

SECTION I: Evaluation, selection and preparation of the potential transplant recipient

I.1 Epidemiological data concerning end-stage renal failure (ESRF) and its treatment in Europe

Guideline

A. In estimating the number of patients in need of renal transplantation, one should integrate the basic epidemiological data concerning end-stage renal failure (ESRF), and in particular the currently linear increase of the point prevalence by ~7.5% each year. (Evidence level B)

Commentary on Guideline I.1: Epidemiological data concerning end-stage renal failure (ESRF) and its treatment in Europe

Guideline A. The incidence of new patients with ESRF during 1996 was 118 per million population (pmp) for the European Union, which currently includes 15 countries with a total population of 373.3 million (response rate=88%) corresponding to 44 140 new patients per annum.

The death rate from ESRF during 1996 was 69 pmp for the EU, corresponding to 25 830 deaths per annum.

On 31st December 1996, the prevalence of live ESRF Patients was 655 pmp for the EU, corresponding to 244 508 patients on dialysis.

The dynamics were as follows [1,2,3]:

- Flow-in rate of new patients: $K_i = +18.1\%$ of the active pool.
- Flow-out rate (crude death rate): $K_o = -10.6\%$ of the active pool.
- Linear increase for 1996 compared with 1995: $+7.5\%$ or $+49$ pmp [4].

These 244 508 live patients were treated either by haemodialysis (140 812; 57.6%), peritoneal dialysis (20 390; 8.3%) or with a transplant (83 305; 34.1%).

The number of renal transplants performed during 1996 in the EU was 11 333, (30.4 pmp). The highest activity was for Spain with 1707 (43.4 pmp) and Austria with 362 (44.7 pmp).

There is a large disparity between countries belonging to the EU, but an even greater disparity between countries outside the EU. Comparison between the EU and the USA is given in Table I.1 for 1996.

Clearly, the demand for renal transplantation far

Table I.1. Epidemiological data concerning end-stage renal failure (ESRF) during 1996

	EU ^a	USA ^b	Units
Population	373.3	272.7	millions
Response rate	88	93	%
New patients:			
Ni (in)	44 140	78 592	number
Ni/P (incidence)	118	288	pmp
Ki (Ni/Ns)	+18.1	+25.7	%
Dead patients:			
No (out)	25 830	55 658	number
No/P (incidence)	69	204	pmp
Ko (No/Ns)	-10.6	-18.2	%
Live patients:			
Ns (stock)	244 508	305 303	number
Ns/P (point prevalence)	655	1120	pmp
K [(Ni-No)/Ns]	+7.5	+7.5	%
Modalities of treatment:			
Ns HD	140 812	190 814	number
Haemodialysis	57.6	62.5	%
Ns PD	20 390	30 225	number
Peritoneal dialysis	8.3	9.9	%
Ns Tx	83 305	84 264	number
Functioning transplant	34.1	27.6	%
Transplant activity:			
N Tx	11 333	12 238	number
N Tx/P	30.4	44.9	pmp

Ni, new patients; P, population; Ki, input rate; No, dead patients; Ko, output (death) rate; Ns, live patients in stock; K, linear increase rate in the stock of patients; HD, Haemodialysis; PD, peritoneal dialysis; Tx, renal transplantation.

^aERA Registry Report (Madrid, Sept 99).

^bUSRDS 1998 Report.

exceeds the availability. Every effort should be made to increase the number of donors, but the solution may reside in xenotransplantation with modified pigs as donors.

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I.2 General evaluation

Guidelines

A. All patients with end-stage renal disease (ESRD) should be considered for renal transplantation unless they have absolute contra-indications, because renal transplantation offers a better life expectancy and quality of life than dialysis.

(Evidence level A)

B. Long duration of dialysis, previous incidence of recurrent infections, cancer, cardiovascular disease or gastrointestinal complications should not be considered as absolute contra-indications to renal transplantation, despite these conditions increasing the risk of post-transplant morbidity and mortality.

(Evidence level B)

C. Psychological evaluation of transplant candidates may be useful in assessing compliance with future immunosuppressive treatment. Poor compliance significantly worsens the outcome of renal allografts.

(Evidence level B)

Commentary on Guideline I.2: General evaluation

Guideline A. Although dialysis once offered a greater chance of survival than transplantation, particularly in the short term, recent studies have reported a lower risk of mortality among renal transplant recipients vs dialysis patients. UNOS data reveal that despite the increased risk of death in the early post-transplant period, the 1-year mortality rate of transplant recipients was 59–67% lower, depending on the degree of HLA compatibility, than that of dialysis patients remaining on the waiting list [1]. A long-term follow-up study also confirmed the lower mortality rate associated with transplantation vs dialysis: adopting a hazard rate of 1.0 for age, gender and underlying disease for patients on the waiting list, the relative risk of mortality at 8 years post-transplant was 0.31 for transplanted patients [2].

Guideline B. The history of the transplant candidate is very important. Previous chronic or recurrent infections, cancer, gastrointestinal complications, viral hepatitis, myocardial infarction and/or lower limb arteriopathy does not always represent an absolute contra-indication to transplantation, but they indicate the need for a particularly careful work-up. Long duration dialysis is an independent variable associated with poorer long-term results [3] and increased mortality [4]. These patients therefore require a thorough investigation, particularly of the cardiovascular system.

Patients with a long history of uncontrolled hypertension have a greater risk of cardiovascular disease.

The renal history should focus on the diagnosis and duration of the original renal disease. Correct diagnosis is important to evaluate the possible risk of recurrent disease. Some patients, for example those with vasculitis, lupus, rapidly progressive nephritis or previous transplantation, will have received vigorous or prolonged immunosuppressive treatments. In such cases renal transplantation may be postponed for several months after starting dialysis, and immunosuppressive agents may be stopped or reduced to avoid the risk of over-immunosuppression.

A general screening examination should be conducted following the interview. Attention must be paid to the exit site of any peritoneal catheter or to the arteriovenous fistula, which represent potential sites of infection. In patients with adult polycystic kidney disease, the size of the kidneys should be evaluated to determine whether or not a nephrectomy is required.

As well as cardiac auscultation, murmurs of carotid arteries, aorta or lower limb arteries should be investigated. Physical examination should include palpation of the prostate in men and a gynaecological examination in women.

Guideline C. The use of psychiatric screening in transplantation is not universally adopted, despite the fact that many transplant candidates have active psychiatric disorders, psychiatric pre-disposition, psychiatric symptoms or a history of substance abuse, and require psychiatric attention [5]. An important aim of the psychological evaluation is to predict patient compliance with post-transplant treatment care. Poor compliance is common [6] and is one of the most frequent causes of graft loss [7]. Patients with a history of attempted suicide, with prior medical non-compliance, psychosis, inadequate neurocognitive functions, or alcohol or drug abuse are poor candidates for transplantation [8]. With the exception of a few cases of absolute non-compliance, which almost inevitably leads to graft failure, ~22% of patients take some but not all the prescribed drugs. Even in these cases, late rejection episodes eventually leading to graft loss may occur [9].

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I.3 Information for the transplant recipient

Guidelines

A. Comprehensive information on renal transplantation should be given to all potential candidates with ESRF, including mortality, morbidity, results compared with dialysis, and also data concerning the different sources of kidneys, including marginal organs.

(Evidence level C)

B. The specific transplant evaluation should only be performed after this information is delivered and clear acceptance is given by the patient. Inclusion on the waiting list is the final step of the procedure and requires formal informed consent (often legal) from the prospective recipient.

(Evidence level C)

C. All critical aspects concerning kidney donor selection for transplantation, including the use of marginal organs, need clear informed consent from the prospective candidate, both in advance, whenever possible, and at the time of an offer.

(Evidence level C)

Commentary on Guideline I.3: Information for the transplant recipient

Guideline A. This information should concern donor availability and quality, possibility of live donation, waiting time, allocation algorithm, operative risks, risk of infection, risk of rejection, graft and recipient survival (compared with other treatment modalities), increased risk of *de novo* malignancies, need for lifelong medication and aspects of fertility and childbearing, if appropriate.

Guidelines B and C. Most organ allocation agencies currently use kidneys from an extended donor pool due to organ shortage. Kidneys are used from donors older than 65 years of age, from diabetic donors, from hypertensive donors, from donors tested positive for hepatitis B or C and, at least in some countries, from non heart-beating donors.

Although it is well known that the outcome of transplant using organs from the extended donor pool is inferior to those from younger and more healthy donors, under certain circumstances it is acceptable to

use these organs in older recipients, in recipients with very long waiting times or in recipients with life-limiting concomitant diseases. Nevertheless the decision must be made in advance and informed consent must be obtained at a time unrelated to an offer in line with practices for other critical informed consent issues [1].

Reference

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I.4 Contra-indications for transplantation

Guideline

A. There are few absolute contra-indications to renal transplantation. These include uncontrolled cancer, HIV positivity, active systemic infections and/or any condition with a life expectancy <2 years.

(Evidence level B)

Commentary on Guideline I.4: Contra-indications for transplantation

Guideline A. The main goal of renal transplantation is to improve the quality of life of patients with ESRF and to offer life expectancy at least as good as that provided by regular dialysis.

Patients with active cancer despite treatment may have an increased risk of metastasis and spread with immunosuppressive therapy [1]. Thus, these patients should not be listed for transplantation until the cancer is treated and a sufficient time has passed (see section I.5).

HIV-positive patients maintain the capacity to reject organ transplants and would therefore require standard immunosuppressive therapy, which can aggravate the course of AIDS [2]. About half of the transplant patients who received a kidney from HIV-positive donors died within 1 year [3]. Although the prognosis of patients with AIDS has recently improved, there is consensus that these patients should not be transplanted.

Patients with sepsis, active tuberculosis but effectively treated, or any other form of potentially life-threatening infection should be excluded from transplantation until complete recovery in view of the deleterious effect of immunosuppressive treatment.

For patients with a short life expectancy related to extra-renal diseases or complications, renal transplantation does not offer any advantage and may instead accelerate the death.

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I.5 Risk factors/relative contra-indications

I.5.1 Work-up for cancer and waiting time for pre-existing cancer

Guidelines

A. Candidates for renal transplantation, particularly those older than 50 years of age, should be screened for the presence of pre-existing cancer.

(Evidence level C)

B. In patients with previous cancer, renal transplantation should only be considered if there is no evidence of persistent cancer. It is recommended that the waiting time between tumour treatment and transplantation be based on the type of cancer.

(Evidence level B)

C. After renal transplant, general preventive measures of surveillance for occurrence of *de novo* cancer are recommended.

(Evidence level C)

Commentary on Guideline I.5.1: Work-up for cancer and waiting time for pre-existing cancer

Guideline A. Evaluation of the transplant candidates may include an exhaustive history and physical examination for cancer, in addition to routine radiological and echographic investigations. Pre-transplant screening may include faeces occult blood testing in all patients and mammography in women over 40 years of age or with a family history of breast carcinoma. Regardless of age, women should have a pelvic examination and a pap-test. Men aged over 50 years should be screened for prostate carcinoma, with PSA evaluation and prostate echography. The search for renal carcinoma should be particularly thorough in patients with analgesic nephropathy. This disorder is frequently associated with malignancies, mostly transitional cell carcinoma [1]. Another frequent cause of cancer in the native kidneys is acquired cystic disease, which may occur in 30–95% of patients receiving long-term dialysis [4]. Because of the high prevalence (3–4%) of renal cell carcinomas associated with acquired cystic disease [2], it is recommended that long-term dialysis patients who are candidates for transplantation are screened with kidney ultrasonography and/or computed tomography [3].

Guideline B. Whether patients with a previous history of cancer, but without evidence of active disease should be considered suitable for transplantation is a difficult decision. With the exception of non-invasive basal cell

carcinoma, fully excised squamous cell carcinoma or *in situ* bladder neoplasias, caution is required. About a quarter of renal cell carcinomas are discovered incidentally during work-up for other disorders, nephrectomy or operations for other reasons. When small and non-metastasized, these incidentally discovered carcinomas usually do not recur [4]. *In situ* uterine cervical carcinomas also have a low risk of recurrence. For these tumours, a waiting time of 2 years is considered to be sufficient to minimize the risk. Women with non-*in situ* carcinomas should wait at least 4–5 years before being accepted for transplantation [5].

It is difficult to decide whether and when to accept women for transplantation who have had breast cancer, because in most cases recurrence happens after >3 years. For patients with *in situ* bladder cancer, a 1-year wait before transplantation may be sufficient, but at least 5 years should pass before patients with diffuse bladder cancers should be considered for transplantation. In the case of an isolated malignant prostate, a 1–2 year waiting time may be sufficient. Transplantation should be avoided in cases of diffuse prostate cancer. A waiting time of at least 5 years is recommended for carcinomas of the colon or rectum, while for other cancers a wait of 2 years is sufficient [5].

Penn [5] has estimated that the risk of recurrence depends on the type of cancer (Table I.2) and on the waiting period between treatment of cancer and transplantation. The risk of recurrence is 53% if the transplant is performed within 2 years of apparent recovery from neoplasia. The risk is 34% if the time interval is between 25 and 60 months and is 13% if the period is 5 years. Penn [5] indicates that in most cases, a transplant may be performed 2 years after recovery from cancer (Table I.3).

Guideline C. General preventive measures for the detection of *de novo* cancer include regular surveillance, maybe once a year (dermatological, gynaecological or

Table I.2. Risk of recurrence after transplantation of pre-existing malignancies (adapted from ref. 5)

● Low recurrence rate (0–10%)

Incidentally discovered renal tumors
Lymphomas
Testicular, uterine cervical, thyroid carcinomas

● Intermediate recurrence rate (11–25%)

Carcinoma of the uterine body
Wilms' tumours
Carcinomas of colon, prostate, breast

● High recurrence rate (>26%)

Carcinomas of bladder
Sarcomas
Skin cancers (melanomas and non-melanomas)
Symptomatic renal carcinomas
Myelomas

Table I.3. Waiting period between treatment of cancer and transplantation (adapted from ref. 5)**A • Less than 2 years**

Incidentally discovered renal carcinomas
In situ carcinomas
 Small single focal neoplasms
 Low-grade bladder cancer
 Basal cell skin cancers

B • 2 years

Most cancers except A and C

C • More than 2 years

Malignant melanomas
 Breast carcinomas
 Colorectal carcinomas
 Non-*in situ* carcinoma of the uterus

prostatic evaluation, native kidney ultrasonography, occult blood in the stools), stopping of smoking, minimizing sun exposure, and self-examination of breasts and testes.

