefit of transplantation [11].

Living donor vs cadaveric transplantation. Patient survival is better after living donor transplantation than after cadaveric transplantation [12,13]. The 1-year

patient survival following live donor transplantation is between 93 and 98% compared with 93 and 94% for recipients of a cadaveric graft. The 5-year survival for these donor categories is between 83 and 94% and 81 and 85%, respectively.

In Europe, patient survival following transplantation with a kidney from a related donor is 98% at 1 year, 97% at 2 years, 96% at 3 years and 94% at 5 years; following transplantation of a graft from a spousal donor, patient survival is 95, 93, 93 and 92%, and following transplantation of a kidney from a cadaveric donor 94, 92, 90 and 85% at the same time points [Source: Collaborative Transplant Study registry, Prof Opelz] (Figure III.2). It is important to stress that these differences are not necessarily due to differences in the donor source.

Transplantation mortality compared with the general population. The survival rate of kidney transplant patients is significantly lower than in age-matched controls in the general population [14,15]. The relatively higher mortality in renal transplant patients is, in part, due to co-morbid medical illnesses, pre-transplant dialysis treatment and factors unique to transplantation, including immunosuppression and other drug effects [16–18]. Death with graft function has been reported in 9–30% of patients [15,19–21].

A recent study showed a marked and significant improvement since 1990 in the survival of renal transplant recipients [22], despite a substantial increase in the number of high-risk ESRD patients undergoing renal transplantation. Cardiovascular disease, specifically acute myocardial infarction, is the predominant cause of death with graft function and supersedes infection.

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