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I.5.2 Infectious risk**• Hepatitis C virus (HCV) infection in kidney transplant recipients and kidney donors****Guidelines**

A. All transplant candidates should be tested for anti-HCV antibodies. Anti-HCV-positive patients with negative HCV viraemia are at very low risk of liver disease after renal transplantation. The presence of HCV-RNA in serum may be searched for in all prospective recipients with liver disease, even in cases where anti-HCV antibodies are not detectable.
(Evidence level C)

B. All HCV-positive patients should be considered for renal transplantation, as this procedure is not associated

with increased mortality compared with dialysis, at least not during the first post-transplant decade.

(Evidence level B)

C. HCV-infected transplant candidates with elevated transaminase levels (alanine aminotransferase, ALT) should undergo a liver biopsy. It is desirable, but not essential, to perform a liver biopsy in HCV-infected patients who display consistently normal liver enzymes, because HCV liver disease is often undetected.

(Evidence level C)

D. Transplant candidates with existing cirrhosis should not be considered for isolated renal transplantation, but should be considered for combined kidney and liver graft.

(Evidence level C)

E. Patients with chronic active hepatitis (CAH) might be offered a treatment with interferon (IFN- α) prior to transplantation. They may be maintained on the active transplant waiting list during the period of IFN- α administration, the drug being stopped if transplantation occurs before the end of planned therapy. Patients without improvement after IFN- α therapy may still be put on the waiting list for transplantation, but only after careful consideration and information.

(Evidence level C)

F. Kidneys from HCV-infected living or cadaveric donors may be offered to HCV RNA-positive recipients with their consent and when permitted by the national law. Obtaining the donor and recipient HCV genotypes is desirable for further careful evaluation of the results.

(Evidence level B)

Commentary on Guideline I.5.2: Infectious risk (hepatitis C virus infection in kidney transplant recipients and kidney donors)

Guideline A. Infection with HCV is the major cause of liver disease after renal transplantation. The most frequent sources of infection in kidney transplant recipients, before HCV screening became available, were contaminated blood products, nosocomial transmission within dialysis units and previous organ transplantation [1,2]. Among renal transplant candidates, the prevalence of patients positive for anti-HCV antibodies (anti-HCV+) by ELISA-2 assays varies from 10 to 30% [3]. The vast majority of these patients (70–95%) have detectable HCV-RNA in the serum [3]. A very small proportion of HCV-infected patients are positive only for HCV RNA in serum and not for anti-HCV antibodies.

Guideline B. Although patients with normal renal function who acquired HCV through transfusion do not show increased mortality up to 18 years after infection [4], it is now clear that anti-HCV+ renal transplant recipients are at increased risk of death compared with non-infected transplanted patients [5–8]. The increased death rate was progressive, being ~5% at 5 years, 10% at 10 years, and 20% at 20 years [6–8]. Increased mortality was mainly related to infections, although

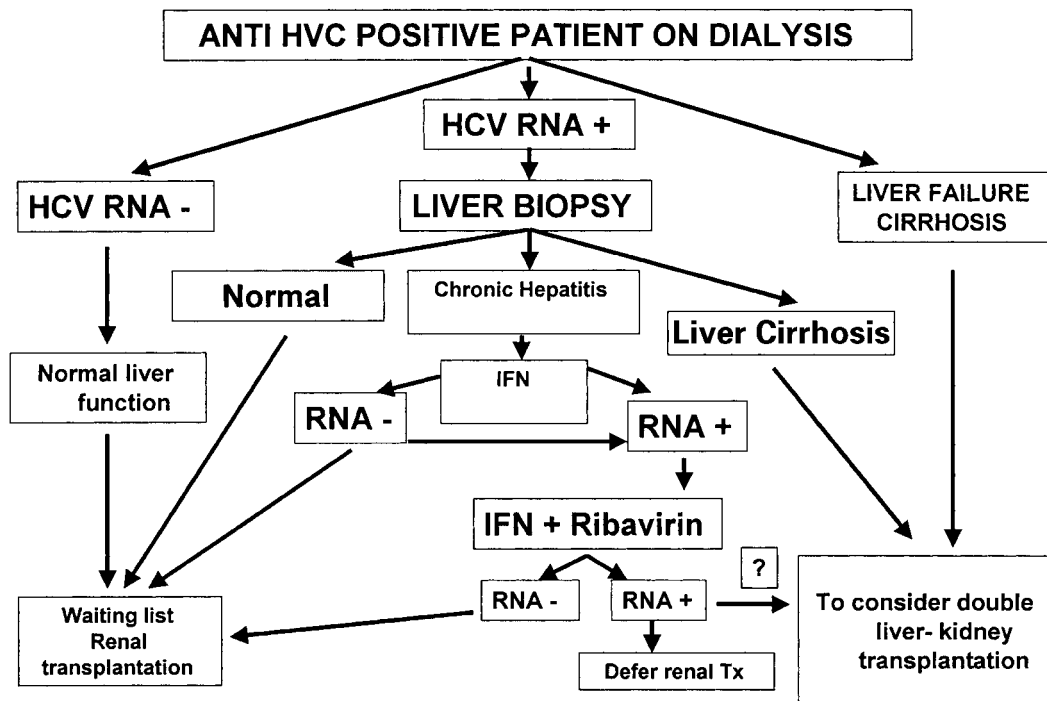


Fig. I.1. Algorithm for renal transplantation in anti-HCV-positive dialysed patients (reprinted with permission from ref. 43).

liver diseases such as cirrhosis or liver carcinoma also contributed. Nevertheless, two recent studies suggest that transplantation is still the best option for HCV+ patients. Firstly, a cohort of HCV+ patients on the renal transplant waiting list had an increased risk of death irrespective of whether they received a kidney or remained on dialysis [9]. However, transplantation was associated with a beneficial rather than an adverse effect on long-term survival in anti-HCV+ patients. Secondly, HCV+ patients who remained on the transplant waiting list had a significantly decreased survival rate compared with those who received transplants [10]. *Guideline C.* The aim of pre-transplant evaluation is mainly to identify patients with advanced liver disease, such as those with chronic active hepatitis or cirrhosis. These patients are at increased risk of death from liver failure after transplantation [11]. IFN- α , a mainstay of HCV therapy, is contra-indicated after renal transplantation. Indeed, administration of IFN- α triggers acute renal allograft rejection in a considerable number of patients [12–14]. In general, in HCV infection there is an association between liver enzyme elevations and histological liver disease [15]. Nevertheless, liver biopsy of dialysis patients with normal transaminase levels may indicate chronic hepatitis [16], and patients with elevated liver enzymes may sometimes have essentially normal liver histology [17]. Similarly, there is no good correlation between liver histology and either the presence or absence of HCV viraemia [3]. It is clear that transplant candidates with abnormal liver enzymes should undergo a liver biopsy (Figure I.1).

Guidelines D and E. The small proportion of patients with cirrhosis found at biopsy may be further evaluated for combined kidney and liver transplantation. Those

with chronic hepatitis may be candidates for a trial of IFN- α therapy if it proves to be well tolerated. Indeed, several pilot studies indicate that the response rate to IFN- α in dialysis patients is comparable to that of the general population, with normalization of liver enzymes, improvement of liver histology and disappearance of HCV viraemia in a minority of patients [18–22]. These encouraging results may be related to an increased exposure to IFN- α because of its reduced clearance in dialysis patients [23]. It must be stressed, however, that as yet there are no data showing that a course of IFN- α therapy, given when the patient is on dialysis, improves survival after transplantation. In general, genotype 1b appears to be more aggressive for the liver compared with other genotypes.

Guideline F. Whether kidneys from HCV+ donors are suitable for transplantation depends on the HCV status of the recipient. When transplanted into HCV-negative recipients, primary HCV infection almost always ensues [24], and approximately half of the recipients will develop abnormal liver enzyme levels. Despite this, no increased mortality was seen 3–5 years after transplantation, probably because HCV-induced diseases become apparent only after decades. Nevertheless, the general opinion is that this kind of transplantation should not be performed. On the other hand, transplantation of HCV+ organs into HCV+ recipients appears safe and does not result in an increased incidence of elevated hepatic transaminase when compared with HCV+ recipients who received a kidney from an HCV-negative donor [25,26]. Of concern, however, is the fact that most of the recipients free of HCV RNA in serum at transplantation became positive for HCV RNA after grafting [25]. Finally, super-

infection of the recipient with the HCV genotype of the donor has been reported to occur, although the long-term consequences of this process remain unknown [27]. From a practical point of view, it seems unrealistic at present to perform HCV genotyping in cadaveric HCV+ donors with the aim of finding a recipient matched for the donor HCV genotype.

- **Hepatitis B virus (HBV) infection in kidney transplant recipients and kidney donors**

Guidelines

G. All transplant candidates should be tested for HBV infection. Hepatitis B surface antigen (HBsAg)-positive patients are at increased risk of death over the long term after renal transplantation compared with HBsAg-negative patients, and should therefore be informed.
(Evidence level B)

H. Renal transplant candidates infected with HBV and who present with markers of viral replication, such as Hepatitis B envelope antigen (HBeAg)-positive and/or HBV-DNA positivity, should undergo a complete evaluation for liver disease, including a liver biopsy (when ALT is elevated), because they are at increased risk of progressive liver disease after renal transplantation.
(Evidence level B)

I. Transplant candidates with existing cirrhosis should not be considered for isolated renal transplantation, but might be considered for a combined kidney/liver graft whenever possible.
(Evidence level C)

J. Transplant candidates with active liver disease (including chronic active hepatitis) should be offered treatment with interferon (IFN- α) and/or lamivudine prior to renal transplantation. Patients without improvement after treatment may be registered for transplantation, but after very careful consideration and information.
(Evidence level C)

K. Kidneys from HBV-infected living or cadaveric donors may be offered to already HBsAg-positive recipients or HBV well protected recipients (active and passive immunization) with their consent and when permitted by the national law.
(Evidence level C)

Commentary on Guideline I.5.2: Infectious risk (hepatitis B virus infection in kidney transplant recipients and kidney donors)

Guideline G. HBV infection is the second most common cause of liver disease after renal transplantation [28,29]. Most patients acquire the infection before transplantation. Fortunately, the incidence of HBV infection in dialysis patients has been markedly reduced by the isolation of HBsAg-positive patients in special

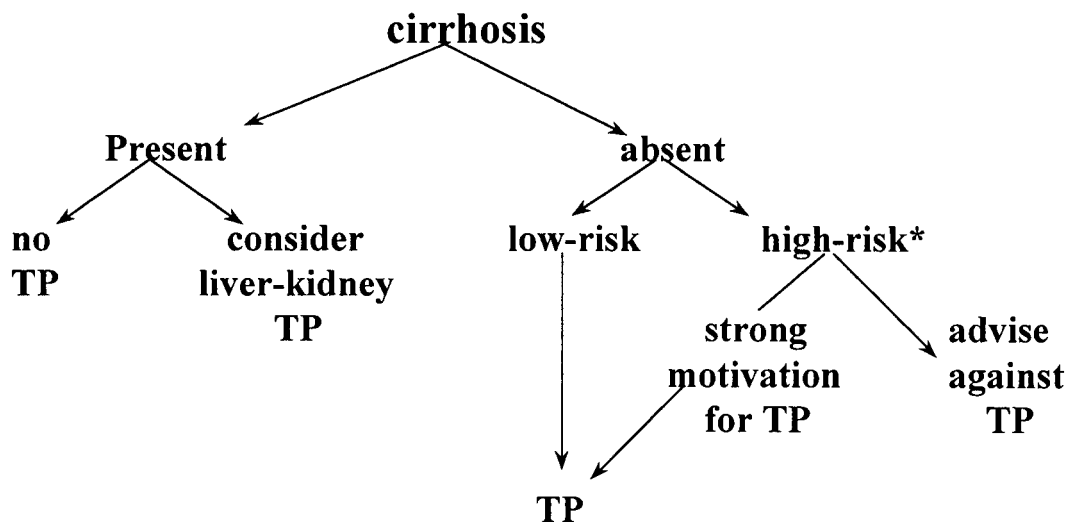
units and by the systematic vaccination of pre-dialysis patients. In fact, in Europe the yearly incidence of HBV infection in dialysis patients on the waiting list for transplantation is <0.1% [30].

Following HBV infection in dialysis patients, 80% become carriers and this situation is more frequently associated with liver disease. However, chronic HBV infection is not an important cause of death on dialysis and survival of HBsAg-positive patients is similar to HBsAg-negative patients [31].

The clinical course and complications of HBV infection after renal transplantation are completely different. The clinical course is typically symptomatic with a moderate elevation of alanine aminotransferase (ALT) showing more severe morphological forms of liver disease than HBV-negative patients [32]. Also, a progressive worsening of liver disease evidenced by repeated biopsies has been documented [31–33]. The experience of the largest single centre showed that a histological deterioration was observed in 85 out of 101 HBsAg-positive patients who had repeat biopsies after a mean interval of 66 months: 28% showed cirrhosis and 42% chronic active hepatitis [34]. Older age, female sex and the presence of CAH were associated with progressive worsening of liver disease to cirrhosis [32]. Hepatocellular carcinoma developed mainly in cirrhotic patients and it has been suggested that the incidence of carcinoma could be greater in renal transplant patients than in the HBsAg-positive general population. To date there has been no effective therapy. Recently, antiviral therapy such as lamivudine has been administered to a small number of patients with elevated transaminases and with HBV DNA in the serum with normalization of transaminases and a rapid disappearance of HBV DNA from the serum [35]. Therefore, lamivudine could be a promising therapy in these patients.

Guideline H. The association of a higher mortality at 10 years in renal transplant patients with HBs antigenaemia has been confirmed by most authors [36–38]. Mathurin *et al.* showed that age and HBsAg-positivity were independent prognostic factors for patient survival [28]. Liver failure and infection are the most frequent causes of death. However, other authors did not find any significant difference in patient survival among HBsAg-positive and -negative groups despite viral replication and worsening of liver disease [34]. Differences in liver disease severity at transplantation and different immunosuppressive protocols might explain the discrepancies between the studies.

The spontaneous disappearance rates of HBsAg, HBeAg and HBV DNA (the gold standard for diagnosis of viral replication) after renal transplantation is clearly lower than in the general population. Persistent viral replication (HBV DNA positive) may be seen in 50% of patients, and reactivation (reappearance of HBeAg) in 30% of patients [30]. Therefore, renal transplantation is associated with long-lasting HBV replication, probably due to immunosuppression. HBsAg-positive patients with HBV DNA and/or HBeAg at transplantation are also considered to be at



***high risk: HBsAg (+), DNA polymerase (++)**

Fig. I.2. Algorithm for renal transplantation in the HBsAg(+) patient with or without cirrhosis (reprinted with permission from ref. 30). TP, transplantation.

high risk of developing fatal liver disease. There is also considerable focus on the role of several mutant forms of HBV in the development of fibrosing cholestatic hepatitis [29,30].

Guidelines I and J. A multicentre study in Canada showed that transplanted HBsAg patients develop chronic hepatitis and die from liver disease more frequently than those on dialysis [39]. Therefore, the question remains whether HBsAg-positive patients should be included on the waiting list for renal transplantation or whether they should stay permanently on chronic dialysis. To answer this question it would be necessary to conduct a study comparing evolution of the disease whilst on dialysis with that after transplantation in a large number of patients. Until this information becomes available, several authors [30] suggest that HBsAg carriers should be approached as candidates for renal transplantation as shown in Figure I.2.

If a patient presents with cirrhosis, portal hypertension or liver failure, in the absence of viral replication, continuation on dialysis or a combined liver and kidney transplantation should be discussed. Rao also suggested to extend this approach to patients who are at risk of developing cirrhosis, i.e. older females with chronic active hepatitis (CAH) [32].

If a patient is free of the above complications, the decision should be made based on serology and liver biopsy results. If a patient is HBeAg-positive or HBV DNA-positive or has severe CAH, he/she is at high risk of developing fatal liver failure, and therefore renal transplantation is contraindicated. If the patient has no serological markers of high risk, most doctors would consider renal transplantation [40].

Therefore, HBV positivity is not an absolute contraindication for inclusion on the waiting list for renal transplantation. In each case, the physician and the well informed patient have to weigh the risks and

benefits of transplantation compared with the expected course and life on dialysis [40]. Most patients prefer renal transplantation because of the improved quality of life. In fact, most of these patients have a good quality of life and can maintain normal renal function for 8–10 years after transplantation [30].

Guideline K. Whether kidneys from HBV-positive donors are suitable for transplantation depends on the HBV status of the recipient. When transplanted into HBV-negative patients, transmission of HBV infection normally occurs and some patients develop chronic liver disease [30]. Therefore, this practice is generally contra-indicated, except in some countries where both passive and active immunization of the recipient [41] (specific anti-HBs immunoglobulins and booster vaccination) are practiced. Transplantation of kidneys from HBV-positive donors into HBV-positive recipients has been explored in Spain, and has shown a similar clinical course to HBV-positive recipients who receive organs from HBV-negative donors [42].

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Hepatitis C virus

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- ### I.5.3 Recurrence of original renal disease
- #### Recurrence of primary glomerulonephritis
- #### Guidelines
- A. Focal and segmental glomerulosclerosis (FSGS) is not a contra-indication to renal transplantation despite the high risk of recurrence. Patients with recurrence have reduced graft survival. In case of living donation, the possibility of early recurrence leading to graft loss should be clearly explained to the potential donor. Approximately 15–50% of patients develop early recurrence of FSGS in the first allograft. It is almost impossible to predict which patient will have a recurrence after**

transplantation. Plasmapheresis and increased dosage of cyclosporine may be of value in severe cases.

(Evidence level B)

B. Membranous glomerulonephritis (MN) is not a contra-indication to renal transplantation despite the fact that there is no effective treatment for recurrent MN and ~20–30% of adult patients may develop recurrence after transplantation.

(Evidence level B)

C. Membranoproliferative glomerulonephritis (MPGN) is not a contra-indication to renal transplantation. Type I MPGN may recur in children where it accounts for ~6% of graft failures, and in adults where the recurrence rate is ~50% and graft survival is poorer at 4 years. Most patients with type II MPGN show histological recurrence. Clinical recurrence is less common, ~10% in adults and 28% in children.

(Evidence level C)

D. IgA glomerulonephritis (IgAGN) is not a contra-indication to transplantation. The risk of recurrence is related to the length of post-transplant follow-up, being almost 100% by 10–20 years. Patients with histological signs of recurrence have a lower probability of long-term graft survival than patients without recurrence.

(Evidence level B)

E. In anti-glomerular basement membrane glomerulonephritis (anti-GBM GN), it is recommended to wait until the circulating anti-GBM antibodies measured by specific techniques (RIA or ELISA) have disappeared before transplantation. Anti-GBM GN tends to recur only in patients with circulating anti-GBM antibodies. Recurrence does not usually lead to graft loss.

(Evidence level C)

Commentary on Guideline I.5.3: Recurrence of original renal disease (recurrence of primary glomerulonephritis)

Guideline A. Focal and segmental glomerulosclerosis (FSGS)

Patients with FSGS are at high risk of recurrence after renal transplantation. Approximately 15–50% of patients develop recurrence of FSGS after the first allograft [1]. At present, it is almost impossible to predict which patients will have a recurrence after transplantation and which patients will not. However, it seems that the risk of recurrence is greater in recipients with better HLA matching [2], in patients with collapsing variant of FSGS, and in those with rapid progression to uraemia [3]. Second grafts in those who have had recurrence during their first graft are accompanied by further recurrence in 85% of cases [4].

In patients with recurrence, proteinuria and the initial lesions of FSGS usually develop early, with a median time of 10–18 days after transplantation [5]. However, presentation of recurrence varies from patient to patient, from immediate massive proteinuria

to milder forms which develop after several years. Spontaneous remission of proteinuria is exceptional. Patients with recurrence of FSGS have reduced graft survival. In a European paediatric survey, the median survival of the graft from appearance of nephrotic syndrome was 5 months [6]. A retrospective analysis of the literature showed that 50–85% of patients with recurrence lost their allograft within 2 years [1]. A study of the Renal Allograft Registry (RAR) showed a relative risk for graft failure of 2.25 for post-transplant FSGS [2]. It is possible that the high rate of acute renal failure and acute rejection observed in patients with recurrence may have contributed to this poor survival [7].

The frequent occurrence of rapid or even immediate relapse of proteinuria after transplantation suggests that at least some patients with FSGS have circulating factor(s) capable of altering glomerular permeability in the normal graft. In patients with recurrent FSGS after transplantation, Savin *et al.* [8] identified a circulating factor with an apparent molecular mass of ~50 Da, which might be responsible for initiating renal injury. Recently, Dantal *et al.* [9] reported that the albuminuric factor(s) are part of a complex with immunoglobulins. However, no firm evidence to implicate a direct role of immunoglobulins is available.

The management of patients with a recurrence of FSGS and nephrotic syndrome is difficult. Three large studies have examined the frequency of recurrence in recipients treated with azathioprine or with cyclosporine. There was no difference in incidence between any of the three studies or in the pooled data [4,10,11]. In children, it is now recommended to give high-doses of cyclosporin intravenously (target blood level 250–350 ng/ml) to maintain a steady-state blood level [5,12]. However, the long-term efficacy and tolerance of such a therapy remains to be established. Artero *et al.* [13] treated nine patients with ACE inhibitors. Of these, five had lasting remission of proteinuria and stable renal function during treatment.

Another approach is the use of early plasmapheresis. A review of the literature showed that of 17 adults with renal transplants treated with plasmapheresis following a relapse of nephrotic syndrome, five (29%) showed complete absence of proteinuria and another five showed a reduction of daily urine protein excretion to <3 g/day [1]. Response was better in patients treated earlier and more intensively. After stopping plasma exchange, almost half of those who responded relapsed. Some patients, however, responded to a new course of treatment. The results in children are even better. The same review reported 17 cases of complete remission and four partial remissions in 23 children given plasmapheresis and concomitant intensified immunosuppression. More specific apheresis, namely immunoadsorption with protein A, followed by intravenous infusion of human immunoglobulins has been proposed by Dantal *et al.* [14]. However, among eight patients treated with this technique, only one showed sustained remission and one had only a transient improvement in proteinuria. On the basis of the avail-

able results, patients with recurrent FSGS and severe nephrotic syndrome may be offered an early and intensive course of plasmapheresis (three exchanges per week for the first 2 weeks, then two per week for another 2 weeks, then one per week). If proteinuria completely disappears, plasmapheresis may be stopped. If proteinuria improves but remains $>2\text{--}3$ g/day, plasma exchanges may be continued with longer intervals. A further course of plasmapheresis may be attempted in the case of relapse of nephrotic proteinuria. The administration of high-dose ACE-inhibitors may also be recommended due to the anti-proteinuric effect of these agents. Whether a reinforcement of immunosuppressive therapy might allow a more stable remission is still uncertain. Due to the risk of over-immunosuppression, the benefit of a more aggressive immunosuppressive therapy should be determined on an individual basis.

Despite the risk of recurrence, FSGS is not considered a contra-indication to a cadaveric renal transplant. There are more doubts about living donation. The risk of recurrence should be discussed extensively with both donor and recipient.

Guideline B. Membranous nephropathy (MN)

The frequency of recurrence of MN is difficult to assess [15] because a *de novo* form may develop in transplant recipients already with idiopathic MN, with an indistinguishable histological pattern. Recurrence of MN is very uncommon in children. The rate of recurrence in adults averages 20–30% in the largest series [16,17]. The risk of recurrence appears higher in patients receiving a transplant from a living related donor than in those receiving a cadaveric kidney. The time of recurrence also appears to be earlier in recipients of a living donor allograft at 9.3 ± 3 months after transplantation compared with 18.2 ± 7.5 months in cadaveric transplant recipients [18]. Recurrence is not inhibited by cyclosporine [19]. Obermiller *et al.* [20] suggested that a more aggressive disease is more likely to recur after transplantation, but others have not found any relationship between the duration of original disease and rate of recurrence [17].

Clinically, recurrence of MN is heralded by the appearance of proteinuria, which is often in the nephrotic range (>3.5 g/day). It is rare that proteinuria spontaneously improves or disappears [21]. With the exception of these cases, the nephrotic syndrome is usually resistant to any treatment and approximately two-thirds of patients progress to ESRF within 4.1 ± 2.6 years after recurrence is diagnosed [18]. Renal vein thrombosis may also complicate the course of recurrent MN [22]. A poor prognosis is not always entirely attributable to MN because many patients also show histological evidence of rejection. At present, MN is not considered a contra-indication to renal transplantation.

Guideline C. Membranoproliferative glomerulonephritis (MPGN)

The recurrence rate of type I MPGN is difficult to estimate because the features of type I MPGN under light microscopy may mimic those of allograft glomerulopathy [23]. However, with immunofluorescence microscopy, patients with recurrent type I MPGN show a greater intensity of C3, whereas there is greater intensity of IgM in patients with allograft glomerulopathy. Under electron microscopy, type I MPGN shows subendothelial electron-dense deposits whereas transplant glomerulopathy shows an electron-lucent zone in the subendothelial space [24]. Retrospective review of the Renal Allograft Registry showed a relative risk of graft failure of 2.37 for post-transplant MPGN [2]. In children, a French study reported recurrence of MPGN in seven of 11 renal allograft recipients with graft loss in two patients [10], while an American study found graft loss in only one child out of 13 [25]. A recent survey of the EDTA registry [26] showed 6% of graft failure due to recurrence of MPGN with a survival at 2 years of 86%. In adults, the recurrence rate reached 48% at 4 years in one series [27]. There are no clinical features prior to transplantation that can be used to predict the risk of recurrence. Cyclosporin does not appear to prevent recurrence [19] but may be protective against crescentic transformation [28]. The major clinical feature of MPGN recurrence is proteinuria, leading to the nephrotic syndrome and progression to renal insufficiency. Graft survival is poorer in patients with recurrence, averaging only 40 months after recurrence is diagnosed [27].

In type II MPGN, histological recurrence of dense deposits after renal transplantation ranges from 85 to 100% [10,29,30] while clinical recurrence is much less common. Graft failure due to recurrent disease is 10–13% in adults [31,30] and $\sim 28\%$ in children [10], but these data are approximations as the number of reported cases is small and follow-up variable.

Type III MPGN is very rare. One reported case involved a patient who progressed to dialysis within 3 months of diagnosis and lost a second transplant after 7 years due to recurrence [32].

There is no effective therapy for recurrent MPGN. At present, no type of MPGN is considered to be a contra-indication to kidney transplantation.

Guideline D. IgA glomerulonephritis (IgAGN)

Histological recurrence of the mesangial IgAGN is observed in $\sim 60\%$ of renal allografts in patients with primary IgAGN [33,34]. These figures may be an underestimate because not all recipients are biopsied and, of those who are, IgA is often not examined in the biopsy [29]. Moreover, the prevalence of recurrent deposits depends largely on the timing of renal biopsy, being $\sim 50\%$ at 2–5 years but approaching 100% at 10–20 years after renal transplantation [35]. The risk of recurrence is similar for recipients of living related

donor and cadaveric renal allografts. No pre-transplant characteristics are predictive of recurrence [36,37].

Haematuria and low-grade proteinuria are characteristic of recurrence. The occurrence of rapidly progressive renal failure, caused by an underlying crescentic glomerulonephritis, is rare [38].

Some papers have reported more favourable outcomes of the renal allograft in patients with IgAGN [39,40] but others have found graft survival in IgA groups similar to that in non-IgA renal transplant recipients [41,42]. It now seems clear that the risk of graft loss caused by recurrence depends on the length of follow-up. Hartung *et al.* [43] found a 15% lower cumulative graft survival rate at 5 years after transplantation in patients showing a recurrence compared with those without recurrence. Odum *et al.* [33] followed 17 patients with recurrence IgAGN for 72 months. Graft loss occurred in five patients (29%). Bumgardner *et al.* [42] followed 18 renal transplant recipients with clinical and histological signs of recurrence of IgAGN. With a mean follow-up of 61 months, six patients (33%) lost their allograft and another four showed deteriorating renal function. Kimata *et al.* [44] reported that almost all patients with recurrent disease who had proteinuria of >1 g/day and >30% glomerulosclerosis at renal biopsy developed graft loss by 6 years post-transplant. Thus, despite early reports that recurrent IgAGN is a benign process and despite the indolent course of the disease, it is now clear that in the long-term IgAGN may be associated with deteriorating renal function and graft loss in a substantial proportion of patients. Living-related transplantation and HLA matching do not appear to confer an advantage for graft survival [42].

There is no specific therapy for recurrent IgAGN. ACE-inhibitors may be prescribed if hypertension and/or proteinuria are present, as these agents have been shown to be protective in primary IgAGN [45]. If recurrent crescentic IgAGN develops, trial treatment with high-dose corticosteroids, cyclophosphamide and plasmapheresis may be attempted. Bumgardner *et al.* [42] reported the outcome of five patients retransplanted because of recurrence of IgAGN and graft loss. Despite second recurrence of IgAGN in three patients, all patients had good graft function at an average follow-up of 54 months after their second transplant.

Despite the potential recurrence of the disease, there is general agreement that patients with IgAGN are good candidates for renal transplantation.

Guideline E. Anti-glomerular basement membrane glomerulonephritis (anti-GBM GN)

Linear deposits of IgG on glomerular capillary walls is necessary to make the diagnosis of recurrence of this disease but is not specific (as could be seen in recipients with Alport's syndrome). Anti-GBM GN recurs in 10–30% of allografts, particularly if circulating anti-GBM antibodies are present at the time of transplanta-

tion [46]. Conversely, in patients where antibodies cannot be detected, there is no recurrence [4].

Clinical manifestations of the glomerular deposits of anti-GBM antibodies occur in <10% of cases and only rarely lead to graft loss. Bilateral nephrectomy proposed in the past, is no longer recommended. Most clinicians prefer to check the titre of circulating anti-GBM antibodies at regular intervals and wait for 6–12 months before transplantation, or until anti-GBM antibodies disappear. With this policy, the recurrence of anti-GBM GN has almost disappeared.

Recurrence of systemic diseases

Guidelines

F. Lupus nephritis is not a contra-indication to transplantation because the risk of recurrence after transplantation is low and does not affect prognosis.
(Evidence level B)

G. Henoch-Schönlein purpura (HSP) is not a contra-indication to renal transplantation despite the risk of recurrence. Histological recurrence may occur in about half of the cases and is more frequent in children than in adults. Graft survival rates are lower in patients with recurrence.
(Evidence level B)

H. At the moment, no recommendation can be proposed for fibrillary/immunotactoid glomerulopathy (FG) because little information is available on the subject: however recurrence seems to be frequent, although some cases showed good function in spite of recurrence.
(Evidence level C)

I. Renal amyloidosis associated with familial Mediterranean fever (FMF) is not a contra-indication to renal transplantation despite the fact that amyloidosis may recur after kidney allograft, because it can be prevented by early administration of colchicine. No recommendation can be proposed for the other causes of amyloidosis which overall, carry a 10–40% recurrence rate after renal transplantation.
(Evidence level C)

J. Light-chain deposition disease (LCDD) should be considered a contra-indication to renal transplantation because recurrence is frequent and associated with poor prognosis.
(Evidence level C)

K. Haemolytic-uraemic syndrome (HUS) is not a contra-indication to renal transplantation despite the well-established risk of recurrence although this risk is poorly defined. The effect of cyclosporine and tacrolimus on recurrence is still unclear.
(Evidence level B)

L. Anti-neutrophilic cytoplasmic antibody-associated (ANCA) vasculitis is not a contra-indication to transplantation: there is a low but substantial risk of recurrence, which is independent of the presence of circulating

ANCA or type of vasculitis. Graft survival is similar in patients with ANCA-associated vasculitis and those with other causes of renal failure.

(Evidence level B)

M. Idiopathic mixed cryoglobulinemic nephritis (MCN) is not an absolute contra-indication to renal transplantation when there is no severe liver involvement. However, the risk of recurrence after transplantation is high, but it remains unclear whether recurrence is detrimental to graft survival, as very few cases have been described.

(Evidence level C)

Commentary on Guideline I.5.3: Recurrence of original renal disease (recurrence of systemic diseases)

Guideline F. Lupus nephritis

Recurrence of lupus nephritis seems very rare. A review of the literature shows only eight cases of recurrence out of 823 patients transplanted for lupus nephritis [47]. A higher number of histological recurrences in iterative renal allograft biopsy has been reported by Nyberg *et al.* [48] although morphological lesions were usually mild. It is possible that the rate of recurrence has been underestimated due to under-reporting, insufficient length of follow-up and/or failure to diagnose recurrence [49]. Even if recurrence of lupus nephritis is slightly more frequent than the 1% reported in the literature, this event still occurs in only a small minority of cases.

From a clinical point of view, many patients who were previously unresponsive to immunosuppression show little or no sign of active disease after transplantation [50,51]. Even in patients where recurrence has been clearly identified, it is usually of little clinical relevance and does not justify increasing immunosuppression, which should be reserved for exceptional cases of severe episodes of lupus nephritis. Although lupus nephritis *per se* does not represent a contra-indication to transplantation, the work-up of the candidate should be thorough. Particular attention should be paid to cardiovascular complications, bone mineral density and the possible existence of an underlying cancer in patients with a long history of immunosuppression or corticosteroid therapy. In heavily immunosuppressed patients it may be appropriate to wait 1–2 years before transplantation, to allow a wash-out of corticosteroid and immunosuppressive agents.

Guideline G. Henoch-Schönlein purpura (HSP)

Review of the literature shows recurrence of IgA mesangial deposits in 53% of renal allografts in patients with HSP. Clinical recurrence with microscopic haematuria and proteinuria occurred in 18% of cases and graft loss from recurrence occurred in 11% of cases at 5 years [52]. Recurrence is more frequent in children

than in adults [53]. Some papers report a higher risk of recurrence in living related donor grafts than in cadaver kidney recipients [54] but this was not confirmed by Meulders *et al.* [52]. Recurrence can take place despite a delay of > 1 year between disappearance of proteinuria and transplantation.

Clinical signs and symptoms of HSP recurrence may be absent. In patients with clinical evidence of recurrence, haematuria (sometimes macroscopic), moderate proteinuria, and hypertension are common. Histological recurrence is characterized by focal and segmental necrotizing GN and mesangial IgA deposits. The prognosis is worse in adults than in children [52,55]. Graft survival in patients with recurrence is 57% at 2 years [26].

Guideline H. Fibrillary/immunotactoid glomerulopathy (FG)

This rare disease is characterized by extracellular deposition of non-branching microfibrils or microtubules within the mesangium and on the capillary walls of renal glomeruli. Proteinuria, generally in the nephrotic range, haematuria, hypertension and a progressive course to renal failure are the main clinical features.

There is limited information on the results of renal transplantation in FG, in part because diagnosis is difficult without electron microscopy. Fibril deposition has been reported to recur in 50% of cases, with allografts functioning satisfactorily for > 5 years in the majority of cases. Interestingly, the rate of decline of renal function in allografts was slower than in native kidneys, suggesting some benefit of immunosuppressive therapy [56].

Guideline I. Amyloidosis

Both primary and secondary amyloidosis may recur in kidney allografts with a reported frequency of 10–40% [57,58].

Recurrence develops within 3 years. In the secondary form, the risk of recurrence is correlated with the activity of the underlying primary disease, usually rheumatoid arthritis. Not all patients with recurrence of amyloid deposits show signs of renal disease. Proteinuria, usually causing a nephrotic syndrome, is the principal clinical sign. It often heralds progressive renal dysfunction. Unfortunately, many patients die of infections or cardiovascular complications even if allograft function remains stable. However, acceptable results can be obtained in young patients with rheumatoid arthritis. An extensive cardiological work-up is needed in candidates with amyloidosis.

Recurrence of amyloidosis may also occur in patients with familial Mediterranean fever (FMF). Early administration of colchicine, 1 mg/day indefinitely, can prevent the deposit of amyloid substance in the transplanted kidney [59].

Guideline J. Light-chain deposition disease (LCDD)

LCDD is characterized by the deposition of κ or λ -immunoglobulin light chains in the kidneys and in other organs. About one-third of patients have no associated systemic illness, while in two-thirds LCDD is associated with multiple myeloma or other lymphoplasmacytic disease.

Recurrence of multiple myeloma and LCDD after renal transplantation is frequent and is associated with poor prognosis. However, a few cases of prolonged allograft survival have been reported in patients who attained remission with melphalan and prednisone before transplantation [60]. LCDD is considered a contra-indication to kidney transplantation.

Guideline K. Haemolytic-uremic syndrome (HUS)

The possibility of recurrence of HUS after renal transplantation is well established but the risk is poorly defined. The frequency of recurrence has been estimated to range from 10 to 45% [29,61] and recurrence is more frequent in children.

At biopsy, thrombotic microangiopathy can be seen early following transplantation but may also occur after several months. Clinically, the recurrence of HUS may be associated with haemolytic microangiopathy, anaemia, thrombocytopenia, hypertension and progression to renal failure. In some cases clinical signs and symptoms may be absent, and the outcome may be benign. However, in most cases recurrence of HUS leads to loss of the allograft [62]. A retrospective study of the North American Pediatric Renal Transplant Cooperative Group showed that the relative risk of graft failure was 5.36 for patients with post-transplant HUS [2]. The differential diagnosis between recurrence and a *de novo* HUS, caused by cyclosporine or by malignant hypertension, can be difficult.

There are no formal contra-indications to renal transplantation in patients with HUS, but patients with ongoing haemolysis and thrombocytopenia should remain on dialysis until quiescence. Hypertension should be treated vigorously and bilateral nephrectomy may be considered in cases of refractory treatment. It has been suggested that the use of cyclosporine and antilymphocyte antibodies should be avoided to reduce the risk of recurrence. Whether the use of tacrolimus does or does not prevent the recurrence of HUS after transplantation is controversial. Some authors found a benefit of replacing cyclosporine with tacrolimus [63] but others reported cases of HUS in patients treated with tacrolimus [64]. There is no definite treatment for recurrent HUS. Withdrawal of cyclosporine might result in resolution of disease in a few cases [65]. Fresh plasma infusions may be helpful for alleviating severe thrombocytopenia [10].

Guideline L. Anti-neutrophilic cytoplasmic antibody-associated (ANCA) vasculitis

There is a substantial rate of recurrence of ANCA-associated vasculitis, ~17% [66,67]. A few patients may even have recurrence several years after transplantation.

The risk of recurrence is not influenced by treatment with cyclosporine, by the presence of circulating ANCA, or by the type of underlying vasculitis. Despite the risk of recurrence, ANCA-associated vasculitis is not considered a contra-indication to transplantation.

Many patients with Wegener granulomatosis (WG) or microscopic polyarteritis have successfully received transplants [68,69]. The optimal timing for transplantation in these patients is unclear. A successful outcome has been obtained in patients with a short interval between clinical onset and transplantation and in patients with symptoms of active disease [70]. Cyclophosphamide and corticosteroids may stabilize renal function in most patients with recurrence [71]. Survival rate and graft function has been reported to be similar in patients with WG compared to other kidney transplant recipients [72]. However, many of these patients were older, and cardiovascular and extra-renal complications caused most deaths.

Guideline M. Mixed cryoglobulinemic nephritis (MCN)

Only a few patients with MCN have undergone renal transplantation. By reviewing the literature, Tarantino *et al.* [73] found recurrence of MCN in 70% of cases. However, it is still unclear whether the recurrence of MCN interferes with the evolution of the transplanted kidney.

Recurrence of metabolic disease

Guidelines

N. Diabetic nephropathy:

Renal transplantation should be considered as the treatment of choice for many patients with diabetes mellitus despite almost inevitable histological recurrence a few years after renal transplantation. However, overt clinical nephropathy leading to late graft loss occurs in only a minority of patients.

(Evidence level B)

O. Type 1 primary hyperoxaluria:

Patients with type I primary hyperoxaluria should generally be considered for combined kidney and liver transplantation because renal transplantation alone is associated with rapid recurrent deposition of oxalate and graft loss, and liver grafting corrects the enzyme deficiency. Few patients with pyridoxine-sensitive hyperoxaluria may receive preemptive kidney transplantation

alone but in association with forced diuresis and early/prolonged pyridoxine administration.

(Evidence level B)

P. Cystinosis:

Renal transplantation should be recommended in patients (usually children) with cystinosis, because the disease does not recur.

(Evidence level B)

Q. Fabry's disease (alpha galactosidase defect):

Fabry's disease is not a contra-indication to renal transplantation; limited information is available regarding recurrence.

(Evidence level C)

Commentary on Guideline I.5.3: Recurrence of original renal disease (recurrence of metabolic disease)

Guideline N. Diabetic nephropathy

Recurrence of diabetic arteriolar lesions, mesangial expansion and glomerular basement thickening occurs in 100% of diabetic patients within 4 years of transplantation [74]. In patients with proteinuria and renal insufficiency, the typical nodular intercapillary glomerulosclerosis is seen infrequently but vascular changes are common [75].

Progression of histological lesions in the transplanted kidney is usually slow, but is often more rapid than in the original disease, perhaps because of lower nephron mass, use of nephrotoxic agents such as cyclosporine or tacrolimus, or the frequent presence of hypertension. Microalbuminuria indicates the presence of renal morphological abnormalities. Overt proteinuria and nephrotic syndrome develop later and precede the onset of progressive renal failure. Despite the high frequency of recurrence, this accounted for only 1.8% of graft losses in the largest study of renal transplants in diabetic recipients [76]. This is probably due to the fact that the mean interval from transplantation to the development of overt nephropathy is at least 7–8 years [75].

Despite many problems, renal transplantation is the treatment of choice for many diabetics with ESRF. However, pre-transplant investigations should be particularly thorough. Patients with a cardiac ejection fraction <30% or severe peripheral arteropathy [77] should be excluded from transplantation as the risk of mortality is excessively high.

Successful transplantation of both pancreas and kidney can prevent the development of diabetic nephropathy [78]. In the case of kidney transplantation alone, strict glycaemic control should be recommended. ACE-inhibitors and/or angiotensin receptor antagonists may be helpful in slowing the progression of renal disease and should be started as early as possible.

Guideline O. Type 1 primary hyperoxaluria

This rare innate error of metabolism is due to deficiency of the hepatic enzyme glyoxylate aminotransferase. In infancy the disease is characterized by nephrocalcinosis and widespread oxalate deposition, particularly in blood vessel walls and in bone. The disease is characterized by severely recurrent nephrolithiasis. After renal transplantation, patients may show rapid recurrence with deposition of oxalate in the allograft resulting in its loss. Pre-emptive transplantation, forced diuresis and early administration of pyridoxine can be helpful in reducing oxalate deposition in the kidney. Measures to prevent progressive oxalate deposition include early transplantation in patients with a glomerular filtration rate (GFR) around 20 ml/min to minimize oxalate retention, pre-operative dialysis to deplete the oxalate pool, forced diuresis, administration of pyridoxine which may decrease the oxalate pool by converting glyoxylate to glycine, and avoidance of cyclosporine in the early post-transplant period [79]. Good results with isolated kidney allografts have been reported in pyridoxine-responsive patients [80,81]. However, European meta-analysis indicates a graft survival of 10% at 1 year with isolated kidney transplantation vs 80% at 5 years with combined liver and kidney transplantation [82]. Thus the preferred treatment is combined liver and kidney transplantation, not only in pyridoxine-resistant patients [83] but in all cases [84]. The transplanted liver can restore the missing enzyme and prevent cardiovascular disease, which is the major cause of death. Radiological and histological improvement of osteopathy has also been reported [85].

In summary, renal transplantation alone may be indicated in only a minority of patients (those with pyridoxine sensitivity and low plasma levels of oxalate) whereas pre-emptive liver–kidney transplantation when patients have a GFR ~20–30 ml/min, is the treatment of choice in most cases.

Guideline P. Cystinosis

This is a rare metabolic disease inherited as an autosomal recessive trait and characterized by intracellular accumulation of free cystine in many organs, including the kidney. Renal transplantation in children with cystinosis produces results comparable to those in children with other renal diseases [86]. Cystinosis does not recur, even if some accumulation of cystine may be observed in the renal interstitium. These cystine deposits are thought to derive from macrophage invasion of host origin and have no clinical consequences for the graft. Despite successful transplantation, accumulation of cystine in other organs continues with associated manifestations. Early and continuous administration of cysteamine, however, may lower the content of cystine in leukocytes and improve growth rate. Cysteamine eye-drops may prevent corneal accumulation.

Guideline Q. Fabry's disease

This disease is caused by a deficiency of the enzyme alpha-galactosidase, with consequent accumulation of glycosphingolipids in many tissues, including kidney. Angiokeratomata, corneal dystrophy, acroparesthesias, mitral valve defects and cardiovascular disease are frequent clinical features. Renal failure is the most common cause of death.

Poor results with renal transplantation were reported in the 1970s, but more recent data show good graft survival [87,88]. Recurrence of the disease in the kidney allograft may occur, but this does not appear to impede graft survival, exemplified by a report of survival up to 11 years in one patient [89]. On the basis of limited experience, Fabry's disease should not be considered a contra-indication to renal transplantation.

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1.5.4 Work-up and preventive measures for thrombotic complications

Guidelines

A. General measures such as subcutaneous heparin, early mobilization and graduate compression stockings to reduce the risk of deep vein thrombosis and consequences should be recommended for renal transplantation because of an increased risk associated with the surgery and the immunosuppressive treatment.
(Evidence level B)

B. Specific measures (see commentary) to reduce the risk of vascular thrombosis of the graft after renal transplant surgery should be recommended because it is an early cause of graft complication in 2–7% of cases, more frequently in children, in patients with delayed graft function and in grafts with multiple arteries.
(Evidence level B)

C. A specific work-up to identify increased thrombotic risk should be performed in transplant candidates with

a previous history of venous thrombosis, in women taking oral contraceptives, in patients with diabetes mellitus, and in patients with atherosclerosis.
(Evidence level C)

Commentary on Guideline I.5.4: Work-up and preventive measures for thrombotic complications

Guideline A. Deep venous thrombosis is relatively frequent after transplantation [1]. Following transplantation, fibrinolysis may be impaired and coagulation remains activated as a consequence of tissue trauma, inflammation and expression of tissue factor. Cyclosporine has a procoagulant activity and may theoretically predispose to vein thrombosis. While some studies actually found a hypercoagulable state in cyclosporine-treated renal transplant recipients [2,3], others failed to find any difference between transplant patients who took cyclosporine and those who did not [4,5]. In a randomized study comparing tacrolimus with cyclosporine, patients assigned to tacrolimus had a significantly higher risk of deep vein thrombosis (5%) than those assigned to cyclosporine (0.5%), suggesting a potential thrombogenic effect of tacrolimus [6]. The risk for vein thrombosis in renal transplant patients ranges between 4 and 8%, and is maximal in the first 6 months after transplantation [7]. Thus, general measures to reduce the risk of deep vein thrombosis are recommended. These include subcutaneous heparin, early mobilization, calf-stimulators and graduate compression stockings. Although controlled studies evaluating the role of anticoagulation for prevention of venous thrombosis are lacking, a recent series reported no cases of thrombosis or haemorrhage in renal transplant recipients given delteparin, 2500–5000 U daily for 1 month [8].

Guideline B. Renal allograft thrombosis is responsible for 2–7% of early allograft losses [9]. Graft thrombosis is characterized by anuria and irreversible loss of function. Venous thrombosis in the transplanted kidney is more common than arterial thrombosis. The risk of graft thrombosis is particularly high in small children [10,11]. In addition to age, several other factors may contribute, such as abnormalities of coagulation, excessive dehydration, hypovolaemia caused by dialysis or polyuria, obese recipient, atherosclerosis of donor or recipient, or technical error. The donor kidney endothelium may also suffer from reperfusion injury and activation of a pro-coagulant surface from cytokines and the recipient immune response [9]. Renal graft thrombosis may be triggered by the administration of OKT3, which can lead to graft loss in 3–14% of cases [12]. The risk is increased in patients pre-treated with high-dose intravenous methylprednisolone. Thus, it is recommended that the dose of methylprednisolone, for pre-medication, should not exceed 8 mg/kg [13].

Arterial allograft thrombosis is particularly frequent in cases with delayed graft function [14] and in allografts with multiple renal arteries; up to 36% reported

in one series [15]. Furthermore, arterial allograft thrombosis also appears to be more frequent in CAPD (7.1%) than in haemodialysis (1.8%) patients [16]. However, other studies have reported no difference in the incidence of renal graft thrombosis in CAPD or haemodialysis patients [5,14]. Nevertheless, it is likely that in most cases of renal allograft thrombosis there is an interaction between acquired hypercoagulability as a result of the renal disease, genetic risk of thrombosis and environmental stress, such as surgery [9].

Guideline C. The presence of thrombophilic disorders, such as factor V Leiden mutation, protein C, protein S and antithrombin deficiency, may be associated not only with venous thromboembolic complications including cerebral or coronary vascular disease but also a higher rate of acute rejection [17] and acute vascular rejection [18]. In patients with a family or personal history of venous thrombosis, in women taking oral contraceptives, in patients with diabetes mellitus [19,20] and in patients with atherosclerosis, it may be of particular importance to search for thrombophilic factors to prevent thrombotic complications. Investigations should include factor V Leiden mutation deficiency of protein C, S or antithrombin III, lupus anticoagulant, and/or antiphospholipid antibodies.

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I.5.5 Co-morbid conditions

• Diabetes mellitus

Guidelines

A. Kidney transplantation should be considered as the first therapeutic choice for all suitable patients with end-stage renal disease (ESRD) due to diabetes mellitus, because kidney transplantation is able to significantly extend survival as compared with dialysis.

(Evidence level B)

B. Diabetic ESRD patients should be considered for an early and pre-emptive transplantation of either a simultaneous pancreas–kidney transplantation (SPK), a living related donor graft, or an early cadaver graft when residual glomerular filtration rate (GFR) decreases to < 20 ml/min.

(Evidence level B)

C. Diabetes mellitus should be considered as a serious co-morbid condition affecting transplant success and patient morbidity/mortality, mainly because of increased cardiovascular and infectious risks.

(Evidence level B)

D. Therefore, a thorough evaluation of diabetic transplant candidates is recommended with particular attention to the cardiovascular risk.

(Evidence level C)

Commentary on Guideline I.5.5: Co-morbid conditions (diabetes mellitus)

Guideline A. ESRD due to diabetic nephropathy is of increasing importance in all Western countries. More than 40% of all cases of ESRD are due to diabetic nephropathy, making it the most common cause [1]. Within this increasing population, most cases are due to type II diabetes mellitus, whereas the incidence of cases due to type I diabetes mellitus has remained relatively constant. ESRD due to diabetes mellitus

carries the highest risk for early death due to cardiovascular complications. The pathogenetic background consists of hypertension, lipid disorders, the accumulation of AGE (advanced glycation end products) substances, and autonomic neuropathy. All forms of renal or combined transplantation have been proven to have a better patient survival rate than dialysis, although prospective investigations are not available [2].

Guideline B. For diabetics with progressive renal failure, when the creatinine clearance decreases to <20 ml/min the patient's suitability for a combined pancreas and kidney transplant should be evaluated. If the patient is found to be unsuitable, the possibility of a living donated kidney graft should be evaluated. Evaluation should begin when kidney function is <25 ml/min GFR and the transplant should be pre-emptively scheduled for the time point when function deteriorates to <20 ml/min GFR. If a combined transplant is not possible and a living related donor (LRD) graft is not available, pre-emptive registration on a waiting list is mandatory. This process is supported by the superior results of LRD grafts compared to CAD in diabetics [3].

Guideline C. Efforts should be made to offer diabetic patients a graft as early as possible. Dialysis treatment has the most inferior outcome compared with all types of transplantation. Although renal transplantation alone cannot halt or improve extrarenal diabetic complications such as retinopathy, neuropathy and microangiopathy, there is often an improvement of life expectancy as shown by data from the USRDS [2]. Registry data have also shown improved survival of transplant recipients after a first myocardial infarction compared with dialysis patients [4]. The number of amputations and amauroses may be increased [5]. Recurrence of diabetic nephropathy in the graft has been reported, although it is very rarely a cause of graft failure [6,7]. Special attention should be directed to diabetic sequelae, such as impaired gastric emptying and diabetic cystopathy. Gastroparesis may result in unpredictable absorption of immunosuppressive drugs [8,9]. Impaired bladder voiding predisposes to urosepticemia [10]. Peripheral neuropathy may cause foot ulcers and infectious complications such as gangrene.

Guideline D. The previously observed increase in perioperative risk in diabetic patients has disappeared in recent years and has become similar to non-diabetic patients [11].

Diabetic transplant candidates should undergo an intensive evaluation of all co-morbid conditions in general, and cardiovascular risk factors in particular. Coronary artery disease and pelvic and peripheral vessel disease must be investigated by all appropriate means. Because most of the recipients have a low exercise capacity, adequate exercise ECG cannot be performed and should be replaced by pharmacological stress echocardiography [12]. In most centres, the policy is to perform a coronary angiography in candidates for SPK or LRD. Pre-existing coronary artery disease carries an increased risk, and coronary bypass grafting (or stenting) should be performed before

placing the patient on the waiting list. Patients with cardiac autonomic neuropathy, detectable by heart rate variability recording, should be considered to have increased cardiovascular risk. Evaluation should include investigation of the gastric emptying capacity, detection of residual bladder content and observation of foot injuries.

• Cardiovascular disease

Guidelines

E. As cardiovascular disease is the main cause of mortality after transplantation, careful evaluation is mandatory to detect and treat symptomatic coronary artery disease, congestive heart failure due to valvular failure or cardiomyopathy and pericardial constriction.

(Evidence level B)

F. As technical graft failure and impaired patient survival is often due to symptomatic peripheral artery disease, extensive pelvic vessel calcification, aortic and pelvic vessel dissection and symptomatic cerebral vascular disease should be excluded or treated in advance.

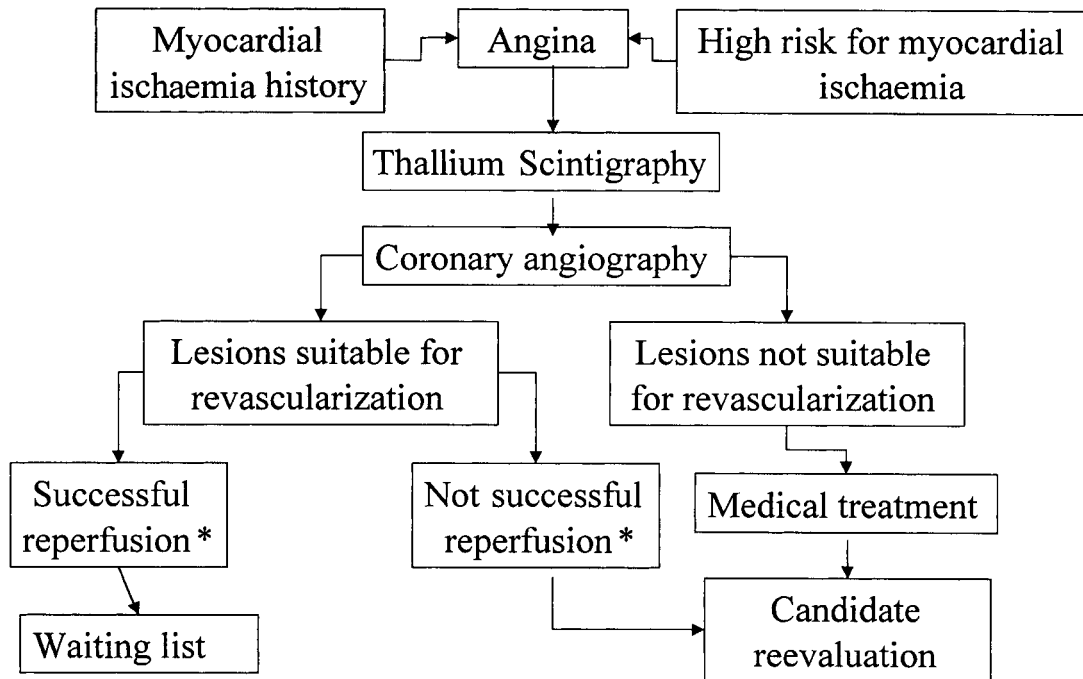
(Evidence level B)

G. As venous vessel disease such as post-thrombotic occlusion of the pelvic veins, radiation injury and retroperitoneal fibrosis of the pelvic and lower abdominal region carry a high risk of technical graft failure, these conditions should be excluded or treated in advance.

(Evidence level C)

Commentary on Guideline I.5.5: Co-morbid conditions (cardiovascular disease)

Guideline E. Convincing evidence is available showing the impact of cardiovascular risk factors on patient survival after kidney transplantation. Attempts have been made to reduce the risk by careful pre-transplant evaluation [13,14]. Investigations have been performed to select the best available method for cardiovascular work-up in transplant candidates (Figure I.3). Echocardiography, although not prospectively tested, seems to be of pivotal importance to screen for cardiac abnormalities such as valvular disease, cardiomyopathy, pericardial disease and impaired cardiac wall movement after myocardial infarction [15–17]. Exercise testing to detect coronary artery diseases is limited because of the impaired exercise capacity of dialysis patients. This applies to both exercise ECG and thallium myocardial imaging [18]. Exercise testing is only of use in patients with normal exercise capacity. Dobutamine stress testing appears to be a useful method, although somewhat observer dependent [19–21]. Prospective use of coronary angiography detects a high number of lesions not identified by non-invasive measures [15,22]. The use of coronary angiography in any suspicious case is therefore recommended. In appropriate cases, pre-transplant cardiac surgery is



* Surgical or by coronary angioplasty

Fig. I.3. Algorithm for cardiovascular evaluation of patients for the waiting list.

recommended and improves the outcome for the recipients [23].

Guideline F. The increasing age of the patient population makes peripheral vascular occlusive disease a significant cause of morbidity in transplant patients. In particular the presence of pelvic vessel disease is an important factor for surgery [24] and the risk of amputation is high in diabetics. Special attention must be paid to vascular occlusive disease of the carotid arteries [25].

Guideline G. Although not extensively studied, diseases of venous return in pelvic veins after thrombosis with and without previous access catheters may cause technical failures and early graft thrombosis.

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I.5.6 Individual risk factors

Older recipients

Guidelines

A. Advanced age *per se* is not a contra-indication to renal transplantation.

(Evidence level B)

B. In elderly (older) patients, renal transplantation should be offered because it increases the chance of survival compared with dialysis.

(Evidence level B)

C. In older recipients, careful assessment of their cardiovascular status and tailored immunosuppression are both recommended after renal transplantation because cardiovascular disease and infections are frequent causes of death and older recipients usually have less rejection.

(Evidence level C)

Commentary on Guideline I.5.6: Individual risk factors (older recipients)

Guidelines A and B. Although life-expectancy is obviously less in elderly than in younger transplant recipients, a number of studies have shown that in well selected elderly recipients, graft survival may be similar

to that observed in young adults [1–3]. Some investigators report that graft survival is inferior when older recipients are transplanted with an older donor kidney [4]. However, others have found that when deaths are excluded, graft survival is similar in older recipients who received kidneys from a donor older than 60 years and younger recipients given kidneys from donors younger than 59 years [5]. Some papers reported that pure graft survival (excluding death) is even better in older recipients than in younger adults [6,7]. A recent paper showed that improvements in results since 1983 now make transplantation in older patients a viable option. The risk of graft failure (including death) of a 20-year-old patient who underwent transplantation between 1983 and 1990 was greater than that of a 70-year-old patient who underwent transplantation between 1994 and 1997 [8]. The improving results in recent times appear to surpass the increased risk of donor age [8]. This justifies an extension of renal transplantation to elderly patients.

When only patients eligible for transplantation are considered, the 5-year patient survival rate is better in older patients who receive a transplant than in those who remain on dialysis [9,10].

Guideline C. Cardiovascular disease is the leading cause of death in elderly transplant patients [11]. However, approximately half of the elderly patients who die of a cardiovascular accident after transplantation are asymptomatic for cardiovascular disease at the time of inclusion on the waiting list [12].

Infection is another major cause of death in older patients [7]. However, despite an increased risk of cardiovascular and infectious complications in elderly patients, the incidence and the severity of acute rejection are lower than that observed in younger patients [13].

Two main measures can be adopted to reduce mortality: accurate recipient selection and preparation and immunosuppression tailored to the older patient.

The risk of death is mainly related to the presence of co-morbid conditions. Although the leading causes of death in older transplant patients are cardiovascular diseases and infections, colonic perforation [2,12], gastric haemorrhage or acute cholecystitis [14] are also frequent causes of mortality in this population. Cardiac risk may be evaluated by thallium scintigraphy and/or dobutamine echocardiography, but some investigators advocate routine coronary angiography, particularly in diabetic patients. Coronary revascularization may reduce post-transplantation cardiovascular events and silent cardiac infarcts, which represent frequent causes of death in the elderly [15]. Identification and treatment of infections is also needed. Pre-emptive treatment with ganciclovir can reduce the risk of cytomegalovirus (CMV) infections, and thus reduce the risk of opportunistic, life-threatening infections. Antiviral therapy may be suggested for seronegative recipients receiving seropositive CMV transplants. Colonic perforation most often results from diverticulitis. Colonic perforation should be suspected in the presence of abdominal pain and unexplained fever.

Gallbladder ultrasound should be performed before transplantation to identify any cholelithiasis, and cholecystectomy may be considered.

A possible advantage of renal transplantation in older recipients is represented by their blunted inflammatory and immune responses and by the lower incidence of rejection [2,6,11,16]. This may allow a reduction in the intensity of immunosuppression, thus decreasing post-transplant morbidity and mortality. However, hypersensitized patients and those who lost a previous transplant because of an early acute rejection should receive adequate immunosuppression.

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I.6 Immunogenetic work-up of the recipient (and donor)

I.6.1 ABO blood grouping and HLA typing

Guidelines

A. The ABO blood group should be ascertained for all candidates awaiting transplantation.
(Evidence level A)

B. The HLA-A, -B and -DR phenotypes should be ascertained for all candidates awaiting transplantation.
(Evidence level A)

C. Cells for HLA typing should be obtained from ~20 ml of recipient's peripheral blood using an appropriate anticoagulant (e.g. ACD, EDTA or PFH).
(Evidence level C)

D. Comprehensive sets of reagents capable of detecting all commonly occurring HLA antigens within the relevant ethnic groups should be used and results should be accepted only if HLA antigens are unequivocally defined. If only one allele is identified at an HLA-locus, additional techniques (see details in commentary) should be employed to confirm true homo- or heterozygosity due to a hitherto undetected allele.
(Evidence level B)

E. If the patient has been heavily transfused especially with non-leukodepleted blood within the previous 7 days, care should be taken in interpreting the level of mismatch since there is a risk of a 'mixed field' result giving more than two alleles per HLA locus.
(Evidence level C)

F. When a relative is being evaluated for live donation and there is ambiguity with regard to the level of HLA matching, the immediate family members may be typed to obtain accurate HLA haplotype assignments and to identify any recombination between HLA genes.
(Evidence level C)

Commentary on Guideline I.6.1: ABO blood grouping and HLA typing

Guideline A: ABO typing

See commentary to guideline on: ABO blood group matching and mismatching (section III.1.1).

Guidelines B, C and D: Short guide to HLA

To appreciate the role of HLA in transplantation, brief consideration needs to be given to the structural and functional aspects of HLA molecules. These are coded by a series of genes on the short arm of chromosome 6. The genes and their products are classified into two major categories: first, class I molecules which include products of the HLA-A, -B and -C loci, and secondly, class II molecules which include products of the HLA-DR, -DQ and -DP loci. Class I molecules are expressed on the cell membrane of all nucleated cells. In the absence of inflammatory stimuli, class II expression is limited to a few cell types (e.g. dendritic cells, B-cells and activated T-cells), but expression is induced in many tissues, including renal vascular endothelium, when exposed to inflammatory cytokines. A mismatched transplant induces the recipient to produce allo-specific helper (CD4 positive) and killer (CD8 positive) T-cells. These in turn induce B-cells to produce allo-antibodies. All these cells contribute to graft rejection. For pragmatic reasons, tissue typing tends to be restricted to products of the HLA-A, -B and

-DRB1 loci. Clear evidence exists for the influence of these genes on graft outcome. The other HLA genes have never been fully evaluated and are not uniformly included in routine typing for kidney transplantation, one exception being a possible role for HLA-DP mismatches in regrafts (see below).

HLA is a cell membrane glycoprotein intimately involved in cell-cell interactions in the immune response. The membrane-proximal part of the molecule forms a peptide-binding groove that presents small peptides to T-cells via a specific T-cell receptor (TCR). Non-self or 'foreign' peptides transmit signals via the TCR that activate T-cells and induce them to undergo clonal expansion and differentiation. The clonal progeny interact with specific B-cells that also undergo clonal expansion and differentiation. B-cells differentiate into plasma cells that produce antibodies against non-self epitopes carried by the original proteins from which the non-self peptides were derived. At a certain point, the expanded clones undergo programmed cell death or apoptosis except for a few specialized memory cells that persist in prolonged G₀ phase of the cell cycle. In sensitized patients, it is both the memory T- and memory B-cells that maintain lifelong immunity to HLA and other histocompatibility antigens.

When a kidney transplant is performed, the donor's foreign HLA molecules activate the recipient's immune system. The vast polymorphism of HLA makes it very difficult to find unrelated individuals who are exactly matched at each locus. In contrast, within families, siblings may be completely matched for both HLA haplotypes. There is in fact a 25% probability of two siblings being HLA identical for all HLA genes. This difference contributes to the superior outcome of living related donor transplants compared with cadaver donor transplants.

Terminology of HLA

All HLA terminology should conform to the latest report of the WHO Committee on Nomenclature [1]. This publication and its regularly published updates summarize current knowledge on the HLA system. It contains an ordered listing of the known HLA loci or genes and the molecular characteristics of the gene products. For each gene all the alleles so far discovered are listed, each being confirmed by DNA sequencing. Alongside each allele is the HLA specificity as originally defined by antibody. The genes that are of potential importance in rejection in transplantation are listed below and those that are most commonly used for matching in kidney transplantation are underlined: HLA-A, -B, -C, -DRA, -DRB1, -DRB3, -DRB4, -DRB5, -DQA1, -DQB1, -DPA1, -DPB1. HLA phenotypes may be reported either as alleles or specificities. The nomenclature used for alleles is based on DNA sequence information and is logical and simple to understand. The nomenclature used for specificities is a language that has evolved over 30 years. As new specificities were defined by serological research they

were allotted the next unused number irrespective of their locus of origin. Hence numbers assigned to specificities accord with the historical epoch in which they were discovered. Thus HLA-A1, -A2, -B4 and -B6 were amongst the first specificities to be defined, and incidentally amongst the most frequent in the population. All HLA specificities can be deduced from HLA alleles, but the reverse does not always apply since certain alleles are non-immunogenic and fail to induce unique antibodies making them difficult to place within a known grouping of serological specificities. In allelic nomenclature, the gene/locus followed by * precedes the allele numbers, thus: HLA-A*, -B*, -Cw*, -DRA*, -DRB1*, -DRB3*, -DRB4*, -DRB5*, -DQA1*, -DQB1*, -DPA1*, -DPB1*. The allele number that follows the gene designation may have two to four or more digits. Where there is a strong association between an allele and a previously defined specificity this is reflected in the first two digits of the allelic number (e.g. the DNA defined allele HLA-A*02 is associated with the serologically defined specificity HLA-A2). Shorter allele numbers imply low-resolution typing and longer allele numbers (e.g. HLA-A*0204) imply high-resolution typing. An alternative reporting style for low-resolution typing is to list all the members of the allele family to which the type belongs (e.g. HLA-A*0201-23/25/26).

A haplotype such as HLA-A1, -B8, -DR3 is a cluster of HLA specificities inherited from one parent which, because of close linkage on the same segment of chromosome, is normally inherited *en bloc*. Each somatic cell has two haplotypes: one inherited from the father and one inherited from the mother. When both haplotypes have been defined in an individual by family segregation studies, it is possible to designate the HLA genotype. For example family segregation studies of the results in Table I.4 allow the haplotypes shown in Table I.5 to be identified. Furthermore it can be seen that there is substantially more complexity identifiable at the allelic level than at the level of specificities.

HLA typing in practice

HLA typing techniques were first developed in the 1960s using methods that relied on naturally occurring anti-HLA sera collected from parous women, sensitized to paternal HLA mismatches expressed on foetal cells [2-6]. Today typing is increasingly performed by DNA-based techniques that rely on nucleotide sequence differences between alleles. Many more alleles have been detected using DNA typing techniques than specificities identified by serology [7,8]. In theory, if the alleles at each locus would segregate completely independently of each other, and if each one was equally represented in the population, the number of possible combinations of alleles as HLA-A, -B, -DR phenotypes would exceed the population of the world! (Table I.6). In reality two features of the HLA system make matching a more achievable goal than would

Table I.4. Typical HLA phenotype reported either as specificities or alleles

Serologically defined HLA specificities		HLA alleles defined by DNA typing	
Locus	Type ^a	Gene	Allele ^b
HLA-A	2	HLA-A*	0201–23/25/26
HLA-A	24(9)	HLA-A*	2402–07/10/14
HLA-B	44(12) (Bw4)	HLA-B*	4402–04
HLA-B	8 (Bw6)	HLA-B*	0801–03
HLA-DR	17(3)	HLA-DRB1*	0301/02/06/08/11
HLA-DR	4	HLA-DRB1*	0401–07/10–12/ 15–17/21/22/24/25

^aSpecificity and broad cross reactive group in parentheses.

^bAllelic families: from–to, inclusive; and either/or.

Table I.5. Typical HLA genotype reported either as specificities or alleles

Serologically defined HLA specificities		HLA alleles defined by DNA typing	
Locus	Type ^a	Locus	Allele ^b
Paternally derived haplotype:			
HLA-A	2	HLA-A*	0201–23/25/26
HLA-B	44(12) (Bw4)	HLA-B*	4402–04
HLA-DR	17(3)	HLA-DRB1*	0301/02/06/08/11
Maternally derived haplotype:			
HLA-A	24(9)	HLA-A*	2402–07/10/14
HLA-B	8 (Bw6)	HLA-B*	0801–03
HLA-DR	4	HLA-DRB1*	0401–07/10–12/ 15–17/21/22/24/25

^aSpecificity and broad cross reactive group in parentheses.

^bAllelic families: from XXXX–to XXXX, inclusive; and either/or.

Table I.6. Comparison of HLA specificities and alleles at the A, B and DR loci

HLA locus	Antibody defined specificities	Alleles defined DNA sequencing
HLA-A	27	124
HLA-B	60	258
HLA-DRB1	18	221
Theoretical number of HLA-A, -B, -DR phenotypes	8.5×10^8	5.0×10^{13}

otherwise be expected. First, certain HLA specificities occur much more frequently in the population than others. For example HLA-A2 occurs in 40–50% of the Caucasian population. Secondly, certain specificities at adjacent loci occur together within the population more often than would be expected if they were segregating at the normal rates of crossing over and recombination between loci. This permits the increase of certain common haplotypes within populations. For example HLA-A1, -B8, -DR3 is a common haplotype within the caucasian population with a frequency of 4–9%.

HLA molecules are polypeptide chains made up of amino acid residues, segments of which are shared with other HLA molecules. For example, a molecule coded by an HLA-B allele contains a chain of 180 amino acids. Each HLA-B molecule has two alternative amino acids at position 82 (lysine or arginine), in combination with one of four amino acids at position

45, in combination with one of two at position 41 and so on along the chain. Different HLA molecules owe their uniqueness to these site-specific amino acid substitutions. However, the fact that many substitutions are widely shared with other HLA molecules leads to cross reactivity between HLA alleles at the level where antibodies react with specificities (epitopes). Since there are fewer serologically defined epitopes than DNA defined alleles, a large discrepancy exists between phenotypes identified by the two methods (Table I.6). This is discussed further under cross-reactive group (CREG) matching below.

The accuracy of HLA typing in practice depends on the comprehensiveness of the reagents used and their ability to detect all commonly occurring alleles within the population [9–11]. Caucasian serological reagents are less accurate when used for typing black patients. These differences are largely overcome by using DNA typing techniques. When typing with intent to match,

the same degree of accuracy should be applied to both donor and recipient. Recent blood transfusions may cause persistent DNA from the transfusion donor to give misleading typing results. Typing may be 'high resolution' or 'low resolution' according to the comprehensiveness of the reagent set used. Typing of family members with a view to selecting a living donor only requires low resolution typing because the main requirement is to get a marker on the HLA haplotypes shared between family members.

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I.6.2 Antibody screening to evaluate sensitization status

Guidelines

A. From time to time anti-HLA antibodies appear in a patient's blood that react against a potential donor. If unrecognized, these antibodies may cause hyperacute rejection of the transplant. Hence sequential serum samples should be routinely collected from the transplant candidate immediately before dialysis and at intervals no greater than 3 months.
(Evidence level B)

B. Sequential serum samples should be analysed for antibody and freeze-stored ready for cross-matching against a potential donor. Samples should be screened against a reference panel of cells selected to cover the majority of the HLA alleles in the donor population. The results should be expressed both as percentage panel reactive antibody (%PRA) and as the HLA specificity(s) that they react against.
(Evidence level B)

C. In serum samples with a high %PRA, careful analysis of the reaction patterns against the panel can often reveal allelic products against which the patient failed to make antibody. These 'windows of non-reactivity' may be used to predict and select cross-match negative donors.
(Evidence level B)

D. The most reactive sera available (highest %PRA) either after rejection and/or nephrectomy of a previously rejected graft, or after blood transfusion, should be identified by testing sera at frequent intervals in the 4 subsequent weeks after the event. The highest %PRA sera should be used in any subsequent cross-match test with a potential donor.
(Evidence level B)

E. A system should exist whereby the laboratory is notified every time a patient receives either a transfusion or treatment with anti-thymocyte or -lymphocyte globulin or monoclonal antibodies such as OKT3. Antibodies may linger in the serum and interfere with the antibody screening and cross-match tests.
(Evidence level B)

Commentary on Guideline I.6.2: Antibody screening to evaluate sensitization status

Guidelines A and B. Up to 47% of patients awaiting a transplant have anti-HLA antibodies mostly as a result of prior pregnancies, transfusions or previously failed transplants [1–5]. In rare cases, antibody may appear even in the absence of prior exposure to non-self HLA. Antibody may be directed to class I or II specificities. Not all antibody is detectable by the standard lymphocytotoxicity test, which is most sensitive to anti-class I specificities for complement fixing IgG₁, IgG₃ and IgM antibodies. It is less sensitive for anti-class II and weak anti-class I specificities. It does not detect non-complement fixing antibodies of the IgG₂, IgG₄ and IgA types [6]. Non-complement fixing allo-antibodies are better detected in alternative assays including ELISA, flow cytometry, anti-globulin tests or by using alternative cell targets such as lymphoblastoid cell lines or B cells [6–19].

Guidelines C–E. A minority of patients awaiting transplantation are 'highly sensitized'. The level of sensitization is expressed as %PRA. This is the proportion of individuals that react positively against a reference panel of accurately typed cells selected to represent the distribution of donor HLA phenotypes within the population. Thus, a highly sensitized patient would be

someone with one or more sera reacting with 80% or more of the panel cells (>80% PRA). These patients make up ~12–20% of national waiting lists. In some cases %PRA may be reduced following treatment of the serum with dithiothreitol (DTT) which selectively destroys IgM antibody [20,21]. In cases <100% PRA, it is possible to deduce the targeted epitope(s) from the HLA genotypes of the negatively reacting panel cells [22–24]. High %PRA may often be attributed to highly focused antibodies that react against no more than 2–3 epitopes [25]. Highly sensitized patients require special treatment because it is difficult to find cross-match negative kidneys for them. Some organ sharing organizations have special schemes that give higher priority to highly sensitized patients [26–30]. A small fraction of highly sensitized patients have 100% PRA due to IgG antibody and are ineligible for these schemes. In these cases, the only option is to use techniques that involve antibody removal coupled to immunosuppression of antibody production [31].

Some harmless antibodies may have the additional property of being associated with a beneficial effect on the transplant, but most have not been confirmed or evaluated in prospective studies. Sometimes, these antibodies may co-exist with lymphocytotoxic antibodies. They include cold lymphocytotoxic antibodies [32,33], Fc receptor II blocking antibodies [34], auto-reactive IgA [6] and anti-idiotypic antibodies [35–38].

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I.7 Pre-emptive transplantation

Guidelines

A. Pre-emptive transplantation from either live or cadaveric donors results in equivalent or even better patient and graft survivals than transplantation performed after the start of dialysis. Pre-emptive renal transplantation should be encouraged for all patients whenever a living donor is available. Pre-emptive cadaveric transplantation may ideally be offered to all transplant candidates but is of particular importance for children and patients with diabetes mellitus; however cadaveric organ shortage makes this unlikely. (Evidence level B)

B. Patients should have progressive deterioration in renal function and a creatinine clearance <15 ml/min/1.73 m² to be eligible for pre-emptive transplantation. (Evidence level C)

Commentary on Guideline I.7: Pre-emptive transplantation

Guideline A. Transplantation is said to be pre-emptive if it takes place before the initiation of chronic dialysis. Pre-emptive transplantation has the potential to avoid the morbidity and the burden of chronic dialysis. In addition, the costs of dialysis are spared. There has been some concern in the past that pre-emptive transplantation might be associated with an increased risk of graft loss from rejection because these patients would not experience the immunosuppressive effects of uraemia. A number of recent reports indicate that this is not the case [1–12]. In one series of adult cadaveric recipients immunosuppressed with cyclospor-

ine A, both patient and graft survival were significantly higher when transplantation was pre-emptive rather than performed after dialysis (graft survival: 72 vs 60% at 5 years) [7]. Furthermore, the risk of rejection was not greater after pre-emptive transplantation [7]. Along the same line, adults who received live-related pre-emptive transplantation had similar patient and graft survival at 2 years compared to a control group transplanted after dialysis [11]. Data reported to the EDTA Registry again indicate that adult transplant recipients who receive pre-emptive transplantation, from either live or cadaveric donors, fare as well as those who did not [6].

The same conclusions were reached with respect to pre-emptive transplantation in children, with results for patient and graft survival being either equivalent or even better than those recorded in patients transplanted after dialysis has started [2,4,5,8,9,12].

Guideline B. Two conditions should be fulfilled to perform a pre-emptive transplant. First, the recipient should have a renal disease which is definitely irreversible and clearly progressive. Secondly, the renal function must be less than a certain value, for instance a creatinine clearance <15 ml/min/1.73 m² [13]. However, some categories of patients derive major benefits from transplantation with regard to quality of life and improved life expectancy, such as children and patients with diabetes mellitus [14].

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1.8 Waiting list

1.8.1 Assignment to the transplant waiting list

Guidelines

A. Assignment to the transplant waiting list is the first crucial step for the patient, and this process should be seen to be transparent and to follow objective scientific principles after careful evaluation of the patient's medical history.

(Evidence level C)

B. The process of assignment should balance the possible success of a graft with the personal needs of the patient.

(Evidence level C)

C. Discrimination by age, gender, social and ethnic background is not acceptable.

(Evidence level C)

Commentary on Guideline I.8.1: Assignment to the transplant waiting list

Guidelines A–C. There are no evidence-based rules on the policies for assignment to the transplant waiting list and daily practice differs somewhat from institution to institution [1,2]. Volume and experience may play an important role. In general patients who tend not to be accepted are older, more often female, diabetic and carriers of viral disease such as hepatitis C [3]. In some countries consensus conferences or medical associations have issued rules or guidelines to support decision making. In view of the very long waiting lists in most countries, there is no evidence that acceptance rates are low or influenced by non-medical criteria, although specific individual patients may be unfairly treated [4–6]. In the US there is ongoing discussion on acceptance rates in minority groups.

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I.8.2 Regular check-up while on waiting list

Guidelines

A. Due to the possible rapid change in the waiting recipient's medical condition, an update at regular intervals is recommended to avoid unexpected risks at the time of an offer of transplantation.

(Evidence level C)

B. The updated record available to the transplant centre should contain information on the cardiovascular condition, on new infectious and viral diseases and on the lower urinary tract.

(Evidence level C)

C. Assessment may be performed every 6–12 months depending on the age and condition of the recipient.

(Evidence level C)

Commentary on Guideline I.8.2: Regular check-up while on waiting list

Guidelines A–C. Regular follow up on the waiting list is particularly important in countries and patient populations with waiting times exceeding 1–2 years. The accelerated cardiovascular disease of dialysis patients and concomitant conditions such as hyperparathyroidism make it unlikely that the status of the patient remains stable for long periods. It is therefore highly recommended that regular follow-up checks are performed, to avoid complications during surgery and perioperatively.

The status of infectious disease must also be monitored. In patients at risk of infectious or malignant disease of the urinary tract, ultrasound, culture and cytology must be performed.

I.8.3 Principles of organ sharing

Guidelines

A. Centres undertaking cadaveric kidney transplantation should participate in a national (regional) or international organ sharing scheme that gives priority to HLA matching in kidney allocation. This will increase the proportion of well matched transplants performed in all participating centres.

(Evidence level B)

B. The organ sharing organization should maintain accurate, confidential and up-to-date central records containing the HLA-A, -B and -DR types, %PRA,

gender, parity, previous transplants and other basic information on patients from the participating centres.

(Evidence level C)

C. The degree of resolution and the accuracy of HLA typing should be at a uniform level throughout all participating centres and should be regularly monitored.

(Evidence level B)

D. All HLA typing results on cadaveric donors should be recorded by the organ sharing organization and any discrepancies or errors investigated. The different typings include the 'offer typing' originating from the donor centre, the 'typing at transplant' performed at the recipient centre and any retrospective typings.

(Evidence level C)

Commentary on Guideline I.8.3: Principles of organ sharing

Guidelines A–D. Minimizing the HLA mismatch between donor and recipient clearly improves the survival of kidney transplants, but the vast polymorphism of the HLA system ensures that good matches rarely happen by chance. Hence, organ sharing schemes have been developed on the principle that the larger the pool of patients waiting, the wider the range of HLA types to choose between and the greater the chance of transplants being well matched [1–9]. Table I.7 illustrates this principle in a computer simulation study [1]. It shows that the higher the number of patients

Table I.7. Simulation^a of proportion of ABO and beneficially matched^b transplants

Pool size	HLA-A, -B, -DR mismatch level				Donor
	000 (%)	100 (%)	010 (%)	Other (%)	
100	3	4	5	88	1000
500	7	11	12	70	1000
1000	10	14	17	59	1000
3000	17	22	22	39	1000
5000	28	24	21	26	1000

^aSimulations assume: (i) all donors and recipients are typed for HLA-A, -B and -DR; (ii) both kidneys from each donor are offered to the pool initially for the best matched recipient on the waiting list; (iii) all offers are for ABO identical recipients; and (iv) no exclusions due to positive cross matches, and ethnic matching between donor and recipient populations.

^b'Beneficial matching' is defined as either 000 or 100 or 010 mismatches for HLA-A, -B and -DR genes, respectively. The lowest risk of graft loss is associated with zero HLA-A, -B or -DR mismatches (000), the next lowest risk is associated with one HLA-A or -B mismatch (100 or 010), and the highest risk is associated with one or more HLA-DR mismatches irrespective of number of HLA-A and -B mismatches (**1 or **2). The range of HLA mismatching with cadaveric donor transplants extends from 000 through several grades to 222. Whereas in family donor transplants results are classifiable into one of three levels of mismatch, otherwise termed 0, 1 or 2 HLA haplotypes mismatched, cadaveric transplant results are spread across 27 grades given by three possible mismatches at HLA-A, -B and -DR loci ($3 \times 3 \times 3 = 27$). For further discussion see text.

on the waiting list, the higher the proportion of beneficially matched transplants. With a waiting list of 100 only 12% can be beneficially matched, whereas with a waiting list of 5000 patients, 74% can be beneficially matched.

Most organs are redistributed on the basis of ABO and HLA compatibility and %PRA. Additional weighting is often given to other factors such as time on the waiting list, balance of trade between centres and age. In theory, the polymorphism of HLA is so vast that even a global sharing scheme would only result in a minute proportion of HLA-matched grafts. But in practice, certain combinations of alleles at adjacent HLA loci occur commonly in the population (e.g. HLA-A1, -B8, -DR3), and a high proportion of matched transplants can be achieved [9]. Unfortunately, common HLA haplotypes in one ethnic group may be uncommon in another; hence minority ethnic groups tend to have a much lower chance of well matched cadaveric kidneys. Theoretically, this could be overcome by matching for cross reactive groups (CREG) rather than HLA alleles or specificities (for further discussion see section on matching below). Other reasons why the overall proportion of well matched transplants is sub-optimal include logistics, age, distance, high sensitization and 'balance of trade' [10]. Nonetheless, schemes that redistribute kidneys equitably between participating centres ensure that the proportion of well matched transplants in all centres approaches the optimum [11]. Matchability is the calculation of a patient's expected waiting time to receive a beneficially matched graft. It can be useful for the clinician in deciding whether to wait for a well matched donor or to accept a lesser grade of match [12–14].

Current best practice is for each transplant centre to participate fully in an organ-sharing scheme by registering all their waiting patients. Should a local donor become available both of the kidneys retrieved from a single donor should be offered for export through the organ sharing service for patients who are beneficially matched for HLA-A, -B and -DR alleles.

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1.9 Pre-operative transfusion

Guidelines

A. Administration of random blood transfusions to first cadaveric kidney transplant candidates improved graft survival in patients immunosuppressed with azathioprine and steroids, and an effect, although reduced, was still observed in the early cyclosporine A (CyA) era. However, graft survival and rejection rates in non-transfused recipients are better today with the new immunosuppressive drugs than in previously transfused patients. As transfusion still carries a small risk of allo-immunization and transmission of infectious diseases, there are no robust indications at present to systematically give pre-transplant blood transfusion to all transplant candidates. If contemplated, administration of pre-transplant transfusion should preferably be performed in the context of a clinical study.

(Evidence level C)

B. Administration of donor-specific transfusion (DST) from living donor to non-HLA-identical recipient improved graft survival in the azathioprine era. This beneficial effect appears still to prevail in the early CyA era, but there are no data about the possible impact of DST with the present immunosuppressive regimens. Even with azathioprine or CyA pre-treatment, DST carries a risk of anti-donor sensitization precluding transplantation in up to 10% of patients. The decision to perform a DST should be made on a case-per-case basis.

(Evidence level C)

C. In patients with previous exposure to alloantigens, such as multiparous women, previously transplanted patients and those already HLA-sensitized, both random and donor-specific transfusions carry an increased risk of anti-HLA sensitization. The risks and benefits of transfusing these patients should be carefully evaluated.

(Evidence level B)

D. The blood transfusions, whether random or HLA semi-identical or donor-specific, should meet the following requirements: (i) they should not be leukocyte free; (ii) the number of units administered should be ≤ 3 ; (iii) fresh rather than frozen blood should be given; and (iv) the blood should be transfused at least several weeks before transplantation, as perioperative blood transfusions have no consistent effects.

(Evidence level B)

Commentary on Guideline 1.9: Pre-operative transfusion

Guideline A. The interest of transfusions for kidney transplant recipients was first pointed out in 1973 by Opelz, who made the unexpected observation that patients who had received blood transfusions prior to transplantation enjoyed a major improvement of graft survival as compared with non-transfused recipients [1]. Numerous studies, mainly retrospective, performed during the seventies confirmed these findings [2]. What was striking was the magnitude of the transfusion effect: the 1-year graft survival, which was in many series as low as 30% in untransfused recipients, often reached >60 or even 70% in transfused recipients. Therefore, one may say that the need to transfuse anaemic patients on dialysis in the pre-erythropoietin era has played a major role in the development of solid organ transplantation, because the results were so poor in untransfused recipients at that time.

The transfusion effect, however, has been unambiguously apparent only during the early days of transplantation, and in patients immunosuppressed with azathioprine and steroids. For several reasons, the favourable impact of blood transfusions on graft loss from rejection declined sharply during the mid-eighties. The main factor was the availability of cyclosporine A, which prevented immunological graft loss much better than azathioprine. This allowed for a considerable improvement in graft survival in both transfused as well as non-transfused recipients, with the difference between both groups being either reduced to $\pm 5\%$ [3,4], or even no more apparent [5]. Furthermore, transplant teams gained experience in the early diagnosis and treatment of rejection. This translated into an increase in graft survival of >20% between 1982 and 1984 even in non-transfused recipients treated with azathioprine [3]. Finally, progresses in matching for HLA-DR antigens also contributed to the decrease of the transfusion effect. Indeed, registry data revealed that under CsA therapy, a beneficial effect of transfusion on graft survival, approximating $\pm 5\%$, was still seen, but only in patients having one or two HLA-DR antigen mismatches with their kidney donors [4]. No transfusion effect was seen in donor–recipients pairs with no HLA-DR mismatches, or in those with HLA-A or HLA-B mismatches [4].

What remains of the transfusion effect in the early cyclosporine era between 1985 and 1995? The best data come from a prospective study in which candidates for

a first cadaveric graft received either no or three transfusions [6]. Immunosuppression consisted of CyA (classical formulation), azathioprine and steroids. The transfused group had a significant increase in graft survival at 1 year (90 vs 82% in the non-transfused patients). Nevertheless, >50% of patients in both groups experienced a rejection episode, a figure much higher than the present 15–25% rejection rates observed with the more recent immunosuppressive regimens developed since 1995, including tacrolimus, mycophenolate mofetil or rapamycin [7]. Furthermore, the most recent trials with the new drugs showed 1 year graft survival rates of $\geq 90\%$ [7], thus equivalent or better than the results obtained in the transfused recipients under CyA (classical formulation), azathioprine and steroids [6]. While we clearly lack data on random transfusions in cadaveric recipients treated with the newly developed immunosuppressive drugs, this procedure could still prove useful in improving a number of clinical outcomes, such as the incidence or severity of acute and chronic rejection rates, or in allowing for a reduction of the amount of immunosuppression given long term. Only careful prospective studies will help to make progress in this field.

Guideline B. With regard to living-donor transplantation, the pioneering work of Salvatierra showed that the transfusion of blood from the prospective donor (donor-specific transfusion-DST) led to a considerable improvement in the survival of one haplotype-mismatched grafts under azathioprine-steroid therapy [8]. This finding was soon confirmed by others, and extended to recipients of two haplotype-mismatched grafts [9]. One of the drawbacks of this procedure was the occurrence in 20–30% of recipients of anti-donor lymphocytotoxic antibodies that precluded transplantation from the prospective donor [8,10–12]. Administration of azathioprine [9,10,11,13,14] or later CyA [15] during the pre-transplant transfusion period sharply reduced the incidence of this complication to <10%. Once CyA was administered after transplantation, the effect of DST on graft survival disappeared in some [12,15] but not all studies [11,13], and the general feeling is that the case for donor-specific transfusion in non-HLA identical living related transplantation is somewhat stronger than for random blood transfusions in cadaveric transplantation. Without data available on DST in patients receiving the new, more potent immunosuppressive drugs, the indication for DST must be carefully made on an individual basis, taking into account factors such as the risks of rejection and sensitization.

Guideline C. The main drawback of blood transfusions is the risk of sensitization to HLA antigens. Both donor-specific (see above) and random transfusions are associated with a small but definite risk of sensitization to alloantigens. This occurs more frequently in already HLA-sensitized patients, in multiparous women, and in previously transplanted patients than in unsensitized male recipients awaiting their first transplant [17,18]. Among these latter patients, between 10 and 20% developed lymphocytotoxic antibodies (panel

reactive antibodies (PRA) >10%) after five random transfusions; this occurred in >50% of multiparous women [17]. The figures for highly sensitized patients (PRA >90%) reached 10–30% for multiparous women, but <3% for HLA-naïve recipients [17]. As a matter of fact, being either HLA-sensitized or having had a previous transplant has been an almost universal exclusion criteria from the transfusion studies.

In addition, there are a number of other problems associated with the deliberate use of blood products in kidney transplant candidates. First, there is still a legitimate concern about the possible transmission of viral infection through transfusion. While the present risk of acquisition of either HIV, HCV or HBV is at all lower than one in 50 000 [19,20], the possible contamination by a new, presently unknown virus can never be ruled out. Secondly, whether the transfused blood should share HLA class II DR antigens with the recipient in order to induce immunological unresponsiveness has been a matter of debate. Initial work showed that patients who were transfused with 1 unit of blood sharing one HLA-DR antigen with them displayed a major improvement in graft survival compared with non-transfused recipients [21]. Importantly, patients transfused with 1 unit of blood mismatched for two HLA-DR loci experienced no improvement in graft survival [21]. However, these results on graft survival were obtained in patients treated with azathioprine and steroids, and were not confirmed later in patients treated by calcineurin inhibitors [22–24]. At best, some [22,23], but not all [24] retrospective studies showed a lower incidence of rejection in recipients of HLA-DR-matched vs HLA-DR-mismatched blood. Finally, the immunological mechanisms underlying the blood transfusion effect have never been fully elucidated. It has even been difficult, on theoretical grounds, to explain how the infusion to a recipient A of random blood from a donor B would lead to a reduced immune response towards the alloantigens of the unrelated graft donor C. As a result, it has been impossible to evaluate by any kind of *in vitro* assay whether the transfused patient did develop the desired unresponsiveness towards alloantigens.

Guideline D. Early studies [1,2,25–36] established that the pre-transplant transfusions had to fulfil several conditions in order to be beneficial: (i) leukocytes had to be present within the transfused blood unit, although their precise number has never been precisely quantified [25]. (ii) Already a single transfusion appeared to confer a major benefit with regard to graft survival [25], although some studies showed a stepwise increase in graft survival with increasing numbers of transfused blood units [26]. One to 3 units seem a reasonable range. (iii) Fresh blood was more consistently beneficial than frozen blood [26], although this was not observed in all studies [27,28]. (iv) The classical pre-transplant blood transfusion [26,29] was more clearly beneficial than blood transfused solely on the day of transplant surgery [30–33]. Finally, the transfusion effect does not vanish with time: longer periods between

transfusion and transplantation did not compromise the benefit from blood transfusion [6,25].

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I.10 Specific groups

I.10.1 Simultaneous transplantation of kidney and pancreas

Guidelines

A. Simultaneous transplantation of kidney and pancreas should be offered to young recipients with juvenile onset diabetes mellitus as a first therapeutic option to prolong their survival.

(Evidence level B)

B. Simultaneous transplantation of kidney and pancreas may be carried out pre-emptively or early after the start of renal replacement therapy to avoid or retard serious diabetic sequelae.

(Evidence level C)

Commentary on Guideline I.10.1: Simultaneous transplantation of kidney and pancreas

Guidelines A, B. Numerous data are available on the impaired life expectancy of diabetic patients who start renal replacement therapy [1–5]. The interpretation of these data is somewhat hampered by mixing or misclassification of juvenile onset diabetics with type II diabetics; clear evidence is available for juvenile onset diabetics only. No prospective trial has been carried out to compare dialysis therapy, renal transplantation from different donor sources (LRD vs CAD), and simultaneous pancreas and kidney transplantation (SPK), although some single-centre studies have been published [6]. There is one prospective trial comparing kidney-only transplantation and SPK [7]. A regional retrospective analysis from the Netherlands showed increased survival of patients from transplant programs offering SPK compared with KTA (kidney transplant alone) programs [8]. Single-centre studies, such as that reported by Sollinger *et al.* [9], have shown comparable long-term survival with SPK as with KTA and LRD, and superior results for SPK compared with CAD transplant. This effect was most pronounced in recipients under 45 years of age at the time of transplant [9]. It must be borne in mind that even highly efficient pancreas transplant programs commonly have observation times of <10 years [10]. Important data have been obtained from a retrospective analysis using the USRDS database [11]. The authors analysed survival in patients on a waiting list (considered as intent to treat with respect to selection bias), who received a transplant or not from 1991 to 1996. The analysis showed that regardless of the method of transplantation used (SPK, KTA) renal transplantation resulted in a highly significant extension of survival and projected life expectancy.

There are additional data which show that early or even pre-emptive transplantation without commencing dialysis gives improved results [12,13].

The recommendation to transplant the pancreas as early as possible is supported by evidence from a database of pancreas transplants alone (PTA), showing improvement of diabetic nephropathy [14]. Additional beneficial effects on other diabetic sequelae have been observed after SPK. Diabetic retinopathy was halted or even improved slightly, particularly with respect to acute proliferative changes [15]. Some improvements have also been reported in diabetic neuropathy [16,17], a strong negative predictor of outcome if severely prolonged [18]. Some recent evidence also suggests that diabetic microangiopathy improved after SPK if capillary microscopy was applied [19].

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I.10.2 Combined transplants with liver, heart and lung

Guidelines

A. Combined kidney and liver transplants should be offered to carefully selected recipients suffering from simultaneous renal and hepatic failure secondary to viral

hepatitis, extensive polycystic liver disease and primary hyperoxaluria.

(Evidence level C)

B. Combined kidney and heart (lung) transplants should be offered to carefully selected groups of recipients suffering from both chronic renal failure and severe heart failure irrespective of the cause (valvular, myocardial, coronary artery disease).

(Evidence level C)

Commentary on Guideline I.10.2: Combined transplants with liver, heart and lung

Guideline A. A few patients with ESRD also suffer from liver disease, which may or may not be related to the kidney disease. In carefully selected groups, successful combined transplants have been reported, supporting the offering of this procedure to some patients [1–3]. Because of a protective effect of the concomitantly transplanted liver on the kidney graft the functional survival of the kidney is excellent. Due to dialysis-related HBV or HBC infection some patients on RRT (renal replacement therapy) have end-stage liver cirrhosis.

The rate of survival following a combined transplant is related to the recipient's condition. Combined transplants should be considered even earlier than a liver transplant alone, when liver function is not too compromised (Child classification, stages A–B). Poor results have been reported for Child C stage.

Another indication for a combined transplant is extensive polycystic disease of both liver and kidneys [4–7]. The disabling mass of cysts that sometimes exceed 20 kg, leads to malnutrition and cachexia. Although the polycystic liver almost never fails to function, the procedure is indicated when the patients can no longer perform daily life functions. The reported results are encouraging.

An additional indication for a combined liver and kidney transplant exists in primary hyperoxaluria type I (PHI) [8–12]. The enzymatic liver defect results in renal stone disease, renal failure and extensive oxalate deposits in bone, vessels, eyes and skin. Because the prognosis of patients with PHI is poor and a kidney transplant alone has a very high risk of failure, liver transplantation is recommended at an early stage, either alone or, if the renal function is impaired, combined.

Guideline B. Combined heart and kidney transplants have been reported in a number of circumstances [13,14]. Cardiomyopathy combined with some kind of renal disease, coronary or valvular heart disease in young RRT patients, and an increasing number of kidney transplants were performed because of nephrotoxic renal failure following heart transplants [15]. Successful transplants have been reported but the available data is sparse. Rare cases of combined lung and kidney transplants have been reported in cases of kidney disease associated with cystic fibrosis as glomerulonephritis, amyloidosis and nephrotoxic renal fail-

ure. In experienced centres, this procedure can be successful. In addition, in a certain number of lung/heart transplant recipients, kidney failure occurs due to nephrotoxic injury. The prognosis of transplants in these patients is currently poor.

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I.10.3 Retransplants

Guidelines

A. Retransplants after early loss of a previous graft from rejection should be considered to be at increased risk of graft failure. Preventive measures such as improved HLA compatibility and adequate immunosuppression should be undertaken.

(Evidence level B)

B. Retransplants after early loss of a previous graft for technical reasons or late graft loss for any reason give similar results to first grafts and do not require special precautions. For retransplantation, nephrectomy of asymptomatic grafts is not necessary.
(Evidence level C)

Commentary on Guideline I.10.3: Retransplants

Guideline A. Between 10 and 20% of renal transplants performed annually are retransplants [1–3] with up to 20% of patients on waiting lists awaiting a repeat graft. Despite these statistics, a relatively small proportion of patients who lose their first graft are subsequently put on a waiting list, either because of early death after graft loss, because patients may not wish to undergo retransplantation, or as a result of transplant centre selection procedures [4]. In patients being considered for repeat transplantation, the reasons for the loss of the first graft must be investigated (i.e. whether graft loss was due to technical failure, primary non-function, early or late acute rejection, chronic rejection, recurrence of the original disease or non-compliance). A major reason for graft failure may be the development of anti-HLA antibodies, although this remains controversial. Where anti-HLA antibodies developed after a first transplant, preventive measures as flow-cytometry cross-matching, avoiding the mismatched antigens of the previous graft, aiming for a high HLA compatibility, and extended induction immunosuppression, have all been recommended [5–7]. The outcome in immunized retransplants is comparable to recipients immunized for other reasons.

Guideline B. The question of accepting patients after a graft loss due to non-compliance has been discussed

extensively. The available data do not support the exclusion of these patients.

Patients retransplanted with either living or cadaveric donor kidneys after late allograft loss have an almost identical outcome as first grafts, irrespective of donor source. There is no proof that nephrectomy of an asymptomatic failed graft has a beneficial effect [8], and in fact the contrary has also been reported [9]. However, third and subsequent retransplants do worse than first and second grafts.

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